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Evidence-Base to Support
Food Supplement Health Claims

Maintenence of Wellness
Restoration of Wellness

Prevention of Disease
Disease Risk Reduction
Treatment of Disease

Presented to
Codex Committee on Food Labelling

By South African Government

May 2004

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1. Acne

Preventative and curative options include:

Chromium, zinc, vitamin B6, vitamin E, vitamin A

Acne vulgaris: therapy directed at pathophysiologic defects.

Ayres S Jr, Mihan R

Cutis 1981 Jul;28(1):41-2

An effective therapeutic regimen for the treatment of acne vulgaris is presented. The emphasis is based upon correcting a defect in keratinization of the sebaceous follicles with a combination of vitamins A and E. This prevents the formation of milia and comedones, thus depriving the Propionibacterium acnes of a culture medium. Vitamin E also prevents irritating lipid peroxidation of sebum, damaged by bacterial growth, which may be responsible for the inflammatory aspects of acne. No antibiotics were employed in the series of 98 consecutive cases examined herein.

Endotoxin-induced changes in copper and zinc metabolism in the Syrian hamster.

Etzel KR, Swerdel MR, Swerdel JN, Cousins RJ

J Nutr 1982 Dec;112(12):2363-73

The temporal response of zinc and copper metabolism to endotoxin administration was examined in Syrian hamsters over a 144-hour period. Serum copper was significantly elevated at 12, 24 and 72 hours after endotoxin, whereas serum zinc was reduced 4-48 hours after treatment. A brief elevation (8 hours) in liver copper concentration and a sustained (72 hours) increase in liver zinc concentration were also observed. The amount of zinc associated with liver metallothionein (MT) progressively increased with time, to a plateau by 24 hours and persisted at the elevated level until 72 hours after endotoxin treatment. In vitro translation of poly (A)+ RNA from liver polyribosomes showed that following endotoxin treatment MTmRNA activity was maximally elevated 6 hours after endotoxin administration and remained elevated 24 and 48 hours thereafter. Slab gel electrophoresis of serum proteins indicated changes in a stainable protein comigrating with purified ceruloplasmin after endotoxin administration. Pooled gingival tissue from endotoxin-treated hamsters demonstrated a consistently elevated copper content 12-144 hours after treatment. Endotoxin isolated from Bacteroides melaninogenicus was more effective in elevating gingival and serum copper and gingival zinc than Escherichia coli endotoxin. It was concluded that endotoxin administration elicits responses that result in enhanced metaollthionein

mRNA activity. In addition, Cu and Zn concentrations in serum, liver and gingival tissue are influenced by different endotoxins to different degrees.

[Current aspects about the role of zinc in nutrition]. [Article in French]

Favier A Groupe de recherche sur les pathologies oxydatives, Universite de Grenoble, La Tronche.

Rev Prat 1993 Jan 15;43(2):146-51

The role played by zinc in biology is now better known, and numerous biochemical mechanisms, such as immunity or actions on several hormones and more than 200 enzymes, have proved to be zinc-dependent. Thus, many functions are disturbed when this trace metal is deficient, including, for example, taste and appetite, cell multiplication, growth, pregnancy, fertility, defence against bacteria and brain functions. Zinc intake has been found to be unexcessive and indeed, at the limit of sufficiency in the French population. Groups at risk, such as neonates, growing children, pregnant women and elderly people, should have a higher zinc intake provided by dietary measures or supplementation. Zinc supplementation has been shown to exert a beneficial effect in randomized studies concerning children's growth, acne, old people's immunity or low female fertility. Such supplementation must be balanced and given in moderate doses since zinc interacts with other foodstuffs, and an excess of zinc can be as bad as its deficiency in our nutrition.

Nutrition-endocrine interactions: induction of reciprocal changes in the delta 4-5 alpha-reduction of testosterone and the cytochrome P-450-dependent oxidation of estradiol by dietary macronutrients in man.

Kappas A, Anderson KE, Conney AH, Pantuck EJ, Fishman J, Bradlow HL

Proc Natl Acad Sci U S A 1983 Dec;80(24):7646-9

The in vivo biotransformations of drugs known to be metabolized by enzymes localized in the endoplasmic reticulum of liver can be greatly altered by diet in humans, as we have shown previously. Steroid hormones also are metabolized extensively by hepatic microsomal enzymes; therefore, we examined the possibility that testosterone and estradiol biotransformations, as assessed with radiolabeled tracer methods, could be influenced by dietary macronutrients. Normal males were fed a high-protein diet for 2 weeks, followed by a high-carbohydrate diet for an additional 2 weeks. The delta 4-5 alpha-reduction of testosterone was considerably diminished, while the cytochrome P-450-dependent hydroxylation of estradiol at the C2 position was substantially enhanced during ingestion of the high-protein diet as compared with the high-carbohydrate diet. These results indicate that dietary macronutrients can significantly alter major metabolic pathways for testosterone and estradiol in man. The mechanism by which reciprocal changes in the delta 4-5 alpha-reduction of testosterone and the cytochrome P-450-mediated oxidation of estradiol are produced by diets is not known. Similar changes in steroid delta 4-5 alpha-reduction and cytochrome P-

450-dependent chemical oxidations have been observed in circumstances in which the mixed-function oxidase system in liver is induced by agents such as phenobarbital, hexachlorobenzene, dioxin, and polyhalogenated biphenyls. Thus, the alterations in steroid hormone metabolism produced by dietary macronutrients in man mimic those that can be produced by drugs and environmental chemicals.

Oral vitamin A in acne vulgaris. Preliminary report.

Kligman AM, Mills OH Jr, Leyden JJ, Gross PR, Allen HB, Rudolph RI

Int J Dermatol 1981 May;20(4):278-85

Oral vitamin A (retinol) is generally not considered useful in the treatment of acne vulgaris. We conducted a study which showed that retinol was indeed ineffective at the usual doses of 50,000 to 100,000 IU daily. Retinol was highly efficacious in doses of 300,000 units for women and 400,000 to 500,000 units for men, toxicity was slight and limited mainly to skin (xerosis) and mucous membranes (cheilitis). The danger of hypervitaminosis A in this dosage range has been exaggerated. Retinol is a valuable drug for treating stubborn, severely inflammatory acne vulgaris. It is administered until the disease is brought under control, usually within three to four months. Then the dosage is progressively reduced relying on conventional drugs to keep the disease in abeyance.

Pantothenic acid deficiency as the pathogenesis of acne vulgaris.

Leung LH. Department of General Surgery, Hong Kong Central Hospital, Hong Kong.

Med Hypotheses 1995 Jun;44(6):490-2

For years, the pathogenesis of acne vulgaris has been known to be strongly influenced by hormonal factors. However, the exact role of and the interrelationship among the various hormones in question have not been well elucidated. Here, I wish to suggest a radically different theory for its pathogenesis and relate its basic pathology to a deficiency in pantothenic acid, a vitamin hitherto not known to cause any deficiency syndrome in humans. Hence, the effect of hormonal factors in this disease entity becomes secondary to that of the availability of pantothenic acid. A complete cure of this condition is effected by a very liberal replacement therapy with the vitamin.

High-chromium yeast for acne?

McCarty M

Med Hypotheses 1984 Jul;14(3):307-10

Many dermatologists have reported that insulin and tolbutamide are therapeutically effective in acne. This rationalizes a recent observation that high-chromium yeast appears to have value as an acne treatment.

Effects of oral zinc and vitamin A in acne.

Michaelsson G, Juhlin L, Vahlquist A

Arch Dermatol 1977 Jan;113(1):31-6

The effects of oral zinc sulfate (corresponding to 135 mg of zinc daily) alone and in combination with vitamin A (300,000 international units) daily on acne lesions have been compared with those of vitamin A alone and of a placebo. The number of comedones, papules, pustules, and infiltrates were counted at each visit. After four weeks, there was a significant decrease in the number of papules, pustules, and infiltrates in the zinc-treated groups. The effect of zinc plus vitamin A was not better than zinc alone. After 12 weeks of treatment, the mean acne score had decreased from 100% to 15%. The mechanism for the effect of zinc therapy in acne, to our knowledge, is not presently known.

Serum zinc and retinol-binding protein in acne.

Michaelsson G, Vahlquist A, Juhlin L

Br J Dermatol 1977 Mar;96(3):283-6

The serum levels of zinc and retinol-binding protein (RBP) have been determined in 173 patients with acne and compared with those of a control group. The RBP is a specific transport protein and its level in plasma reflects the amount of vitamin A available to the tissues. Patients with severe acne were found to have lower levels of RBP than either patients with mild acne or healthy subjects of the same age. In the case of males with severe acne, the mean serum zinc level was significantly lower than that of the control group. No such difference was observed for girls. The observed condition of low levels of zinc and vitamin A in the serum of patients with severe acne may provide a rationale for the clinically good effect of oral zinc treatment.

A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris.

Michaelsson G, Juhlin L, Ljunghall K

Br J Dermatol 1977 Nov;97(5):561-6

With a double-blind technique, the effects of oral zinc and tetracyclines were compared in 37 patients with moderate and severe acne. No difference in effect between the treatments was seen and no side-effects were noted in any group. After 12 weeks of treatment, the average decrease in the acne score was about 70% in both groups.

Erythrocyte glutathione peroxidase activity in acne vulgaris and the effect of selenium and vitamin E treatment.

Michaelsson G, Edqvist LE

Acta Derm Venereol 1984;64(1):9-14

The glutathione-peroxidase (GSH-Px) activity in erythrocytes was determined in 42 men with severe acne and 47 women with acne--26 of a moderate degree and 21 severe. The male acne patients had significantly lower GSH-Px levels than the controls. The women with acne did not differ significantly from the controls in this respect when patients and controls using oral contraceptives were excluded. Both the female controls and the women with acne using oral contraceptives had significantly higher GSH-Px values than the corresponding groups not using the pill. The pubertal acne girls had the same high GHSH-Px activity as women on oral contraceptives. In an open trial 29 patients were given 0.2 mg of selenium (as Na2Se O3) + 10 mg of tocopheryl succinate for their acne twice daily for 6-12 weeks. A good result was obtained, especially in patients with pustular acne and low GSH-Px activity, and the beneficial effect was usually paralleled by a slow rise of the GSH-Px activity. Some 6-8 weeks after withdrawal of the treatment the GSH-Px values had returned to the pretreatment levels.

A double-blind controlled evaluation of the sebosuppressive activity of topical erythromycin-zinc complex.

Pierard-Franchimont C, Goffin V, Visser JN, Jacoby H, Pierard GE Department of Dermatopathology, University of Liege, Belgium.

Eur J Clin Pharmacol 1995;49(1-2):57-60

In a double-blind randomised study, 14 volunteers applied 4% erythromycin plus 1.2% zinc (Zineryt lotion) and 4% erythromycin lotions, each on half of the forehead twice daily for 3 months. The sebum output was evaluated at 3-week intervals using the photometric and the lipid-sensitive film methods. Evaluations of casual level (CL) and sebum excretion rate (SER) were made with a Sebumeter, and total area of lipid spots (TAS) was measured on Sebutapes. Compared to baseline values, the formulation of the erythromycin-zinc complex induced significant reductions in SER after 6 and 9 weeks, and in CL and TAS at 3, 6, 9 and 12 weeks. The mean reduction in TAS was over 20% for four successive 1-h samplings on completion of the study. Significant reductions in CL, SER and TAS were observed for the erythromycin-zinc formulation compared to the control lotion at 6 and 9 weeks, and also at 3 weeks for SER and TAS, and at 12 weeks for CL and TAS. This study indicates that sebum output is significantly reduced by the erythromycin-zinc complex. This reduction is theoretically beneficial for the acneic patient.

Increased target tissue uptake of, and sensitivity to, testosterone in the vitamin B6 deficient rat.

Symes EK, Bender DA, Bowden JF, Coulson WF

J Steroid Biochem 1984 May;20(5):1089-93

Six-week old male rats were maintained for 4 weeks on a vitamin B6-free diet to cause a moderately severe degree of vitamin B6 depletion. This led to a significant reduction in the circulating concentration of testosterone in plasma (control = 8.36 +/- 1.68, deficient = 2.13 +/- 0.54 nmol/l), but had no effect on circulating concentrations of luteinizing hormone, or, in intact males, on the weight of the prostate relative to body weight. In both intact and 24-h castrated animals vitamin B6 deficiency resulted in a significant increase in the uptake of [3H]testosterone into the prostate, and both increased and prolonged the specific nuclear retention of the steroid, as assessed by the ratio of radioactivity in the nuclear pellet: the high speed supernatant fraction. The results suggest that vitamin B6 has a function in the action of testosterone (and other steroid hormones), possibly in the recycling of receptors from the nucleus back into the cytosol after initial translocation. Vitamin B6 deficient animals have either a reduced rate of synthesis of testosterone or an increased rate of metabolic clearance compared with vitamin B6 supplemented controls, and this appears to be associated with enhanced target organ response to the hormone.

High-dose vitamin A therapy for Darier's disease.

Thomas JR 3d, Cooke JP, Winkelmann RK

Arch Dermatol 1982 Nov;118(11):891-4

Three patients with Darier's disease were treated with 1 X 10(6) IU of orally administered vitamin A daily for 14 days. In all patients, 50% to 80% improvement in the skin lesions was noted. Desquamation was minimal, and side effects consisted of drowsiness, mild frontal headache, dry lips and dry nose. During therapy, all patients had a transient, mild increase in the serum triglyceride level, and two patients had a minimal increase in the serum cholesterol concentration.

Zinc sulfate in acne vulgaris.

Weimar VM, Puhl SC, Smith WH, tenBroeke JE

Arch Dermatol 1978 Dec;114(12):1776-8

The effects of orally administered zinc sulfate in 52 patients with mild to moderate acne vulgaris were compared to those of a placebo capsule. The numbers of comedones, papules, pustules, infiltrates, and cysts were counted at each visit over a 12-week period. Forty patients completed the study. Zinc appeared to have a somewhat beneficial effect on pustules but not on comedones, papules, infiltrates, or cysts. Fourteen patients (50%) in the zinc group had side effects of nausea, vomiting, or diarrhea. Six patients (21%) in the zinc group could not tolerate the nausea and withdrew from the study.

Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc.

Bojar RA, Eady EA, Jones CE, Cunliffe WJ, Holland KT Department of Microbiology, University of Leeds, U.K.

Br J Dermatol 1994 Mar;130(3):329-36

Propionibacteria resistant to high concentrations of erythromycin [minimal inhibitory concentration (MIC) < or = 0.5 mg/ml] are now commonly isolated from the skin of antibiotic-treated acne patients. This double-blind study was carried out to assess the ability of 4% w/v erythromycin with and without 1.2% w/v zinc acetate to reduce the numbers of erythromycin-resistant propionibacteria in vivo, and also to monitor the acquisition of resistant strains de novo during therapy. Under laboratory conditions, erythromycin-resistant propionibacteria were shown to be as sensitive to zinc acetate as fully sensitive strains. In vivo, the erythromycin/zinc complex and erythromycin alone produced highly significant reductions in total propionibacteria ($P < 0.001$) and in the number of erythromycin-resistant strains ($P < 0.001$ at 8 weeks). After 12 weeks, resistant propionibacteria were reacquired, or acquired de novo, by three patients treated with erythromycin alone and four patients treated with the erythromycin/zinc complex. In contrast, changes in numbers of Micrococcaceae were slight and, after 12 weeks, erythromycin-resistant strains were predominant in both treatment groups. In vitro MIC determinations suggested that this finding might be explained by the exceptionally high degree of erythromycin resistance displayed by some staphylococcal strains (MIC < 4 mg/ml) and by the relative insensitivity of all staphylococcal strains to zinc acetate. Erythromycin with and without zinc was clinically effective, and both preparations produced significant reductions in acne grade, and inflamed and non-inflamed lesion counts ($P < 0.001$).

Endotoxin-induced changes in copper and zinc metabolism in the Syrian hamster.

Etzel KR, Swerdel MR, Swerdel JN, Cousins RJ

J Nutr 1982 Dec;112(12):2363-73

The temporal response of zinc and copper metabolism to endotoxin administration was examined in Syrian hamsters over a 144-hour period. Serum copper was significantly elevated at 12, 24 and 72 hours after endotoxin, whereas serum zinc was reduced 4-48 hours after treatment. A brief elevation (8 hours) in liver copper concentration and a sustained (72 hours) increase in liver zinc concentration were also observed. The amount of zinc associated with liver metallothionein (MT) progressively increased with time, to a plateau by 24 hours and persisted at the elevated level until 72 hours after endotoxin treatment. In vitro translation of poly (A)+ RNA from liver polyribosomes showed that following endotoxin treatment MTmRNA activity was maximally elevated 6 hours after endotoxin administration and remained elevated 24 and 48 hours thereafter. Slab gel electrophoresis of serum proteins indicated changes in a stainable protein comigrating with purified ceruloplasmin after endotoxin administration. Pooled gingival tissue from endotoxin-treated hamsters demonstrated a consistently elevated copper content 12-144 hours after treatment. Endotoxin isolated from

Bacteroides melaninogenicus was more effective in elevating gingival and serum copper and gingival zinc than Escherichia coli endotoxin. It was concluded that endotoxin administration elicits responses that result in enhanced metaollthionein mRNA activity. In addition, Cu and Zn concentrations in serum, liver and gingival tissue are influenced by different endotoxins to different degrees.

The effect of zinc on the 5 alpha-reduction of testosterone by the hyperplastic human prostate gland.

Leake A, Chisholm GD, Habib FK

J Steroid Biochem 1984 Feb;20(2):651-5

The present studies were performed to evaluate the role of zinc in the regulation of testosterone 5 alpha-reduction by the 800 g supernatants prepared from human benign prostate hyperplasia specimens. The results show that when zinc is added at low concentrations the 5 alpha-reduction of testosterone is increased but at higher cation concentrations the metabolism is significantly inhibited. This decrease was mediated by both a non-competitive inhibition of the binding of testosterone to the 5 alpha-reductase enzyme and by a reduction in the formation of the NADPH cofactor. We have also demonstrated that the decreased synthesis of NADPH was produced by a competitive inhibition of both G6P and NADP binding to the G6PD enzyme. The data also suggests that the increase in testosterone metabolism observed at low zinc concentrations does not produce any changes in the binding of testosterone to the 5 alpha-reductase enzyme. In spite of the above observations we were unable to establish any correlation between the endogenous zinc content of the tissue and the in vitro capacity of the BPH samples to 5 alpha-reduce testosterone. The present study suggests a possible physiological role for the regulation of testosterone metabolism by zinc in the human prostate gland.

Toxic doses of vitamin A for pityriasis rubra pilaris.

Randle HW, Diaz-Perez JL, Winkelmann RK

Arch Dermatol 1980 Aug;116(8):888-92

Seven patients who were disabled by pityriasis rubra pilaris were given toxic doses of oral vitamin A (1 million IU/day in six of the seven patients) for five to 14 days. Within 72 hours, the patients began to exfoliate the hyperkeratotic and keratodermatous lesions. The desquamative process was completed between ten and 14 days. The skin remained erythematous for several months before assuming a normal color. The skin of six of the seven patients was virtually cleared by the treatment, and none suffered a relapse of the pityriasis rubra pilaris. Serial skin biopsy specimens showed evidence suggestive of an accelerated turnover rate of epidermal cells during treatment. Transient abnormalities of liver function test results were noted in two patients.

[Retinotherapy of skin diseases]. [Article in French]

Saurat JH

Presse Med 1994 Nov 5;23(34):1551-3

The discovery of retinoid receptors has contributed greatly to our understanding of the mechanism of action of vitamin A. The organism produces at least two ligands from ingested vitamin A which act as hormones modulating the activity of numerous genes via their nuclear receptor. These ligands are produced locally by target cells from retinol and retinaldehyde. These advances do not respond to the clinicians' interrogation as to why 13cis retinoic acid blocks sebaceous secretion and cures severe acne while other known retinoids are uneffective. Current research would suggest that the expression of nuclear receptors is not altered in skin diseases but that upstream anomalies in the intracrine system (enzymes and binding proteins) could be involved. Clinically, teratogenic risks are a major obstacle to the oral administration of retinoids and the future in skin diseases lies most likely in topical applications.

2. Allergies

Preventative and curative options include:
Omega 3 and 6 fatty acids, co enzyme Q10, vitamin C, vitamin E, magnesium, DHEA, n-acetyl cysteine, bifido bacteria, grape seed extract, ginkgo biloba, glutamine, nettle leaf, aloe vera, pantothenic acid, quercitin,

Thiols decrease cytokine levels and down-regulate the expression of CD30 on human allergen-specific T helper (Th) 0 and Th2 cells.

Bengtsson A, Lundberg M, Avila-Carino J, Jacobsson G, Holmgren A, Scheynius A. Department of Medicine, Unit of Clinical Allergy Research, Karolinska Institutet, Stockholm, Sweden. asa.bengtsson@mb.ki.se

Clin Exp Immunol 2001 Mar;123(3):350-360

The thiol antioxidant N-acetyl- L-cysteine (NAC), known as a precursor of glutathione (GSH), is used in AIDS treatment trials, as a chemoprotectant in cancer chemotherapy and in treatment of chronic bronchitis. In vitro, GSH and NAC are known to enhance T cell proliferation, production of IL-2 and up-regulation of the IL-2 receptor. The 120-kD CD30 surface antigen belongs to the tumour necrosis factor (TNF) receptor superfamily. It is expressed by activated T helper (Th) cells and its expression is sustained in Th2 cells. We have analysed the effect of GSH and NAC on the cytokine profile and CD30 expression on human allergen-specific T cell clones (TCC). TCC were stimulated with anti-CD3 antibodies in the presence of different concentrations of GSH and NAC. Both thiols caused a dose dependent down-regulation of IL-4, IL-5 and IFN-gamma levels in Th0 and Th2 clones, with the most pronounced decrease of IL-4. Furthermore, they down-regulated the surface expression of CD30, and the levels of soluble CD30 (sCD30) in the culture supernatants were decreased. In contrast, the surface expression of CD28 or CD40 ligand (CD40L) was not significantly changed after treatment with 20 m M NAC. These results indicate that GSH and NAC favour a Th1 response by a preferential down-regulation of IL-4. In addition, the expression of CD30 was down regulated by GSH and NAC, suggesting that CD30 expression is dependent on IL-4, or modified by NAC. In the likely event that CD30 and its soluble counterpart prove to contribute to the pathogenesis in Th2 related diseases such as allergy, NAC may be considered as a future therapeutic agent in the treatment of these diseases.

Effects of Orally consumed aloe vera juice on gastrointestinal function in normal humans

Jeffrey Bland Linus Pauling Institute of Science & Medicine

Preventive Medicine March/April 1985

This study evaluated the effect of oral Aloe Vera juice supplemented on gastric pH, stool specific gravity, protein digestion/absorption, and stool microbiology. Results indicate that supplemental oral Aloe Vera juice is well toledrated by most individuals and has a favorable effects upon a number of gastrointestinal parameters. A discussion of the potential role of Aloe Vera juice on inflammatory bowel disorders based upon this work presented.

Effect of vitamin C on histamine bronchial responsiveness of patients with allergic rhinitis

Bucca C.; Rolla G.; Oliva A.; Farina J.-C. Clinica Medica I, Dpt. Scienz Biomediche e Oncologia Umana, Via Genova3, 10126 Torino Italy

Ann. Allergy (USA), 1990, 65/4 (311-314)

The effect of acute oral administration of 2 g vitamin C on bronchial responsiveness to inhaled histamine in 16 patients with allergic rhinitis was compared with placebo on two consecutive days in double-blind, crossover design. The PC15FEV1 was significantly increased one hour after treatment with vitamin C but not after placebo.

Pretreatment of skin with a Ginkgo biloba extract/sodium carboxymethyl-beta-1,3-glucan formulation appears to inhibit the elicitation of allergic contact dermatitis in man

Castelli D.; Colin L.; Camel E.; Ries G. D. Castelli, RoC Laboratoires de Dermo-esthetique, 50 Rue de Seine, 92704 Colombes France

Contact Dermatitis (Denmark), 1998, 38/3 (123-126)

The clinical efficiency of mitigating contact dermatitis with a Ginkgo biloba extract and carboxymethyl-beta-1,3-glucan formulation was investigated in a double-blind versus placebo study using 22 subjects (Caucasian women aged 22-55 years) with allergic contact dermatitis from various substances in the European standard series. The formulation was applied to intact skin 2 x a day for 2 weeks ('in use' application) prior to a single application of a selected contact allergen under a Finn Chamber for 24 h. Readings were carried out in a blind study by a dermatologist 2 and 3 days after patch removal. Representative photographs were taken of treated, placebo and untreated test areas. 68.2% of the panelists showed significantly reduced skin reactivity ($p = 0.037$*) on the treated site 2 days after patch removal, versus untreated and/or placebo sites. This finding indicates that the Ginkgo biloba/carboxymethyl-beta-1,3-glucan formulation can mitigate against allergic contact dermatitis.

The potential role of tocopherol in asthma and allergies: modification of the leukotriene pathway.

Centanni S, Santus P, Di Marco F, Fumagalli F, Zarini S, Sala A. Respiratory Unit, San Paolo Hospital, University of Milan, Milan, Italy. stefano.centanni@unimi.it

BioDrugs 2001;15(2):81-86

Metabolism of arachidonic acid via the 5-lipoxygenase (5-LO) pathway leads to the formation of hydroperoxyeicosatetraenoic acids (HPETEs) and leukotriene (LT) A4. This unstable allylic epoxide can be further converted by secondary enzymes into LTB(4) and cysteinyl LTs. LTs represent a family of potent biologically active compounds synthesised by specific cell types and by transcellular biosynthetic mechanisms. Cysteinyl LTs are involved in the pathogenesis of asthma, and recent data indicate that individuals with asthma may have enhanced basal excretion of urinary LTE4 compared with normal individuals. Tocopherol (vitamin E) and tocopherol acetate strongly inhibit potato 5-LO in an irreversible and noncompetitive way, and, by affecting the redox state of cells possessing 5-LO, they may influence the production of biologically active LTs. It has been reported that normal plasma levels of tocopherol may enhance the lipoxygenation of arachidonic acid, whereas higher tocopherol levels exert a suppressive effect that is consistent with its role as a hydroperoxide scavenger. Receptor-mediated activation of neutrophils in individuals with asthma results in the synthesis of LTs. This activation is inhibited by tocopherol in a concentration-dependent manner. Additional controlled studies are needed to assess the effect of tocopherol on leukotriene production in asthmatic individuals. The results of these studies may be useful in developing new therapeutic approaches in asthmatic/allergic patients.

Increase of intestinal Bifidobacterium and suppression of coliform bacteria with short-term yogurt ingestion.

Chen RM, Wu JJ, Lee SC, Huang AH, Wu HM. Department of Pathology, National Cheng Kung University Medical College, Tainan, Taiwan, Republic of China.

J Dairy Sci 1999 Nov;82(11):2308-2314

To determine whether ingestion of yogurt would alter human intestinal bacterial composition and whether Bifidobacterium numbers would increase in the intestine, 34 healthy volunteers were studied. The experimental period was 26 d, including an initial 8 d without yogurt, 10 d with three bottles (230 ml each) of AB yogurt per day (President Enterprise Corporation, Tainan, Taiwan), and 8 d without yogurt. Stool samples were taken at 3- to 4-d intervals. The bacteria of each fresh stool sample were promptly analyzed by dilution and culture on blood, MacConkey, Center for Disease Control and NNLP agars, the agar contained nalidixic acid, neomycin sulfate, LiCl, and paromomycin sulfate for aerobes, coliforms, anaerobes, and bifidobacteria, respectively. The number of bacteria

was determined as colony-forming units per gram of dried stool. Results indicated that ingestion of AB yogurt increased the counts of anaerobic bacteria, suppressed aerobic bacteria, and significantly elevated the bifidus to coliform ratio. Arbitrarily primed polymerase chain reaction was used to differentiate the identity of bifidobacteria in four volunteers before and after yogurt ingestion and confirmed that B. bifidum ingested from the yogurt survived and proliferated in the stool throughout the experiment. However, the elevated bifidus to coliform ratio gradually diminished and disappeared after yogurt consumption was discontinued. In conclusion, ingestion of yogurt increased the numbers of stool bifidobacteria and suppressed coliform bacteria. The ingested bifidobacteria survived for more than 8 d after yogurt consumption was discontinued.

Influence of glutamine on cytokine production by human gut in vitro.

Coeffier M, Miralles-Barrachina O, Le Pessot F, Lalaude O, Daveau M, Lavoinne A, Lerebours E, Dechelotte P. Appareil Digestif Environnement et Nutrition group (ADEN), France.

Cytokine 2001 Feb 7;13(3):148-154

BACKGROUND: glutamine modulates cytokine production by immune cells in vitro and protects the gut from experimental enterocolitis, but data on the effect of glutamine on cytokine production in human gut are lacking. AIM: to assess the effect of glutamine pre-treatment in vivo and in vitro on cytokine production by intestinal mucosa.

METHODS: nine fasted volunteers received either enteral glutamine or saline over 6 h in a cross-over design. Duodenal biopsies were cultured for 24 h with or without glutamine. Cytokine content of culture media was analysed by ELISA, and the expression of cytokine mRNA in biopsies was assessed by semi-quantitative RT-PCR. Results: glutamine given in vivo and in vitro significantly decreased IL-6 [1.4 (0.8-8.5) vs 8.9 (1.0-43.9)] and IL-8 production [5.8 (0-51.4) vs. 53.0 (2.5-114.6), pg/mg wet tissue], median (range), both < or =0.01, in comparison to no glutamine experiments. Glutamine did not influence IL-4 production. IL-1beta, IL-10 and TNF-alpha were not detectable in culture media. The expression of any cytokine mRNA was not influenced by glutamine.

CONCLUSIONS: glutamine reduces pro-inflammatory cytokine production by human intestinal mucosa, probably by a post-transcriptional pathway. Glutamine could be useful to modulate inflammatory conditions with imbalanced cytokine production.

Increased nitrosothiols in exhaled breath condensate in inflammatory airway diseases.

Corradi M, Montuschi P, Donnelly LE, Pesci A, Kharitonov SA, Barnes PJ. Institute of Respiratory Diseases, University of Parma, Italy.

Am J Respir Crit Care Med 2001 Mar;163(4):854-858

Nitrosothiols (RS-NOs) are formed by interaction of nitric oxide (NO) with glutathione and may limit the detrimental effect of NO. Because NO generation is increased in airway inflammation, we have measured RS-NOs in exhaled breath condensate in patients with asthma, cystic fibrosis, or chronic obstructive pulmonary disease (COPD). We also measured exhaled NO and nitrite (NO(2-)) in the same subjects. RS-NOs were detectable in exhaled breath condensate of all subjects. RS-NOs were higher in subjects with severe asthma (0.81 0.06 microM) when compared with normal control subjects (0.11 0.02 microM, < 0.01) and with subjects with mild asthma (0.08 0.01 microM, < 0.01). Elevated RS-NOs values were also found in patients with cystic fibrosis (0.35 0.07 microM, < 0.01), in those with COPD (0.24 0.04 microM, p < 0.01) and in smokers (0.46 0.09 microM, < 0.01). In current smokers there was a correlation (r = 0.8, < 0.05) between RS-NOs values and smoking history (pack/year). We also found elevated concentrations of NO(2-) in patients with severe asthma, cystic fibrosis, or COPD, but not in smokers or patients with mild asthma. This suggests that exhaled NO(2-) is less sensitive than exhaled RS-NOs. This study has shown that RS-NOs are detectable in exhaled breath condensate of healthy subjects and are increased in patients with inflammatory airway diseases. As RS-NOs concentrations in exhaled breath condensate vary in the different airway diseases and increase with the severity of asthma, their measurement may have clinical relevance as a noninvasive biomarker of nitrosative stress.

Can immunoregulatory lactic acid bacteria be used as dietary supplements to limit allergies?

Cross ML, Gill HS. Milk & Health Research Centre, Institute of Food, Nutrition and Human Health, Massey University, Palmerston North, New Zealand.

Int Arch Allergy Immunol 2001 Jun;125(2):112-119

Studies in gnotobiotic animals have suggested that the intestinal bacterial flora may play an important role in priming the immune system during ontogeny to limit dysfunctional responses, including allergy. Prospective clinical studies have identified a higher incidence of allergy expression in early childhood among children who have low enteric populations of lactic acid bacteria (LAB), such as lactobacilli and bifidobacteria, further supporting a role for gut-colonizing bacteria in regulating immunological atopy. There is some evidence to suggest that supplementing the human diet with probiotic LAB might combat both allergy development and expression of atopy in allergy sufferers; however, definitive information, in the form of controlled intervention trials, remains scant. Recent immunological evidence has indicated that certain strains of LAB can stimulate the production of type I and II interferons and pro-interferon monokines (IL-12 and IL-18), following contact with the immune system; therefore, probiotic forms of immunoregulatory LAB could be used as dietary supplements to modify the gut microflora and provide pro-T helper cell 1 (Th1) STAT-activating signals sufficient to deviate the immune phenotype and correct the Th2-type bias which promotes allergy. This review outlines the clinical and laboratory evidence of a role for LAB in combating allergies, and attempts to explain this phenomenon in

terms of our current understanding of immunoregulatory signals produced by gut-colonizing microbes. Copyright 2001 S. Karger AG, Basel

Quercetin inhibits anaphylactic contraction of guinea pig ileum smooth muscle.

Fanning MJ, Macander P, Drzewiecki G, Middleton E Jr.

Int Arch Allergy Appl Immunol 1983;71(4):371-3

Certain flavonoids inhibit antigen-induced release of histamine from mast cells and basophils and also inhibit contraction of guinea pig ileum induced by histamine, acetylcholine, and PGE2. We examined the effect of one flavonoid, quercetin, on anaphylactic smooth muscle contraction of ileum from guinea pigs sensitized to egg albumin. Quercetin inhibited both the phasic and tonic components of anaphylactic contraction in a concentration-dependent fashion (IC50 approximately 10 microM). Whether this is primarily an effect on mast cell mediator release or inhibition of mediator effects on smooth muscle has not been established.

TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression.

Fukatsu K, Kudsk KA, Zarzaur BL, Wu Y, Hanna MK, DeWitt RC. The University of Tennessee Health Science Center, Memphis 38163, USA.

Shock 2001 Apr;15(4):318-322

Total parenteral nutrition (TPN) decreases intestinal IgA and levels of Th2 cytokines, interleukin (IL)-4, and IL-10 within the supernatants of intestinal homogenates. These cytokines are known to stimulate IgA production in vitro by cells of the gut-associated lymphoid tissue (GALT). Glutamine (GLN) supplementation of TPN normalizes GALT mass and cytokine levels. Because intestinal homogenates contain mucosa which itself is a source of cytokines, it was unclear whether cytokines change within the GALT itself. This study investigates dietary effects on IL-4 and IL-10 cytokine mRNA expression within isolated GALT lamina propria cells after lipopolysaccharide (LPS) stimulation. Prospective randomized experimental trials were used in this study. Fifty-nine mice were randomized to chow, intravenous TPN (IV-TPN), intragastric TPN (IG-TPN), complex enteral diet (CED), or 2% GLN-supplemented TPN (GLN-TPN). In experiment 1, animals were fed chow, IV-TPN, IG-TPN, or CED for 5 days and received intraperitoneal LPS (100 microg/kg BW), and then were sacrificed 1 h later. Intestine was harvested for GALT lamina propria. Total RNA was extracted from lamina propria cells and cytokine mRNA for IL-4, and IL-10 was measured by reverse transcriptase polymerase chain reaction. IgA levels of intestinal washing were also measured with ELISA. In experiment 2, mRNA for IL-4 and IL-10, and intestinal IgA levels were measured in mice fed chow, IV-TPN, or GLN-TPN as in experiment 1. Both IL-4 and IL-10 mRNA expression

decreased significantly in IV-TPN mice compared to chow or CED feeding. IG-TPN resulted in IL-10 mRNA expression significantly lower than chow or CED but significantly better than IV-TPN. GLN preserved IL-4 and IL-10 mRNA levels, which correlated with intestinal IgA levels. Route and type of nutrition as well as GLN influence message for the Th2 type IgA-stimulating cytokines, IL-4 and IL-10, within the primary site of GALT IgA production, the lamina propria.

Enrichment of bifidobacteria from human gut contents by oligofructose using continuous culture.

Gibson GR, Wang X. Medical Research Council, Dunn Clinical Nutrition Centre, Cambridge, UK.

FEMS Microbiol Lett 1994 May 1;118(1-2):121-127

Chemostat cultures of human faecal bacteria were used to determine the bifidogenic effect of oligofructose, a fermentable carbohydrate found in a number of plants. In single stage continuous culture, oligofructose preferentially enriched for bifidobacteria, in comparison to sucrose and inulin. This stimulatory effect was enhanced at a high dilution rate, high substrate concentration and low pH. These parameters are likely to approximate to those that occur in the proximal colon. Studies with a three-stage continuous culture model of the large intestine confirmed the bifidogenic effect of oligofructose. These in vitro data indicate that an increase in the concentration of fructose-based oligosaccharides in the diet may alter the balance of the gut microflora towards bifidobacteria, a purported health-promoting genus.

Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin.

Gibson GR, Beatty ER, Wang X, Cummings JH. Medical Research Council, Dunn Clinical Nutrition Centre, Cambridge, England.

Gastroenterology 1995 Apr;108(4):975-982

BACKGROUND/AIMS: Oligofructose and inulin are naturally occurring indigestible carbohydrates. In vitro they selectively stimulate the growth of species of Bifidobacterium, a genus of bacteria considered beneficial to health. This study was designed to determine their effects on the large bowel microflora and colonic function in vivo.

METHODS: Eight subjects participated in a 45-day study during which they ate controlled diets. For the middle 15 days, 15 g.day-1 oligofructose was substituted for 15 g.day-1 sucrose. Four of these subjects went on to a further period with 15 g.day-1 inulin. Bowel habit, transit time, stool composition, breath H2 and CH4, and the predominant genera of colonic bacteria were measured.

RESULTS: Both oligofructose and inulin significantly increased bifidobacteria from 8.8 to 9.5 log10 g stool-1 and 9.2 to 10.1 log10 g stool-1, respectively,

whereas bacteroides, clostridia, and fusobacteria decreased when subjects were fed oligofructose, and gram-positive cocci decreased when subjects were fed inulin. Total bacterial counts were unchanged. Fecal wet and dry matter, nitrogen, and energy excretion increased with both substrates, as did breath H2. Little change in fecal short-chain fatty acids and breath CH4 was observed.

CONCLUSIONS: A 15-g.day-1 dietary addition of oligofructose or inulin led to Bifidobacterium becoming the numerically predominant genus in feces. Thus, small changes in diet can alter the balance of colonic bacteria towards a potentially healthier microflora.

[Role of polyunsaturated fatty acids in diet therapy of children with allergic diseases]. [Article in Russian]

Gorelova ZI, Ladodo KS, Levachev MM, Lupinovich VL, Mamonova LG, Orlova SV, Balabolkin II, Zadkova GF, Arutiunova MB.

Vopr Pitan 1999;68(1):31-35

135 pediatric patients receiving hypoallergic diet were included into the study group. The control group consisted of 20 children. The impact of PUFA omega-3 biologically active supplements (polyen, prima-Oil) was studied in hypoallergic rations. Biochemical indices were simultaneously investigated. The revealed dynamic changes of fatty acid spectrum in plasma and red cell membranes, cellular and humoral immunity status and eicosanoids synthesis were followed by positive clinical changes. Diets enriched with biologically active supplementation (PUPA omega-3) can be recommended for application in pediatric practice.

Nutritional and pharmacological enhancement of gut-associated lymphoid tissue.

Hanna MK, Kudsk KA. The University of Tennessee, Memphis, USA.

Can J Gastroenterol 2000 Nov;14:145D-151D

There has been an explosion of research in the field of nutrition over the past quarter century. Clinical studies have demonstrated the effectiveness of providing nutrition by the enteral route in reducing septic morbidity in critically ill patients. These improved outcomes have been substantiated by animal models that show that enteral nutrition decreases gut permeability while maintaining the gut-associated lymphoid tissue (GALT) in mucosal immunity. Evidence points to the important immunological role of the gut in the maintenance of mucosal immunity at both intestinal and extraintestinal sites. The preservation of this mucosal immunity by enteral nutrition is consistent with the lower morbidity seen in severely injured patients who receive nutrition via the gastrointestinal tract. For patients who are unable to be fed by the enteral route and who require parenteral nutrition, several supplements show promise in enhancing the mucosal immune system defenses. The nutritional and pharmacological tactics that may enhance the GALT and thereby maintain mucosal immunity are examined.

Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia.

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Thorax 2000 Sep;55(9):775-779

BACKGROUND: The causes of the worldwide increases in asthma and allergic diseases in childhood, which seem to relate to increasing prosperity, are unknown. We have previously hypothesised that a reduction in the antioxidant component of the diet is an important factor. An investigation was undertaken of dietary and other risk factors for asthma in Saudi Arabia where major lifestyle differences and prevalences of allergic disease are found in different communities.

METHODS: From a cross sectional study of 1444 children with a mean age of 12 (SD 1) years in Jeddah and a group of rural Saudi villages, we selected 114 cases with a history of asthma and wheeze in the last 12 months and 202 controls who had never complained of wheeze or asthma, as recorded on the ISAAC questionnaire. Risk factors for asthma and allergies (family history, social class, infections, immunisations, family size, and diet) were ascertained by questionnaire. Atopy was assessed by skin prick testing.

RESULTS: In univariate analyses, family history, atopy, and eating at fast food outlets were significant risk factors for wheezy illness, as were the lowest intakes of milk and vegetables and of fibre, vitamin E, calcium, magnesium, sodium, and potassium. These differences were present also in the urban children considered separately. Sex, family size, social class, infections, and parental smoking showed no relationship to risk. In multiple logistic regression analysis, urban residence, positive skin tests, family history of allergic disease, and the lowest intakes of vitamin E, magnesium and sodium related significantly and independently to risk. The lowest tertile of intake of vitamin E was associated with a threefold (95% CI 1.38 to 6.50) increase in risk when adjusted for the other factors. Intake of milk and vegetables both showed inverse linear relationships to being a case.

CONCLUSIONS: This study suggests that dietary factors during childhood are an important influence in determining the expression of wheezy illness, after allowing for urban/rural residence, sex, family history, and atopy. The findings are consistent with previous studies in adults and with the hypothesis that change in diet has been a determinant of the worldwide increases in asthma and allergies.

Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial.

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Lancet 2001 Apr 7;357(9262):1076-1079

BACKGROUND: Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy).

METHODS: In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint.

FINDINGS: Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6).

INTERPRETATIONS: Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

Dietary fatty acids and allergy.

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Ann Med 1999 Aug;31(4):282-287

The increase in the prevalence of atopic diseases has recently been linked to altered consumption of polyunsaturated fatty acids (PUFAs). As typical Western diets contain almost 10 times more linoleic acid (18:2 omega-6) than alpha-linolenic acid (18:3 omega-3), it is the metabolism of the former that predominates. Subsequently produced arachidonic acid-derived eicosanoids alter the balance of T-helper cells type 1 and type 2 thus favouring the production of immunoglobulin (Ig)E. In atopic subjects, the impact of this excessive eicosanoid production may be further strengthened as a result of changes in cyclic nucleotide metabolism exacerbated by substrate availability. Dietary omega-3 fatty acids can have marked influence on both specific and nonspecific immune responses in modifying eicosanoid production and replacing omega-6 fatty acids in cell membranes. Therefore, it is concluded that careful manipulation of dietary PUFAs may play a key role in the successful management of inflammation associated with atopic diseases.

Polyunsaturated fatty acids in maternal diet, breast milk, and serum lipid fatty acids of infants in relation to atopy.

Kankaanpaa P, Nurmela K, Erkkila A, Kalliomaki M, Holmberg-Marttila D, Salminen S, Isolauri E. Departments of Biochemistry and Food Chemistry, and Pediatrics, University of Turku, Turku, Finland.

Allergy 2001 Jul;56(7):633-638

BACKGROUND: The increased consumption of n-6 polyunsaturated fatty acids (PUFA) has been shown to coincide with the increased prevalence of atopic diseases. We aimed to investigate whether maternal diet and atopic status influence the PUFA composition of breast milk and the serum lipid fatty acids of infants.

METHODS: Maternal diet was assessed by a food questionnaire. The PUFA composition of breast milk obtained at 3 months from 20 allergic and 20 healthy mothers and of their infants' (10 atopic and 10 nonatopic/group of mothers) serum lipids was analyzed.

RESULTS: Although no differences in maternal PUFA intake were observed, the breast milk of allergic mothers contained less gamma-linolenic acid (18:3 n-6) than that of healthy mothers. Similarly, atopic infants had less gamma-linolenic acid in phospholipids than healthy infants, although n-6 PUFA were elevated in other serum lipid fractions in atopic infants. The serum lipid fatty acids in atopic infants did not correlate with those in maternal breast milk.

CONCLUSION: Our results suggest that dietary n-6 PUFA are not as readily transferred into breast milk or incorporated into serum phospholipids, but may be utilized for other purposes, such as eicosanoid precursors, in allergic/atopic individuals. Subsequently, high dietary proportions of n-6 PUFA, or reduced proportions of regulatory PUFA, such as gamma-linolenic acid and n-3 PUFA, may be a risk factor for the development of atopic disease.

Aloe vera.

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J Am Acad Dermatol 1988 Apr;18(4 Pt 1):714-720

We review the scientific literature regarding the aloe vera plant and its products. Aloe vera is known to contain several pharmacologically active ingredients, including a carboxypeptidase that inactivates bradykinin in vitro, salicylates, and a substance(s) that inhibits thromboxane formation in vivo. Scientific studies exist that support an antibacterial and antifungal effect for substance(s) in aloe vera. Studies and case reports provide support for the use of aloe vera in the treatment of radiation ulcers and stasis ulcers in man and burn and frostbite injuries in animals. The evidence for a potential beneficial effect associated with the use of

aloe vera is sufficient to warrant the design and implementation of well-controlled clinical trials.

Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels.

Kudsk KA, Wu Y, Fukatsu K, Zarzaur BL, Johnson CD, Wang R, Hanna MK. University of Tennessee, Memphis, USA.

JPEN J Parenter Enteral Nutr 2000 Sep;24(5):270-274

BACKGROUND: Total parenteral nutrition (TPN) prevents progressive malnutrition but fails to maintain intestinal gut-associated lymphoid tissue (GALT) or established respiratory antiviral or antibacterial mucosal immunity. Our previous work demonstrated that decreases in intestinal immunoglobulin A (IgA) were associated with decreases in Th2-type IgA-stimulating cytokines, interleukin (IL)-4 and IL-10. Because glutamine supplementation of TPN partially preserves respiratory defenses and normalizes GALT, we investigated the ability of parenteral glutamine to normalize respiratory and intestinal IgA levels and measured Th2 cytokines in intestinal homogenates.

METHODS: Animals were cannulated and randomly assigned to receive chow (n = 17), TPN (n = 18), or an isonitrogenous, isocaloric TPN solution formulated by removing the appropriate amount of amino acids and replacing them with 2% glutamine (n = 18) for 5 days. Respiratory tract and intestinal washings were obtained for IgA and the intestine homogenized and analyzed for IL-4 and IL-10.

RESULTS: TPN decreased intestinal and respiratory IgA in association with decreases in intestinal IL-4 and IL-10 compared with chow-fed animals. Glutamine significantly improved respiratory and intestinal IgA levels, significantly improved IL-4 compared with TPN animals, and maintained IL-10 levels midway between chow-fed and TPN animals.

CONCLUSIONS: Glutamine-enriched TPN preserved both extraintestinal and intestinal IgA levels and had a normalizing effect on Th2-type IgA-stimulating cytokines.

Oligosaccharides in human milk: structural, functional, and metabolic aspects.

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Annu Rev Nutr 2000;20:699-722

Research on human milk oligosaccharides (HMOs) has received much attention in recent years. However, it started about a century ago with the observation that oligosaccharides might be growth factors for a so-called bifidus flora in breast-fed

infants and extends to the recent finding of cell adhesion molecules in human milk. The latter are involved in inflammatory events recognizing carbohydrate sequences that also can be found in human milk. The similarities between epithelial cell surface carbohydrates and oligosaccharides in human milk strengthen the idea that specific interactions of those oligosaccharides with pathogenic microorganisms do occur preventing the attachment of microbes to epithelial cells. HMOs may act as soluble receptors for different pathogens, thus increasing the resistance of breast-fed infants. However, we need to know more about the metabolism of oligosaccharides in the gastrointestinal tract. How far are oligosaccharides degraded by intestinal enzymes and does oligosaccharide processing (e.g. degradation, synthesis, and elongation of core structures) occur in intestinal epithelial cells? Further research on HMOs is certainly needed to increase our knowledge of infant nutrition as it is affected by complex oligosaccharides.

[Effects of ginkgo leave concentrated oral liquor in treating asthma]. [Article in Chinese]

Li MH, Zhang HL, Yang BY. Qingdao Hospital of Integrated Traditional and Western Medicine, Shandong.

Zhongguo Zhong Xi Yi Jie He Za Zhi 1997 Apr;17(4):216-218

OBJECTIVE: To determine the effects of Ginkgo leave concentrated oral liquor (GLC) on airway inflammation.

METHODS: Airway hyperreactivity and clinical symptoms and pulmonary functions of asthma patients were determined.

RESULTS: In contrast to placebo group, GLC significantly reduced airway hyperreactivity (< 0.05) and improved clinical symptoms (< 0.05), pulmonary functions (< 0.05) of the asthmatic patients.

CONCLUSION: GLC is an effective drug of anti airway inflammation.

In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A.

Mahmoud F, Abul H, Onadeko B, Khadadah M, Haines D, Morgan G. Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences and Nursing, Kuwait University, Sulaibekhat.

Jpn J Pharmacol 2000 Jul;83(3):241-245

The effects of Ginkgolide B (BN52021) on in vitro activation responses of human peripheral blood mononuclear cells (PBMC) from asthmatic patients was measured using 2-channel flow cytometric analysis of activation-associated cell surface antigens or ELISA assays for cytokines known to be expressed by PBMC during T1 or T2 immunological activation. BN52021 is an anti-inflammatory

extract of Ginkgo biloba and has been used therapeutically. It is a known inhibitor of platelet activating factor (PAF), which is important in the pathogenesis of asthma, and may synergise with cyclosporin A (CyA) to inhibit pathogenic immune activation in asthmatics. We compared the inhibitory effects of BN52021 and CyA (1 microM each) on activation of PBMC of asthmatic patients stimulated by phorbol myristate acetate and calcium ionophore. Inhibition of production of the cytokines IL-4 and IL-5 by BN52021 was insignificant compared to CyA. However, BN52021 significantly reversed the increase in activation-associated CD45RA expression, with a trend towards decreased expression of HLA-DR. Lymphocyte activation markers were not significantly altered by CyA. Since they appear to have differing effects on activated cells, the anti-inflammatory effects of CyA and BN52021 in atopic asthma is potentially additive. The present approach may be useful for preliminary evaluation of novel therapeutic modalities for asthma treatment.

Study of the effect of Lactobacillus paracasei and fructooligosaccharides on the faecal microflora in weanling piglets.

Nemcova R, Bomba A, Gancarcikova S, Herich R, Guba P Research Institute of Veterinary Medicine, Kosice, Slovak Republic.

Berl Munch Tierarztl Wochenschr 1999 Jun-Jul;112(6-7):225-8

The influence of administration of Lactobacillus paracasei alone and mixture of Lactobacillus paracasei and fructooligosaccharide on faecal bacteria counts in the weanling pigs was investigated. The administration of Lactobacillus paracasei alone significantly decreased Clostridium (< 0.05) and Enterobacteriaceae (< 0.05) counts as compared to the control. Lactobacillus paracasei administered in combination with fructooligosaccharide significantly increased Lactobacillus (< 0.01-< 0.05), Bifidobacterium (< 0.05), total anaerobes (< 0.05), and total aerobes (< 0.05) counts compared to control group as well as Lactobacillus paracasei group and significantly decreased Clostridium (< 0.05) and Enterobacteriaceae (< 0.01) counts compared to control group. The results obtained point out to a synergic effect of the combination of Lactobacillus paracasei and fructooligosaccharide on numbers of bacterial populations observed in the faeces of the weanling pigs.

Clinical applications of probiotic agents.

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Am J Clin Nutr 2001 Jun;73(6):1147S-1151S

In the past century the beneficial roles of nonpathogenic bacteria in the intestinal lumen were described. In the past decade there has been a dramatic increase in scientific work supporting the concept that there are clinical benefits to ingesting specific nonpathogenic organisms (probiotics). The potential benefits of modifying the intestinal flora composition of certain high-risk groups, eg,

premature infants, travelers, and children receiving antibiotics, are emerging in the literature. Studies documenting prophylactic and therapeutic benefits in acute viral gastroenteritis and in atopic disease point not only to the potential applications, but also to the fact that the mechanisms of action of these agents may be due to their interaction with the gut as an immunologic organ. The benefits documented thus far are of varying degree and are most likely dependent on the number of agents, the dose, the dosing patterns, and the characteristics of the host and its underlying luminal microbial environment. Consequently, the safety and specification of a particular probiotic agent and methods of delivery to a particular population for a particular purpose should be carefully documented before making broad recommendations. The cost-benefit assessment of adding probiotics to our diet for prophylactic or therapeutic purposes, as well as better regulation of these agents as commercial products, is also needed.

Consequences of magnesium deficiency on the enhancement of stress reactions; Preventive and therapeutic implications (A review)

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J. Am. Coll. Nutr. (USA), 1994, 13/5 (429-446)

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress . Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA). A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA metabolism and the endothelium), that are vasoconstrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress , whether physical (i.e. exertion, heat, cold, trauma-accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress .

Continuous culture selection of bifidobacteria and lactobacilli from human faecal samples using fructooligosaccharide as selective substrate.

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J Appl Microbiol 1998 Oct;85(4):769-77

The human large intestine contains a large and diverse population of bacteria. Certain genera, namely Bifidobacterium and Lactobacillus, are thought to exert health-promoting effects. Prebiotics such as fructooligosaccharides (FOS) have been shown to stimulate the growth of endogenous bifidobacteria. In this study, changes of lactic acid producing bacteria in continuous culture fermentors (semi-defined, anaerobic medium containing 5 g 1(-1) FOS, dilution rate of 0.1 h-1, pH 5.5) were followed over a 21 d period after inoculation with blended human faeces from four healthy adults. Samples were also taken every 3 d for influent/effluent FOS, short chain fatty acid (SCFA), lactate and microbiological analyses. Results showed that SCFA concentrations decreased abruptly 1 d after inoculation while lactate concentrations increased. Classical methods of enumeration using selective media showed that the proportion of total culturable count represented by bifidobacteria and lactobacilli increased from 11.9% on day 1 to 98.1% on day 21. However, molecular methods using genus-specific 16S rRNA oligonucleotide probes indicated that the bifidobacterial population maintained a level between 10 and 20% of total 16S rRNA during the first 6 d and disappeared rapidly when the maximum concentration of lactate was reached. Lactobacilli, which were initially present in low numbers, increased until day 9 and remained at high levels (20-42% of total 16S rRNA) to day 21, with the exception of day 18. Although FOS has usually been regarded as a selective substrate for bifidobacteria, these observations suggest that: (1) lactobacilli are also able to use FOS, (2) lactobacilli can out-compete bifidobacteria in continuous culture at pH 5.2-5.4 when FOS is the primary carbon and energy source, and (3) bifidobacteria can grow faster on FOS than lactobacilli under controlled conditions.

Protective effect of bifidus milk on the experimental infection with Salmonella enteritidis subsp. typhimurium in conventional and gnotobiotic mice.

Silva AM, Bambirra EA, Oliveira AL, Souza PP, Gomes DA, Vieira EC, Nicoli JR. Departamento de Microbiologia, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

J Appl Microbiol 1999 Feb;86(2):331-336

The ability of Bifidobacterium bifidum from a commercial bifidus milk to antagonize Salmonella enteritidis subsp. typhimurium in vivo, and to reduce the pathological consequences for the host, was determined using conventional and gnotobiotic mice. Conventional animals received daily, by gavage, 0.1 ml bifidus milk containing about 10(9) cfu B. bifidum and germ-free animals received a single 0.1 ml dose. The conventional and gnotobiotic groups were challenged orally with 10(2) cfu of the pathogenic bacteria 5 and/or 10 d after the beginning of treatment. Control groups were treated with milk. Bifidus milk protected both animal models against the challenge with the pathogenic bacteria, as demonstrated by survival and histopathological data. However, to obtain the protective effect in gnotobiotic animals, the treatment had to be initiated 10 d

before the challenge. In experimental and control gnotobiotic mice, Salm. enteritidis subsp. typhimurium became similarly established at levels ranging from 10(8) to 10(9) viable cells g-1 of faeces and remained at these high levels until the animals died or were sacrificed. It was concluded that the protection against Salm. enteritidis subsp. typhimurium observed in conventional and gnotobiotic mice treated with bifidus milk was not due to the reduction of the intestinal populations of the pathogenic bacteria.

[Effects of oral administration of bifidobacteria on intestinal microflora in premature and newborn infants]. [Article in German]

Uhlemann M, Heine W, Mohr C, Plath C, Pap S. Kinder- und Jugendklinik der Universitat Rostock.

Z Geburtshilfe Neonatol 1999 Sep;203(5):213-217

In a prospective, randomised study the effects of orally administered bifidobacteria on the intestinal microflora were investigated in 100 preterm and term neonates under intensive care conditions during the first 21 days of life. The 50 infants (group with bifidobacteria) received lyophilized bifidobacteria (Topfer Bifidus) via nasogastral tube with an initial dosage of 3 times daily 1.25 x 10(8) bifidobacteria on day 2 of life and a daily dosage of 6 times 1.25 x 10(8) bifidobacteria on day 3 until day 21 of life. The other 50 infants (control group) did not receive bifidobacteria. The preterm and term neonates were fed either with pasteurized mother's milk or milk from healthy female donors (n = 79) or with an infant formula (Alfare, n = 13) or initially with Alfare and thereafter with mother's milk (n = 8). The intestinal microflora of preterm and term neonates under intensive care conditions could be influenced by the oral administration of bifidobacteria. The administration of bifidobacteria resulted in the group of inoculated infants in a significantly earlier colonization of bifidobacteria (8.1 3.9 days of life) than in the control group (11.3 4.7 days of life). On day 7 a bifidobacterial dominance (< 90% of the intestinal microflora) could be found in 26% of infants with inoculation of bifidobacteria and only in 2% of the control group (< 0.001). These significant differences could be shown until day 21 of life. A difference in septicemia frequency between the two groups could not be demonstrated. At the beginning of the infection a bifidobacterial dominance was found in only one of 23 cases of septicemia.

The effect of a newly developed ointment containing eicosapentaenoic acid and docosahexaenoic acid in the treatment of atopic dermatitis.

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J Med Invest 1999 Aug;46(3-4):173-177

While various therapeutic modalities have been tried for atopic dermatitis (AD), numerous obstinate cases exist in which sufficient effects cannot be obtained. Therefore, we developed and prepared an ointment containing docosahexaenoic

acid and eicosapentaenoic acid as a topical therapeutics for AD. We applied this ointment to 64 patients with AD (aged between 2 months and 29 years) who showed poor responses to conventional therapies and obtained satisfactory results. This ointment is considered a new topical preparation for AD.

Immune senescence and adrenal steroids: Immune dysregulation and the action of dehydroepiandrosterone (DHEA) in old animals

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Eur J Clin Pharmacol 1993;45 Suppl 1:S21-3; discussion S43-4

Immune senescence is characterized by dysregulation of the immune system. The disorder occurs during old age and is manifested by an increased production of autoantibodies and a decreased production of antibodies to most foreign antigens. These events seem to reflect an altered ratio of activity between the CD5+ and CD5- B cell subsets. Likewise, there is dysregulation of cytokine production with an increased production of IL-4, IL-5 and IL-6 associated with a decreased production of IL-2. This appears to reflect an altered ratio of activity between the Th1 and Th2 cell subsets. Dehydroepiandrosterone (DHEA) is one of the three principal adrenal steroids; its serum concentration declines with age. Recent results suggest that in vitro culture of lymphocytes, from aged donors, with DHEA or in vivo treatment of old mice with DHEA sulphate results in the augmentation of the antibody response to foreign antigens and a reversal in the dysregulated cytokine production by T cells. Thus, a decline in one of the three principal adrenal steroids is associated with age-associated changes in the immune system. Some of these changes can be reversed by exposure to DHEA.

Reduced levels of glutathione S-transferases in patch test reactions to dithranol and sodium lauryl sulphate as demonstrated by quantitative immunocytochemistry: evidence for oxidative stress in acute irritant contact dermatitis.

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Eur J Dermatol 2001 Mar;11(2):99-104

There is increasing evidence that oxidative stress plays a role in the pathogenesis of acute irritant contact dermatitis. As part of on-going studies into the effect of irritant chemicals on the anti-oxidant enzyme systems in the skin, we have examined the changing levels of two classes of glutathione S-transferase in patch test reactions to dithranol and sodium lauryl sulphate, using quantitative immunocytochemistry. Although no changes were evident after 6 hrs, significant reductions in the density of staining for glutathione S-transferase alpha were seen with both irritants after 48 hrs and 96 hrs. Glutathione S-transferase pi levels were reduced to a lesser degree, reaching significance for dithranol at the 96 hrs time

point only, and for sodium lauryl sulphate at 48 hrs only. The results support the hypothesis that oxidative stress plays a role in chemically-induced inflammation, not only in the case of irritants such as dithranol which are known to directly generate reactive oxygen species, but also with chemicals not generally associated with free radical generation.

Metabolic support of the gastrointestinal tract: potential gut protection during intensive cytotoxic therapy.

Wilmore DW. Department of Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

Cancer 1997 May 1;79(9):1794-1803

BACKGROUND: Potentially curative options involving cytoablative therapies are now available for the treatment of almost all human tumors, but major toxicities represent the rate-limiting step in achieving a cure with these therapies. With successful hematoprotective strategies now in use, it is apparent that the gastrointestinal tract will be the rate-limiting organ system that prevents further dose escalation in many cancer patients.

METHODS: A review of the English language literature was conducted. Paperchase, a computer-based application that reviews the data bases of the National Library of Medicine and the National Cancer Institute, was used to obtain pertinent literature.

RESULTS: A variety of gut-protective nutrients and growth factors were identified. These substances may be useful in preventing dose-limiting gastrointestinal symptoms. Animal studies and some patient data suggest that the amino acid glutamine stimulates mucosal growth and promotes gut health. When nutrient administration is coupled with growth factors, such as growth hormone, insulin-like growth factor-1, glucagon-like peptide-2, and interleukin-11, a high level of bowel protection should be attained.

CONCLUSIONS: Therapy is evolving that may be useful in protecting the intestinal mucosa and preventing dose-limiting gastrointestinal symptoms.

A modified determination of coenzyme Q10 in human blood and CoQ10 blood levels in diverse patients with allergies.

Ye CQ, Folkers K, Tamagawa H, Pfeiffer C Institute for Biomedical Research, University of Texas, Austin.

Biofactors 1988 Dec;1(4):303-6

Two situations required a modified determination of coenzyme Q10 (CoQ10) in human blood and organ tissue. Blood from patients with AIDS and cancer raised apprehensions about safety to an analyst, and the number of specimens for analysis is increasing enormously. A modified determination replaces silica gel-

TLC with disposable Florisil columns, and steps were simplified to allow more analyses per unit time. Data from the modified determination are quantitatively compatible with data from older and tedious procedures. This determination was used for blood from 36 diverse patients with allergies. The mean CoQ10 blood level of these patients is not different from the mean level of so-called normal individuals, but approximately 40% (14/36) of these allergic patients had levels up to 0.65 micrograms/ml, which is the level of dying class IV cardiac patients. The biosynthesis of CoQ10 in human tissues is a complex process that requires several vitamins and micronutrients, so that countless vitamin-unsupplemented Americans may be deficient in CoQ10. The relationship of allergies to autoimmune mechanisms and immunity, and the established relationship of CoQ10 to immune states, may be a rationale for therapeutic trials of administering CoQ10 to patients with allergies who have low CoQ10 blood levels and are very likely deficient.

3. Alzheimers Disease

Preventative and curative options include:

Acetylcholine, Ginkgo biloba, Vitamin E, Vitamin C, N-acetyl cysteine, Essential fatty acids, Curcumin, Vitamin B12, Vitamin B6, Folic acid, SAMe, Methylcobalamin, Phosphatidylserine, Acetyl-L-carnitine, Melatonin, Carnosine, DHEA, Vitamin K.

The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease.
Allison AC. SurroMed Corporation, Mountain View, California 94043, USA.

Med Hypotheses 2001 Aug;57(2):151-5

The incidence of Alzheimer's disease (AD) increases with age and in carriers of the apolipoprotein E4 genotype. A relative deficiency of vitamin K, affecting the extrahepatic functions of the vitamin, is common in ageing men and women. The concentration of vitamin K is lower in the circulating blood of APOE4 carriers than in that of persons with other APOE genotypes. Evidence is accumulating that vitamin K has important functions in the brain, including the regulation of sulfotransferase activity and the activity of a growth factor/tyrosine kinase receptor (Gas 6/Axl). The hypothesis is now proposed that vitamin K deficiency contributes to the pathogenesis of AD and that vitamin K supplementation may have a beneficial effect in preventing or treating the disease. Vitamin K may also reduce neuronal damage associated with cardiovascular disease. Copyright 2001 Harcourt Publishers Ltd.

[A new interventional strategy for Alzheimer's disease by Japanese herbal medicine]. [Article in Japanese]

Arai H, Suzuki T, Sasaki H, Hanawa T, Toriizuka K, Yamada H Department of Geriatric Medicine, Tohoku University School of Medicine.

Nippon Ronen Igakkai Zasshi 2000 Mar;37(3):212-5

A Japanese herbal medicine termed "Kami-Umtan-To (KUT)" was first described in Japanese literature in 1626, KUT consists of 13 different herbs, and it has been used for a long time in the treatment of a variety of neuropsychiatric problems including neurosis and insomnia. Recently, Yabe et al. have demonstrated that KUT increased both choline acetyltransferase (ChAT) and nerve growth factor at the protein and mRNA levels in cultured rat brain cells. Moreover, the same research group has reported that KUT improved mean latency on passive avoidance test in both basal forbrain lesioned and aged rats. KUT significantly

improved the survival rate, and increased the number of ChAT-positive neurons in aged rats. Here, we report a 12-month open clinical trial of KUT and combination of estrogen, vitamin E and NSAID to aim at slowing down the progression of Alzheimer's disease (AD). Twenty AD patients (MMSE score: 18.6 +/- 5.8) received extracts from original KUT herbs, and 7AD patients (MMSE score: 21.3 +/- 2.8) were placed on the combination therapy. Rate of cognitive decline as measured by change in MMSE score per year was significantly slower (p = 0.04, ANOVA) in the KUT group (1.4 points) and the combination group (0.4 points) as compared to 4.1 points in 32 control AD patients (MMSE score: 20.8 +/- 5.6) who received no medicines for AD. Any of CSF measures including tau. and A beta 1-42 did not differ significantly after KUT theraopy. The efficacy of the KUT therapy was most obvious at 3 months. Our results suggest that traditional Japanese herbal medicine(s) may serve a new interventional strategy for AD.

Inositol treatment of Alzheimer's disease: a double blind, cross-over placebo controlled trial.

Barak Y, Levine J, Glasman A, Elizur A, Belmaker RH. Abarbanel Mental Health Center, Bat Yam, Israel.

Prog Neuropsychopharmacol Biol Psychiatry 1996 May;20(4):729-35

1. A double-blind controlled crossover trial of 6 gm of inositol daily vs glucose for one month each was carried out in 11 Alzheimer patients. 2. Overall CAMCOG scores showed a trend for greater improvement with inositol that was not significant. 3. Language and orientation improved significantly more on inositol than on placebo. There were no serious side effects. 4. Higher doses of inositol should be studied in Alzheimer's Disease for longer periods.

The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid.

Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R Douglas Hospital Research Centre, Department of Psychiatry, McGill University, 6875 Bld LaSalle, Verdun, Quebec, Canada.

Eur J Neurosci 2000 Jun;12(6):1882-90

Substantial evidence suggests that the accumulation of beta-amyloid (Abeta)-derived peptides, and to a lesser extent free radicals, may contribute to the aetiology and/or progression of Alzheimer's disease (AD). Ginkgo biloba extract (EGb 761) is a well-defined plant extract containing two major groups of constituents, i.e. flavonoids and terpenoids. It is viewed as a polyvalent agent with a possible therapeutic use in the treatment of neurodegenerative diseases of multifactorial origin, e.g. AD. We have investigated here the potential effectiveness of EGb 761 against toxicity induced by (Abeta)-derived peptides (Abeta25-35, Abeta1-40 and Abeta1-42) on hippocampal primary cultured cells, this area being severely affected in AD. A co-treatment with EGb 761

concentration-dependently (10-100 microg/mL) protected hippocampal neurons against toxicity induced by Abeta fragments, with a maximal and complete protection at the highest concentration tested. Similar, albeit less potent protective effects were seen with the flavonoid fraction of the extract (CP 205), while the terpenes were ineffective. Most interestingly, EGb 761 (100 microg/mL) was even able to protect (up to 8 h) hippocampal cells from a pre-exposure to Abeta25-35 and Abeta1-40. EGb 761 was also able to both protect and rescue hippocampal cells from toxicity induced by H2O2 (50-150 microM), a major peroxide possibly involved in mediating Abeta toxicity. Moreover, EGb 761 (10-100 microg/mL), and to a lesser extent CP 205 (10-50 microg/mL), completely blocked Abeta-induced events, e.g. reactive oxygen species accumulation and apoptosis. These results suggest that the neuroprotective effects of EGb 761 are partly associated with its antioxidant properties and highlight its possible effectiveness in neurodegenerative diseases, e.g. AD via the inhibition of Abeta-induced toxicity and cell death.

Mitochondria, NO and neurodegeneration.

Beal MF Neurochemistry Laboratory, Neurology Service/WRN 408, Massachusetts General Hospital, Boston, USA.

Biochem Soc Symp 1999;66:43-54

A role for mitochondrial dysfunction in neurodegenerative disease is gaining increasing support. Mitochondrial dysfunction may be linked to neurodegenerative diseases through a variety of different pathways, including free-radical generation, impaired calcium buffering and the mitochondrial permeability transition. This can lead to both apoptotic and necrotic cell death. Recent evidence has shown that there is a mitochondrial defect in Friedreich's ataxia, which leads to increased mitochondrial iron content, that appears to be linked to increased free-radical generation. There is evidence that the point mutations in superoxide dismutase which are associated with amyotrophic lateral sclerosis may contribute to mitochondrial dysfunction. There is also evidence for bioenergetic defects in Huntington's disease. Studies of cybrid cell lines have implicated mitochondrial defects in both Parkinson's disease and Alzheimer's disease. If mitochondrial dysfunction plays a role in neurodegenerative diseases then therapeutic strategies such as coenzyme Q10 and creatine may be useful in attempting to slow the disease process.

Vitamin E protects neurons against oxidative cell death in vitro more effectively than 17-beta estradiol and induces the activity of the transcription factor NF-kappaB.

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J Neural Transm 2000;107(4):393-407

Antioxidants can function as powerful protectants for neurons in vitro. Here, the neuroprotective activity of lipophilic free radical scavengers synthetic (+/-) alpha-tocopherol (synthetic vitamin E) and natural (+) alpha-tocopherol (natural vitamin E) against oxidative stress was investigated and compared to the neuroprotective effect of the female sex hormone estradiol. Employing mouse clonal hippocampal HT22 cells and rat cerebellar granule neurons, we found that both types of alpha-tocopherol exerted a higher neuroprotective antioxidant activity than 17-beta estradiol. At concentrations as low as 100 nM, synthetic (+/-) alpha-tocopherol and natural (+) alpha-tocopherol protected neurons effectively against the oxidative cell death caused by the Alzheimer's disease-associated amyloid beta protein, hydrogen peroxide, and the excitatory amino acid glutamate. Moreover, vitamin E induced the activity of the redox-sensitive transcription factor NF-kappaB, which is involved in the control of nerve cell survival and, therefore, may play also a role in vitamin E-induced neuroprotection. These results may have implications regarding the prevention and treatment of oxidative stress-related degenerative disorders such as Alzheimer's disease.

Thiamine pyrophosphate and pyridoxamine inhibit the formation of antigenic advanced glycation end-products: comparison with aminoguanidine.

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Biochem Biophys Res Commun 1996 Mar 7;220(1):113-9

Nonenzymatic glycation of proteins by glucose leading to the formation of toxic and immunogenic advanced glycation end products (AGEs) may be a major contributor to the pathological manifestations of diabetes mellitus, aging, and, possibly, neurodegenerative diseases such as Alzheimer's. We tested the in vitro inhibition of antigenic AGE formation on bovine serum albumin, ribonuclease A, and human hemoglobin by various vitamin B1 and B6 derivatives. Among the inhibitors, pyridoxamine and thiamine pyrophosphate potently inhibited AGE formation and were more effective than aminoguanidine, suggesting that these two compounds may have novel therapeutic potential in preventing vascular complications of diabetes. An unexpected finding was that aminoguanidine inhibited the late kinetic stages of glycation much more weakly than the early phase.

In vitro kinetic studies of formation of antigenic advanced glycation end products (AGEs). Novel inhibition of post-Amadori glycation pathways

Booth A.A.; Khalifah R.G.; Todd P.; Hudson B.G. USA

Journal of Biological Chemistry (USA), 1997, 272/9 (5430-5437)

Nonenzymatic protein glycation (Maillard reaction) leads to heterogeneous, toxic, and antigenic advanced glycation end products ('AGEs') and reactive precursors

that have been implicated in the pathogenesis of diabetes, Alzheimer's disease, and normal aging. In vitro inhibition studies of AGE formation in the presence of high sugar concentrations are difficult to interpret, since AGE-forming intermediates may oxidatively arise from free sugar or from Schiff base condensation products with protein amino groups, rather than from just their classical Amadori rearrangement products. We recently succeeded in isolating an Amadori intermediate in the reaction of ribonuclease A (RNase) with ribose (Khalifah, R. G., Todd, P., Booth, A. A., Yang, S. X., Mott, J. D., and Hudson, B. G. (1996) Biochemistry 35, 4645- 4654) for rapid studies of post-Amadori AGE formation in absence of free sugar or reversibly formed Schiff base precursors to Amadori products. This provides a new strategy for a better understanding of the mechanism of AGE inhibition by established inhibitors, such as aminoguanidine, and for searching for novel inhibitors specifically acting on post-Amadori pathways of AGE formation. Aminoguanidine shows little inhibition of post-Amadori AGE formation in RNase and bovine serum albumin, in contrast to its apparently effective inhibition of initial (although not late) stages of glycation in the presence of high concentrations of sugar. Of several derivatives of vitamins B1 and B6 recently studied for possible AGE inhibition in the presence of glucose (Booth, A. A., Khalifah, R. G., and Hudson, B. G. (1996) Biochem. Biophys. Res. Commun. 220, 113-119), pyridoxamine and, to a lesser extent, thiamine pyrophosphate proved to be novel and effective post-Amadori inhibitors that decrease the final levels of AGEs formed. Our mechanism- based approach to the study of AGE inhibition appears promising for the design and discovery of novel post-Amadori AGE inhibitors of therapeutic potential that may complement others, such as aminoguanidine, known to either prevent initial sugar attachment or to scavenge highly reactive dicarbonyl intermediates.

[Vitamin B12 deficiency in geriatrics]. [Article in German]

Bopp-Kistler I, Ruegger-Frey B, Grob D, Six P Klinik fur Geriatrie und Rehabilitation, Stadtspital Waid, Zurich. irene.bopp@waid.stzh.ch

Schweiz Rundsch Med Prax 1999 Nov 4;88(45):1867-75

Cobalamin deficiency increases with advancing age. The cut-off point of serum concentration should be raised, because many elderly people with "normal" serum vitamin B12 concentrations are metabolically deficient in cobalamin. The measurement of the metabolites homocysteine and/or methylmalonic acid is recommended. Cobalamin deficiency may result in a variety of atypical symptoms. Hematological changes typical of megaloblastic anemia are absent in a majority of patients with neuropsychiatric disorders. Generally underlying pernicious anemia is not the main cause of cobalamin deficiency in the elderly. Protein-bound cobalamin malabsorption due to atrophic gastritis with hypo- or achlorhydria is a common cause of cobalamin deficiency in elderly people. An important manifestation of cobalamin deficiency is cognitive impairment. Much controversy exists on the subject of the association of dementia of the Alzheimer type with cobalamin deficiency. In several studies dementia has been related to low serum cobalamin levels. Physicians should be liberal of cobalamin therapy. The window of opportunity for effective intervention may be as short as one year

from the onset of medical symptoms. At last a compilation of recommendations is given.

S-adenosylmethionine levels in psychiatric and neurological disorders: a review.

Bottiglieri T, Hyland K. Metabolic Disease Center, Baylor Research Institute, Dallas, TX 75226.

Acta Neurol Scand Suppl 1994;154:19-26

INTRODUCTION--S-adenosylmethionine (SAMe) is an important methyl donor in over 35 methylation reactions involving DNA, proteins, phospholipids and catechol- and indole-amines.

MATERIAL AND METHODS--This article reviews the studies that have examined brain and blood levels of SAMe in several psychological, neurological and metabolic disorders.

RESULTS--Although studies have found no consistent changes in whole blood SAMe levels in psychiatric patients, other investigators have found low cerebrospinal fluid (CSF) SAMe levels in patients with neurological disorders such as Alzheimer's dementia, subacute combined degeneration of the spinal cord (SACD), and HIV-related neuropathies, as well as in patients with metabolic disorders such as 5, 10-CH2-H4 folate reductase deficiency.

CONCLUSION--Intravenous or oral administration of SAMe thus represents a possible treatment for these neurological and metabolic disorders.

Effect of melatonin in selected populations of sleep-disturbed patients.

Brusco LI, Fainstein I, Marquez M, Cardinali DP. Departamento de Fisiologia, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina.

Biol Signals Recept 1999 Jan-Apr;8(1-2):126-31

In an open pilot study on the efficacy of melatonin in the treatment of sleep disorders, patients with sleep disturbances alone, patients with sleep disturbances and signs of depression and patients with sleep disorders and dementia received 3 mg melatonin p.o. for 21 days, at bed time. After 2-3 days of treatment, melatonin significantly augmented sleep quality and decreased the number of awakening episodes in patients with sleep disturbances associated or not with depression. Estimates of next-day alertness improved significantly only in patients with primary insomnia. Agitated behavior at night (sundowning) decreased significantly in dementia patients. In a second retrospective study, 14 Alzheimer's disease (AD) patients received 9 mg melatonin daily for 22-35 months. A significant improvement of sleep quality was found, while there were no significant differences between initial and final neuropsychological evaluation (Functional Assessment Tool for AD, Mini-Mental). The results indicate that

melatonin can be useful to treat sleep disturbances in elderly insomniacs and AD patients.

Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease.

Brusco LI, Marquez M, Cardinali DP. Departamento de Fisiologia, Facultad de Medicina, Universidad de Buenos Aires, Argentina.

Neuroendocrinol Lett 2000;21(1):39-42

OBJECTIVES: A retrospective study on the efficacy of melatonin in treatment of sleep and cognitive disorders of Alzheimer's disease was conducted.

METHODS: Fourteen patients (8 females, 6 males), mean +/- S.D. age 72 +/- 9 years were included. All patients received 9 mg gelatin melatonin capsules p.o. daily at bedtime for 22 to 35 months. Overall quality of sleep was assessed from sleep logs filled in by the patients or their caretakers. Neuropsychological evaluation was performed by Functional Assessment Tool For Alzheimer's Disease (FAST), Mini-Mental, Alzheimer's Disease Assessment Scale (ADAS), and Mattis' and Blessed's scales. At diagnosis, all patients had cognitive and neuroimaging alterations (cortical and bitemporal atrophy) compatible with different evolutionary stages of the disease.

RESULTS: At the time of assessment, a significant improvement of sleep quality was found in all cases examined. There were no significant differences between initial and present evaluation in scores of FAST, Mini-Mental, and ADAS, and of Mattis' and Blessed's scales. Clinically, the patients exhibited lack of progression of the cognitive and behavioral signs of the disease during the time they received melatonin. Sundowning was no longer detectable in 12 patients and persisted, although attenuated, in 2 patients.

CONCLUSION. The results suggest that melatonin can be useful for treatment of Alzheimer's disease.

Evidence for forebrain cholinergic neuronal loss in congenital ornithine transcarbamylase deficiency.

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Metab Brain Dis 2000 Mar;15(1):83-91

Congenital ornithine transcarbamylase (OTC) deficiency in humans results in failure to thrive, hypotonia, seizures and mental retardation. Neuropathologic evaluation reveals significant cerebral cortical atrophy, delayed myelination and Alzheimer type II astrocytosis. Using an animal model of congenital OTC deficiency, the sparse fur (spf) mouse, studies reveal convincing evidence of a loss of forebrain cholinergic neurons in this condition. Evidence includes (i)

reduced activities of the cholinergic nerve terminal enzyme choline acetyltransferase (ChAT), (ii) a 25% loss of ChAT immunostaining, (iii) reduced high affinity transport of [3H]choline by cortical synaptosomes and (iv) a selective reduction in densities of presynaptic muscarinic M2 binding sites, in spf mouse brain compared to controls. A partial correction of the cholinergic deficit was observed following treatment with acetyl-L-carnitine. Possible mechanisms responsible for cholinergic neuronal loss in congenital OTC deficiency include decreased synthesis of the ChAT substrate acetyl CoA, impaired cerebral energy metabolism and NMDA receptor-mediated excitotoxicity. Loss of forebrain cholinergic neurons is consistent with the severe cognitive impairment characteristic of congenital OTC deficiency.

Relationships between dehydroepiandrosterone sulfate (DHEAS) and cortisol (CRT) plasma levels and everyday memory in Alzheimer's disease patients compared to healthy controls.

Carlson LE, Sherwin BB, Chertkow HM Department of Psychology, McGill University, Montreal, Canada.

Horm Behav 1999 Jun;35(3):254-63

Fifty-two age-matched Alzheimer's disease (AD) patients (26 men, 26 women), mean age 76.2 years, were assessed with the Rivermead Behavioural Memory Test, a test of everyday memory, coincident with the measurement of plasma cortisol (CRT) and dehydroepiandrosterone sulfate (DHEAS) via radioimmunoassay. The AD patients were compared to a control group of age- and gender-matched healthy elderly men and women. No differences were found between the AD patients and the controls in DHEAS or CRT levels, or in the DHEAS/CRT ratio. There were no gender differences in DHEAS or CRT levels, or in the DHEAS/CRT ratio in subjects with AD. However, AD patients with higher levels of DHEAS scored better than those with lower levels on the subtests of Remembering a Name associated with a picture, Digit Span Total and Forward, and the Mini Mental Status Exam. AD patients with higher CRT levels performed worse on Delayed Route Recall than those with lower levels. These findings suggest that AD patients with higher endogenous levels of DHEAS may perform better on some memory tasks than those with lower levels, while AD patients with lower levels of CRT may perform better than those with higher CRT.

Oxidative stress and Alzheimer disease.

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Am J Clin Nutr 2000 Feb;71(2):621S-629S

Research in the field of molecular biology has helped to provide a better understanding of both the cascade of biochemical events that occurs with Alzheimer disease (AD) and the heterogeneous nature of the disease. One hypothesis that accounts for both the heterogeneous nature of AD and the fact that

aging is the most obvious risk factor is that free radicals are involved. The probability of this involvement is supported by the fact that neurons are extremely sensitive to attacks by destructive free radicals. Furthermore, lesions are present in the brains of AD patients that are typically associated with attacks by free radicals (eg, damage to DNA, protein oxidation, lipid peroxidation, and advanced glycosylation end products), and metals (eg, iron, copper, zinc, and aluminum) are present that have catalytic activity that produce free radicals. beta-Amyloid is aggregated and produces more free radicals in the presence of free radicals; beta-amyloid toxicity is eliminated by free radical scavengers. Apolipoprotein E is subject to attacks by free radicals, and apolipoprotein E peroxidation has been correlated with AD. In contrast, apolipoprotein E can act as a free radical scavenger and this behavior is isoform dependent. AD has been linked to mitochondrial anomalies affecting cytochrome-c oxidase, and these anomalies may contribute to the abnormal production of free radicals. Finally, many free radical scavengers (eg, vitamin E, selegeline, and Ginkgo biloba extract EGb 761) have produced promising results in relation to AD, as has desferrioxamine-an iron-chelating agent-and antiinflammatory drugs and estrogens, which also have an antioxidant effect.

Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease.

Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM Clinical Trial Service Unit, Nuffield Department of Clinical Medicine, Oxford, England.

Arch Neurol 1998 Nov;55(11):1449-55

BACKGROUND: Recent studies suggest that vascular disease may contribute to the cause of Alzheimer disease (AD). Since elevated plasma total homocysteine (tHcy) level is a risk factor for vascular disease, it may also be relevant to AD.

OBJECTIVE: To examine the association of AD with blood levels of tHcy, and its biological determinants folate and vitamin B12. DESIGN: Case-control study of 164 patients, aged 55 years or older, with a clinical diagnosis of dementia of Alzheimer type (DAT), including 76 patients with histologically confirmed AD and 108 control subjects. SETTING: Referral population to a hospital clinic between July 1988 and April 1996.

MAIN OUTCOME MEASURES: Serum tHcy, folate, and vitamin B12 levels in patients and controls at entry; the odds ratio of DAT or confirmed AD with elevated tHcy or low vitamin levels; and the rate of disease progression in relation to tHcy levels at entry. RESULTS: Serum tHcy levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with DAT and patients with histologically confirmed AD than in controls. The odds ratio of confirmed AD associated with a tHcy level in the top third (< or = 14 micromol/L) compared with the bottom third (< or = 11 micromol/L) of the control distribution was 4.5 (95% confidence interval, 2.2-9.2), after adjustment for age, sex, social class, cigarette smoking, and apolipoprotein E epsilon4. The orresponding odds ratio for the lower third compared with the upper third of

serum folate distribution was 3.3 (95% confidence interval, 1.8-6.3) and of vitamin B12 distribution was 4.3 (95% confidence interval, 2.1-8.8). The mean tHcy levels were unaltered by duration of symptoms before enrollment and were stable for several years afterward. In a 3-year follow-up of patients with DAT, radiological evidence of disease progression was greater among those with higher tHcy levels at entry.

CONCLUSIONS: Low blood levels of folate and vitamin B12, and elevated tHcy levels were associated with AD. The stability of tHcy levels over time and lack of relationship with duration of symptoms argue against these findings being a consequence of disease and warrant further studies to assess the clinical relevance of these associations for AD.

Essential fatty acids in Alzheimer's disease.

Corrigan FM, Van Rhijn A, Horrobin DF. Argyll and Bute Hospital, Lochgilphead, Scotland.

Ann N Y Acad Sci 1991;640:250-2

Concentrations of essential fatty acids (EFAs) in plasma and red blood cell phospholipids were found to be abnormal in patients with Alzheimer's disease. A double-blind, placebo-controlled trial of treatment with EFAs plus appropriate antioxidants was carried out in 36 patients with Alzheimer's disease. After 20 weeks both the EFA and placebo groups had improved, but the degree of improvement was consistently greater in the EFA group.

Alzheimer's disease risk factors as related to cerebral blood flow: additional evidence.

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Med Hypotheses 1998 Jan;50(1):25-36

In a previous report, Alzheimer's disease risk factors, including alcohol abuse, depression, Down's syndrome, cerebral glucose metabolism defect, head trauma, old age, Parkinson's disease, sleep disturbance, and underactivity, were shown to have an association with reduced cerebral blood flow. In this report an attempt is made to strengthen a hypothesis that reduced cerebral blood flow may be a required cofactor in the cause of Alzheimer's disease with examples of additional putative risks, including aluminum, ApoE 4 alleles, estrogen deficiency, family history of dementia, low education-attainment, olfactory deficit, and underactivity coupled with gender, considered to have a relationship or potential relationship with reduced cerebral blood flow. Factors, believed to ameliorate Alzheimer's disease, associated with improved or stabilized cerebral blood flow are tabulated. A tentative cerebral blood flow nomogram is shown as a potential model to possibly help predict Alzheimer's disease susceptibility.

Alzheimer's disease risk factors as related to cerebral blood flow.

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Med Hypotheses 1996 Apr;46(4):367-77

Inconsistencies within results of case-control studies on Alzheimer's disease risk factors led to a search of the literature for a potential cofactor. Reduced cerebral blood flow was selected and literature was surveyed for evidence of a cerebral blood flow linkage with the more than 40 putative risks. Alcohol abuse, depression, head trauma, underactivity, old age, sleep disturbance, glucose utilization, Down's syndrome, and Parkinson's disease are risk factors where an association with reduced cerebral blood flow is documented. Studies were cited showing that improved cerebral blood flow is associated with factors thought to be helpful in Alzheimer's disease, such as education or occupational attainment, exercise, headache, smoking, and arthritis/anti-inflammatory drugs to the extent that aspirin is used. Sugar consumption is identified as a potential risk factor with glucose management in Alzheimer's disease also shown to involve reduced cerebral blood flow. An hypothesis is developed showing how compromised regional cerebral blood flow could fit as a cofactor for genetic, autoimmune, and neurotoxic aspects of Alzheimer's disease.

Effects of phosphatidylserine in Alzheimer's disease

Crook T, Petrie W, Wells C, Massari DC Memory Assessment Clinics, Inc., Bethesda, MD 20814. USA

Psychopharmacol. Bull. (USA), 1992, 28/1 (61-66)

We studied 51 patients meeting clinical criteria for probable Alzheimer's disease (AD). Patients were treated for 12 weeks with a formulation of bovine cortex phosphatidylserine (BC-PS; 100 mg t.i.d.) or placebo, and those treated with the drug improved on several cognitive measures relative to those administered placebo. Differences between treatment groups were most apparent among patients with less severe cognitive impairment. Results suggest that phosphatidylserine may be a promising candidate for study in the early stages of AD.

Treatment of Alzheimer's disease.

Cummings JL. UCLA Alzheimer's Disease Center, UCLA School of Medicine, Los Angeles, California, USA.

Clin Cornerstone 2001;3(4):27-39

A growing consensus indicates that Alzheimer's disease (AD) results from an increase in the production or accumulation of beta-amyloid protein (A beta) leading to nerve cell death. Mechanisms by which A beta accumulation leads to

neuronal death include oxidative damage and inflammation. This article discusses the management of AD patients with antioxidants, cholinesterase inhibitors, and psychotropic agents. Studies show that these agents can slow the progression of the disease, improve cognition, and reduce behavioral disturbances. A therapeutic alliance between physician and caregiver is an essential element in successfully managing the AD patient. The 3Rs--repeat, reassure, and redirect--can help caregivers reduce behavioral disturbances in patients with AD and limit the need for pharmacologic management.

Impaired cerebromicrovascular perfusion. Summary of evidence in support of its causality in Alzheimer's disease.

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Ann N Y Acad Sci 2000;924:136-52

After nearly a century of inquiry, the cause of Alzheimer's disease (AD) remains to be found. In this review, basic and clinical evidence is presented that assembles and hypothetically explains most of the key pathologic events associated with the development of AD. These pathologic events are triggered in AD by impaired cerebral perfusion originating in the microvasculature that affects the optimal delivery of glucose and oxygen and results in an energy metabolic breakdown of brain cell biosynthetic and synaptic pathways. We propose that two factors must be present before cognitive dysfunction and neurodegeneration is expressed in the AD brain: (1) advanced aging, (2) presence of a condition that lowers cerebral perfusion, such as a vascular risk factor. The first factor introduces a normal but potentially menacing process that lowers cerebral blood flow in proportion to increased aging, while the second factor adds a crucial burden that further lowers brain perfusion and places vulnerable neurons in a state of metabolic compromise leading to a death pathway. These two factors will lead to a critically attained threshold of cerebral hypoperfusion (CATCH). CATCH is a self-sustaining and progressive circulatory insufficiency that will destabilize neurons, synapses, neurotransmission, and cognitive function, creating in its wake a neurodegenerative process characterized by the formation of senile plaques, neurofibrillary tangles, amyloid angiopathy, and, in some cases, Lewy bodies. Since any of a considerable number of vessel-related conditions must be present in the aging individual for cognition to be affected, CATCH supports the heterogeneic disease profile assumed to be characteristic of the AD syndrome. A brief discussion of target therapy based on the proposed pathogenesis of AD is also reviewed.

Double-blind randomized controlled study of phosphatidylserine in senile demented patients.

Delwaide PJ, Gyselynck-Mambourg AM, Hurlet A, Ylieff M.

Acta Neurol Scand 1986 Feb;73(2):136-40

A double-blind randomized controlled study was conducted in 42 hospitalized demented patients to evaluate the therapeutical effect of phosphatidylserine (BS-PS). Half of the patients received 3 X 100 mg of this product, and the other half a placebo of the same appearance. After a wash-out period, prescription lasted for six weeks. To evaluate the patients, two distinct rating scales were used: the Crichton Scale and an original one (Peri Scale) designed in our geriatric unit (see Appendix). A circle crossing test was added. Out of the 35 patients who completed the trial, 18 had received placebo and 17 BC-PS. The results indicated a trend toward improvement in the BC-PS treated patients and an analysis of covariance showed a significant (p less than 0.05) treatment effect on the Peri Scale. The results at the end of the treatment period were compared with those obtained three weeks later. Here again there was a statistically significant difference in the Peri Scale results, indicating that modifications are drug-related. The behavioral improvement shown in this study is in agreement with experimental studies on aged animals.

Ginkgo biloba extract: mechanisms and clinical indications.

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Arch Phys Med Rehabil 2000 May;81(5):668-78

OBJECTIVE: Ginkgo biloba may have a role in treating impairments in memory, cognitive speed, activities of daily living (ADL), edema, inflammation, and free-radical toxicity associated with traumatic brain injury (TBI), Alzheimer's dementia, stroke, vasoocclusive disorders, and aging. The purpose of this review is to provide a synthesis of the mechanisms of action, clinical indications, and safety of Ginkgo biloba extract.

DATA SOURCES: Empirical studies, reviews, chapters, and conference proceedings were identified in the following databases: Medline, the Research Council for Complementary Medicine based on the British Library database, and Psychlnfo. Ginkgo biloba, EGb 761, Tanakan, Tebonin, Rokan, and LI 1370 were the principal index terms.

STUDY SELECTION AND DATA EXTRACTION: Controlled clinical studies with both positive and negative findings are included, in addition to animals studies illustrating mechanisms of activity.

DATA SYNTHESIS: Ginkgo has shown activity centrally and peripherally, affecting electrochemical, physiologic, neurologic, and vascular systems in animals and humans with few adverse side effects or drug interactions. Ginkgo shows promise in patients with dementia, normal aging, and cerebrovascular-related disorders. Clinical indications include memory, information processing, and ADL.

CONCLUSIONS: Ginkgo shows promise in treating some of the neurologic sequelae associated with Alzheimer's disease, TBI, stroke, normal aging, edema, tinnitus, and macular degeneration. Mechanisms of action may include antioxidant, neurotransmitter/receptor modulatory, and antiplatelet activating factor properties. While safe, caution is advised when recommending ginkgo to patients taking anticoagulants. Future studies should examine dose effects, component activity, mechanisms, and clinical applications.

Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuropsychological function.

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Int J Geriatr Psychiatry 2000 Mar;15(3):226-33

BACKGROUND: Vitamin B12 assay is part of the routine investigation of dementia, although few studies have investigated the effects of treatment on cognition. We examined the effects of B12 treatment on neuropsychological function and disease progression in patients presenting with dementia or cognitive impairment.

METHODS: From 1432 patients who were assessed at the Bristol Memory Disorders Clinic, 125 patients with low serum B12 were identified. Sixty-six patients presenting with dementia, and 22 with cognitive impairment were seen for a second assessment after treatment. Changes in neuropsychological test scores were compared with those of patients with normal serum B12, matched by age and diagnosis.

RESULTS: The majority of patients with low serum B12 had normal Hb and MCV values. We found no cases of reversible B12 deficiency dementia. The B12 treatment patients who presented with dementia showed no significant improvement, and no less deterioration, in their neuropsychological function than their matched group. However, a treatment effect was demonstrated among the patients presenting with cognitive impairment. These improved significantly compared to matched patients on the verbal fluency test (p<0.01).

CONCLUSION: All patients with cognitive impairment should be investigated for B12 deficiency. Vitamin B12 treatment may improve frontal lobe and language function in patients with cognitive impairment, but rarely reverses dementia. Copyright 2000 John Wiley & Sons, Ltd.

Immunological mechanisms and the spectrum of psychiatric syndromes in Alzheimer's disease.

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J Psychiatr Res 2002 Sep-Oct;36(5):269-80

Pathological, genetic and epidemiological studies support the opinion that inflammatory mechanisms are involved in the pathogenesis of Alzheimer's disease (AD). Recent pathological and neuroradiological (PET) data show that activation of microglia is an early pathogenic event that precedes the process of severe neuropil destruction in AD brains. In this paper we review the evidence that inflammatory mediators can play a pathogenic role in some behavioural disorders frequently encountered during the clinical course in AD patients. Motivational disturbances are the most striking of the depressive symptoms in AD and can be present in a preclinical stage of the disease. Experimental animal studies and clinical trials in humans have shown that cytokines can induce similar symptoms which were described as 'sickness behaviour' or 'depressive-like' state. Delirious states are frequently observed in more advanced stages of dementia. Delirium is generally considered the result of an imbalance in neurotransmitter systems with severe deficits of the cholinergic systems. Animal studies show that pro-inflammatory cytokines, such as interleukin-1, induce a reduced activity of the cholinergic system. In AD, the release of cytokines would exacerbate any already existing disturbances in the cholinergic neurotransmission. This could explain the susceptibility of demented patients to delirium provoked by a wide variety of trivial incidents that are accompanied by an acute phase response. The data reviewed in this paper suggest that it could be worthwhile employing a neuroimmunological approach to study at molecular level the pathogenesis of a broad spectrum of behavioural disturbances common in the clinical course of AD patients.

Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type . Engel RR, Satzger W, Gunther W, Kathmann N, Bove D, Gerke S, Munch U, Hippius H. Psychiatric Hospital, University of Munich, Germany.

Eur Neuropsychopharmacol 1992 Jun;2(2):149-55

Thirty-three patients with mild primary degenerative dementia according to DSM-III (MMS between 15 and 27) took part in a double-blind cross-over study of phosphatidylserine (Fidia, 300 mg/d) versus placebo. Both treatment phases lasted for 8 weeks with an 8 week washout phase in between and a 4 week washout phase before treatment phase one. Clinical global improvement ratings showed significantly more patients improving under BC-PS than under placebo during treatment phase one. The improvement carried over to the following wash-out and treatment phases. There were no significant improvements in GBS dementia rating scale, psychometric tests or P300-latency. 16-channel EEG mapping findings indicated that the patients initially showed higher power values in all frequency bands (except alpha), when compared to a younger, healthy control group. BC-PS reduced the higher power values compared to placebo, shifting EEG power more towards the normal level.

Treatment of Alzheimer's disease with short- and long-term oral THA and lecithin: a double-blind study.

Fitten LJ, Perryman KM, Gross PL, Fine H, Cummins J, Marshall C. VA Medical Center, Sepulveda, Calif 91343.

Am J Psychiatry 1990 Feb;147(2):239-42

Ten Alzheimer's disease patients underwent a trial of oral tetrahydroaminoacridine (THA) and lecithin. After 3 inpatient weeks there was no clear therapeutic effect. Three of six patients able to continue in long-term treatment showed measurable cognitive improvement, but only one displayed clinically obvious improvement.

The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study.

Giem P, Beeson WL, Fraser GE Department of Preventive Medicine, School of Medicine, Loma Linda University, CA 92350.

Neuroepidemiology 1993;12(1):28-36

We investigated the relationship between animal product consumption and evidence of dementia in two cohort substudies. The first enrolled 272 California residents matched for age, sex, and zip code (1 vegan, 1 lacto-ovo-vegetarian, and 2 'heavy' meat eaters in each of 68 quartets). This design ensured a wide range of dietary exposure. The second included 2,984 unmatched subjects who resided within the Loma Linda, California area. All subjects were enrolled in the Adventist Health Study. The matched subjects who ate meat (including poultry and fish) were more than twice as likely to become demented as their vegetarian counterparts (relative risk 2.18, $p = 0.065$) and the discrepancy was further widened (relative risk 2.99, $p = 0.048$) when past meat consumption was taken into account. There was no significant difference in the incidence of dementia in the vegetarian versus meat-eating unmatched subjects. There was no obvious explanation for the difference between the two substudies, although the power of the unmatched sub-study to detect an effect of 'heavy' meat consumption was unexpectedly limited. There was a trend towards delayed onset of dementia in vegetarians in both substudies.

Early diagnosis of cognitive impairment in the elderly with the focus on Alzheimer's disease.

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J Neural Transm 1998;105(8-9):773-86

In dementia disorders, it can be assumed that the pathological process in the brain has been present for a long time. It is therefore of importance to have a preclinical or an early clinical diagnosis. Obviously, vulnerability genes, such as ApoE-4, can be diagnosed preclinically. As we have no treatment to offer patients with

genetic risk factors, genotyping for ApoE-4 is at present of no clinical use. Trained neuropsychologists have today access to sensitive tests which reveal cognitive impairment before the disturbances reach the level of dementia. Laboratory investigations of cerebrospinal fluid have so far yielded no great results. Tau protein appears to be the most sensitive marker, but it is unspecific. Chromogranin A separates early onset from late onset Alzheimer's disease and seems to be a marker for synaptic degeneration. Synaptotagmin was also found to be reduced in patients with early onset Alzheimer's disease. Still we do not know, however, whether these proteins are early markers for degenerative processes in the brain. Laboratory investigations of blood have not yielded markers of use in early or differential diagnosis of dementia disorders. In a study at our own institute, however, we found serum-homocysteine (S-HCY) to be an early and sensitive marker for cognitive impairment. In patients with dysmentia (mild cognitive impairment), no less than 39% had pathological S-HCY levels, indicating insufficient 1-carbon metabolism.

Vitamin E and Alzheimer disease: the basis for additional clinical trials.

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Am J Clin Nutr 2000 Feb;71(2):630S-636S

Many lines of evidence suggest that oxidative stress is important in the pathogenesis of Alzheimer disease. In particular, beta-amyloid, which is found abundantly in the brains of Alzheimer disease patients, is toxic in neuronal cell cultures through a mechanism involving free radicals. Vitamin E prevents the oxidative damage induced by beta-amyloid in cell culture and delays memory deficits in animal models. A placebo-controlled, clinical trial of vitamin E in patients with moderately advanced Alzheimer disease was conducted by the Alzheimer's Disease Cooperative Study. Subjects in the vitamin E group were treated with 2000 IU (1342 alpha-tocopherol equivalents) vitamin E/d. The results indicated that vitamin E may slow functional deterioration leading to nursing home placement. A new clinical trial is planned that will examine whether vitamin E can delay or prevent a clinical diagnosis of Alzheimer disease in elderly persons with mild cognitive impairment.

The effect of tetrahydrofolate on tetrahydrobiopterin metabolism.

Hamon CG, Blair JA, Barford PA.

J Ment Defic Res 1986 Jun;30 (Pt 2):179-83

5-Methyltetrahydrofolate and vitamin B12 appear to be required for the biosynthesis of tetrahydrobiopterin. A deficiency of either could be sufficient to bring about neurological change which can be corrected by reversing the deficiency. Patients with senile dementia could possibly be benefited by the administration of 5-methyltetrahydrofolate.

Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation

Heiss WD, Kessler J, Mielke R, Szelies B, Herholz K Max-Planck-Institut fur neurologische Forschung.

Dementia 1994 Mar-Apr;5(2):88-98

70 patients with probable Alzheimer's disease were randomly allocated to four groups: 17 patients received only social support. 18 cognitive training twice a week, in 17 cognitive training was combined with pyritinol 2 x 600 mg/day and in 18 cognitive training was combined with phosphatidylserine 2 x 200 mg/day. Treatment duration was 6 months. Before and after treatment, the patients underwent neuropsychological testing as well as measurement of the regional cerebral metabolic rate for glucose using positron emission tomography and 18F-2-fluoro-2-deoxy-D-glucose. Before treatment the groups were comparable in respect to resting and activated glucose pattern achieved by a visual recognition task. Electrophysiological changes were assessed as EEG power, globally and in 4 frequency bands. This 6-month study in four groups of patients with Alzheimer's disease indicated that phosphatidylserine treatment has an effect on different measures of brain function. Since neuropsychological improvements were best documented after 8 and 16 weeks and faded towards the end of the treatment period, it must be concluded that this symptomatic therapy is mainly of short-term benefit and was overcome by the progressive pathological changes at the end of the treatment period.

JC virus infection and Alzheimer's disease: reappraisal of an in situ hybridization approach.

Heinonen O, Syrjanen S, Mantyjarvi R, Syrjanen K, Riekkinen P. Department of Neurology, University of Kuopio, Finland.

Ann Neurol 1992 Apr;31(4):439-41

To assess the validity of the recently reported data on frequent occurrence of latent JC virus (JCV) infections in the brains of patients with Alzheimer's disease, we used in situ hybridization with biotinylated whole genomic JCV probes and the streptavidin-biotinylated alkaline phosphatase method to examine brain sections of such patients. We did not find any signs of JCV either in the brains of the patients with Alzheimer's disease or in those of nondemented, elderly control patients. Non-specific staining of corpora amylacea-like bodies, however, was invariably detected with in situ hybridization using JCV probes.

DHEA-S plasma levels and incidence of Alzheimer's disease.

Hillen T, Lun A, Reischies FM, Borchelt M, Steinhagen-Thiessen E, Schaub RT Department of Internal Medicine-Geriatrics, Medical Faculty, Humboldt University Berlin/Charite, Germany.

Biol Psychiatry 2000 Jan 15;47(2):161-3

BACKGROUND: Cross-sectional studies controlling for age and gender reported a relationship between Alzheimer's disease and low dehydroepiandrosterone sulphate (DHEA-S) plasma levels. Prospective data with sufficient control for confounding factors are lacking.

METHODS: A nested case-control study examined baseline DHEA-S in participants of the Berlin Aging Study. Cases (n = 14) developed dementia of the Alzheimer type within 3 years. Control group A (n = 14) was matched for gender, age, multimorbidity, and immobility. Control group B (n = 13) was matched for gender and age and comprised participants free from multimorbidity, immobility, multimedication, need of help, incontinence, visual impairment, hearing impairment, and depression.

RESULTS: The mean plasma DHEA-S concentration of case subjects was 1.02 0.61 mumol/L. Both control groups had higher mean DEHA-S levels, in control group A, it was 1.89 1.24 mumol/L (p = .012) and in control group B 1.70 1.38 mumol/L (p = .093).

CONCLUSIONS: This population-based prospective study supports the role of DHEA-S as a risk factor for Alzheimer's disease.

Carnosine, a protective, anti-ageing peptide?

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Int J Biochem Cell Biol 1998 Aug;30(8):863-8

Carnosine (beta-alanyl-L-histidine) has protective functions additional to anti-oxidant and free-radical scavenging roles. It extends cultured human fibroblast life-span, kills transformed cells, protects cells against aldehydes and an amyloid peptide fragment and inhibits, in vitro, protein glycation (formation of cross-links, carbonyl groups and AGEs) and DNA/protein cross-linking. Carnosine is an aldehyde scavenger, a likely lipofuscin (age pigment) precursor and possible modulator of diabetic complications, atherosclerosis and Alzheimer's disease.

Pluripotent protective effects of carnosine, a naturally occurring dipeptide.

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Ann N Y Acad Sci 1998 Nov 20;854:37-53

Carnosine is a naturally occurring dipeptide (beta-alanyl-L-histidine) found in brain, innervated tissues, and the lens at concentrations up to 20 mM in humans.

In 1994 it was shown that carnosine could delay senescence of cultured human fibroblasts. Evidence will be presented to suggest that carnosine, in addition to antioxidant and oxygen free-radical scavenging activities, also reacts with deleterious aldehydes to protect susceptible macromolecules. Our studies show that, in vitro, carnosine inhibits nonenzymic glycosylation and cross-linking of proteins induced by reactive aldehydes (aldose and ketose sugars, certain triose glycolytic intermediates and malondialdehyde (MDA), a lipid peroxidation product). Additionally we show that carnosine inhibits formation of MDA-induced protein-associated advanced glycosylation end products (AGEs) and formation of DNA-protein cross-links induced by acetaldehyde and formaldehyde. At the cellular level 20 mM carnosine protected cultured human fibroblasts and lymphocytes, CHO cells, and cultured rat brain endothelial cells against the toxic effects of formaldehyde, acetaldehyde and MDA, and AGEs formed by a lysine/deoxyribose mixture. Interestingly, carnosine protected cultured rat brain endothelial cells against amyloid peptide toxicity. We propose that carnosine (which is remarkably nontoxic) or related structures should be explored for possible intervention in pathologies that involve deleterious aldehydes, for example, secondary diabetic complications, inflammatory phenomena, alcoholic liver disease, and possibly Alzheimer's disease.

Endogenous mechanisms of neuroprotection: role of zinc, copper, and carnosine.

Horning MS, Blakemore LJ, Trombley PQ. Biomedical Research Facility, Department of Biological Science, Florida State University, Tallahassee 32306-4340, USA. horning@neuro.fsu.edu

Brain Res 2000 Jan 3;852(1):56-61

Zinc and copper are endogenous transition metals that can be synaptically released during neuronal activity. Synaptically released zinc and copper probably function to modulate neuronal excitability under normal conditions. However, zinc and copper also can be neurotoxic, and it has been proposed that they may contribute to the neuropathology associated with a variety of conditions, such as Alzheimer's disease, stroke, and seizures. Recently, we demonstrated that carnosine, a dipeptide expressed in glial cells throughout the brain as well as in neuronal pathways of the visual and olfactory systems, can modulate the effects of zinc and copper on neuronal excitability. This result led us to hypothesize that carnosine may modulate the neurotoxic effects of zinc and copper as well. Our results demonstrate that carnosine can rescue neurons from zinc- and copper-mediated neurotoxicity and suggest that one function of carnosine may be as an endogenous neuroprotective agent.

Health benefits of docosahexaenoic acid.

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Pharmacol Res 1999 Sep;40(3):211-25

Docosahexaenoic acid (DHA) is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. The inclusion of plentiful DHA in the diet improves learning ability, whereas deficiencies of DHA are associated with deficits in learning. DHA is taken up by the brain in preference to other fatty acids. The turnover of DHA in the brain is very fast, more so than is generally realized. The visual acuity of healthy, full-term, formula-fed infants is increased when their formula includes DHA. During the last 50 years, many infants have been fed formula diets lacking DHA and other omega-3 fatty acids. DHA deficiencies are associated with foetal alcohol syndrome, attention deficit hyperactivity disorder, cystic fibrosis, phenylketonuria, unipolar depression, aggressive hostility, and adrenoleukodystrophy. Decreases in DHA in the brain are associated with cognitive decline during aging and with onset of sporadic Alzheimer disease. The leading cause of death in western nations is cardiovascular disease. Epidemiological studies have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction. The reduction is approximately 50% with 200 mg day(-1)of DHA from fish. DHA is the active component in fish. Not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias. The association of DHA deficiency with depression is the reason for the robust positive correlation between depression and myocardial infarction. Patients with cardiovascular disease or Type II diabetes are often advised to adopt a low-fat diet with a high proportion of carbohydrate. A study with women shows that this type of diet increases plasma triglycerides and the severity of Type II diabetes and coronary heart disease. DHA is present in fatty fish (salmon, tuna, mackerel) and mother's milk. DHA is present at low levels in meat and eggs, but is not usually present in infant formulas. EPA, another long-chain n-3 fatty acid, is also present in fatty fish. The shorter chain n-3 fatty acid, alpha-linolenic acid, is not converted very well to DHA in man. These longchain n-3 fatty acids (also known as omega-3 fatty acids) are now becoming available in some foods, especially infant formula and eggs in Europe and Japan. Fish oil decreases the proliferation of tumour cells, whereas arachidonic acid, a longchain n-6 fatty acid, increases their proliferation. These opposite effects are also seen with inflammation, particularly with rheumatoid arthritis, and with asthma. DHA has a positive effect on diseases such as hypertension, arthritis, atherosclerosis, depression, adult-onset diabetes mellitus, myocardial infarction, thrombosis, and some cancers.

High brain myo-inositol levels in the predementia phase of Alzheimer's disease in adults with Down's syndrome: a 1H MRS study.

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Am J Psychiatry 1999 Dec;156(12):1879-86

OBJECTIVE: An extra portion of chromosome 21 in Down's syndrome leads to a dementia in later life that is phenotypically similar to Alzheimer's disease. Down's

syndrome therefore represents a model for studying preclinical stages of Alzheimer's disease. Markers that have been investigated in symptomatic Alzheimer's disease are myoinositol and N-acetyl-aspartate. The authors investigated whether abnormal brain levels of myo-inositol and other metabolites occur in the preclinical stages of Alzheimer's disease associated with Down's syndrome.

METHOD: The authors used 1H magnetic resonance spectroscopy (MRS) with external standards to measure absolute brain metabolite concentrations in 19 nondemented adults with Down's syndrome and 17 age- and sex-matched healthy comparison subjects.

RESULTS: Concentrations of myoinositol and choline-containing compounds were significantly higher in the occipital and parietal regions of the adults with Down's syndrome than in the comparison subjects. Within the Down's syndrome group, older subjects (42-62 years, N = 11) had higher myo-inositol levels than younger subjects (28-39 years, N = 8). Older subjects in both groups had lower N-acetylaspartate levels than the respective younger subjects, although this old-young difference was not greater in the Down's syndrome group.

CONCLUSIONS: The approximately 50% higher level of myo-inositol in Down's syndrome suggests a gene dose effect of the extra chromosome 21, where the human osmoregulatory sodium/myo-inositol cotransporter gene is located. The even higher myoinositol level in older adults with Down's syndrome extends to the predementia phase earlier findings of high myoinositol levels in symptomatic Alzheimer's disease.

Inflammatory mechanisms in Alzheimer's disease

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European Archives of Psychiatry and Clinical Neuroscience (Germany) 1996, 246/3 (124-128)

In recent years many studies have indicated an involvement of inflammatory mechanisms in Alzheimer's disease (AD). Acute-phase proteins such as alpha1-antichymotrypsin and c-reactive protein, elements of the complement system, and activated microglial and astroglial cells are consistently found in brains of AD patients. Most importantly, also cytokines such as interleukin-6 (IL-6) have been detected in the cortices of AD patients, indicating a local activation of components of the unspecific inflammatory system. Up to now it has remained unclear whether inflammatory mechanisms represent a primary event or only an unspecific reaction to brain tissue damage. Therefore, we investigated whether IL-6 immunoreactivity could be found in plaques prior to the onset of neuritic changes, or whether the presence of this cytokine is restricted to later stages of plaque pathology. We confirmed our previous observation that IL-6 is detectable in a significant proportion of plaques in the brains of demented patients. In AD patients IL-6 was found in diffuse plaques in a significant higher ratio as would

have been expected from a random distribution of IL-6 among all plaque types. This observation suggests that IL-6 may precede neuritic changes, and that immunological mechanism may be involved both in the transformation from diffuse to neuritic plaques in AD and in the development of dementia.

Cerebrospinal fluid levels of alpha-tocopherol (vitamin E) in Alzheimer' s disease.

Jimenez-Jimenez FJ; de Bustos F; Molina JA; Benito-Leon J; Tallon-Barranco A; Gasalla T; Orti-Pareja M; Guillamon F; Rubio JC; Arenas J; Enriquez-de-Salamanca R. Department of Neurology, Hospital Universitario Principe de Asturias, Alcala de Henares, Spain.

J Neural Transm (Austria) 1997, 104 (6-7) p703-10

We compared CSF and serum levels, and the CST/serum ratio of alpha-tocopherol (vitamin E), measured by HPLC, in 44 apparently well-nourished patients with Alzheimer's disease (AD) and 37 matched controls. CSF and serum vitamin E levels were correlated, both in AD patients and in controls. The mean CSF and serum vitamin E levels were significantly lower in AD patients, and the CSF/serum ratio of AD patients did not differ significantly between the 2 study groups. CSF vitamin E levels did not correlate with age, age at onset, duration of the disease and score of the Minimental State Examination in the AD group. Weight and body mass index were significantly lower in AD patients than in controls. These results suggest that low CSF and serum vitamin E concentrations in AD patients could be related with a deficiency of dietary intake of vitamin E.

Serum levels of beta-carotene, alpha-carotene and vitamin A in patients with Alzheimer's disease.

Jimenez-Jimenez FJ, Molina JA, de Bustos F, Orti-Pareja M, Benito-Leon J, Tallon-Barranco A, Gasalla T, Porta J, Arenas J. Department of Neurology of Hospital 'Principe de Asturias', University of Alcala de Henares, Madrid, Spain.

Eur J Neurol 1999 Jul;6(4):495-7

To elucidate the possible role of carotenoids and vitamin A as risk factors for Alzheimer's disease (AD), we compared serum levels of beta-carotene and alpha-carotene, and vitamin A, measured by isocratic high performance liquid chromatography, of 38 AD patients and 42 controls. The serum levels of alpha-carotene did not differ significantly between AD patients and control groups. However, the serum levels of beta-carotene and vitamin A were significantly lower in the AD-patient group. These values did not correlate to age, age at onset or score on the MiniMental State Examination. Weight and body mass index were significantly lower in AD patients than in controls. These results suggest that low serum beta-carotene concentrations in AD patients could be related to a deficiency in dietary intake of this provitamin, although its possible relationship with risk for AD could not be excluded. Copyright 1999 Lippincott Williams & Wilkins

Effect of curcumin and capsaicin on arachidonic acid metabolism and lysosomal enzyme secretion by rat peritoneal macrophages

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Lipids (United States) 1997, 32/11 (1173-1180)

The inflammatory mediators secreted by macrophages play an-important role in autoimmune diseases. Spice components, such as curcumin from turmeric and capsaicin from red pepper, are shown to exhibit antiinflammatory properties. The influence of these spice components on arachidonic acid metabolism and secretion of lysosomal enzymes by macrophages was investigated. Rat peritoneal macrophages preincubated with 10 muM curcumin or capsaicin for 1 h inhibited the incorporation of arachidonic acid into membrane lipids by 82 and 76%: prostaglandin Einf 2 by 45 and 48%; leukotriene Binf 4 by 61 and 46%, and leukotriene Cinf 4 by 34 and 48%, respectively, but did not affect the release of arachidonic acid from macrophages stimulated by phorbol myristate acetate. However, the secretion of 6-keto PG F(1alpha) was enhanced by 40 and 29% from macrophages preincubated with 10 muM curcumin or capsaicin, respectively, as compared to those produced by control cells. Curcumin and capsaicin also inhibited the secretion of collagenase, elastase, and hyaluronidase to the maximum extent of 57, 61, 66%, and 46, 69, 67%, respectively. These results demonstrated that curcumin and capsaicin can control the release of inflammatory mediators such as eicosanoids and hydrolytic enzymes secreted by macrophages and thereby may exhibit antiinflammatory properties.

Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer' s disease?

Joosten E; Lesaffre E; Riezler R; Ghekiere V; Dereymaeker L; Pelemans W; Dejaeger E Department of Pathophysiology, University Hospitals K. U. Leuven, Belgium.

J Gerontol A Biol Sci Med Sci (United States) Mar 1997, 52 (2) M76-9.

BACKGROUND: It is still unclear whether there is an association between Alzheimer's disease and vitamin B-12 or folate deficiency. This study was designed to investigate whether patients with Alzheimer's disease are particularly prone to metabolically significant cobalamin or folate deficiency as compared to nondemented hospitalized controls and healthy elderly controls living at home.

METHODS: Evaluation for the diagnosis of Alzheimer's disease, routine laboratory tests, serum folate and vitamin B-12, serum methylmalonic acid (MMA), total homocysteine (tHcy), and radiological tests was performed in 52 patients with Alzheimer's disease (AD), 50 nondemented hospitalized controls, and 49 healthy elderly subjects living at home.

RESULTS: Serum vitamin B-12 and folate levels are comparable between patients with AD, hospitalized control patients, and subjects living at home. Patients with AD have the highest serum MMA and tHcy levels. The MMA levels of patients with AD and hospitalized controls are not different, but the mean tHcy level is significantly higher in patients with AD as compared to nondemented patients or subjects living at home.

CONCLUSION: The interpretation of the vitamin B-12 and folate status in patients with AD depends largely on the methodology (i.e., serum vitamin vs metabolite levels) and the selection of the control group. Although patients with AD have the highest tHcy and MMA levels, metabolically significant vitamin B-12 and folate deficiency is also a substantial problem in nondemented elderly patients.

Alzheimer's disease: risk and protection.

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Med J Aust 1997 Oct 20;167(8):443-6

Only four risk factors for Alzheimer's disease can be regarded as confirmed--old age, family history of dementia, apo-E genotype and Down syndrome. Other disputed risk factors with some supporting evidence include ethnic group, head trauma and aluminium in drinking water. Possible protection factors, such as anti-inflammatory drugs, oestrogen replacement therapy and a high education level, are of great interest because they suggest possible preventive action.

A review of nutrients and botanicals in the integrative management of cognitive dysfunction.

Kidd PM

Altern Med Rev 1999 Jun;4(3):144-61

Dementias and other severe cognitive dysfunction states pose a daunting challenge to existing medical management strategies. An integrative, early intervention approach seems warranted. Whereas, allopathic treatment options are highly limited, nutritional and botanical therapies are available which have proven degrees of efficacy and generally favorable benefit-to-risk profiles. This review covers five such therapies: phosphatidylserine (PS), acetyl-l-carnitine (ALC), vinpocetine, Ginkgo biloba extract (GbE), and Bacopa monniera (Bacopa). PS is a phospholipid enriched in the brain, validated through double-blind trials for improving memory, learning, concentration, word recall, and mood in middle-aged and elderly subjects with dementia or age-related cognitive decline. PS has an excellent benefit-to-risk profile. ALC is an energizer and metabolic cofactor which also benefits various cognitive functions in the middle-aged and elderly, but with a slightly less favorable benefit-to-risk profile. Vinpocetine, found in the

lesser periwinkle Vinca minor, is an excellent vasodilator and cerebral metabolic enhancer with proven benefits for vascular-based cognitive dysfunction. Two meta-analyses of GbE demonstrate the best preparations offer limited benefits for vascular insufficiencies and even more limited benefits for Alzheimer's, while "commodity" GbE products offer little benefit, if any at all. GbE (and probably also vinpocetine) is incompatible with blood-thinning drugs. Bacopa is an Ayurvedic botanical with apparent anti-anxiety, anti-fatigue, and memory-strengthening effects. These five substances offer interesting contributions to a personalized approach for restoring cognitive function, perhaps eventually in conjunction with the judicious application of growth factors.

Do raised brain aluminium levels in Alzheimer's dementia contribute to cholinergic neuronal deficits?

King RG.

Med Hypotheses 1984 Jul;14(3):301-6

Raised aluminium levels have been found in brains of patients with Alzheimer's dementia (1,2), a disease in which reductions have been reported in various parameters of presynaptic cholinergic nerve function, including choline uptake, acetylcholine synthesis and choline acetyltransferase activity (3). Aluminium has been found to inhibit choline transport by isolated rat brain nerve endings (4) and human erythrocytes (5), and also to cause an encephalopathy in rabbits with neurofibrillary tangles and reduced neuronal choline acetyltransferase activity (6). It is therefore hypothesised that raised brain aluminium levels in Alzheimer's dementia may contribute to the cholinergic neuronal deficits in this disease. If this is the case, then aluminium chelating agents may be of value in its treatment.

Influence of vitamin E and C supplementation on lipoprotein oxidation in patients with Alzheimer's disease.

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Free Radic Biol Med 2001 Aug 1;31(3):345-54

Because increased oxidation is an important feature of Alzheimer's disease (AD) and low concentrations of antioxidant vitamins C and E have been observed in cerebrospinal fluid (CSF) of AD patients, supplementation with these antioxidants might delay the development of AD. Major targets for oxidation in brain are lipids and lipoproteins. We studied whether supplementation with antioxidative vitamins E and C can increase their concentrations not only in plasma but also in CSF, and as a consequence decrease the susceptibility of lipoproteins to in vitro oxidation. Two groups, each consisting of 10 patients with AD, were for 1 month supplemented daily with either a combination of 400 IU vitamin E and 1000 mg vitamin C, or 400 IU vitamin E alone. We found that supplementation with vitamin E and C significantly increased the concentrations of both vitamins in

plasma and CSF. Importantly, the abnormally low concentrations of vitamin C were returned to normal level following treatment. As a consequence, susceptibility of CSF and plasma lipoproteins to in vitro oxidation was significantly decreased. In contrast, the supplementation with vitamin E alone significantly increased its CSF and plasma concentrations, but was unable to decrease the lipoprotein oxidizability. These findings document a superiority of a combined vitamin E + C supplementation over a vitamin E supplementation alone in AD and provide a biochemical basis for its use.

Music therapy increases serum melatonin levels in patients with Alzheimer's disease.

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Altern Ther Health Med 1999 Nov;5(6):49-57

CONTEXT: Music therapy is known to have healing and relaxing effects. Although these effects appear to be mediated by release of neurotransmitters and neurohormones, the specific neurohormonal systems involved have not been fully investigated.

OBJECTIVE: To assess the effects of a music therapy intervention on concentrations of melatonin, norepinephrine, epinephrine, serotonin, and prolactin in the blood of a group of patients with Alzheimer's disease.

DESIGN: Blood samples were obtained before initiating the therapy, immediately at the end of 4 weeks of music therapy sessions, and at 6 weeks follow-up after cessation of the sessions.

SETTING: Miami Veterans Administration Medical Center, Miami, Fla.

PATIENTS: 20 male inpatients with Alzheimer's disease.

INTERVENTION: 30- to 40-minute morning sessions of music therapy 5 times per week for 4 weeks.

MAIN OUTCOME MEASURES: Changes in melatonin, norepinephrine, epinephrine, serotonin, and prolactin following music therapy.

RESULTS: Melatonin concentration in serum increased significantly after music therapy and was found to increase further at 6 weeks follow-up. A significant increase was found between baseline values and data recorded after the music therapy sessions as well as at 6 weeks follow-up. Norepinephrine and epinephrine levels increased significantly after 4 weeks of music therapy, but returned to pretherapy levels at 6 weeks follow-up. Serum concentration of prolactin and

platelet serotonin levels remained unchanged after 4 weeks of music therapy and at 6 weeks follow-up.

CONCLUSION: Increased levels of melatonin following music therapy may have contributed to patients' relaxed and calm mood.

Melatonin affects the metabolism of the beta-amyloid precursor protein in different cell types.

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J Pineal Res 1999 Apr;26(3):137-46

Melatonin is released in mammals during the dark phase of the circadian cycle, and its production declines with age in animals and humans. Since supplemental administration of melatonin may be beneficial in delaying age-related degenerative conditions, it is necessary to study its effect on neuronal differentiation and the processing of key neuronal proteins, such as beta-amyloid precursor protein (beta APP) and synaptophysin. One of the important pathological hallmarks of Alzheimer's disease (AD) is the cerebrovascular deposition of amyloid plaques. The amyloid in senile plaques is mainly composed of the amyloid beta-peptide (A beta) of 39-43 amino acids derived from a larger beta APP. The proteolytic cleavage by 'alpha-secretase' generate soluble derivatives of beta APP (sAPP), lacking the cytoplasmic tail, transmembrane domain, and a small portion of the extracellular domain. Here levels of sAPP and beta APP were analyzed in cell lines of different origins by Western immunoblot of samples from conditioned media and cell lysates, respectively. Normal levels of secretion of sAPP into conditioned media were severely inhibited by treating different cell lines with a high dose of melatonin. In PC12 cells, levels of the fully matured beta APP forms of the post-Golgi compartment were more drastically decreased than the unglycosylated beta APP of the endoplasmic-reticulum (ER) forms. In other cell types, the unglycosylated ER-bound beta APP derivatives are predominant forms that were marginally affected by melatonin treatment. When the treatment of cells with melatonin was withdrawn, the normal level of secretion of sAPP was restored. Melatonin reduces the secretion of soluble A beta. Melatonin also inhibits the secretion of synaptophysin in PC12 cells. Taken together, these data suggest that melatonin probably affects the secretion of sAPP in the conditioned medium by interfering with its full maturation, and melatonin also affects the presysnaptic terminal marker.

Interactions between melatonin, reactive oxygen species, and nitric oxide.

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Ann N Y Acad Sci 1999;893:325-30

Accumulation of reactive oxygen species is critical for the neuropathology of Alzheimer's disease. Melatonin hormone, an antioxidant, could play a key role in aging and senescence. Nitric oxide, a biologically active unstable radical, is synthesized by nitric oxide synthase when converting L-arginine to L-citrulline. We have investigated whether the treatment of cultured cells with melatonin could possibly reduce the release of free radicals and other ROS. We assayed NO indirectly by measuring the level of its stable end products, nitrite/nitrate (NOx), using the Griess reagent. When the neuroblastoma cells such as N1E-115 were treated with a NO donor such as sodium nitroprusside (SNP), a significant level of NOx was detected in a time- and dose-dependent manner in the conditioned medium compared to the untreated cells or SNP-containing media. In neuroblastoma cells, the release of NOx as mediated by SNP was significantly inhibited by treatment with (i) carboxy-PTIO, a NO scavenger; (ii) SOD-1, superoxide dismutase; and (iii) melatonin. In these cells SNP-mediated NOx release was mediated by superoxide ions and/or free radicals that can be inhibited by melatonin. The ROS-scavenging function of melatonin along with its neuroprotective and neurodifferentiating role can be utilized for the prevention of neurodegenerative disorders such as AD.

A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group.

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JAMA 1997 Oct 22-29;278(16):1327-32

CONTEXT: EGb 761 is a particular extract of Ginkgo biloba used in Europe to alleviate symptoms associated with numerous cognitive disorders. Its use in dementias is based on positive results from only a few controlled clinical trials, most of which did not include standard assessments of cognition and behavior.

OBJECTIVE: To assess the efficacy and safety of EGb in Alzheimer disease and multi-infarct dementia.

DESIGN: A 52-week, randomized double-blind, placebo-controlled, parallel-group, multicenter study.

PATIENTS: Mildly to severely demented outpatients with Alzheimer disease or multi-infarct dementia, without other significant medical conditions.

INTERVENTION: Patients assigned randomly to treatment with EGb (120 mg/d) or placebo. Safety, compliance, and drug dispensation were monitored every 3 months with complete outcome evaluation at 12, 26, and 52 weeks.

PRIMARY OUTCOME MEASURES: Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC).

RESULTS: From 309 patients included in an intent-to-treat analysis, 202 provided evaluable data for the 52-week end point analysis. In the intent-to-treat analysis, the EGbgroup had an ADAS-Cog score 1.4 points better than the placebo group (P=.04) and a GERRI score 0.14 points better than the placebo group (P=.004). The same patterns were observed with the evaluable data set in which 27% of patients treated with EGb achieved at least a 4-point improvement on the ADAS-Cog, compared with 14% taking placebo (P=.005); on the GERRI, 37% were considered improved with EGb, compared with 23% taking placebo (P=.003). No difference was seen in the CGIC. Regarding the safety profile of EGb, no significant differences compared with placebo were observed in the number of patients reporting adverse events or in the incidence and severity of these events.

CONCLUSIONS: EGb was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year. Although modest, the changes induced by EGb were objectively measured by the ADAS-Cog and were of sufficient magnitude to be recognized by the caregivers in the GERRI.

A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 in dementia.

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Dement Geriatr Cogn Disord 2000 Jul-Aug;11(4):230-7

This intent-to-treat (ITT) analysis was performed to provide a realistic image of the efficacy that could be expected after 26 weeks treatment with a 120-mg dose (40 mg t.i.d.) of EGb 761 (EGb). The data were collected during a 52-week, double-blind, placebo-controlled, fixed dose, parallel-group, multicenter study. Patients were mildly to severely impaired and diagnosed with uncomplicated Alzheimer's disease or multi-infarct dementia according to ICD-10 and DSM-III-R criteria. The primary outcome measures included the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI) and Clinical Global Impression of Change. From 309 patients included in the ITT analysis, 244 patients (76% for placebo and 73% for EGb) actually reached the 26th week visit. In comparison to the baseline values, the placebo group showed a statistically significant worsening in all domains of assessment, while the group receiving EGb was considered slightly improved on the cognitive assessment and the daily living and social behavior. Mean treatment differences favored EGb with 1.3 and 0.12 points, respectively, on the ADAS-Cog ($p = 0.04$) and the GERRI ($p = 0.007$). In the group receiving EGb, 26% of the patients achieved at least a 4-point improvement on the ADAS-Cog, compared to 17% with placebo ($p = 0.04$). On the GERRI, 30% of the EGb group improved and 17% worsened, while the placebo group showed an opposite trend with 37% of patients worsening for 25% improved ($p = 0.006$). Regarding safety, no differences between EGb and placebo were observed.

Hyperhomocysteinemia in dementia.

Leblhuber F, Walli J, Artner-Dworzak E, Vrecko K, Widner B, Reibnegger G, Fuchs D. Department of Gerontology, Landesnervenklinik Wagner Jauregg, Linz, Austria.

J Neural Transm 2000;107(12):1469-74

Hyperhomocysteinemia is a strong risk factor for atherosclerotic vascular disease, and elevated serum homocysteine is correlated with vitamin B deficiency. In this pilot study, significantly elevated homocysteine levels were found in patients with Alzheimer's disease as well as in patients with vascular dementia, probably indicating similar pathophysiological pathways. We found significant correlations between low folic acid concentrations as well as high homocysteine concentrations and cognitive decline. Supplementation with folic acid may be an inexpensive way to reduce elevated homocysteine levels in demented patients.

Identification of cognitive impairment in the elderly: homocysteine is an early marker.

Lehmann M, Gottfries CG, Regland B. Goteborg University, Institute of Clinical Neuroscience, Department of Psychiatry and Neurochemistry, Molndal, Sweden.

Dement Geriatr Cogn Disord 1999 Jan-Feb;10(1):12-20

In 336 consecutive patients attending a university-affiliated memory unit, clinical and psychological findings, neuroimaging and laboratory tests were analyzed. The patients were diagnosed with early Alzheimer's disease 3%, senile dementia (SDAT) 16%, vascular dementia (VAD) 20%, other dementias 9%, minor cognitive impairment (dysmentia) 32% and subjective symptoms only 21%. Increases in vascular risk factors, serum homocysteine, ApoE4 load and neuroimaging pathology were found in dementia but also in dysmentia and in patients with subjective symptoms only. The homocysteine levels correlated inversely with cognitive performance. The increases in serum homocysteine, which were pathological in VAD, Dysmentia and SDAT, may be indicative of a disturbed cerebral one-carbon metabolism and signal-accelerated development of cognitive disease.

A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease.

Little A, Levy R, Chuaqui-Kidd P, Hand D.

J Neurol Neurosurg Psychiatry 1985 Aug;48(8):736-42

The first long-term double-blind placebo controlled trial of high dose lecithin in senile dementia of the Alzheimer type is reported. Fifty one subjects were given 20-25 g/day of purified soya lecithin (containing 90% phosphatidyl plus lysophosphatidyl choline) for six months and followed up for at least a further six

months. Plasma choline levels were monitored throughout the treatment period. There were no differences between the placebo group and the lecithin group but there was an improvement in a subgroup of relatively poor compliers. These were older and had intermediate levels of plasma choline. It is suggested that the effects of lecithin are complex but that there may be a "therapeutic window" for the effects of lecithin in the condition and that this may be more evident in older patients.

Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype.

Liu RY, Zhou JN, van Heerikhuize J, Hofman MA, Swaab DF. Netherlands Institute for Brain Research, Amsterdam.

J Clin Endocrinol Metab 1999 Jan;84(1):323-7

Sleep disruption, nightly restlessness, sundowning, and other circadian disturbances are frequently seen in Alzheimer's disease (AD) patients. Changes in the suprachiasmatic nucleus and pineal gland are thought to be the biological basis for these behavioral disturbances. Melatonin is the main endocrine message for circadian rhythmicity from the pineal. To determine whether melatonin production was affected in AD, melatonin levels were determined in the cerebrospinal fluid (CSF) of 85 patients with AD (mean age, 75 +/- 1.1 yr) and in 82 age-matched controls (mean age, 76 +/- 1.4 yr). Ventricular postmortem CSF was collected from clinically and neuropathologically well defined AD patients and from control subjects without primary neurological or psychiatric disease. In old control subjects (>80 yr of age), CSF melatonin levels were half of those in control subjects of 41-80 yr of age [176 +/- 58 (n = 29) and 330 +/- 66 (n = 53) pg/mL, respectively; P = 0.016]. We did not find a diurnal rhythm in CSF melatonin levels in control subjects. In AD patients the CSF melatonin levels were only one fifth (55 +/- 7 pg/mL) of those in control subjects (273 +/- 47 pg/mL; P = 0.0001). There was no difference in the CSF melatonin levels between the presenile (42 +/- 11 pg/mL; n = 21) and the senile (59 +/- 8 pg/mL; n = 64; P = 0.35) AD patients. The melatonin level in AD patients expressing apolipoprotein E-epsilon3/4 (71 +/- 11 pg/mL) was significantly higher than that in patients expressing apolipoprotein E-epsilon4/4 (32 +/- 8 pg/ml; P = 0.02). In the AD patients no significant correlation was observed between age of onset or duration of AD and CSF melatonin levels. In the present study, a dramatic decrease in the CSF melatonin levels was found in old control subjects and even more so in AD patients. Whether supplementation of melatonin may indeed improve behavioral disturbances in AD patients should be investigated.

Association between changes in adrenal secretion and cerebral morphometric correlates in normal aging and senile dementia.

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Dement Geriatr Cogn Disord 2000 Mar-Apr;11(2):90-9

The circadian organization of adrenal secretion was studied in 23 healthy elderly subjects, 23 elderly demented patients and 10 healthy young subjects, in order to investigate the relationships between the hypothalamic-pituitary-adrenal axis and some cerebral morphometric parameters. The cerebral morphometric analysis was performed in some subjects of the three groups by MRI. A significant increase in cortisol levels during evening and nighttime was found in both groups of the aged subjects. In elderly subjects, particularly if demented, the mean serum dehydroepiandrosterone sulfate (DHEAs) levels throughout the 24-hour cycle were significantly lower than in young controls. A significant reduction of the hippocampal and temporal volume and an enlargement of the lateral ventricles were found in aged subjects, these changes being significantly related to subjects' age. Moreover, the hippocampal volume was positively correlated with the circadian mesor of DHEAs (i.e., the circadian rhythm adjusted mean) and with the cortisol nocturnal increase. Our data may suggest the existence of a link between the selective impairment of cortisol secretion and DHEAs levels, and the progression of hippocampal degeneration.

The therapeutic potential for tryptophan and melatonin: possible roles in depression, sleep, Alzheimer's disease and abnormal aging.

Maurizi CP.

Med Hypotheses 1990 Mar;31(3):233-42

Evidence suggests that stress and/or a dietary lack of tryptophan may make deficiencies of serotonin and melatonin common. In addition, older animals and human beings have a reduced ability to synthesize melatonin. Disorders of melatonin levels and rhythms are suggested to be a cause of affective disease, abnormal sleep, Alzheimer's disease, and some age related disorders. If these ideas prove to be true, then preventive measures are possible.

Analogues, ageing and aberrant assimilation of vitamin B12 in Alzheimer's disease.

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Dement Geriatr Cogn Disord 2001 Mar-Apr;12(2):133-7

Vitamin B12 assimilation might be disrupted in patients with Alzheimer's disease. We therefore measured B12 carrier protein saturation and inactive B12 'analogues' in patients compared with healthy elderly individuals in a prospective case-controlled survey. Twenty-three patients, aged 60 or over, with features compatible with DSM-IV criteria for primary degenerative dementia of the Alzheimer type were recruited together with 18 cognitively intact age-matched control subjects. Total vitamin B12 (active corrinoids), holo- and apo-haptocorrin

and transcobalamin were measured in serum. B12 analogues (inactive corrinoids) were estimated from the difference between R-binder-determined corrinoids and an intrinsic factor based B12 assay. Alzheimer patients had significantly lower active corrinoid than control subjects and the analogue/corrinoid ratio was significantly higher in the Alzheimer group. The inter-relationship between age, analogues and transcobalamin polarised patients into two distinct groups. Two disparate mechanisms might exist for the development of cerebral B12 deficiency in Alzheimer's disease, although both imply a disruption of selective B12 assimilation and analogue elimination in such patients. Copyright 2001 S. Karger AG, Basel

Total serum homocysteine in senile dementia of Alzheimer type.

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Int J Geriatr Psychiatry 1998 Apr;13(4):235-9

OBJECTIVE: The main hypothesis was that subtle vitamin B12 deficiencies occur more commonly in senile dementia of Alzheimer type (SDAT) that in healthy elderly individuals, and may be revealed by elevated total serum homocysteine (tHcy). A subsidiary hypothesis was that such deficiencies would be nutritionally independent as determined by retinol binding protein (RBP).

DESIGN: A prospective case-controlled survey.

SETTING: A Welsh urban psychogeriatric assessment centre and local general practice.

PATIENTS: Thirty patients, aged 65 or over, seen consecutively in 1994 with features compatible with DSM-III-R criteria for primary degenerative dementia of Alzheimer type and 30 cognitively intact age-matched control subjects.

MEASURES: Diagnosis was assessed using the CAMDEX. Cognitive scores were evaluated with the CAMCOG scale for patients and MMSE scores for control subjects. THcy was measured using high performance liquid chromatography (HPLC), and RBP assayed by a radial immunodiffusion method.

RESULTS: Patients had a highly significant elevation of tHcy compared with control (p < 0.0001). Multiple regression highlighted the interrelated effects of tHcy and total serum cobalamin on cognitive scores. RBP did not differ between groups. Macrocytosis was absent, and neutrophil hypersegmentation uncommon, in hyperhomocysteinaemic patients.

CONCLUSIONS: SDAT patients have significantly elevated tHcy. This is independent of RBP determined nutritional status. 'Classical' haematological changes of cobalamin or folate deficiency are poor predictors of tHcy in these patients. Aberrant cobalamin tissue delivery appears to contribute to SDAT

cognitive decline. Relative contributions of other tHcy determinants require further investigation.

Homocysteine and cognitive decline in healthy elderly.

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Dement Geriatr Cogn Disord 2001 Sep-Oct;12(5):309-13

Serum homocysteine is increased, and correlates inversely with cognitive scores, in Alzheimer's disease (AD), vascular dementia and "age-associated memory impairment". Elevated levels might signal accelerated cognitive decline, although this remains to be established. We therefore repeated Mini-Mental State Examinations, together with additional ADAS-Cog assessments, in 32 healthy elderly individuals to determine whether prior homocysteine levels predicted cognitive changes over a 5-year period. Homocysteine predicted follow-up cognitive scores and rate of decline in cognitive performance independently of age, sex, education, renal function, vitamin B status, smoking and hypertension (p < 0.001). Homocysteine predicted word recall (p = 0.01), orientation (p = 0.02) and constructional praxis scores (p < 0.0001). One subject, with the second highest initial homocysteine, had developed probable AD at follow-up. Fasting total serum homocysteine appears to be an independent predictor of cognitive decline in healthy elderly and exerts a maximal effect on spatial copying skills.

Vascular nitric oxide, sex hormone replacement, and fish oil may help to prevent Alzheimer's disease by suppressing synthesis of acute-phase cytokines.

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Med Hypotheses 1999 Nov;53(5):369-74

The neurodegenerative plaques of Alzheimer's disease (AD) are characterized by a self-sustaining acute-phase reaction in which both interleukin-1 (IL-1) and interleukin-6 (IL-6) are up-regulated. The fact that IL-6 is detectable in early stage diffuse plaques encourages the speculation that the acute-phase process is crucial to the pathogenesis of AD. The epidemiological association of AD with estrogen deficiency, as well as with various disorders characterized by vascular endotheliopathy, suggest a protective role for vascular nitric oxide (NO). NO has an autocrine anti-inflammatory impact on endothelium, owing in part to antagonism of NF-kappaB activity; since induction of IL-6 is dependent on NF-kappaB, this may explain recent evidence that NO inhibits macrophage IL-6 production. It is reasonable to postulate that, analogously, cerebrovascular NO decreases IL-6 production in the brain. Vascular NO may also have direct europrotective activity. Estrogen, in addition to promoting vascular NO synthesis, can block IL-6 production by a more direct mechanism in cells expressing

estrogen receptors; since such receptors have been reported in brain glia and astrocytes, estrogen has the potential to limit brain IL-1 activity. Testosterone likewise can inhibit IL-6 induction in androgen-responsive cells, which may include brain glia and astrocytes. Since fish oil and gamma linolenic acid (GLA) suppress IL-1 production by stimulated monocytes, they conceivably could exert this effect in the brain as well; the comparatively low prevalence of AD in elderly Japanese is intriguing in this regard. These considerations suggest that a healthy cerebrovascular endothelium, sex hormone activity, and dietary fish oil/GLA may slow or prevent AD onset by dampening acute-phase mechanisms in the brain.

Subnormal serum vitamin B12 and behavioural and psychological symptoms in Alzheimer's disease.

Meins W, Muller-Thomsen T, Meier-Baumgartner HP Memory-Clinic, Department of Geriatric Medicine, Albertinen Hospital, Hamburg, Germany.

Int J Geriatr Psychiatry 2000 May;15(5):415-8

The objective of this study was to examine whether patients with Alzheimer's disease (AD) with subnormal vitamin B12 levels show more frequent behavioural and psychological symptoms of dementia (BPSD) than AD patients with normal vitamin B12 levels. The design was a prospective case-control study. The study took place at a memory-clinic of a department of geriatric medicine in a teaching hospital. There were seventy-three consecutive outpatients with probable AD, including 61 patients with normal and 12 patients with subnormal (<200 pg/ml) vitamin B12. BPSD were measured using the subscales disturbed behaviour and mood of the Nurses' Observation Scale for Geriatric Patients (NOSGER), the Cornell Scale for Depression and the four criteria for personality change in dementia from the International Classification of Diseases (ICD-10). Controlling for dementia duration and degree of severity of the cognitive deficits, there were significant inverse associations between vitamin B12 status and ICD-10 irritability (p=0.045) and NOSGER subscale disturbed behaviour (p=0.015). Low vitamin B12 serum levels are associated with BPSD in AD. Vitamin B12 could play a role in the pathogenesis of behavioural changes in AD.

Homocysteine and Alzheimer's disease.

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Nutr Rev 1999 Apr;57(4):126-9

In a recent case-control study of 164 patients with clinically diagnosed Alzheimer's disease (AD), including 76 patients with the AD diagnosis confirmed postmortem, mean total serum homocysteine concentration was found to be significantly higher than that of a control group of elderly individuals with no evidence of cognitive impairment. Because homocysteine is considered an independent risk factor for vascular disease, this finding is consistent with the

emerging hypothesis that vascular disease is a contributing factor in the pathogenesis of AD.

Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease.

Morris MC, Beckett LA, Scherr PA, Hebert LE, Bennett DA, Field TS, Evans DA. Rush Institute for Healthy Aging and Rush Alzheimer's Disease Center, Rush University, Chicago, Illinois, USA.

Alzheimer Dis Assoc Disord 1998 Sep;12(3):121-6

Oxidative stress may play a role in neurologic disease. The present study examined the relation between use of vitamin E and vitamin C and incident Alzheimer disease in a prospective study of 633 persons 65 years and older. A stratified random sample was selected from a disease-free population. At baseline, all vitamin supplements taken in the previous 2 weeks were identified by direct inspection. After an average follow-up period of 4.3 years, 91 of the sample participants with vitamin information met accepted criteria for the clinical diagnosis of Alzheimer disease. None of the 27 vitamin E supplement users had Alzheimer disease compared with 3.9 predicted based on the crude observed incidence among nonusers ($p = 0.04$) and 2.5 predicted based on age, sex, years of education, and length of follow-up interval ($p = 0.23$). None of the 23 vitamin C supplement users had Alzheimer disease compared with 3.3 predicted based on the crude observed incidence among nonusers ($p = 0.10$) and 3.2 predicted adjusted for age, sex, education, and follow-up interval ($p = 0.04$). There was no relation between Alzheimer disease and use of multivitamins. These data suggest that use of the higher-dose vitamin E and vitamin C supplements may lower the risk of Alzheimer disease.

Hippocampal perfusion and pituitary-adrenal axis in Alzheimer's disease.

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Neuropsychobiology 2000;42(2):51-7

The hippocampus is involved in Alzheimer's disease (AD) and regulates the hypothalamus-pituitary-adrenal axis (HPAA). Enhanced cortisol secretion has been reported in AD. Increased cortisol levels affect hippocampal neuron survival and potentiate beta-amyloid toxicity. Conversely, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are believed to antagonize noxious glucocorticoid effects and exert a neuroprotective activity. The present study was aimed at investigating possible correlations between hippocampus perfusion - evaluated by SPECT - and HPAA function in AD. Fourteen patients with AD and 12 healthy age-matched controls were studied by (99m)Tc-HMPAO high-resolution brain SPECT. Plasma adrenocorticotropin, cortisol, and DHEAS levels were determined at 2.00, 8.00, 14.00, 20.00 h in all subjects and their mean values

were computed. Cortisol/DHEAS ratios (C/Dr) were also calculated. Bilateral impairment of SPECT hippocampal perfusion was observed in AD patients as compared to controls. Mean cortisol levels were significantly increased and DHEAS titers were lowered in patients with AD, as compared with controls. C/Dr was also significantly higher in patients. Using a stepwise procedure for dependent SPECT variables, the variance of hippocampal perfusional data was accounted for by mean basal DHEAS levels. Moreover, hippocampal SPECT data correlated directly with mean DHEAS levels, and inversely with C/Dr. These data show a relationship between hippocampal perfusion and HPAA function in AD. Decreased DHEAS, rather than enhanced cortisol levels, appears to be correlated with changes of hippocampal perfusion in dementia.

Congeners of N(alpha)-acetyl-L-cysteine but not aminoguanidine act as neuroprotectants from the lipid peroxidation product 4-hydroxy-2-nonenal.

Neely MD, Zimmerman L, Picklo MJ, Ou JJ, Morales CR, Montine KS, Amaranth V, Montine TJ. Departments of Pathology and Pharmacology, and the Center for Molecular Neurosciences, Vanderbilt University Medical Center, Nashville, TN 37232, USA.

Free Radic Biol Med 2000 Nov 15;29(10):1028-36

Increased generation of neurotoxic lipid peroxidation products is proposed to contribute to the pathogenesis of Alzheimer's disease (AD). Current antioxidant therapies are directed at limiting propagation of brain lipid peroxidation. Another approach would be to scavenge the reactive aldehyde products of lipid peroxidation. N(alpha)-acetyl-L-cysteine (NAC) and aminoguanidine (AG) react rapidly and irreversibly with 4-hydroxy-2-nonenal (HNE) in vitro, and both have been proposed as potential scavengers of HNE in biological systems. We have compared NAC, AG, and a series of congeners as scavengers of HNE and as neuroprotectants from HNE. Our results showed that while both NAC and AG had comparable chemical reactivity with HNE, only NAC and its congeners were able to block HNE-protein adduct formation in vitro and in neuronal cultures. Moreover, NAC and its congeners, but not AG, effectively protected brain mitochondrial respiration and neuronal microtubule structure from the toxic effects of HNE. We conclude that NAC and its congeners, but not AG, may act as neuroprotectants from HNE.

Could diet be one of the causal factors of Alzheimer's disease?

Newman PE.

Med Hypotheses 1992 Oct;39(2):123-6

Recent developments show that the brains of persons who have died from Alzheimer's Disease (AD) have a deficiency of Essential Fatty acids in one of the principal classes of phospholipids. It is hypothesized that faulty brain cell membranes resulting from this deficiency may allow passage of an enzyme into the bilayer membrane space which cuts beta amyloid precursor proteins attached

to such cells at a critical intramembrane position releasing a complete sequence of beta amyloid protein into the extracellular space. Beta amyloid protein appears to be the principal active constituent of senile plaques thought to be a probable cause of brain damage resulting in AD. Treatment of persons suffering from AD with desferrioxamine, a trivalent ion chelator to remove aluminium has shown results in slowing the progression of this disease, implicating aluminium and/or other chelated substances in its etiology. Both EFA deficiency and aluminium build-up may be prevented by dietary precautions.

Alzheimer's disease revisited.

Newman PE. Paris, France.

Med Hypotheses 2000 May;54(5):774-6

In a previous paper, it was suggested that a relative deficiency of essential fatty acids might play a role in the etiology of sporadic or non-familial Alzheimer's disease. A recent article regarding dementia in the Rotterdam Study reinforces this suggestion. It is also hypothesized that this relative deficiency could facilitate passage of aluminum into the brain, aluminum being increasingly suggested as one of the possible pathogenic factors in AD. It is further suggested that hypomethylation caused by a deficiency of S-adenosylmethionine might also play a role in the etiology of this disease and perhaps even of Parkinson's disease. Copyright 2000 Harcourt Publishers Ltd.

[Analysis of dietary factors in Alzheimer's disease: clinical use of nutritional intervention for prevention and treatment of dementia] [Article in Japanese]

Otsuka M. Department of Neurology, Jichi Medical School, Omiya Medical Center.

Nippon Ronen Igakkai Zasshi 2000 Dec;37(12):970-3

To determine dietary factors involved in the pathological process of Alzheimer's disease (AD), we analyzed food consumption and intake of nutrients using Self-administered Diet History Questionnaire (DHQ) developed for Japanese. Sixty four AD patients and 80 age-matched healthy subjects were enrolled in this study. AD was diagnosed according to the criteria of DSM-IV. Dietary behaviors of AD patients was markedly deviated from those of age-matched healthy elderly. AD patients disliked fish and green-yellow vegetables and took more meats than controls. Energy-adjusted analysis of nutrients revealed that AD patients took less vitamin C and carotene. Most conspicuously, AD patients took significantly smaller amount of n-3 polyunsaturated fatty acid (PUFA) reflecting low consumption of fish, and their n-6/n-3 ratio was significantly increased. These habits started from 3 months to 44 years before the onset of dementia, suggesting these dietary abnormalities are not merely the consequence of dementia. Rather, it implies that AD might be a life style-related disease such as coronary heart disease, western style diet-associated cancer and hyperallergy. To see if cognitive function was improved by correcting the n-6/n-3 ratio, we prescribed

eicossapentaenoic acid (EPA), one type of n-3 PUFA, for AD patients. Cognitive function was evaluated using MMSE. Administration of EPA (900 mg/day) improved MMSE significantly with maximal effects at 3 months and the effects lasted 6 months. However, the score of MMSE decreased after 6 months. The present study showed that nutritional intervention is useful for the prevention of AD, and also for the therapy of dementia, though it has some limitation.

Alzheimer beta protein mediated oxidative damage of mitochondrial DNA: prevention by melatonin.

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J Pineal Res 1999 Nov;27(4):226-9

Most contemporary progress in Alzheimer's disease (AD) stems from the study of a 42 43 amino acid peptide. called the amyloid beta protein (Abeta), as the main neuropathologic marker of the disorder. It has been demonstrated that Abeta has neurotoxic properties and that such effects are mediated by free-radicals. Exposure of neuronal cells to Abeta results in a spectrum of oxidative lesions that are profoundly harmful to neuronal homeostasis. We had previously shown that Abeta25-35 induces oxidative damage to mitochondrial DNA (mtDNA) and that this modality of injury is prevented by melatonin. Because Abeta25 35 does not occur in AD and because the mode of toxicity by Abeta25-35 may be different from that of Abeta1-42 (the physiologically relevant form of Abeta), we extended our initial observations to determine whether oxidative damage to mtDNA could also be induced by Abeta1-42 and whether this type of injury is prevented by melatonin. Exposure of human neuroblastoma cells to Abeta1-42 resulted in marked oxidative damage to mtDNA as determined by a quantitative polymerase chain reaction method. Addition of melatonin to cell cultures along with Abeta completely prevented the damage. This study supports previous findings with Abeta25-35, including a causative role for Abeta in the mitochondrial oxidative lesions present in AD brains. Most important, the data confirms the neuroprotective role of melatonin in Abeta-mediated oxidative injury. Because melatonin also inhibits amyloid aggregation, lacks toxicity, and efficiently crosses the blood-brain barrier, this hormone appears superior to other available antioxidants as a candidate for pharmacologic intervention in AD.

Acetylcholine in mind: a neurotransmitter correlate of consciousness?

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Trends Neurosci 1999 Jun;22(6):273-80

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and controls activities that depend on selective attention,

which are an essential component of conscious awareness. Psychopharmacological and pathological evidence supports the concept of a 'cholinergic component' of conscious awareness. Drugs that antagonize muscarinic receptors induce hallucinations and reduce the level of consciousness, while the nicotinic receptor is implicated as being involved in the mechanism of action of general (inhalational) anaesthetics. In degenerative diseases of the brain, alterations in consciousness are associated with regional deficits in the cholinergic system. In Alzheimer's disease (AD), there is a loss of explicit (more than implicit) memory and hypoactivity of cholinergic projections to the hippocampus and cortex, while the visual hallucinations experienced by subjects with Dementia with Lewy bodies (DLB) are associated with reductions in neocortical ACh-related activity. In Parkinson's disease, the additional loss of pedunculopontine cholinergic neurones, which control REM (rapid eye movement) sleep or dreaming, is likely to contribute to REM abnormalities, which also occur in DLB. Widespread basal-forebrain and rostral brainstem cholinergic pathways, which include converging projections to the thalamus, appear to be located strategically for generating and integrating conscious awareness. Alleviation of a range of cognitive and non-cognitive symptoms by drugs that modulate the cholinergic system, which are being developed for the treatment of AD and related disorders, could be caused by changes in consciousness.

Effects of physostigmine and lecithin on memory in Alzheimer disease.

Peters BH, Levin HS.

Ann Neurol 1979 Sep;6(3):219-21

Because there is evidence that central cholinergic mechanisms are depleted in dementia, we studied the effects of central cholinergic augmentation on the memory of 5 patients with Alzheimer disease. Patients received placebo, lecithin, physostigmine, or lecithin plus physostigmine in a double-blind study using titrated doses of the acetylcholinesterase inhibitor physostigmine. Memory was evaluated with alternate forms of the selective reminding procedure. Compared with lecithin alone, the combination of physostigmine and lecithin consistently enhanced memory storage and retrieval; physostigmine without lecithin produced no memory facilitation. The strategy of combining a cholinergic agonist and precursor holds promise, although a larger clinical trial is needed.

Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy.

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J Pharm Pharmacol 1999 May;51(5):527-34

The use of complementary medicines, such as plant extracts, in dementia therapy varies according to the different cultural traditions. In orthodox Western medicine, contrasting with that in China and the Far East for example,

pharmacological properties of traditional cognitive- or memory-enhancing plants have not been widely investigated in the context of current models of Alzheimer's disease. An exception is Gingko biloba in which the gingkolides have antioxidant, neuroprotective and cholinergic activities relevant to Alzheimer's disease mechanisms. The therapeutic efficacy of Ginkgo extracts in Alzheimer's disease in placebo controlled clinical trials is reportedly similar to currently prescribed drugs such as tacrine or donepezil and, importantly, undesirable side effects of Gingko are minimal. Old European reference books, such as those on medicinal herbs, document a variety of other plants such as Salvia officinalis (sage) and Melissa officinalis (balm) with memory-improving properties, and cholinergic activities have recently been identified in extracts of these plants. Precedents for modern discovery of clinically relevant pharmacological activity in plants with long-established medicinal use include, for example, the interaction of alkaloid opioids in Papaver somniferum (opium poppy) with endogenous opiate receptors in the brain. With recent major advances in understanding the neurobiology of Alzheimer's disease, and as yet limited efficacy of so-called rationally designed therapies, it may be timely to re-explore historical archives for new directions in drug development. This article considers not only the value of an integrative traditional and modern scientific approach to developing new treatments for dementia, but also in the understanding of disease mechanisms. Long before the current biologically-based hypothesis of cholinergic derangement in Alzheimer' s disease emerged, plants now known to contain cholinergic antagonists were recorded for their amnesia- and dementia-inducing properties.

Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression.

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Mol Psychiatry 2000 Nov;5(6):616-32

Acetyl-L-carnitine (ALCAR) contains carnitine and acetyl moieties, both of which have neurobiological properties. Carnitine is important in the beta-oxidation of fatty acids and the acetyl moiety can be used to maintain acetyl-CoA levels. Other reported neurobiological effects of ALCAR include modulation of: (1) brain energy and phospholipid metabolism; (2) cellular macromolecules, including neurotrophic factors and neurohormones; (3) synaptic morphology; and (4) synaptic transmission of multiple neurotransmitters. Potential molecular mechanisms of ALCAR activity include: (1) acetylation of -NH2 and -OH functional groups in amino acids and N terminal amino acids in peptides and proteins resulting in modification of their structure, dynamics, function and turnover; and (2) acting as a molecular chaperone to larger molecules resulting in a change in the structure, molecular dynamics, and function of the larger molecule. ALCAR is reported in double-blind controlled studies to have beneficial effects in major depressive disorders and Alzheimer's disease (AD), both of which are highly prevalent in the geriatric population.

In-vivo glutathione elevation protects against hydroxyl free radical-induced protein oxidation in rat brain.

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Neurochem Int 2000 Mar;36(3):185-91

Glutathione deficiency has been associated with a number of neurodegenerative diseases including Lou Gehrig's disease, Parkinson's disease, and HIV. A crucial role for glutathione is as a free radical scavenger. Alzheimer's disease (AD) brain is characterized by oxidative stress, manifested by protein oxidation, lipid oxidation, oxidized glutathione, and decreased activity of glutathione S-transferase, among others. Reasoning that elevated levels of endogenous glutathione would offer protection against free radical-induced oxidative stress, rodents were given in vivo injections of N-acetylcysteine (NAC), a known precursor of glutathione, to study the vulnerability of isolated synaptosomal membranes treated with Fe2+/H2O2, a known hydroxyl free radical producer. Protein carbonyls, a marker of protein oxidation, were measured. NAC significantly increased endogenous glutathione levels in cortical synaptosome cytosol (P < 0.01). As reported previously, protein carbonyl levels of the Fe2+/H2O2-treated synaptosomes were significantly higher compared to that of non-treated controls (P < 0.01), consistent with increased oxidative stress. In contrast, protein carbonyl levels in Fe2+/H2O2-treated synaptosomes isolated from NAC-injected animals were not significantly different from saline-injected non-treated controls, demonstrating protection against hydroxyl radical induced oxidative stress. These results are consistent with the notion that methods to increase endogenous glutathione levels in neurodegenerative diseases associated with oxidative stress, including AD, may be promising.

Cognitive deficit induced by acute tryptophan depletion in patients with Alzheimer's disease.

Porter RJ, Lunn BS, Walker LL, Gray JM, Ballard CG, O'Brien JT. Academic Department of Psychiatry, University of Newcastle upon Tyne, England.

Am J Psychiatry 2000 Apr;157(4):638-40

OBJECTIVE: The study assessed the effects on global cognitive function and mood of a reduction of brain serotonin by means of acute tryptophan depletion in 16 patients with dementia of the Alzheimer type and in 16 cognitively intact comparison subjects.

METHOD: In a double-blind, crossover design, subjects received a tryptophan-free amino acid drink to induce acute tryptophan depletion and, on a separate occasion, a placebo drink containing a balanced mixture of amino acids. On each occasion, ratings of depressed mood were made at baseline and 4 and 7 hours later, and the Modified Mini-Mental State was administered at baseline and 4 hours later.

RESULTS: Patients with dementia of the Alzheimer type had a significantly lower mean score on the Modified Mini-Mental State after acute tryptophan depletion than after receiving placebo. The comparison group showed no difference in mean score on the Modified Mini-Mental State after acute tryptophan depletion and after receiving placebo. No significant changes in mood were found in either group.

CONCLUSIONS: Acute tryptophan depletion significantly impaired cognitive function in patients with dementia of the Alzheimer type. Compromised serotonergic function, in combination with cholinergic deficit, may make an important contribution to cognitive decline in dementia of the Alzheimer type.

Toxic effects of beta-amyloid(25-35) on immortalised rat brain endothelial cell: protection by carnosine, homocarnosine and beta-alanine.

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Neurosci Lett 1998 Feb 13;242(2):105-8

The effect of a truncated form of the neurotoxin beta-amyloid peptide (A beta25-35) on rat brain vascular endothelial cells (RBE4 cells) was studied in cell culture. Toxic effects of the peptide were seen at 200 microg/ml A beta using a mitochondrial dehydrogenase activity (MTT) reduction assay, lactate dehydrogenase release and glucose consumption. Cell damage could be prevented completely at 200 microg/ml A beta and partially at 300 microg/ml A beta, by the dipeptide carnosine. Carnosine is a naturally occurring dipeptide found at high levels in brain tissue and innervated muscle of mammals including humans. Agents which share properties similar to carnosine, such as beta-alanine, homocarnosine, the anti-glycating agent aminoguanidine, and the antioxidant superoxide dismutase (SOD), also partially rescued cells, although not as effectively as carnosine. We postulate that the mechanism of carnosine protection lies in its anti-glycating and antioxidant activities, both of which are implicated in neuronal and endothelial cell damage during Alzheimer's disease. Carnosine may therefore be a useful therapeutic agent.

Melatonin as a pharmacological agent against neuronal loss in experimental models of Huntington's disease, Alzheimer's disease and parkinsonism.

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Ann N Y Acad Sci 1999;890:471-85

This review summarizes the experimental findings related to the neuroprotective role of melatonin. In particular, it focuses on research directed at models of Huntington's disease, Alzheimer's disease and Parkinsonism. Melatonin has been shown to be highly effective in reducing oxidative damage in the central nervous

system; this efficacy derives from its ability to directly scavenge a number of free radicals and to function as an indirect antioxidant. In particular, melatonin detoxifies the highly toxic hydroxyl radical as well as the peroxyl radical, peroxynitrite anion, nitric oxide, and singlet oxygen, all of which can damage macromolecules in brain cells. Additionally, melatonin stimulates a variety of antioxidative enzymes including superoxide dismutase, glutathione peroxidase and glutathione reductase. One additional advantage melatonin has in reducing oxidative damage in the central nervous system is the ease with which to crosses the blood-brain barrier. This combination of actions makes melatonin a highly effective pharmacological agent against free radical damage. The role of physiological levels of melatonin in forestalling oxidative damage in the brain is currently being tested.

Nutritional status of free-living Alzheimer's patients.

Renvall MJ, Spindler AA, Ramsdell JW, Paskvan M. Department of Medicine, University of California Medical Center, San Diego 92103-1990.

Am J Med Sci 1989 Jul;298(1):20-7

Self-reported, dietary intake and biochemical estimates of thiamine, riboflavin, folate, vitamin B-12, protein, and iron were compared in 22, free-living elders by individuals who had senile dementia of the Alzheimer's type (SDAT) and in 41 who were cognitively normal (CN). The two groups did not differ significantly in their intake of these nutrients or the number of deficiency states for intake (less than 67% RDA). Low serum transketolase (thiamin; p less than 0.055), red blood cell (RBC) folate (p less than 0.06), and serum vitamin B-12 (p less than 0.05) levels occurred more often in SDAT patients than in CN subjects. Individuals in both groups who used multivitamin supplements had significantly higher biochemical values for thiamine (p less than 0.03), riboflavin (p less than 0.01), and vitamin B-12 (p less than 0.003) than nonsupplement users. Because of the differences in vitamin B-12 and RBC folate levels between groups, a retrospective analysis was performed on a larger group of subjects drawn from a geriatric assessment clinic. Patients with SDAT had significantly lower serum vitamin B-12 (p less than 0.01) and lower RBC folate (p less than 0.03) values than CN subjects. Which mean values for vitamin B-12 and RBC folate were grouped by degree of impairment in SDAT subjects, vitamin B-12 was significantly lower in mildly and moderately impaired subjects than in those with normal cognition. Mean values for both nutrients did not differ significantly between severely impaired and CN subjects. There was a significant quadratic relationship between cognitive impairment and biochemical values for vitamin B-12.(ABSTRACT TRUNCATED AT 250 WORDS)

Low plasma vitamin C in Alzheimer patients despite an adequate diet.

Riviere S, Birlouez-Aragon I, Nourhashemi F, Vellas B. Hopital La Grave-Casselar, Toulouse, France.

Int J Geriatr Psychiatry 1998 Nov;13(11):749-54

OBJECTIVE: To compare the vitamin C and E plasma levels in patients with Alzheimer's disease (AD) and to assess the vitamin C intake and nutritional status.

DESIGN: Case-control study. Four groups of sex- and age-matched subjects were compared: severe AD and moderate AD, in patients with moderate AD and controls.

SETTING: Community and hospitalized patients in the region of Toulouse, France.

PARTICIPANTS: Patients with dementia who fulfilled criteria for Alzheimer's disease: severe Alzheimer group (N = 20), Mini-Mental State Examination (MMSE) score range 0-9; moderate Alzheimer group (N = 24), MMSE 10-23; hospitalized Alzheimer group (N = 9), MMSE 10-23. Control group (N = 19), MMSE 24-30.

MEASURES: Plasma vitamin E and C were quantified by HPLC-fluorescence. Consumption of raw and cooked fruit and vegetables was evaluated in order to determine the mean vitamin C intakes. Mini Nutritional Assessment (MNA) and plasma albumin were used to measure nutritional status.

RESULTS: Institutionalized and community subjects were analysed separately. MNA scores were normal in home-living Alzheimer subjects with moderate dementia and significantly lower in those with severe disease, despite normal plasma albumin levels. In the home-living Alzheimer subjects, vitamin C plasma levels decreased in proportion to the severity of the cognitive impairment despite similar vitamin C intakes, whereas vitamin E remained stable. The hospitalized Alzheimer subjects had lower MNA scores and albumin levels but normal vitamin C intakes, but their plasma vitamin C was lower than that of community-living subjects. Institutionalized Alzheimer subjects had significantly lower MNA scores but normal vitamin C and albumin levels and vitamin C intakes compared with community-dwelling subjects of similar degree of cognitive impairment.

CONCLUSION: Plasma vitamin C is lower in AD in proportion to the degree of cognitive impairment and is not explained by lower vitamin C intake. These results support the hypothesis that oxygen-free radicals may cause damage.

A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer ' s disease. The Alzheimer' s Disease Cooperative Study

Sano M; Ernesto C; Thomas RG; Klauber MR; Schafer K; Grundman M; Woodbury P; Growdon J; Cotman CW; Pfeiffer E; Schneider LS; Thal LJ
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N Engl J Med (United States) Apr 24 1997, 336 (17) p1216-22

BACKGROUND: There is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease.

METHODS: We conducted a double-blind, placebo-controlled, randomized, multicenter trial in patients with Alzheimer's disease of moderate severity. A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3).

RESULTS: Despite random assignment, the baseline score on the Mini-Mental State Examination was higher in the placebo group than in the other three groups, and this riable was highly predictive of the primary outcome (P<0.001). In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. In analyses that included the base-line score on the Mini-Mental State Examination as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline (median time, 655 days; P=0.012), alpha-tocopherol (670 days, P=0.001) or combination therapy (585 days, P=0.049), as compared with the placebo group (440 days).

CONCLUSIONS: In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease.

Tyrosine hydroxylase, tryptophan hydroxylase, biopterin, and neopterin in the brains of normal controls and patients with senile dementia of Alzheimer type.

Sawada M, Hirata Y, Arai H, Iizuka R, Nagatsu T.

J Neurochem 1987 Mar;48(3):760-4

The activities of tyrosine hydroxylase and tryptophan hydroxylase, and the concentrations of the biopterin cofactor and the precursor neopterin were measured in 14 regions of postmortem brains from four histologically verified patients of senile dementia of the Alzheimer type (SDAT) and eight histologically normal controls. Neopterin concentrations were measured in the human brain for the first time. The activities of tyrosine hydroxylase and tryptophan hydroxylase in the brains of patients with SDAT were significantly reduced in the substantia nigra and in the lateral segment of the globus pallidus, locus ceruleus, and substantia nigra, respectively. The concentrations of total biopterin in the brains of patients with SDAT were significantly reduced in the putamen and substantia nigra, but the total neopterin concentrations did not change significantly. These results suggest that the reduction in biogenic amines in SDAT might be related to reductions in biosynthetic enzymes associated with biogenic amines, due to destruction of monoaminergic neurons.

Phenolic antioxidants attenuate neuronal cell death following uptake of oxidized low-density lipoprotein.

Schroeter H, Williams RJ, Matin R, Iversen L, Rice-Evans CA. Wolfson Centre for Age-Related Diseases, Guy's, King's, and St. Thomas's School of Biomedical Sciences, King's College, Guy's Campus, London, England.

Free Radic Biol Med 2000 Dec 15;29(12):1222-33

Oxidative stress is implicated in neuronal loss associated with neurodegeneration such as in Parkinson's disease, Alzheimer's disease and age-related cognitive decline. Recent reports indicate that the consumption of flavonoid-rich fruits partly reverses the age-related neuronal and cognitive decline. In this study, cultured striatal neurons were exposed to oxidized lipids in the form of low-density lipoprotein (oxLDL) as a model for the induction of oxidative injury, and the abilities of phenolic antioxidants, flavonoids and hydroxycinnamic acid derivatives, to attenuate this neuronal damage were examined. OxLDL was demonstrated to enter neuronal cells and to be capable of eliciting neurotoxicity in a dose- and time-dependent manner, inducing DNA fragmentation and cell lysis. Flavonoids exert protective effects, which appear to be related to specific structural characteristics, particularly relevant being those defining their reduction potentials and partition coefficients. In summary, these data suggest a possible role for flavonoids in reducing neurodegeneration associated with chronic disorders in which oxidative stress is implicated.

CSF-folate levels are decreased in late-onset AD patients.

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J Neural Transm 2001;108(1):93-9

Folates are involved in the cerebral metabolism of cobalamine, methionine, L-tyrosine and acetylcholine. Remarkably CSF-folate levels are 3 to 4 times higher than blood-folate levels. To reach the brain, folates are actively transported by choroid plexus (CP) as well as vitamins B6, B12, C and E. Epithelial atrophy having been reported in aging and in Alzheimer's disease (AD), we measured the CSF folate-levels of 126 patients, including 30 AD consecutive patients to evaluate whether CP functions of folate-transport were impaired. CSF-folate concentrations did not vary with age (10.47 +/- 1.93ng/ml between 20 and 60 years; 9.96 +/- 2.01 ng/ml in elderly control patients older than 60 years of age, p > 0.05) while late-onset AD patients had significantly lower CSF-folate levels (8.26 +/- 1.82 ng/ml, p < 0.001). These data support a specific alteration of CP transport function in AD patients.

The pathogenesis of Alzheimer's disease.

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J Clin Psychiatry 1998;59 Suppl 9:7-14

Despite consensus on clinical and neuropathologic definitions of Alzheimer's disease, limited information is available on its causes and pathogenesis. Current data suggest interactions among the various possible biological and environmental influences that result in a common pathway leading to the disease. Biological influences include genetic mutations causing the disease phenotype and polymorphisms contributing to disease risk. Alterations in immune or inflammatory responses may also represent biological influences. Various environmental influences that may interact with endogenous biological factors include education, traumatic injury, oxidative stress, drugs, and hormone replacement. The author describes some recent findings that suggest possible pathogenic mechanisms, which may eventually have important treatment implications.

Vitamin E for Alzheimer's disease.

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Cochrane Database Syst Rev 2000;(4):CD002854

BACKGROUND: Vitamin E is a dietary compound that functions as an antioxidant scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes in Alzheimer's disease has led to interest in the use of vitamin E in the treatment of this disorder.

OBJECTIVES: To examine the effects of vitamin E treatment for people with Alzheimer's disease.

EARCH STRATEGY: The Cochrane Dementia Group Register of Clinical Trials was searched with the following terms: vitamin E, Alzheimer's disease, dementia, alpha-tocopherol, cognitive impairment, cognitive function and controlled trials. The latest search was carried out in July 2000.

SELECTION CRITERIA: All unconfounded, double blind, randomized trials in which treatment with vitamin E at any dose was compared with placebo for patients with Alzheimer's disease.

DATA COLLECTION AND ANALYSIS: Two reviewers independently applied the selection criteria an assessed study quality. One reviewer extracted and analysed the data. For each outcome measure data were sought on every patient randomized. Where such data were not available an analysis of patients who completed treatment was conducted.

MAIN RESULTS: Only one study was identified which met the inclusion criteria (Sano 1997). The primary outcome used in this study of 341 participants was survival time to the first of 4 endpoints, death, institutionalisation, loss of 2 out of 3 basic activities of daily living, or severe dementia, defined as a global Clinical Dementia Rating of 3. The investigators reported the total numbers in each group who reached the primary endpoint within two years for participants completing the study ("completers"). There appeared to be some benefit from vitamin E with fewer participants reaching endpoint - 58% (45/77) of completers compared with 74% (58/78) - a Peto odds ratio of 0.49, 95% confidence interval 0.25 to 0.96. However, more participants taking vitamin E suffered a fall (12/77 compared with 4/78; odds ratio 3.07, 95% CI 1.09 to 8.62). It was not possible to interpret the reported results for specific endpoints or for secondary outcomes of cognition, dependence, behavioural disturbance and activities of daily living.

REVIEWER'S CONCLUSIONS: There is insufficient evidence of efficacy of vitamin E in the treatment of people with with Alzheimer's disease. The one published trial of acceptable methodology (Sano 1997) was restricted to patients with moderate disease, and the published results are difficult to interpret. There is sufficient evidence of possible benefit to justify further studies. There was an excess of falls in the vitamin E group compared with placebo which requires further evaluation.

Huperzine A (shuangyiping): a promising drug for Alzheimer's disease.

Tang XC. Department of Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China.

Zhongguo Yao Li Xue Bao 1996 Nov;17(6):481-4

Hup A, a novel alkaloid isolated from Chineses herb Huperzia serrata, is a potent and selective inhibitor of AChE, with a rapid absorption and penetration into the brain in experimental animals. The inhibition is reversible with a longer duration of action. Hup A exhibited memory-enhancing activities in a broad range of animal cognitive model. Compared to Phy, Tac, and Gal, Hup A has better therapeutic indices, and peripheral cholinergic side effects are minimal at therapeutic doses. These findings suggest that Hup A is a promising candidate for clinical development as a symptomatic treatment for AD.

A 1-year controlled trial of acetyl-l-carnitine in early-onset AD.

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Neurology 2000 Sep 26;55(6):805-10

OBJECTIVE: To determine the efficacy of acetyl-l-carnitine (ALCAR) on the rate of decline in early-onset AD patients.

METHODS: A 1-year, multicenter, double-blind, placebo-controlled, randomized trial was conducted. Subjects were 45 to 65 years old, with a diagnosis of probable AD according to National Institute of Neurological Communicative Disorders-Alzheimer's Disease and Related Disorders Association criteria and had a Mini-Mental State Examination (MMSE) score between 12 and 26. They were treated with ALCAR (1 g tid) or placebo. Primary outcome measures were the Alzheimer's Disease Assessment Scale-Cognitive Component and the Clinical Dementia Rating Scale. Secondary measures included the ADAS Non-Cognitive Subscale, the MMSE, an Activities of Daily Living Scale (ADL), and a Clinician-Based Impression of Change (CIBIC).

RESULTS: Two-hundred twenty-nine patients were enrolled and randomized to drug treatment, with 117 taking placebo and 112 taking ALCAR. There were no significant differences between the two groups at baseline. For the primary outcome measures, there were no significant differences between the treatment groups on the change from baseline to endpoint in the intent-to-treat analysis. In the completer sample only, there was less deterioration in the MMSE for the ALCAR-treated subjects. There was no difference in rate of decline on the CIBIC and the ADL scale. There were no significant differences in the incidence of adverse events by treatment arm.

CONCLUSION: Overall, in a prospectively performed study in young-onset AD patients, ALCAR failed to slow decline. Less decline was seen on the MMSE in the completer sample only, with the difference being mediated by reducing decline in attention. A combination of ALCAR and a cholinesterase inhibitor should be tested for additivity.

Oral physostigmine and lecithin improve memory in Alzheimer disease.

Thal LJ, Fuld PA, Masur DM, Sharpless NS.

Ann Neurol 1983 May;13(5):491-6

Eight patients with early Alzheimer disease were treated with gradually increasing multiple daily doses of oral physostigmine and supplemental lecithin. Six individuals showed improvement in total recall and retrieval from long-term storage (LTR), with a decrease in intrusions (a measure of inaccurate recall). The optimal individual dose was either 2.0 or 2.5 mg of physostigmine for each responding patient. Results of this open trial were subsequently replicated during a double-blind crossover trial comparing physostigmine treatment to placebo. All six patients again demonstrated improvement in total recall and LTR, with a decrease in intrusions. The decrease in intrusions was strongly correlated with increasing inhibition of cholinesterase activity in cerebrospinal fluid, suggesting that the degree of improvement in the patient's memory was related to the amount of physostigmine that reached the brain. Other neurotransmitters and metabolites in cerebrospinal fluid were unaffected by the physostigmine therapy, suggesting a specific effect of physostigmine on the cholinergic system. The results suggest that small oral doses of physostigmine combined with lecithin ingestion have therapeutic benefit for some patients with Alzheimer disease.

Interactions between carnosine and zinc and copper: implications for neuromodulation and neuroprotection.

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Biochemistry (Mosc) 2000 Jul;65(7):807-16

This review examines interactions in the mammalian central nervous system (CNS) between carnosine and the endogenous transition metals zinc and copper. Although the relationship between these substances may be applicable to other brain regions, the focus is on the olfactory system where these substances may have special significance. Carnosine is not only highly concentrated in the olfactory system, but it is also contained in neurons (in contrast to glia cells in most of the brain) and has many features of a neurotransmitter. Whereas the function of carnosine in the CNS is not well understood, we review evidence that suggests that it may act as both a neuromodulator and a neuroprotective agent. Although zinc and/or copper are found in many neuronal pathways in the brain, the concentrations of zinc and copper in the olfactory bulb (the target of afferent input from sensory neurons in the nose) are among the highest in the CNS. Included in the multitude of physiological roles that zinc and copper play in the CNS is modulation of neuronal excitability. However, zinc and copper also have been implicated in a variety of neurologic conditions including Alzheimer's disease, Parkinson's disease, stroke, and seizures. Here we review the modulatory effects that carnosine can have on zinc and copper's abilities to influence neuronal excitability and to exert neurotoxic effects in the olfactory system. Other aspects of carnosine in the CNS are reviewed elsewhere in this issue.

Vitamin E supplementation prevents spatial learning deficits and dendritic alterations in aged apolipoprotein E-deficient mice.

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Eur J Neurosci 2000 Dec;12(12):4541-6

Recent studies have suggested that altered function of apolipoprotein E might lead to Alzheimer's disease via oxidative stress. In this context, the objective of this study was to determine if antioxidative treatment with vitamin E was neuroprotective in apolipoprotein E-deficient mice. For this purpose, 1-month-old control and apolipoprotein E-deficient mice received dietary vitamin E for 12 months. We showed that, compared to apolipoprotein E-deficient mice who received a regular diet, mice treated with vitamin E displayed a significantly improved behavioural performance in the Morris water maze. This improved performance was associated with preservation of the dendritic structure in vitamin E-treated apolipoprotein E-deficient mice. In addition, whilst untreated apolipoprotein E-deficient mice displayed increased levels of lipid peroxidation

and glutathione, vitamin E-treated mice showed near normal levels of both lipid peroxidation and glutathione. These results support the contention that vitamin E prevents the age-related neurodegenerative alterations in apolipoprotein E-deficient mice.

The action of acetyl-L-carnitine on the neurotoxicity evoked by amyloid fragments and peroxide on primary rat cortical neurones.

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Ann N Y Acad Sci 2001 Jun;939:162-78

The amyloid beta-peptides have been implicated in the excitotoxic mechanism of neuronal injury in the pathogenesis of Alzheimer's disease. In this paper we examine the effect of different amyloid fragments (beta A1-40, A1-28, and A25-35), as well as potential neuroprotective compounds on rat cortical neuron viability. Exposure of neurones to beta A25-35 or A1-40 at concentrations as low as 1 microgram/ml inhibited, significantly, the MTT response and this level of inhibition was similar after 24-h or three-day exposure. Furthermore, the level of inhibition was not affected by the presence or absence of 5% horse serum in the medium. Preexposure (10 min) of neurones to ALC at concentrations of 0.1, 1, 5, and 10 mM attenuated the inhibition of the MTT response caused by beta A25-35 (50 micrograms/ml) in serum free medium for 24 h. The treatment of cells with vitamin E (100 microM), catalase (4 mg/ml), NGF (0.1 and 10 ng/ml), or cycloheximide (0.1 microgram/ml) significantly restored the MTT response that was inhibited by beta A25-35. The mechanism for the protective actions of these compounds against beta A25-35 toxicity is not clear but may involve free radical scavenger action and preservation of energy production, although other mechanisms, especially for ALC, such as a direct effect on A-beta interaction with charged anionic phospholipids and/or stabilizing action on membranes, are also possible.

Vitamin B(12) and folate in relation to the development of Alzheimer's disease.

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Neurology 2001 May 8;56(9):1188-94

OBJECTIVE: To explore the associations of low serum levels of vitamin B(12) and folate with AD occurrence.

METHODS: A population-based longitudinal study in Sweden, the Kungsholmen

PROJECT: A random sample of 370 nondemented persons, aged 75 years and older and not treated with B(12) and folate, was followed for 3 years to detect incident AD cases. Two cut-off points were used to define low levels of vitamin B(12) (< or =150 and < or =250 pmol/L) and folate (< or =10 and < or =12 nmol/L), and all analyses were performed using both definitions. AD and other types of dementia were diagnosed by specialists according to DSM-III-R criteria.

RESULTS: When using B(12) < or =150 pmol/L and folate < or =10 nmol/L to define low levels, compared with people with normal levels of both vitamins, subjects with low levels of B(12) or folate had twice higher risks of developing AD (relative risk [RR] = 2.1, 95% CI = 1.2 to 3.5). These associations were even stronger in subjects with good baseline cognition (RR = 3.1, 95% CI = 1.1 to 8.4). Similar relative risks of AD were found in subjects with low levels of B(12) or folate and among those with both vitamins at low levels. A comparable pattern was detected when low vitamin levels were defined as B(12) < or =250 pmol/L and folate < or =12 nmol/L.

CONCLUSIONS: This study suggests that vitamin B(12) and folate may be involved in the development of AD. A clear association was detected only when both vitamins were taken into account, especially among the cognitively intact subjects. No interaction was found between the two vitamins. Monitoring serum B(12) and folate concentration in the elderly may be relevant for prevention of AD.

Tryptophan degradation and immune activation in Alzheimer's disease.

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J Neural Transm 2000;107(3):343-53

Alzheimer's disease (AD) is likely associated with systemic immune activation. During immune response, interferon-gamma stimulates indoleamine 2,3-dioxygenase (IDO) converting tryptophan to N-formylkynurenine followed by kynurenine in an ensuing step. Thus, IDO activity is estimated by the kynurenine per tryptophan quotient (Kyn/Trp). In 21 patients suffering from AD, in 20 controls of similar age, and in 49 blood donors we measured serum tryptophan and kynurenine concentrations by HPLC. Lower tryptophan concentrations were found in elderly control subjects compared to blood donors (62.1 vs. 73.0 microM, p < 0.005). Tryptophan concentrations tended to be still lower in AD patients (54.4 microM, p = 0.07) compared to elderly controls. Enhanced tryptophan degradation in patients was reflected by significantly increased Kyn/Trp (46.1 vs. 34.1 in elderly controls, p < 0.05). Correlations were found in patients between Kyn/Trp and concentrations of soluble immune markers in serum, i.e., neopterin, interleukin-2 receptor and tumor necrosis factor receptor (all p < 0.001). Increased Kyn/Trp was associated with reduced cognitive performance. Tryptophan degradation due to immune activation may exert impact on the pathogenesis of AD.

The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial

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J Am Geriatr Soc 2000 Oct;48(10):1183-94

OBJECTIVES: To evaluate the efficacy, the dose-dependence, and the durability of the effect of the ginkgo biloba special extract EGb 761 (ginkgo) in older people with dementia or age-associated memory impairment.

DESIGN: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.

SETTING: Homes for the elderly in the southern part of the Netherlands.

PARTICIPANTS: Older persons with dementia (either Alzheimer's dementia or vascular dementia; mild to moderate degree) or age-associated memory impairment (AAMI). 214 Participants were recruited from 39 homes for the elderly.

INTERVENTION: The participants were allocated randomly to treatment with EGb 761 (2 tablets per day, total dosage either 240 (high dose) or 160 (usual dose) mg/day) or placebo (0 mg/d). The total intervention period was 24 weeks. After 12 weeks of treatment, the initial ginkgo users were randomized once again to either continued ginkgo treatment or placebo treatment. Initial placebo use was prolonged after 12 weeks.

MEASUREMENTS: Outcomes were assessed after 12 and 24 weeks of intervention. Outcome measures included neuropsychological testing (trail-making speed (NAI-ZVT-G), digit memory span (NAI-ZN-G), and verbal learning (NAI-WL)), clinical assessment (presence and severity of geriatric symptoms (SCAG), depressive mood (GDS), self-perceived health and memory status (report marks)), and behavioral assessment (self-reported level of instrumental daily life activities).

RESULTS: An intention-to-treat analysis showed no effect on each of the outcome measures for participants who were assigned to ginkgo (n = 79) compared with placebo (n = 44) for the entire 24-week period. After 12 weeks of treatment, the combined high dose and usual dose ginkgo groups (n = 166) performed slightly better with regard to self-reported activities of daily life but slightly worse with regard to self-perceived health status compared with the placebo group (n = 48). No beneficial effects of a higher dose or a prolonged duration of ginkgo treatment were found. We could not detect any subgroup that benefited from ginkgo. Ginkgo use was also not associated with the occurrence of (serious) adverse events.

CONCLUSIONS: The results of our trial suggest that ginkgo is not effective as a treatment for older people with mild to moderate dementia or age-associated memory impairment. Our results contrast sharply with those of previous ginkgo trials.

Cholinesterase inhibitors and Gingko extracts--are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration.

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Phytomedicine 2000 Jan;6(6):393-401

The efficacy of four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, metrifonate) and Ginkgo special extract EGb 761 in Alzheimer's disease were compared. The differences in the effects of the active substance and placebo on cognition were measured on the ADAS-Cog scale, taking into account the different degrees of dementia in the various studies and the dropout rate due to adverse drug reactions. Efficacy, expressed as the delay in symptom progression or the difference in response rate between active substance and placebo, showed no major differences between the four cholinesterase inhibitors and the Ginkgo special extract. Only tacrine exhibited a high dropout rate due to adverse drug reactions. In view of this, the subject of new prescriptions should be critically reviewed. Second-generation cholinesterase inhibitors (donepezil, rivastigmine, metrifonate) and Ginkgo special extract EGb 761 should be considered equally effective in the treatment of mild to moderate Alzheimer's dementia.

Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1-42)-induced learning and memory deficits in rats: implication of oxidative stress in beta-amyloid-induced neurotoxicity in vivo.

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Eur J Neurosci 1999 Jan;11(1):83-90

Amyloid beta-peptide (A beta), the major constituent of the senile plaques in the brains of patients with Alzheimer's disease, is cytotoxic to neurons and has a central role in the pathogenesis of the disease. Previous studies have suggested that oxidative stress is involved in the mechanisms of A beta-induced neurotoxicity in vitro. In the present study, we examined whether oxidative stress contributes to learning and memory deficits caused by continuous intracerebroventricular infusion of A beta-(1-42). In the A beta-(1-42)-infused rats, spontaneous alternation behaviour in a Y-maze and spatial memory in a water maze task were significantly impaired, as compared with A beta-(40-1)-infused control rats. The retention of passive avoidance learning was also significantly impaired by treatment with A beta-(1-42). Potent antioxidants idebenone and alpha-tocopherol prevented the behavioural deficits in Y-maze and

water maze, but not passive avoidance, tasks in A beta-(1-42)-infused rats when they were repeatedly administered by mouth once a day from 3 days before the start of A beta infusion to the end of behavioural experiments. Lipid peroxide levels in the hippocampus and cerebral cortex of A beta-(1-42)-infused rats did not differ from those in control animals, and neither idebenone nor alpha-tocopherol affected the lipid peroxide levels. These results suggest that treatment with antioxidants such as idebenone and alpha-tocopherol prevents learning and memory deficits caused by A beta.

Free radicals and lipid peroxidation do not mediate beta-amyloid-induced neuronal cell death.

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Brain Res 1999 Nov 20;847(2):203-10

"beta Amyloid (Abeta)-induced free radical-mediated neurotoxicity" is a leading hypothesis as a cause of Alzheimer's disease (AD). Abeta increased free radical production and lipid peroxidation in PC12 nerve cells, leading to increased 4-hydroxy-2-nonenal (HNE) production and modification of specific mitochondrial target proteins, apoptosis and cell death. Pretreatment of the cells with isolated ginkgolides, the anti-oxidant component of Ginkgo biloba leaves, or vitamin E, prevented the Abeta-induced increase of reactive oxygen species (ROS). Ginkgolides, but not vitamin E, inhibited the Abeta-induced HNE modification of mitochondrial proteins. However, treatment with these anti-oxidants did not rescue the cells from Abeta-induced apoptosis and cell death. These results indicate that free radicals and lipid peroxidation may not mediate Abeta-induced neurotoxicity.

The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands.

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Brain Res 2001 Jan 19;889(1-2):181-90

beta Amyloid (Abeta) treatment induced free radical production and increased glucose uptake, apoptosis and cell death in PC12 nerve cells. Addition of the standardized extract of Ginkgo biloba leaves, EGb 761 together with the Abeta protein prevented, in a dose-dependent manner, the Abeta-induced free radical production, increased glucose uptake, apoptosis and cell death. However, pretreatment of the cells with EGb 761 did not rescue the cells from the Abeta-induced toxicity although it prevented the Abeta-induced reactive oxygen species generation. Moreover, the terpene and flavonoid-free EGb 761 extract, HE 208,

although inhibited the Abeta-induced increased glucose uptake, it failed to protect the cells from apoptosis and cytotoxicity induced by Abeta. In conclusion, these results indicate that the terpenoid and flavonoid constituents of EGb 761, acting probably in combination with components present in HE 208, are responsible for rescuing the neuronal cells from Abeta-induced apoptosis and cell death; their mechanism of action being distinct of their antioxidant properties. Because pre- and post-treatment with EGb 761 did not protect the cells from Abeta-induced neurotoxicity, we examined whether EGb 761 interacts directly with Abeta. Indeed, in vitro reconstitution studies demonstrated that EGb 761 inhibits, in a dose-dependent manner, the formation of beta-amyloid-derived diffusible neurotoxic soluble ligands (ADDLs), suggested to be involved in the pathogenesis of Alzheimer's disease.

Alzheimer's amyloid beta-peptide associated free radicals increase rat embryonic neuronal polyamine uptake and ornithine decarboxylase activity: protective effect of vitamin E.

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Neurosci Lett 1999 Mar 19;263(1):17-20

Recent evidence indicates that alterations in brain polyamine metabolism may be critical for nerve cell survival after a free radical initiated neurodegenerative process. It has been shown previously that A beta(1-42) and A beta(25-35) are toxic to neurons through a free radical dependent oxidative mechanism. Treatment of rat embryonic hippocampal neuronal cultures with A beta-peptides increased ornithine decarboxylase (ODC) activity and spermidine uptake, suggesting that oxidative stress upregulates the polyamine mechanism for the repair of free radical damage. Pretreatment of the cells with vitamin E prior to A beta exposure decreased ODC activity and spermidine uptake to control level. This study is the first to demonstrate that A beta treated cells show an increased polyamine metabolism in response to free radical mediated oxidative stress and that the free radical scavenger vitamin E prevents these attenuations. These results are discussed with reference to Alzheimer's disease.

Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life.

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Int J Neurosci 1996 Nov;87(3-4):141-9

In a number of previous reports we showed the salutary effects on rats of SR-3, a compound comprising a 1:4 ratio of n-3 and n-6 fatty acids. Improvements were noted in learning tasks, thermoregulation, recovery from neurotoxins, and seizure protection. Because we were impressed that these effects are related to changes in

membrane fluidity and neuronal functioning and because Alzheimer's Disease is also associated with lipid defects, we undertook a short term (4 week) double blind study with 100 Alzheimer patients (60 received SR-3 and 40 in a placebo control). The results indicated improvements in mood, cooperation, appetite, sleep, ability to navigate in the home, and short term memory. Overall improvement was reported for 49 patients, and in no case did a guardian report adverse effects to the compound. While not uniform or permanent, and while no mode of action for SR-3 can be precisely identified at this time, the promising results in quality of life for the patient and caregiver warrant further clinical trials and continued basic research into the neuropsychological substrate of the disease and its response to SR-3.

Essential fatty acids and the brain: possible health implications.

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Int J Dev Neurosci 2000 Jul-Aug;18(4-5):383-99

Linoleic and alpha-linolenic acid are essential for normal cellular function, and act as precursors for the synthesis of longer chained polyunsaturated fatty acids (PUFAs) such as arachidonic (AA), eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), which have been shown to partake in numerous cellular functions affecting membrane fluidity, membrane enzyme activities and eicosanoid synthesis. The brain is particularly rich in PUFAs such as DHA, and changes in tissue membrane composition of these PUFAs reflect that of the dietary source. The decline in structural and functional integrity of this tissue appears to correlate with loss in membrane DHA concentrations. Arachidonic acid, also predominant in this tissue, is a major precursor for the synthesis of eicosanoids, that serve as intracellular or extracellular signals. With aging comes a likely increase in reactive oxygen species and hence a concomitant decline in membrane PUFA concentrations, and with it, cognitive impairment. Neurodegenerative disorders such as Parkinson's and Alzheimer's disease also appear to exhibit membrane loss of PUFAs. Thus it may be that an optimal diet with a balance of n-6 and n-3 fatty acids may help to delay their onset or reduce the insult to brain functions which these diseases elicit.

4. Anemia Thrombocytopenia Leukopenia

Preventative and curative options include:

Methylcobalamin, folic acid, iron, zinc, selenium, copper, fish oil, vitamin K, DHEA, nettle leaf extract, melatonin, multinutrient supplements, Vitamin A.

Anemia caused by vitamin B12 deficiency in subjects aged over 75 years: new hypotheses. A study of 20 cases. [Article in French]

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Rev Med Interne 2000 Nov;21(11):946-54

PURPOSE: New hypotheses have recently been developed on vitamin B12 deficiency and the frequently observed occurrence in the elderly subject of food cobalamin malabsorption, i.e., the non-dissociation of B12 and its carrier protein (ND B12), and the possibility of rectifying this imbalance by oral crystalline B12 supplementation. The aim of this study was therefore to confirm these hypotheses in a series of patients aged over 75 years with anemia due to B12 deficiency.

METHODS: A retrospective study was carried out over a 5-year period on patients aged over 75 years presenting with megaloblastic anemia (hemoglobin [Hb] < 12 g/dL) and vitamin B12/cobalamin deficiency (B12 < 160 pg/mL).

RESULTS: Twenty cases were analyzed. The average age of the patient population was 82.5 +/- 6 years, and the F/M sex ratio was 1:2. Mean Hb levels were 7.9 +/- 2.4 g/dL, mean serum B12 levels were 83 +/- 24 pg/mL, and mean homocysteinemic levels were 35 +/- 27 mumol/L. The diagnosis was as follows: food cobalamin malabsorption/ND B12 (n = 10), Biermer's disease/pernicious anemia (n = 5), malabsorption due to pancreatic insufficiency (n = 1), and low dietary B12 levels (n = 1). Disorders associated with ND B12 were: atrophic gastritis and Helicobacter pylori infection (n = 6), antacid or biguanide intake (n = 3), alcohol abuse (n = 2), or idiopathic syndrome (n = 2). In the patients who were followed up (n = 10), i.m. (n = 5) or oral (n = 5) administration of crystalline B12 resulted in the correction of hematological abnormalities.

CONCLUSION: In the elderly subject, food cobalamin/ND B12 malabsorption appears to be the main cause of B12 deficiency, and is frequently associated with atrophic gastritis. In these cases, administration of oral crystalline B12 may be an efficient means of treating this disorder.

Vitamin B12 deficiency in the elderly.

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Annu. Rev. Nutr. 1999. 19:357-377

KEY WORDS: atrophic gastritis, hypochlorhydria, malabsorption of protein-bound vitamin B12, food fortification Vitamin B12 deficiency is estimated to affect 10%-15% of people over the age of 60, and the laboratory diagnosis is usually based on low serum vitamin B12 levels or elevated serum methylmalonic acid and homocysteine levels. Although elderly people with low vitamin B12 status frequently lack the classical signs and symptoms of vitamin B12 deficiency, e.g. megaloblastic anemia, precise evaluation and treatment in this population is important. Absorption of crystalline vitamin B12 does not decline with advancing age. However, compared with the younger population, absorption of protein-bound vitamin B12 is decreased in the elderly, owing to a high prevalence of atrophic gastritis in this age group. Atrophic gastritis results in a low acid-pepsin secretion by the gastric mucosa, which in turn results in a reduced release of free vitamin B12 from food proteins. Furthermore, hypochlorhydria in atrophic gastritis results in bacterial overgrowth of the stomach and small intestine, and these bacteria may bind vitamin B12 for their own use. The ability to absorb crystalline vitamin B12 remains intact in older people with atrophic gastritis. The 1998 recommended daily allowance for vitamin B12 is 2.4 µg, but elderly people should try to obtain their vitamin B12 from either supplements or fortified foods (e.g. fortified ready-to-eat breakfast cereals) to ensure adequate absorption from the gastrointestinal tract. Because the American food supply is now being fortified with folic acid, concern is increasing about neurologic exacerbation in individuals with marginal vitamin B12 status and high-dose folate intake.

The role of copper, molybdenum, selenium, and zinc in nutrition and health.

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Clin Lab Med 1998 Dec;18(4):673-85

Copper, zinc, selenium, and molybdenum are involved in many biochemical processes supporting life. The most important of these processes are cellular respiration, cellular utilization of oxygen, DNA and RNA reproduction, maintenance of cell membrane integrity, and sequestration of free radicals. Copper, zinc, and selenium are involved in destruction of free radicals through cascading enzyme systems. Superoxide radicals are reduced to hydrogen peroxide by superoxide dismutases in the presence of copper and zinc cofactors. Hydrogen peroxide is then reduced to water by the selenium-glutathione peroxidase couple. Efficient removal of these superoxide free radicals maintains the integrity of membranes, reduces the risk of cancer, and slows the aging process. On the other hand, excess intake of these trace elements leads to disease and toxicity; therefore, a fine balance is essential for health. Trace element-deficient patients usually present with common symptoms such as malaise, loss of appetite, anemia,

infection, skin lesions, and low-grade neuropathy, thus complicating the diagnosis. Symptoms for intoxication by trace elements are general, for example, flu-like and CNS symptoms, fever, coughing, nausea, vomiting, diarrhea, anemia, and neuropathy. A combination of observation, medical and dietary history, and analyses for multiple trace elements is needed to pinpoint the trace element(s) involved. Serum, plasma, and erythrocytes may be used for the evaluation of copper and zinc status, whereas only serum or plasma is recommended for selenium. Whole blood is preferred for molybdenum. When trace element levels are inconsistent with medical evaluations, a test for activity of the suspected enzyme(s) would support the differential diagnosis. Furthermore, it is important to differentiate whether trace element deficiency or toxicity is the primary cause of the disorder, or is secondary to other underlying diseases. Only successful treatment of the primary disorder will lead to complete recovery. In the event of sample contamination during collection or analysis, the physician may be misled by falsely elevated results. Royal blue top evacuated tubes containing negligibly low concentrations of the trace element or acid-washed plastic sterilized syringes should be used for blood, serum, or plasma collection. Powdered gloves must be avoided. When possible, mineral supplements are not to be administered to the patient for a minimum of 3 days prior to sample collection. Serum and plasma specimens are to be transported in acid-washed polypropylene and polyethylene tubes. Analysis is performed in a controlled environment to minimize or eliminate contamination. During analysis, all laboratory wares should be acid-washed for decontamination. A detailed description of these precautions may be found in reviews by Aitio and Jarvisalo and by Chan and Gerson. Copper and zinc analysis on serum and plasma are commonly performed by flame atomic absorption spectrometry, inductively coupled plasma-atomic emission spectrometry, and inductively coupled plasma-mass spectrometry. Serum and plasma selenium levels are determined by graphite furnace atomic absorption with Zeeman background correction and neutron activation analysis. Molybdenum levels are best determined by neutron activation and highly sensitive inductively coupled plasma-mass spectrometry. The reader is referred to reviews by Tsalev and Jarvis.

The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells.

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Arterioscler Thromb 1994 Nov;14(11):1829-36

The mechanisms by which dietary fatty acids can modulate atherogenesis and inflammation are poorly understood. Induction in endothelial cells of adhesion molecules for circulating leukocytes and of inflammatory mediators by cytokines probably contributes to the early phases of atherogenesis and inflammation. We report here that incorporation into cellular lipids of docosahexaenoic acid (DHA), a specific fatty acid of the omega 3 family, decreases cytokine-induced expression of endothelial leukocyte adhesion molecules, secretion of inflammatory

mediators, and leukocyte adhesion to cultured endothelial cells. DHA, but not eicosapentaenoic acid, decreased in a dose- and time-dependent fashion the expression of vascular cell adhesion molecule 1 (VCAM-1) induced by interleukin (IL)-1, tumor necrosis factor (TNF), IL-4, or bacterial lipopolysaccharide, with half-maximum inhibition at & 10 mumol/L. This reduction required prolonged (24- to 96-hour) exposure of endothelial cells to DHA and correlated with the degree of DHA incorporation into cellular lipids. DHA also limited cytokine-stimulated endothelial cell expression of E-selectin and intercellular adhesion molecule 1 and the secretion of IL-6 and IL-8 into the medium but not the surface expression of constitutive surface molecules. Cyclooxygenase inhibition did not block the effect of DHA on VCAM-1. In parallel with reduced surface VCAM-1 protein expression, DHA reduced VCAM-1 mRNA induction by IL-1 or TNF. DHA treatment also reduced the adhesion of human monocytes and of monocytic U937 cells to cytokine-stimulated endothelial cells. These properties of DHA may contribute to antiatherogenic and anti-inflammatory effects of omega 3 fatty acids.

Anti-inflammatory effect of warfarin and vitamin K1.

Eichbaum FW, Slemer O, Zyngier SB.

Naunyn Schmiedebergs Arch Pharmacol 1979 Jun 18;307(2):185-90

1. Sodium warfarin, given by oral or by parenteral route, displays a pronounced anti-inflammatory effect in the formaldehyde and carrageenan induced rat paw edema. This effect becomes patent not only when the warfarin application precedes the local injection of the irritant substance (prophylactic effect), but also when it is given to animals with already developed inflammatory reactions (therapeutic effect). 2. The active doses of Na warfarin lie between 0.5 and 5.0 mg/kg. Smaller as well as higher doses show a reduced anti-inflammatory effect. 3. A marked anti-inflammatory effect can be noted already 90 min after drug injection at a still normal prothrombin level. 4. Vitamin K1 (phylloquinone), given by oral or parenteral route, in doses from 1.6 mg/kg upwards, shows a marked anti-inflammatory effect both in the prophylactic and the therapeutic rat paw test. Vitamin K3 is devoid of any anti-inflammatory activity. 5. The anti-inflammatory effect of both sodium warfarin and of vitamin K1 in rats, is not interfered with by previous adrenalectomy.

Congenital dyschromia with erythrocyte, platelet and tryptophan metabolism abnormalities.

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J Am Acad Dermatol 1988 Oct;19(4):642-55

The case of a female child with a unique generalized congenital dyschromia is reported. She had hypopimented skin, with hypomelanosis and hypomelanocytosis, and many pigmented macules, which consisted of epidermal

and dermal hypermelanosis without hypermelanocytosis. Biochemical investigations revealed normal catecholamine metabolism but abnormal tryptophan metabolism, including a decrease in blood serotonin and melatonin. A slight platelet storage pool disease was demonstrated, and a recurrent megaloblastic folate-related anemia occurred. The possible relationship between the pigmentary disease and the biochemical abnormalities is discussed. We suggest that this case represents a previously undescribed association of dyschromia, erythrocyte, platelet, and tryptophan metabolism abnormalities.

Melatonin prevents oxidative stress resulting from iron and erythropoietin administration.

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Am J Kidney Dis 2001 Apr;37(4):750-7

Intravenous iron (Fe) and recombinant human erythropoietin (rHuEPO) are routine treatments in the management of anemia in patients with chronic renal failure. We investigated the oxidative stress acutely induced by these therapies and whether pretreatment with oral melatonin (MEL) would have a beneficial effect. Nine patients (four women) were studied within 1 month of entering a chronic hemodialysis program in the interdialytic period. Plasma malondialdehyde (MDA), red blood cell glutathione (GSH), and catalase (CAT) activity were measured in blood samples obtained before (baseline) and 1, 3, and 24 hours after the administration of Fe (100 mg of Fe saccharate intravenously over 1 hour) or rHuEPO (4,000 U intravenously). One hour before these treatments, patients were administered a single oral dose of MEL (0.3 mg/kg) or placebo. Each patient was studied on four occasions, corresponding to studies performed using either placebo or MEL in association with intravenous Fe and rHuEPO administration. Baseline data showed increased oxidative stress in patients with end-stage renal failure. Increments in oxidative stress induced by Fe were more pronounced at the end of the administration: MDA, baseline, 0.74 +/- 0.09 nmol/mL; 1 hour, 1.50 +/- 0.28 nmol/mL (< 0.001); GSH, baseline, 2.51 +/- 0.34 nmol/mg of hemoglobin (Hb); 1 hour, 1.66 +/- 0.01 nmol/mg Hb (< 0.001); and CAT activity, baseline, 27.0 +/- 5.7 kappa/mg Hb; 1 hour, 23.3 +/- 4.2 kappa/mg Hb (< 0.001). rHuEPO-induced increments in oxidative stress were more pronounced (< 0.001) at 3 hours (MDA, 1.24 +/- 0.34 nmol/mL; GSH, 1.52 +/- 0.23 nmol/mg Hb; CAT activity, 18.0 +/- 3.1 kappa/mg Hb). MEL administration prevented the changes induced by Fe and rHuEPO and had no adverse side effects. These studies show that intravenous Fe and rHuEPO in doses commonly used to treat anemia in chronic hemodialysis patients acutely generate significant oxidative stress. Oral MEL prevents such oxidative stress and may be of clinical use.

Effect of all-trans and 9-cis retinoic acid on growth and metastasis of xenotransplanted canine osteosarcoma cells in athymic mice.

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Am J Vet Res 2000 Oct;61(10):1241-4

OBJECTIVE: To determine effects of all-trans and 9-cis retinoic acid (RA) on tumor growth and metastatic ability of canine osteosarcoma cells transplanted into athymic (nude) mice. ANIMALS: Forty-five 5-week-old female BALB/c nude mice.

PROCEDURE: 1 X 10(7) POS osteosarcoma cells were transplanted subcutaneously into the intrascapular region of mice. All-trans RA (3 or 30 microg/kg of body weight in 0.1 ml of sesame oil), 9-cis RA (3 or 30 mg/kg in 0.1 ml of sesame oil), or sesame oil (0.1 ml; control treatment) were administered intragastrically 5 d/wk for 4 weeks beginning 3 days after transplantation (n = 4 mice/group) or after formation of a palpable tumor (5 mice/group). Tumor weight was estimated weekly by measuring tumor length and width, and retinoid toxic effects were evaluated daily. Two weeks after the final treatment, mice were euthanatized, and number of mice with pulmonary metastases was determined.

RESULTS: Adverse treatment effects were not detected. Tumor weight was less in mice treated with either dose of 9-cis RA than in control mice, although this difference was not significant. Treatment with 30 mg of 9-cis RA/kg initiated after tumor formation significantly reduced the incidence of pulmonary metastasis, compared with the control group.

CONCLUSIONS AND CLINICAL RELEVANCE: 9-cis RA decreased the incidence of pulmonary metastasis in nude mice transplanted with canine osteosarcoma cells and may be a potential adjunct therapy for treatment of osteosarcoma in dogs.

Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.

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Int J Dev Neurosci 1999 Dec;17(8):765-75

Dehydroepiandrosterone (DHEA) is a native neurosteroid with immunomodulating activity. DHEA effectively protects animals from several viral, bacterial and parasitic infections and it was suggested that its age-associated decline is related with immunosenescence. In the present study we examined the ability of DHEA to inhibit the production of inflammatory mediators by mycoplasma-stimulated glial cells and to change the course of acute central nervous system (CNS) inflammatory disease in vivo. Addition of DHEA (10 microg/ml) markedly inhibited tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) production (98 and 95%, respectively), whereas nitric oxide

(NO) and prostaglandin E2 (PGE2) production was not affected. However, daily administration of 0.5 mg DHEA to mice or 5 mg to rats did not change the clinical outcome of experimental autoimmune encephalomyelitis (EAE).

Meta-analysis of efficacy and tolerability data on iron protein succinylate in patients with iron deficiency anemia of different severity.

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Arzneimittelforschung 1995 Nov;45(11):1211-6

Iron proteinsuccinylate (ITF 282, CAS 93615-44-2) is an iron derivative for the oral treatment of iron deficiency anemia. Its efficacy and tolerability have been proved in about 1800 patients, enrolled in 3 multicenter clinical trials. The first aim of this meta-analysis is to verify the increase of hemoglobin (Hb) in these patients (891 treated with ITF282, 644 treated with iron sulphate and 236 treated with iron-polysterene sulphonate). The 3 studies show homogeneous Hb increases. ITF 282 appeared to provide, from time 0 to the 30th day of treatment, a similar or lesser increase in Hb in comparison to the reference drugs, while from the 30th day of treatment to the 60th day its efficacy was always greater than that of the reference medications. The data have been further analyzed by subdividing the patients in three classes, according to the severity of the anemia: basal Hb < or = < or = 11 g/dl, < g/dl. During the 60-day treatment, both ITF 282 and the reference drugs induced the most significant increase in Hb in the patients affected by the most severe anemia. The meta-analytic evaluation of the 3 trials results has been extended to tolerability data. Most side effects were related to the gastrointestinal tract. Their incidence resulted signficantly lower for ITF 282 than that for the reference drugs (9.4% vs. 20.4%, < 0.01). The comparative sub-analysis of the side effect distribution into the patients populations shows that ITF 282 is definitely better tolerated in pregnant women (relative risk 0.321, < 0.01). The time course of Hb increases and the tolerability data suggest a different mechanism by which ITF 282 and the reference drugs are effective. Since the main difference between ITF 282 and the reference drugs is the form in which the iron is presented to the gastrointestinal mucosa, it may be supposed that the reference drugs, providing free divalent iron ions for absorption, could induce some kind of irritative condition of the gastrointestinal mucosa, which results in a reduced long-term absorption capacity, as well as in a higher incidence of gastroenteric adverse events. ITF 282, providing protein-bound iron, would not permit the process supposed with divalent iron, thus resulting in prolonged absorption capacity (that is higher hemoglobin recovery) and higher gastrointestinal tolerability.

Is there a role for melatonin in supportive care?

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Support Care Cancer 2002 Mar;10(2):110-6

Melatonin (MLT) is the main hormone released from the pineal gland and has proved to have physiological antitumor activity. MLT has been shown to exert anticancer activity through several biological mechanisms: antiproliferative action, stimulation of anticancer immunity, modulation of oncogene expression, and anti-inflammatory, anti-oxidant and anti-angiogenic effects. Several experimental studies have shown that MLT may inhibit cancer cell growth, and preliminary clinical studies seem to confirm its anticancer property in humans. In addition, MLT may have other biological effects, which could be useful in the palliative therapy of cancer, namely anticachectic, anti-asthenic and thrombopoietic activities. On this basis, the present clinical investigation was performed in an attempt at better definition of the therapeutic properties of MLT in human neoplasms. In a first clinical study, we evaluated the effects of MLT in a group of 1,440 patients with untreatable advanced solid tumors, who received supportive care alone or supportive care plus MLT. In a second study, we evaluated the influence of MLT on the efficacy and toxicity of chemotherapy in a group of 200 metastatic patients with chemotherapy-resistant tumor histotype, who were randomized to receive chemotherapy alone or chemotherapy plus MLT. In both studies, MLT was given orally at 20 mg/day during the dark period of the day. The frequency of cachexia, asthenia, thrombocytopenia and lymphocytopenia was significantly lower in patients treated with MLT than in those who received supportive care alone. Moreover, the percentage of patients with disease stabilization and the percentage 1-year survival were both significantly higher in patients concomitantly treated with MLT than in those treated with supportive care alone. The objective tumor response rate was significantly higher in patients treated with chemotherapy plus MLT than in those treated with chemotherapy alone. Moreover, MLT induced a significant decline in the frequency of chemotherapy-induced asthenia, thrombocytopenia, stomatitis, cardiotoxicity and neurotoxicity. These clinical results demonstrate that the pineal hormone MLT may be successfully administered in medical oncology in the supportive care of untreatable advanced cancer patients and for the prevention of chemotherapy-induced toxicity.

Immunotherapy with subcutaneous low-dose interleukin-2 plus melatonin as salvage therapy of heavily chemotherapy-pretreated ovarian cancer.

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Oncol. Rep. 1996; 3(5): 947-9.

Preliminary results showed that IL-2 immunotherapy may be effective in the treatment of recurring advanced ovarian cancer. The pineal neurohormone melatonin (MLT) has been proven to amplify IL-2 efficacy by counteracting macrophage-mediated immunosuppression. On this basis, a pilot phase II study of low-dose IL-2 plus MLT was performed in advanced ovarian cancer patients progressing after at least 3 previous polychemotherapeutic lines. The study included 12 evaluable patients. IL-2 was injected subcutaneously at 3 million IU/day for 6 days/week for 4 weeks, by repeating the cycle after a 21-day rest

period in nonprogressing patients, MLT was given orally at 40 mg/day. No complete response was seen. A partial response was achieved in 2/12 (16%) patients. A stable disease was obtained in 5 other patients, whereas the remaining 5 patients progressed. The treatment was well tolerated. This preliminary study suggests that immunotherapy with low-dose IL-2 plus MLT may represent a well tolerated and promising therapy of advanced ovarian cancer progressing on standard medical treatments.

Efficacy of the concomitant administration of the pineal hormone melatonin in cancer immunotherapy with low-dose IL-2 in patients with advanced solid tumors who had progressed on IL-2 alone.

Lissoni P, Barni S, Cazzaniga M, Ardizzoia A, Rovelli F, Brivio F, Tancini G. Division of Radiation Oncology, San Gerardo Hospital, Monza, Italy.

Oncology 1994 Jul-Aug;51(4):344-7

Our preliminary studies in humans have shown that the pineal neurohormone melatonin (MLT) may enhance the antitumor activity of IL-2, by confirming the existence of a neuroendocrine control on cytokine effects. On this basis, a study was started to evaluate the influence of a concomitant administration of MLT and low-dose IL-2 in cancer patients, who had progressed during a previous immunotherapy with IL-2 alone. The study included 14 patients with advanced solid tumors (lung 6; kidney 4; stomach 2; liver 1; melanoma 1). IL-2 was given at a daily dose of 3 million IU s.c. for 6 days/week for 4 weeks. MLT was given orally at a daily dose of 40 mg every day, starting 7 days prior to IL-2. Objective tumor regression, consisting of a partial remission (PR), was achieved in 3/14 (21%) patients (lung 1; kidney 1; liver 1). Six other patients had a stable disease (SD), while the remaining 5 cases progressed. PR and SD were associated either with a significantly longer survival at 1 year, or with a significantly higher increase in lymphocyte and eosinophil mean number with respect to the patients with disease progression. This preliminary study suggests that advanced solid neoplasms resistant to IL-2 may become responsive to IL-2 therapy by a concomitant administration of the pineal hormone MLT, which could act by enhancing IL-2 antitumor immune effect and/or by increasing the susceptibility of cancer cells to the cytolysis mediated by IL-2-induced cytotoxic lymphocytes.

A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state.

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J Pineal Res (Denmark) Aug 1997, 23 (1) p15-9

Recent studies suggest that the pineal hormone melatonin may reduce chemotherapy -induced immune and bone marrow damage. In addition, melatonin may exert potential oncostatic effects either by stimulating host anticancer immune defenses or by inhibiting tumor growth factor production. On this basis, we have performed a randomized study of chemotherapy alone vs. chemotherapy plus melatonin in advanced non-small cell lung cancer patients (NSCLC) with poor clinical status. The study included 70 consecutive advanced NSCLC patients who were randomized to receive chemotherapy alone with cisplatin (20 mg/m2/day i.v. for 3 days) and etoposide (100 mg/m2/day i.v. for 3 days) or chemotherapy plus melatonin (20 mg/day orally in the evening). Cycles were repeated at 21-day intervals. Clinical response and toxicity were evaluated according to World Health Organization criteria. A complete response (CR) was achieved in 1/34 patients concomitantly treated with melatonin and in none of the patients receiving chemotherapy alone. Partial response (PR) occurred in 10/34 and in 6/36 patients treated with or without melatonin, respectively. Thus, the tumor response rate was higher in patients receiving melatonin (11/34 vs. 6/35), without, however, statistically significant differences. The percent of 1-year survival was significantly higher in patients treated with melatonin plus chemotherapy than in those who received chemotherapy alone (15/34 vs. 7/36, < 0.05). Finally, chemotherapy was well tolerated in patients receiving melatonin, and in particular the frequency of myelosuppression, neuropathy, and cachexia was significantly lower in the melatonin group. This study shows that the concomitant administration of melatonin may improve the efficacy of chemotherapy, mainly in terms of survival time, and reduce chemotherapeutic toxicity in advanced NSCLC, at least in patients in poor clinical condition.

Treatment of cancer chemotherapy-induced toxicity with the pineal hormone melatonin.

Lissoni P, Tancini G, Barni S, Paolorossi F, Ardizzoia A, Conti A, Maestroni G. Division of Radiation Oncology, S. Gerardo Hospital, Monza (Milan), Italy.

Support Care Cancer 1997 Mar;5(2):126-9

Experimental data have suggested that the pineal hormone melatonin (MLT) may counteract chemotherapy-induced myelosuppression and immunosuppression. In addition, MLT has been shown to inhibit the production of free radicals, which play a part in mediating the toxicity of chemotherapy. A study was therefore performed in an attempt to evaluate the influence of MLT on chemotherapy toxicity. The study involved 80 patients with metastatic solid tumors who were in poor clinical condition (lung cancer: 35; breast cancer: 31; gastrointestinal tract tumors: 14). Lung cancer patients were treated with cisplatin and etoposide, breast cancer patients with mitoxantrone, and gastrointestinal tract tumor patients with 5-fluorouracil plus folates. Patients were randomised to receive chemotherapy alone or chemotherapy plus MLT (20 mg/day p.o. in the evening). Thrombocytopenia was significantly less frequent in patients concomitantly treated with MLT. Malaise and asthenia were also significantly less frequent in patients receiving MLT. Finally, stomatitis and neuropathy were less frequent in the MLT group, albeit without statistically significant differences. Alopecia and

vomiting were not influenced by MLT. This pilot study seems to suggest that the concomitant administration of the pineal hormone MLT during chemotherapy may prevent some chemotherapy-induced side-effects, particularly myelosuppression and neuropathy. Evaluation of the impact of MLT on chemotherapy efficacy will be the aim of future clinical investigations.

Ambulatory management of common forms of anemia.

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Am Fam Physician 1999 Mar 15;59(6):1598-604

Anemia is a prevalent condition with a variety of underlying causes. Once the etiology has been established, many forms of anemia can be easily managed by the family physician. Iron deficiency, the most common form of anemia, may be treated orally or, rarely, parenterally. Vitamin B12 deficiency has traditionally been treated with intramuscular injections, although oral and intranasal preparations are also available. The treatment of folate deficiency is straightforward, relying on oral supplements. Folic acid supplementation is also recommended for women of child-bearing age to reduce their risk of neural tube defects. Current research focuses on folate's role in reducing the risk of premature cardiovascular disease.

Melatonin as biological response modifier in cancer patients.

Neri B; de Leonardis V; Gemelli MT; di Loro F; Mottola A; Ponchietti R; Raugei A; Cini G Oncological Day Hospital, Department of Internal Medicine, University of Florence, Italy.

Anticancer Res (Greece) Mar-Apr 1998, 18 (2B) p1329-32

The neuroendocrine system modulates the immune response through neuropeptides and neurohormones, findings which point to the existence of a neuro-endocrine-immune system regulatory axis. At the same time, there is growing evidence that the pineal gland has anti-neoplastic properties, which include the action of its principal hormone, melatonin (MLT), on the immune system through the release of cytokines by activated T-cells and monocytes. The present study was carried out on 31 patients (19 males and 12 females, age range 46-73 years) with advanced solid tumors (7 gastric, 9 enteric, 8 renal, 5 bladder, 2 prostate) who either failed to respond to chemotherapy and radiotherapy or showed insignificant responses and were therefore shifted to MLT therapy (10 mg/die orally for 3 months). We obtained blood samples just before the start of MLT administration and after 30 days of therapy. Plasma was collected in EDTA tubes on ice, immediately centrifuged at 4 degrees C and stored frozen at -80 degrees C; samples were measured by immunoradiometric assays (Medgenix-Fleurus, Belgium) for tumor necrosis factor alpha (TNF), interleukin-1, 2 and 6 (IL-1, IL-2, IL-6) and interferon gamma (IFN). We used Student's paired t-test to compare each patient's cytokine circulating levels before and after MLT administration and found a significant differences (< 0.05). After 3 months of

therapy, none of our patients displayed adverse reactions to MLT or had to discontinue treatment. Nineteen patients (61%) showed disease progression. The other 12 (39%), however, achieved disease stabilization with no further growth of either the primary tumor or of secondaries; moreover, they experienced an improvement in their general well-being, in terms of Tchekmedyian's criteria, associated with a significative decrease of IL-6 circulating levels. These findings are consistent with the hypothesis that MLT modulates immune function in cancer patients by activating the cytokine system which exerts growth-inhibitory properties over a wide range of tumor cell types. Furthermore, by stimulating the cytotoxic activity of macrophages and monocytes, MLT plays a critical role in host defence against the progression of neoplasia.

Some biological actions of alkylglycerols from shark liver oil.

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J Altern Complement Med 1998 Spring;4(1):87-99

Shark liver oil has been used for over 40 years as both a therapeutic and preventive agent. The active ingredients in shark liver oil have been found to be a group of ether-linked glycerols known as alkylglycerols. Initial clinical use was for treating leukemias, and later to prevent radiation sickness from cancer x-ray therapy. Studies over the last 30 years have shown that alkylglycerols are multifunctional. The level of natural alkylglycerols rises within tumor cells, apparently in an effort to control cell growth. Recent studies indicate that the activation of protein kinase C, an essential step in cell proliferation, can be inhibited by alkylglycerols. This action suggests a competitive inhibition of 1.2-diacylglycerol by alkylglycerols. Further studies on the immunostimulatory action of alkylglycerols suggest a primary action on the macrophage. The process of macrophage activation has been demonstrated with both synthetic and natural alkylglycerols. While the exact mechanism has not been found, both an autocrine and paracrine system have been suggested. Shark liver is a major natural source of alkylglycerols, which have no known side effects in dosages of 100 mg three times a day. The information presented in this article suggests that alkylglycerols may be used both as an adjunct therapy in the treatment of neoplastic disorders and as an immune booster in infectious diseases.

Retinoids in pancreatic cancer.

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Ann Oncol 1999;10 Suppl 4:197-200

Prognosis of advanced, unresectable pancreatic adenocarcinoma remains dismal and has not significantly improved over the past 20 years. In a broad panel of preclinical experimental settings we have therefore evaluated the effects of retinoids on human pancreatic carcinoma cells in vitro and in vivo. We found that

retinoid treatment results in inhibition of growth, induction of cellular differentiation and decreased adhesion to certain components of the extracellular matrix, all features compatible with a "less malignant" phenotype. Furthermore, retinoids act synergistically antiproliferative when combined with interferon-alpha. Using transient and stable genetic transfer studies we were able to identify two retinoid receptor subtypes responsible for mediating the growth inhibitory effects as well as retinoid sensitivity. In addition we observed a crucial functional interplay between the retinoid signalling pathway and the expression of a distinct protein kinase C isoenzyme, which determines the direction of the growth regulatory effects of retinoids. Based on these encouraging preclinical results we initiated a phase II clinical trial in which patients with advanced pancreatic carcinoma were treated with retinoic acid in combination with interferon-alpha. This therapeutic regimen was well tolerated and resulted in prolonged stable disease in approximately two thirds of the patients. In summary, these studies suggest that retinoids might be beneficial in the treatment of advanced pancreatic carcinoma patients based on their pleiotropic effects on tumor cell biology.

Effectiveness of oral vitamin B12 therapy for pernicious anemia and vitamin B12 deficiency anemia. [Article in Japanese]

Takasaki Y, Moriuchi Y, Tsushima H, Ikeda E, Koura S, Taguchi J, Fukushima T, Tomonaga M, Ikeda S. Department of Hematology, Sasebo City General Hospital, Sasebo, Japan.

Rinsho Ketsueki 2002 Mar;43(3):165-9

We investigated the efficacy of oral vitamin B12 (B12) therapy in patients with B12-deficiency anemia. Between June 1994 and June 2000, 17 patients, who were diagnosed as having B12-deficiency anemia and gave their informed consent, were enrolled in this study. Of these patients, 7 were further treated with a maintenance dose of methylcobalamin (1,500 micrograms daily for 7 days every 1-3 months). Correction of hematological and neurological abnormalities was prompt. The hemoglobin level and serum concentration of B12 were normalized within two months after starting the treatment. Recovery from neurological disturbance was observed within one month. To maintain a normal serum concentration of B12, a 7-day regime of administration was needed every month in 3 patients, every 2 months in 3 patients, and every 3 months in 1 patient. These results demonstrate the effectiveness of oral cobalamin therapy, and also that oral intermittent therapy is useful for maintaining a normal serum B12 concentration. Oral cobalamin therapy might be as effective as conventional injection therapy, and useful for long-term treatment.

Dysregulation of melatonin metabolism in chronic renal insufficiency: role of erythropoietin-deficiency anemia.

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Kidney Int 1996 Aug;50(2):653-6

Chronic renal failure (CRF) is associated with a variety of neurological and endocrine disorders. In this study, we examined the effect of CRF and the associated anemia on circadian variation of pineal hormone, melatonin. Animals were studied six weeks after 5/6 nephrectomy (CRF group, N = 26) or sham operation (control group, N = 28). A group of erythropoietin-treated CRF animals (CRF/EPO, N = 6) was included to discern the possible role of EPO-deficiency anemia. Compared with the normal control group, the CRF group showed a marked attenuation of the nocturnal surge in serum melatonin concentration. In addition, pineal gland melatonin content measured after a 12-hour dark cycle (< or = 2 lux) was significantly depressed in the CRF group when compared to that obtained in the control group. However, the CRF animals exhibited appropriate suppression of serum concentration and pineal tissue melatonin content in response to bright light (< or = 2500 lux). Administration of EPO led to correction of the CRF anemia and a marked improvement of the defective nocturnal rhythm of serum melatonin. Based on our results, experimental CRF is associated with a marked attenuation of the normal nocturnal surge of serum melatonin concentration. Regular EPO administration results in the correction of anemia and substantial reversal of this abnormality suggesting the partial role of EPO deficiency. The possible role of melatonin dysregulation in the pathophysiology of CRF and the potential value of melatonin supplementation in this condition is uncertain and awaits future investigations.

Folic acid deficiency can cause severe anemia and pancytopenia.

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Tidsskr Nor Laegeforen 1990 May 30;110(14):1830-1

Pancytopenia is occasionally a consequence of folate deficiency. The most important differential diagnostic considerations are haematologic malignancies, aplastic anaemia and vitamin B12 deficiency. We discuss the problem as exemplified by three patients. Bone marrow examination and determination of blood concentrations of vitamin B12 and folate will give the correct diagnosis.

n-3 Polyunsaturated fatty acids and cytokine production in health and disease.

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Ann Nutr Metab 1997;41(4):203-34

Arachidonic-acid-derived eicosanoids modulate the production of pro-inflammatory and immunoregulatory cytokines. Overproduction of these cytokines is associated with both septic shock and chronic inflammatory diseases. The n-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid, which are found in fish oils, suppress the production of arachidonic-acid-derived eicosanoids and EPA is a substrate for the synthesis of

an alternative family of eicosanoids. Thus, dietary fats which are rich in n-3 PUFAs have the potential to alter cytokine production. Animal studies have provided a great deal of evidence that feeding plant or fish oils rich in n-3 PUFAs does alter the ex vivo production of tumour necrosis factor (TNF), interleukin 1 (IL-1), IL-6 and IL-2, but many contradictory observations have been made; it is most likely that the discrepancies in the literature result from differences in the cell types and experimental protocols used. Human studies provide more consistent data: several studies have shown that supplementation of the diet of healthy volunteers results in reduced ex vivo production of IL-1, IL-6, TNF and IL-2 by peripheral blood mononuclear cells. Similar findings have been made in patients with rheumatoid arthritis and multiple sclerosis. Animal studies indicate that dietary fish oil reduces the response to endotoxin and to pro-inflammatory cytokines, resulting in increased survival; such diets have been beneficial in some models of bacterial challenge, chronic inflammation and auto-immunity. These beneficial effects of dietary n-3 PUFAs may be of use as a therapy for acute and chronic inflammation and for disorders which involve an inappropriately activated immune response.

Polyunsaturated fatty acids and rheumatoid arthritis.

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Curr Opin Clin Nutr Metab Care 2001 Mar;4(2):115-21

Rheumatoid arthritis is characterized by infiltration of T lymphocytes, macrophages and plasma cells into the synovium, and the initiation of a chronic inflammatory state that involves overproduction of proinflammatory cytokines and a dysregulated T-helper-1-type response. Eicosanoids synthesized from arachidonic acid and cytokines cause progressive destruction of cartilage and bone. The n-6 polyunsaturated fatty acid gamma-linolenic acid is the precursor of di-homo-gamma-linolenic acid. The latter and the n-3 polyunsaturated fatty acid eicosapentaenoic acid, which is found in fish oil, are able to decrease the production of arachidonic acid-derived eicosanoids and to decrease the production of proinflammatory cytokines and reactive oxygen species, and the reactivity of lymphocytes. A number of double-blind, placebo-controlled trials of gamma-linolenic acid and fish oil in rheumatoid arthritis have shown significant improvements in a variety of clinical outcomes. These fatty acids should be included as part of the normal therapeutic approach to rheumatoid arthritis. However, it is unclear what the optimal dosage of the fatty acids is, or whether there would be extra benefit from using them in combination.

Dietary polyunsaturated fatty acids and inflammatory mediator production.

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Am J Clin Nutr 2000 Jan;71(1 Suppl):343S-8S

Many antiinflammatory pharmaceutical products inhibit the production of certain eicosanoids and cytokines and it is here that possibilities exist for therapies that incorporate n-3 and n-9 dietary fatty acids. The proinflammatory eicosanoids prostaglandin E(2) (PGE(2)) and leukotriene B(4) (LTB(4)) are derived from the n-6 fatty acid arachidonic acid (AA), which is maintained at high cellular concentrations by the high n-6 and low n-3 polyunsaturated fatty acid content of the modern Western diet. Flaxseed oil contains the 18-carbon n-3 fatty acid alpha-linolenic acid, which can be converted after ingestion to the 20-carbon n-3 fatty acid eicosapentaenoic acid (EPA). Fish oils contain both 20- and 22-carbon n-3 fatty acids, EPA and docosahexaenoic acid. EPA can act as a competitive inhibitor of AA conversion to PGE(2) and LTB(4), and decreased synthesis of one or both of these eicosanoids has been observed after inclusion of flaxseed oil or fish oil in the diet. Analogous to the effect of n-3 fatty acids, inclusion of the 20-carbon n-9 fatty acid eicosatrienoic acid in the diet also results in decreased synthesis of LTB(4). Regarding the proinflammatory ctyokines, tumor necrosis factor alpha and interleukin 1beta, studies of healthy volunteers and rheumatoid arthritis patients have shown < or = 90% inhibition of cytokine production after dietary supplementation with fish oil. Use of flaxseed oil in domestic food preparation also reduced production of these cytokines. Novel antiinflammatory therapies can be developed that take advantage of positive interactions between the dietary fats and existing or newly developed pharmaceutical products.

Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men.

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Lipids 1999 Apr;34(4):317-24

The purpose of this study was to examine the effects of feeding docosahexaenoic acid (DHA) as triacylglycerol on the fatty acid composition, eicosanoid production, and select activities of human peripheral blood mononuclear cells (PBMNC). A 120-d study with 11 healthy men was conducted at the Metabolic Research Unit of Western Human Nutrition Reach Center. Four subjects (control group) were fed the stabilization diet throughout the study; the remaining seven subjects were fed the basal diet for the first 30 d, followed by 6 g DHA/d for the next 90 d. DHA replaced an equivalent amount of linoleic acid; the two diets were comparable in their total fat and all other nutrients. Both diets were supplemented with 20 mg D alpha-tocopherol acetate per day. PBMNC fatty acid composition and eicosanoid production were examined on day 30 and 113; immune cell functions were tested on day 22, 30, 78, 85, 106, and 113. DHA feeding increased its concentration from 2.3 to 7.4 wt% in the PBMNC total lipids, and decreased arachidonic acid concentration from 19.8 to 10.7 wt%. It also lowered prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) production, in response to lipopolysaccharide, by 60-75%. Natural killer cell activity and in vitro secretion of interleukin-1beta and tumor necrosis factor alpha were significantly reduced by

DHA feeding. These parameters remained unchanged in the subjects fed the control diet. B-cell functions as reported here and T-cell functions that we reported previously were not altered by DHA feeding. Our results show that inhibitory effects of DHA on immune cell functions varied with the cell type, and that the inhibitory effects are not mediated through increased production of PGE2 and LTB4.

Docosahexaenoic and eicosapentaenoic acids inhibit human lymphoproliferative responses in vitro but not the expression of T cell surface activation markers.

Khalfoun B, Thibault G, Lacord M, Gruel Y, Bardos P, Lebranchu Y. Groupe "Interactions Hote-Greffon", Laboratoire d'Immunologie, Faculte de Medecine, Tours, France.

Scand J Immunol 1996 Mar;43(3):248-56

The effects of polyunsaturated fatty acids (PUFAs: docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids) on induced lymphocyte proliferation and expression of CD25alpha chain of interleukin-2 receptor, CD71 and HLA-DR were investigated. PUFAs had no effect on phytohaemagglutinin (PHA)-induced lymphocyte agglutination, but they strongly inhibited the lymphoproliferative response to PHA. This inhibitory effect is PUFA dose-dependent and seems to be more potent with DHA than EPA, Pre-incubation experiments showed that lymphocytes cultured with PUFAs for 6 h then washed and exposed to PHA, still inhibited lymphocyte proliferation. The authors also showed that this inhibitory activity was time dependent but became nonsignificant when PUFAs were added after 48 h lymphocyte culture. The addition of excess exogenous human recombinant rIL-2 partly restored PHA-lymphocyte proliferation inhibited by EPA but not by DHA. On the other hand, the authors showed that PUFAS did not inhibit IL-2 stimulated lymphocyte proliferation. The addition of PUFAs to cell culture medium had no inhibitory action on the PHA-induced lymphocyte expression of CD25, CD71 and HLA-DR. Furthermore, this effect appeared independent of eicosanoid synthesis or peroxide formation. Indeed, the inclusion of aspirin and vitamin E in the culture medium did not prevent the inhibitory effects of PUFAs on lymphocyte proliferation. Regardless of the mechanism of action, the inhibitory effect of PUFAs on activated lymphocytes may explain why some clinical trials of fish oil supplemented diets containing high amounts of DHA and EPA have been successful in improving the health status of patients suffering from inflammatory and autoimmune disorders.

Correlation between traditional Chinese medicine classification of 53 patients with aplastic anemia and varieties of hemopoietic progenitor cells in vitro culture. [Article in Chinese]

Luo XS. Dept. of Hemotology, Affiliated Hospital of Zhejiang College of TCM, Hangzhou.

Zhongguo Zhong Xi Yi Jie He Za Zhi 1992 Mar;12(3):139-41, 131

Aplastic anemia can be classified distinctively three types as progenitor depletive; immunosuppressive and androgenic sensitive. Using bone marrow culture in vitro which had been accomplished in our laboratory, 53 patients with aplastic anemia were also classified according to TCM term in three groups as Yin deficiency, Yang deficiency and both Yin and Yang deficiency, and the correlation was observed between TCM classification and lab character of these patients. The results showed that the number of CFU-GM, CFU-E and BFU-E in Yang deficiency group was significantly higher than that in the other two groups (P less than 0.01 and P less than 0.05). It also showed that the sensitivity of progenitor cells to androgenic hormones of Yang deficiency group was preferential to all (P less than 0.005 and P less than 0.05). The percentage of immunosuppressive type of aplastic anemia in Yin deficiency group was much higher than those in the other two groups (P less than 0.005). These observations suggested that TCM classification for aplastic anemia in this paper has objective material foundation.

Biochemical effects of a diet containing foods enriched with n-3 fatty acids.

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Am J Clin Nutr 2000 Jul;72(1):42-8

BACKGROUND: Results of many studies indicate that consumption of n-3 fatty acids can benefit persons with cardiovascular disease and rheumatoid arthritis. However, encapsulated fish oil is unlikely to be suited to lifetime daily use and recommendations to increase fish intake have not been effective.

OBJECTIVE: The objective was to examine the effectiveness of a diet that incorporates foods rich in n-3 fatty acids in elevating tissue concentrations of eicosapentaenoic acid and in suppressing the production of inflammatory mediators.

DESIGN: Healthy male volunteers were provided with foods that were enriched in alpha-linolenic acid (cooking oil, margarine, salad dressing, and mayonnaise) and eicosapentaenoic and docosahexaenoic acids (sausages and savory dip) and with foods naturally rich in n-3 fatty acids, such as flaxseed meal and fish. Subjects incorporated these products into their food at home for 4 wk. Fatty acid intakes, cellular and plasma fatty acid concentrations, and monocyte-derived eicosanoid and cytokine production were measured.

RESULTS: Analyses of dietary records indicated that intake of eicosapentaenoic acid plus docosahexaenoic acid averaged 1.8 g/d and intake of alpha-linolenic acid averaged 9. 0 g/d. These intakes led to an average 3-fold increase in eicosapentaenoic acid in plasma, platelet, and mononuclear cell phospholipids. Thromboxane B(2), prostaglandin E(2), and interleukin 1beta synthesis decreased by 36%, 26%, and 20% (P < 0.05), respectively.

CONCLUSIONS: Foods that are strategically or naturally enriched in n-3 fatty acids can be used to achieve desired biochemical effects without the ingestion of

supplements or a change in dietary habits. A wide range of n-3-enriched foods could be developed to support large-scale programs on the basis of the therapeutic and disease-preventive effects of n-3 fatty acids.

Clinical roles of vitamins in hematopoietic disorders. [Article in Japanese]

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Nippon Rinsho 1999 Oct;57(10):2349-55

Vitamins are essential organisms which promote various metabolisms and physiological systems. Several vitamins play important roles in hematopoietic system. Vitamin B12, C and folic acid are associated with DNA synthesis of erythroid nucleus, the deficiency of which causes the megaloblastic anemia. Some megaloblatic anemia and sideroblastic anemia might response to vitamin B1 and B6, respectively. Vitamin K participates in some coagulation factors in coagulation-fibrinogenolysis system. It has been reported that vitamins A, D and K potentially differentiate leukemic cells and then induce the apoptosis, suggesting that they would be new therapeutic agents in acute leukemia.

Effect of intravenous infusion of omega-3 and omega-6 lipid emulsions on equine monocyte fatty acid composition and inflammatory mediator production in vitro.

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Shock 2000 Aug;14(2):222-8

The effect of intravenous administration of lipid emulsions enriched with omega-3 (n3) and omega-6 (n6) fatty acids on equine monocyte phospholipid fatty acid composition and the synthesis of inflammatory mediators in vitro was evaluated. In a randomized crossover design, horses were infused intravenously with 20% lipid emulsions containing n3 or n6 fatty acids. Monocytes were isolated from the horses before and 0 h, 8 h, 24 h, and 7 days after lipid infusion. Monocyte fatty acid analysis demonstrated incorporation of the parenteral n3 and n6 fatty acids in monocyte phospholipids immediately after infusion, with changes in the fatty acid composition persisting for up to 7 days after infusion. In vitro production of the inflammatory mediators thromboxane B2/thromboxane B3 (TXB(2/3)) and tumor necrosis factor-alpha (TNFalpha) by peripheral blood monocytes was diminished by n3 lipid infusion and was unchanged or increased by n6 lipid infusion. The results of this study demonstrate that short-term infusions of n3 and n6 fatty acid-enriched lipid emulsions alter the fatty acid composition of equine monocyte phospholipids and modify the inflammatory response of these cells in vitro. These results also support further investigation into the use of parenteral n3 fatty acids as part of the supportive therapy of patients with multiple organ dysfunction (MODS) or systemic inflammatory response syndrome (SIRS).

Effect of zinc supplementation on serum testosterone level in adult male sickle cell anemia subjects.

Prasad AS, Abbasi AA, Rabbani P, DuMouchelle E.

Am J Hematol 1981;10(2):119-27

Previously, we have documented primary testicular failure in adult male subjects with sickle cell anemia. We have also reported the occurrence of zinc deficiency and suggested that androgen deficiency may be related to zinc deficiency in such patients. In this study, we present data with respect to the efferent of oral zinc supplementation on serum testosterone levels in adult male patients with sickle cell anemia. An increase in serum testosterone, neutrophil zinc, and neutrophil alkaline phosphatase activity ws observed in the zinc-supplemented group in comparison with the group on placebo. Additionally, body weight increased and serum lactic dehydrogenase activity decrease in response to zinc supplementation. We conclude that androgen deficiency in adult male subjects with sickle cell anemia is correctable with zinc supplementation and that the determination of neutrophil zinc and alkaline phosphatase activity in the neutrophils may be utilized as good indicators of body zinc status in such subjects.

Interleukin 6 production by lipopolysaccharide-stimulated human fibroblasts is potently inhibited by naphthoquinone (vitamin K) compounds.

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Cytokine 1995 Apr;7(3):287-90

Naphthoquinone vitamins (vitamins K) are widely recognized for their role in the gamma-carboxylation of specific glutamyl residues in coagulation, anti-coagulation and extra-hepatic proteins. Recently, however, there have been reports that these compounds can exert actions other than those normally associated with protein gamma-carboxylation. These observations suggest that naphthoquinones may have effects on the production of inflammatory mediators including cytokines. Fibroblasts are now recognized as a rich source of cytokines and we have examined the effect of various naphthoquinones on the production of interleukin 6 (IL-6) by lipopolysaccharide-stimulated human gingival fibroblasts. Compounds examined in this study include: phylloquinone (K1), menaquinone-4 (K2), menadione (K3), 2,3-dimethoxy-1,4-naphthoquinone (DMK) and a synthetic product of vitamin K catabolism, 2-methyl, 3-(2'methyl)-hexanoic acid-1,4-naphthoquinone (KCAT). All of these compounds are capable of inhibiting IL-6 production with a rank order of potency: KCAT > K3 > DMK > K2 > K1. The most potent compound, KCAT, inhibited IL-6 production with an IC50 of 3 x 10(-7)M. The mechanism of action of these naphthoquinones on fibroblast IL-6 production is unknown. Given that K3 and KCAT are inactive in the gamma-carboxylation reaction, we suggest that this activity is not essential for

the inhibition of IL-6 production and that activity may be related to the redox capacity of these naphthoquinones.

Serum erythropoietin and erythroid activity in vitamin B12 deficiency.

Remacha AF, Bellido M, Garcia-Die F, Marco N, Ubeda J, Gimferrer E. Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Haematologica 1997 Jan-Feb;82(1):67-8

We studied erythropoiesis in 31 patients with vitamin B12 deficiency by measuring serum erythropoietin (s-Epo), serum transferrin receptor (s-TfR, taken as an index of total erythroid activity), reticulocyte count, and the reticulocyte maturation index (RMI). s-Epo and s-TfR were measured with commercial immunoassays, whereas reticulocyte count and RMI were determined by flow cytometry. s-Epo (123 +/- 196 U/L) and s-TfR (4.1 +/- 2 mg/L) levels were increased in patients with vitamin B12 deficiency. The absolute reticulocyte counts were decreased (29 +/- 18 x 10(9)/L) with a relative increase in the most immature fractions (RMI: 29.6 +/- 18%). A significant negative relationship was found between s-Epo and Hb level (r = -0.65, p < 0.0001). On the average, however, s-Epo was inappropriately low for the degree of anemia, since the observed/predicted (O/P) s-Epo ratio was 0.80 +/- 0.28 in vitamin B12 deficiency vs 1.00 +/- 0.16 in a group of patients with iron deficiency anemia. It is concluded that at least a portion of patients with vitamin B12 deficiency have serum erythropoietin levels that are inappropriately low for the degree of anemia.

Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription.

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FEBS Lett 1999 Jan 8;442(1):89-94

Activation of transcription factor NF-kappaB is elevated in several chronic inflammatory diseases and is responsible for the enhanced expression of many proinflammatory gene products. Extracts from leaves of stinging nettle (Urtica dioica) are used as antiinflammatory remedies in rheumatoid arthritis. Standardized preparations of these extracts (IDS23) suppress cytokine production, but their mode of action remains unclear. Here we demonstrate that treatment of different cells with IDS23 potently inhibits NF-kappaB activation. An inhibitory effect was observed in response to several stimuli, suggesting that IDS23 suppressed a common NF-kappaB pathway. Inhibition of NF-kappaB activation by IDS23 was not mediated by a direct modification of DNA binding, but rather by preventing degradation of its inhibitory subunit IkappaB-alpha. Our results suggests that part of the antiinflammatory effect of Urtica extract may be ascribed to its inhibitory effect on NF-kappaB activation.

Alteration of tumor necrosis factor-alpha production by macrophages from mice fed diets high in eicosapentaenoic and docosahexaenoic fatty acids.

Somers SD, Erickson KL. Division of Immunology, James N. Gamble Institute of Medical Research, Cincinnati, Ohio 45319.

Cell Immunol 1994 Feb;153(2):287-97

Dietary exposure to n-3 fats found in marine fish oils are known to reduce certain inflammatory conditions. Although depressed prostaglandin E2 (PGE2) production is thought to be a major mechanism of the beneficial effects, the direct effects of n-3 fatty acids on inflammatory macrophage function are not well understood. In this study, production of the inflammatory monokine, tumor necrosis factor-alpha (TNF alpha), by isolated murine macrophages was assessed following a 3-week feeding with diets containing either 10% menhaden fish oil as a source of n-3 fatty acids or, as a control and source of n-6 fatty acids, 10% safflower oil. Cultures of peritoneal macrophages from mice fed diets with n-3 fatty acids had more TNF alpha activity 24 hr after in vitro stimulation with bacterial lipopolysaccharide than did macrophages from mice fed the n-6-containing diet. The onset and maximal synthesis of bioactive TNF alpha and down-regulation of messenger RNA for TNF alpha appeared to be similar for the two diets, suggesting that macrophages from mice fed a diet high in n-6 but not n-3 fatty acids were capable of removing active TNF alpha from culture media. Experiments in which PGE2 was added exogenously indicated that the removal of TNF alpha from culture supernatant by macrophages was induced by lower concentrations of PGE2 than that associated with termination of production, and that n-3 fatty acid diets caused a selective loss in the clearance mechanism. These results demonstrate a specific alteration of PGE2-mediated regulation of macrophage-produced TNF alpha by n-3 fatty acids.

Dietary supplementation with very long-chain n-3 fatty acids in man decreases expression of the interleukin-2 receptor (CD25) on mitogen-stimulated lymphocytes from patients with inflammatory skin diseases.

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Eur J Clin Invest 1994 Apr;24(4):236-42

T-cell activation and cytokine production play an important role in several chronic inflammatory diseases. Because n-3 fatty acids exert beneficial effects on the clinical state of some of these diseases, we examined the effect of dietary supplementation of n-3 fatty acids on T-cell proliferation, expression of CD25 (interleukin-2 receptor alpha-chain), secretion of interleukin-2, interleukin-6 and tumour necrosis factor from T-cells from patients with psoriasis and atopic dermatitis. During 4 months, 21 patients supplied 6 g of highly concentrated ethyl esters of EPA and DHA in gelatin capsules daily to their diet. In the control group 20 patients supplied 6 g per day of corn oil in gelatin capsules to their diet. Eicosapentaenoic acid (20:5, n-3) of serum phospholipids increased from 14 (min

4-max 42) to 81 (min 59-max 144) mg l-1 (P < 0.01) in patients with atopic dermatitis receiving n-3 fatty acids, and from 25 (min 7-max 66) to 74 (min 46-max 142) mg l-1 (P < 0.01) in patients with psoriasis, whereas docosahexaenoic acid (22:6, n-3) increased from 65 (min 46-max 120) to 92 (min 54-max 121) mg l-1 (P < 0.05) and from 81 (min 38-max 122) to 92 (min 63-max 169) mg l-1 (NS) in atopic and psoriatic patients, respectively. The changes in the serum phospholipid fatty acid profile in the groups receiving n-3 fatty acids, correlate to the dietary intake of corresponding fatty acids. (ABSTRACT TRUNCATED AT 250 WORDS)

Association of humoral markers of inflammation and dehydroepiandrosterone sulfate or cortisol serum levels in patients with chronic inflammatory bowel disease.

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Am J Gastroenterol 1998 Nov;93(11):2197-202

OBJECTIVES: Dehydroepiandrosterone sulfate (DHEAS) and cortisol are multifunctional adrenal hormones with immunomodulating properties. DHEAS levels were found to be very low in chronic inflammatory diseases. This study aimed to shed more light on the interrelation between DHEAS and cortisol (and humoral markers of inflammation) in chronic inflammatory bowel disease.

METHODS: DHEAS and cortisol serum levels were measured by ELISA in the serum of 66 normal subjects, 115 patients with Crohn's disease (CD) and 64 patients with ulcerative colitis (UC). Humoral markers of inflammation and disease activity scores were assessed by standard techniques.

RESULTS: DHEAS was lower in patients with CD (p < 0.005) and UC (p < 0.005) than in controls, which was, in part, dependent on previous corticosteroid treatment (p < 0.01). In CD patients, z-normalized DHEAS was inversely correlated with blood sedimentation rate (p = 0.017). Z-normalized DHEAS was negatively correlated with interleukin-6 (IL-6) in the form of a trend (p = 0.068), and z-normalized DHEAS was significantly positively correlated with hemoglobin (p = 0.001) but not with the Crohn's disease activity index. Cortisol, however, was positively correlated with blood sedimentation rate (p = 0.034) and C-reactive protein (p = 0.006). In contrast, in UC patients no such correlation of z-normalized DHEAS or cortisol and parameters of humoral inflammatory activity or Rachmilewitz index exist.

CONCLUSIONS: DHEAS as a marker of inflammation was low in CD and UC. In CD patients, low DHEAS and high cortisol serum levels were associated with higher humoral inflammatory activity. With respect to humoral inflammatory activity in CD patients, DHEAS and cortisol seem to be inversely regulated, which may have an impact on several immune functions, such as IL-6 secretion.

Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases-substitutes of adrenal and sex hormones.

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Z Rheumatol 2000;59 Suppl 2:II/108-18

A dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis was found in animal models of chronic inflammatory diseases, and the defect was located in more central portions of the HPA axis. This defect of neuroendocrine regulatory mechanisms contributes to the onset of the model disease. Since these first observations in animal models were made, evidence has accumulated that the possible defect in the HPA axis in humans is more distal to the hypothalamus or pituitary gland: In chronic inflammatory diseases, such as rheumatoid arthritis, an alteration of the HPA stress response results in inappropriately low cortisol secretion in relation to adrenocorticotropic hormone (ACTH) secretion. Furthermore, it has recently been shown that the serum levels of another adrenal hormone, dehydroepiandrosterone (DHEA), were significantly lower after ACTH stimulation in patients with rheumatoid arthritis without prior corticosteroids than in healthy controls. These studies clearly indicate that chronic inflammation alters, particularly, the adrenal response. However, at this point, the reason for the specific alteration of adrenal function in relation to pituitary function remains to be determined. Since one of the down-regulated adrenal hormones, DHEA, is an inhibitor of cytokines due to an inhibition of nuclear factor-kappa B (NF-kappa B) activation, low levels of this hormone may be deleterious in chronic inflammatory diseases. We have recently demonstrated that DHEA is a potent inhibitor of IL-6, which confirmed an earlier study in mice. Since IL-6 is an important factor for B lymphocyte differentiation, the missing down-regulation of this cytokine, and others such as TNF, may be a significant risk factor in rheumatic diseases. Since in these patients, administration of prednisolone or the chronic inflammatory process itself alters adrenal function, endogenous adrenal hormones in relation to proinflammatory cytokines change. Furthermore, these mechanisms may also lead to shifts in steroidogenesis which have been demonstrated in chronic inflammatory diseases. It was repeatedly demonstrated that the serum level of the sulphated form of DHEA (DHEAS) was significantly lower in patients with chronic inflammatory diseases. Since DHEAS is the pool for peripheral sex steroids, such as testosterone and 17 beta-estradiol, lack of this hormone leads to a significant sex hormone deficiency in the periphery. This overview will demonstrate mechanisms why DHEAS is reduced in chronic inflammatory diseases. The importance of DHEAS deficiency will be demonstrated with respect to osteoporosis. As a consequence, we suggest a combined therapy with corticosteroids plus DHEA in chronic inflammatory diseases.

Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion

from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence.

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J Clin Endocrinol Metab 1998 Jun;83(6):2012-7

Interleukin-6 (IL-6) is one of the pathogenetic elements in inflammatory and age-related diseases such as rheumatoid arthritis, osteoporosis, atherosclerosis, and late-onset B cell neoplasia. In these diseases or during aging, the decrease in production of sex hormones such as dehydroepiandrosterone (DHEA) is thought to play an important role in IL-6-mediated pathogenetic effects in mice. In humans, we investigated the correlation of serum levels of DHEA, DHEA sulfate (DHEAS), or androstenedione (ASD) and IL-6, tumor necrosis factor-alpha, or IL-2 with age in 120 female and male healthy subjects (15-75 yr of age). Serum DHEA, DHEAS, and ASD levels significantly decreased with age (all P < 0.001), whereas serum IL-6 levels significantly increased with age (P < 0.001). DHEA/DHEAS and IL-6 (but not tumor necrosis factor-alpha or IL-2) were inversely correlated (all patients: r = -0.242/-0.312; P = 0.010/0.001). In female and male subjects, DHEA and ASD concentration dependently inhibited IL-6 production from peripheral blood mononuclear cells (P = 0.001). The concentration-response curve for DHEA was U shaped (maximal effective concentration, 1-5 x 10(-8) mol/L), which may be the optimal range for immunomodulation. In summary, the data indicate a functional link between DHEA or ASD and IL-6. It is concluded that the increase in IL-6 production during the process of aging might be due to diminished DHEA and ASD secretion. Immunosenescence may be directly related to endocrinosenescence, which, in turn, may be a significant cofactor for the manifestation of inflammatory and age-related diseases.

Cytokine secretion in whole blood of healthy subjects following oral dministration of Urtica dioica L. plant extract. [Article in German]

Teucher T, Obertreis B, Ruttkowski T, Schmitz H. Strathmann AG & Co., Hamburg.

Arzneimittelforschung 1996 Sep;46(9):906-10

Twenty healthy volunteers ingested for 21 days 2 capsules b.i.d. of an IDS 23/1 containing nettle leaf extract (Rheuma-Hek). Before and after 7 and 21 days the basal and the lipopolysaccharide (LPS) stimulated tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6) concentrations were measured ex vivo. In vitro the effects of IDS 23/1 on the release of these cytokines were determined. Additionally basal interleukin-4 (IL-4) and interleukin-10 (IL-10) levels were recorded. Orally taken the test drug has ex vivo no effect on basal levels of TNF-alpha, IL-1 beta, IL-4, IL-6 or IL-10 which were always below detection limits. After 7 and 21 days ingestion ex vivo

a decrease of LPS stimulated TNF-alpha release of 14.6 and 24.0%, respectively, was observed. IL-1 beta was reduced for 19.2 and 39.3%. In vitro IDS 23/1 added to whole blood resulted in an exceeded inhibition of LPS stimulated TNF-alpha and IL-1 beta secretion which correlated with the duration of the drug ingestion. Using the highest tested IDS 23/1 concentration the inhibition reached 50.5 (day 0) to 79.5% (day 21) for TNF-alpha and 90.0 (day 0) to 99.2% (day 21) for IL-1 beta, respectively. IDS 23/1 induced a pronounced release of IL-6 in absence of LPS only in vitro. The detected IL-6 concentrations were comparable to those after LPS stimulation, additive effects could not be observed. The absence of detectable IL-6 concentrations in whole blood ex vivo after oral ingestion of the tested drug as well as the differences in the inhibition patterns for TNF-alpha and IL-1 beta ex vivo and ex vivo in vitro suggest that the extract contains different pharmacological effective compounds with varying bioavailabilities.

Dietary docosahexaenoic acid suppresses inflammation and immunoresponses in contact hypersensitivity reaction in mice.

Tomobe YI, Morizawa K, Tsuchida M, Hibino H, Nakano Y, Tanaka Y. Tsukuba Research Laboratory, NOF Corporation, Ibaraki, Japan.

Lipids 2000 Jan;35(1):61-9

This study was designed to examine the immunomodulatory effects of dietary docosahexaenoic acid (DHA) in the absence of eicosapentaenoic acid (EPA). We investigated the effects of feeding dietary DHA ethyl ester (DHA-Et) (97% pure) at levels of 4.8 wt% of the total diet and of feeding EPA ethyl ester (EPA-Et) (99% pure) at 4.8 wt% on the inflammatory response in the challenge phase of the contact hypersensitivity reaction (CHR) in the ears of mice sensitized with 2,4-dinitro-1-fluorobenzene (DNFB). The effect of DHA-Et on T lymphocytes at the CHR site was examined using anti-CD4 antibodies. Furthermore, we examined the cytokines formed at the CHR site on the mRNA level. It was found that 24 h after the challenge, DHA-Et but not EPA-Et reduced the ear swelling. Infiltration of inflammatory cells, in particular, CD4-positive T lymphocytes, into the ears in the challenge phase of CHR was observed. DHA-Et reduced the infiltration of CD4-positive T lymphocytes into the ears. DHA-Et also decreased the expression of interferon-gamma, interleukin (IL)-6, IL-1beta, and IL-2 mRNA in ears. These observations suggest that DHA, but not EPA, may exert an antiinflammatory and immunosuppressive effect. The immunosuppressive ffectiveness of fish oil may be attributed mainly to DHA.

Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin.

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Cancer Chemother Pharmacol 2001;47(1):34-40

PURPOSE: The anticancer activity of omega-3 polyunsaturated fatty acids (omega-3 PUFA) has been shown in a large number of studies. This study was undertaken to analyze the combined effect of omega-3 PUFA and antioxidative vitamins on the level of spontaneous metastatic dissemination. The supportive effect of this dietary combination on chemotherapy with cisplatin (CP) was determined in parallel.

METHODS: C57BL/6J mice bearing the Lewis lung carcinoma 3LL were fed ad libitum one of three isocaloric diets containing 5% soybean oil supplemented with 40 mg/kg alpha-tocopherol acetate (SO diet), or 4% fish oil plus 1% corn oil, and basal amounts of vitamin E (FO diet) or FO diet supplemented with vitamins E and C (FO+E+C diet). These diets were tested in combination with the conventional cytotoxic agent CP in a series of regimens. Tumor growth, feed consumption, body weight, lung metastasis and lung histology were followed.

RESULTS: Both the FO dietary groups showed significantly lower tumor development than the SO group in all examined parameters, indicating that omega-3 PUFA have anticancer activity. However, the FO diet, in comparison with the FO+E+C diet induced a significantly slower rate of tumor growth, and lower metastatic load, as reflected in lung weight. The decrease in the anticancer activity of FO by the addition of vitamins E and C suggests that in situ oxidation of omega-3 PUFA underlies their anticancer action. It is thus proposed that oxidized omega-3 PUFA accumulates in the membranes and the cytosol of tumor cells, reducing their vitality and eventually leading to their death. No signs of anorexia or cachexia were observed in either FO group, in contrast to the SO group. CP treatment with the SO diet had no apparent therapeutic effect, while with the FO diets it reduced the metastatic load. The best regimen of this combined treatment was FO diet followed by CP treatment with FO diet supplemented with vitamins E and C after resection of the primary growth. This regimen could be translated to a combined therapy for human cancer.

CONCLUSIONS: Diets enriched with omega-3 PUFA may have beneficial anticancer effects in particular when containing only basal amounts of antioxidants such as vitamin E or C. Furthermore, the addition of drugs which promote oxidation of omega-3 PUFA, such as ferrous salts (e.g. as prescribed for the treatment of anemia), may further increase these effects. However, the supportive effect of omega-3 PUFA in chemotherapy (e.g. with CP) increases when vitamins E and C are also included.

Folates in human nutrition. Different clinical situations in which folate deficiencies exist. [Article in Spanish]

Zarazaga A, Garcia de Lorenzo A, Montanes P, Culebras JM. Servicio de Cirugia General, Hospital Universitario, La Paz, Madrid.

Nutr Hosp 1991 Jul-Aug;6(4):207-26

The alimentary surveys carried out on various sectors of the population in industrialized countries have shown the existence of chronic clinically silent

deficiency in micronutrients. In some cases, as in folates, their lability against conservation techniques, the change in alimentary habits, the abuse of alcohol and the great quantity of frequently used drugs which interfere in their absorption, diminish their content in the diet and their bio-availability. The appearance of macrocytic anemia is a late deficiency sign, and therefore in situations of an increase need and in patients included in the risk groups, a supplemental intake must be given in order to avoid irreversible lesions if it is not possible to monitor the folate levels. There are risk groups in which various etiological factors come into play, acting at a different metabolic level on the folates and making more difficult their dietetic or pharmacological compensation even if supply is considerably increased. We studied these factors independently and in each specific situation (old people, patients with liver disease, alcoholics, pregnant women and nursing mothers, neonates, children, malabsorption syndromes, gastrectomy, AIDS, anaesthesia and patients being treated with antifolic medication), evaluating their mechanisms of action and their potentiation in determined specific situations

5. Anxiety and Stress

Preventative and curative options include:

Dietary changes, multivitamin and mineral formulas, extra calcium and magnesium, theanine, melatonin, DHEA, kava kava, green tea,

Piper methysticum (kava kava).

Anon.

Altern Med Rev 1998 Dec;3(6):458-60

Piper methysticum (kava kava) is a plant native to the Pacific Island region, and has been used ceremonial for thousands of years. The active ingredients are a group of substances know as kava lactones (AKA kava pyrones). Four lactones in kava have been found to have significant analgesic and anesthetic effects via non-opiate pathways. Kava's most popular application is as a natural anxiolytic, comparing favorably in several studies to a number prescription medications, including benzodiazepines. CNS effects seem to be mediated by several mechanisms. Studies have been conflicting regarding its GABA-receptor-binding capacity, although this has been found to occur in some studies. In vitro kava has been found to block norepinephrine uptake. It also has some anti-convulsant capabilities, which appear to be mediated by Na+ channel receptor sites. The therapeutic dosage is in the range of 50-70 mg kava lactones three times daily. The most common side effect, usually seen only with long-term, heavy usage of the herb, is a scaly skin rash called "kava dermopathy." It has also been know to potentiate other medications such as barbiturates and Xanax.

Effect of green tea rich in gamma-aminobutyric acid on blood pressure of Dahl salt-sensitive rats.

Abe Y, Umemura S, Sugimoto K, Hirawa N, Kato Y, Yokoyama N, Yokoyama T, Iwai J, Ishii M. Second Department of Internal Medicine, Yokohama City University School of Medicine, Japan.

Am J Hypertens 1995 Jan;8(1):74-9

gamma-Aminobutyric acid (GABA) is known to be involved in the regulation of blood pressure by modulating the neurotransmitter release in the central and peripheral sympathetic nervous systems. This study investigated the antihypertensive effect of green tea rich in GABA (GABA-rich tea) in young and old Dahl salt-sensitive (S) rats. GABA-rich tea was made by fermenting fresh green tea leaves under nitrogen gas. In experiment 1, 21 11-month-old rats, fed a 4% NaCl diet for 3 weeks, were given water (group W), an ordinary tea solution (group T), or a GABA-rich tea solution (group G) for 4 weeks. The average GABA intake was 4.0 mg/rat per day. After 4 weeks of the treatment, blood

pressure was significantly decreased in group G (176 +/- 4; <.01) compared with group W (207 +/- 9) or group T (193 +/- 5 mm Hg). Plasma GABA levels were more elevated in group G (111 +/- 54) than in group W (not detectable) or group T (14 +/- 8 ng/mL; < .01 v G). In experiment 2, 21 5-week-old rats, fed a 4% NaCl diet, were divided into groups W, T, and G. The average GABA intake was 1.8 mg/rat per day. Body weight or chow and beverage consumption did not differ significantly among the three groups. After 4 weeks of the treatment, although blood pressure was comparable in groups W and T (165 +/- 3 v 164 +/- 5 mm Hg, mean +/- SE), it was significantly lower in group G (142 +/- 3 mm Hg) than in the other groups (< .01).(ABSTRACT TRUNCATED AT 250 WORDS)

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look.

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J Ethnopharmacol 2000 Oct;72(3):345-93

The adaptogen concept is examined from an historical, biological, chemical, pharmacological and medical perspective using a wide variety of primary and secondary literature. The definition of an adaptogen first proposed by Soviet scientists in the late 1950s, namely that an adaptogen is any substance that exerts effects on both sick and healthy individuals by 'correcting' any dysfunction(s) without producing unwanted side effects, was used as a point of departure. We attempted to identify critically what an adaptogen supposedly does and to determine whether the word embodies in and of itself any concept(s) acceptable to western conventional (allopathic) medicine. Special attention was paid to the reported pharmacological effects of the 'adaptogen-containing plant' Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae), referred to by some as 'Siberian ginseng', and to its secondary chemical composition. We conclude that so far as specific pharmacological activities are concerned there are a number of valid arguments for equating the action of so-called adaptogens with those of medicinal agents that have activities as anti-oxidants, and/or anti-cancerogenic, immunomodulatory and hypocholesteroletic as well as hypoglycemic and choleretic action. However, 'adaptogens' and 'anti-oxidants' etc. also show significant dissimilarities and these are discussed. Significantly, the classical definition of an adaptogen has much in common with views currently being invoked to describe and explain the 'placebo effect'. Nevertheless, the chemistry of the secondary compounds of Eleutherococcus isolated thus far and their pharmacological effects support our hypothesis that the reported beneficial effects of adaptogens derive from their capacity to exert protective and/or inhibitory action against free radicals. An inventory of the secondary substances contained in Eleutherococcus discloses a potential for a wide range of activities reported from work on cultured cell lines, small laboratory animals and human subjects. Much of the cited work (although not all) has been published in peer-reviewed journals. Six compounds show various levels of activity as anti-oxidants, four show anti-cancer action, three show hypocholesterolemic activity,

two show immunostimulatory effects, one has choleretic activity and one has the ability to decrease/moderate insulin levels, one has activity as a radioprotectant, one shows anti-inflammatory and anti-pyretic activities and yet another has shown activity as an antibacterial agent. Some of the compounds show more than one pharmacological effect and some show similar effects although they belong to different chemical classes. Clearly, Eleutherococcus contains pharmacologically active compounds but one wishes that the term adaptogen could be dropped from the literature because it is vague and conveys no insights into the mechanism(s) of action. If a precise action can be attributed to it, then the exact term for said action should obviously be used; if not, we strongly urge that generalities be avoided. Also, comparison of Eleutherococcus with the more familiar Panax ginseng C.A. Meyer (Araliaceae), 'true ginseng' has underscored that they differ considerably chemically and pharmacologically and cannot be justifiably considered as mutually interchangeable. Accordingly, we recommend that the designation 'Siberian ginseng' be dropped and be replaced with 'Eleutherococcus'. In the case of both Eleutherococcus and true ginseng, problems inherent in herbal preparation use include inconsistencies not only in terms of indications for use, but in the nomenclature of constituent chemical compounds, standardization, dosage and product labeling. (ABSTRACT TRUNCATED)

Inhibiting effects of theanine on caffeine stimulation evaluated by EEG in the rat.

Kakuda T, Nozawa A, Unno T, Okamura N, Okai O. Central Research Institute, Itoen Ltd., Shizuoka, Japan. ITN00527@nifty.ne.jp

Biosci Biotechnol Biochem 2000 Feb;64(2):287-93

In this study, the inhibiting action of theanine on the excitation by caffeine at the concentration regularly associated with drinking tea was investigated using electroencephalography (EEG) in rats. First, the stimulatory action by caffeine i.v. administration at a level higher than 5 micromol/kg (0.970 mg/kg) b.w. was shown by means of brain wave analysis, and this level was suggested as the minimum dose of caffeine as a stimulant. Next, the stimulatory effects of caffeine were inhibited by an i.v. administration of theanine at a level higher than 5 micromol/kg (0.781 mg/kg) b.w., and the results suggested that theanine has an antagonistic effect on caffeine's stimulatory action at an almost equivalent molar concentration. On the other hand, the excitatory effects were shown in the rat i.v. administered 1 and 2 micromol/kg (0.174 and 0.348 mg/kg) b.w. of theanine alone. These results suggested two effects of theanine, depending on its concentration.

Exercise intensity and self-efficacy effects on anxiety reduction in healthy, older adults.

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J Behav Med 1999 Jun;22(3):233-47

The purpose of the present study was to examine the effects of varying exercise intensities and changes in self-efficacy on anxiety reduction in a sample of healthy, older adults. Eighty older adults from a randomized controlled exercise trial participated in this study and completed measures of self-efficacy and the State Anxiety Inventory (SAI) prior to and following light-, moderate-, and high-intensity exercise. Latent growth curve modeling analyses revealed that although anxiety was reduced following the light-intensity condition, no significant changes in anxiety occurred following the moderate-intensity condition, and anxiety increased following the high-intensity condition. In addition, changes in self-efficacy were related to anxiety responses only in the moderate-intensity condition. An analysis of SAI items indicated that although the light-intensity condition resulted in decreased arousal and anxiousness, the high-intensity condition resulted in increased arousal and decreased anxiousness. These results are discussed in terms of social cognitive theory and the appropriateness of the SAI for use in exercise settings.

The impact of a new emotional self-management program on stress, emotions, heart rate variability, DHEA and cortisol.

McCraty R, Barrios-Choplin B, Rozman D, Atkinson M, Watkins AD. Institute of HeartMath, Boulder Creek, California 95006, USA. rollin@heartmath.org

Integr Physiol Behav Sci 1998 Apr-Jun;33(2):151-70

This study examined the effects on healthy adults of a new emotional self-management program, consisting of two key techniques, "Cut-Thru" and the "Heart Lock-In." These techniques are designed to eliminate negative thought loops and promote sustained positive emotional states. The hypotheses were that training and practice in these techniques would yield lowered levels of stress and negative emotion and cortisol, while resulting in increased positive emotion and DHEA levels over a one-month period. In addition, we hypothesized that increased coherence in heart rate variability patterns would be observed during the practice of the techniques. Forty-five healthy adults participated in the study, fifteen of whom acted as a comparison group for the psychological measures. Salivary DHEA/DHEAS and cortisol levels were measured, autonomic nervous system function was assessed by heart rate variability analysis, and emotions were measured using a psychological questionnaire. Individuals in the experimental group were assessed before and four weeks after receiving training in the self-management techniques. The experimental group experienced significant increases in the positive affect scales of Caring and Vigor and significant decreases in the negative affect scales of Guilt, Hostility, Burnout, Anxiety and Stress Effects, while no significant changes were seen in the comparison group. There was a mean 23 percent reduction in cortisol and a 100 percent increase in DHEA/DHEAS in the experimental group. DHEA was significantly and positively related to the affective state Warmheartedness, whereas cortisol was significantly and positively related to Stress Effects. Increased coherence in heart rate variability patterns was measured in 80 percent of the experimental group during the use of the techniques. The results suggest that techniques designed to eliminate negative thought loops can have important positive effects on stress,

emotions and key physiological systems. The implications are that relatively inexpensive interventions may dramatically and positively impact individuals' health and well-being. Thus, individuals may have greater control over their minds, bodies and health than previously suspected.

Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review.

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Altern Med Rev 2000 Aug;5(4):334-46

OBJECTIVE: The objective of this paper is to review the literature regarding Withania somnifera (ashwagandha, WS) a commonly used herb in Ayurvedic medicine. Specifically, the literature was reviewed for articles pertaining to chemical properties, therapeutic benefits, and toxicity.

DESIGN: This review is in a narrative format and consists of all publications relevant to ashwagandha that were identified by the authors through a systematic search of major computerized medical databases; no statistical pooling of results or evaluation of the quality of the studies was performed due to the widely different methods employed by each study.

RESULTS: Studies indicate ashwagandha possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hemopoietic, and rejuvenating properties. It also appears to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems. The mechanisms of action for these properties are not fully understood. Toxicity studies reveal that ashwagandha appears to be a safe compound.

CONCLUSION: Preliminary studies have found various constituents of ashwagandha exhibit a variety of therapeutic effects with little or no associated toxicity. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using ashwagandha for a variety of conditions should also be conducted.

Efficacy of kava extract for treating anxiety: systematic review and meta-analysis.

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J Clin Psychopharmacol 2000 Feb;20(1):84-9

Synthetic anxiolytic drugs are effective for treating anxiety, but they are burdened with adverse effects. Constraints on resources and time often render therapies

such as psychologic interventions impracticable. Thus, an effective oral medication with few adverse effects would be a welcome addition to the therapeutic repertoire. This systematic review and meta-analysis was aimed at assessing the evidence for or against the efficacy of kava extract as a symptomatic treatment for anxiety. Systematic literature searches were performed in the computerized databases MEDLINE, EMBASE, BIOSIS, AMED, CISCOM, and the Cochrane Library (all from their respective inception to June 1998). The search terms used were kava, kawa, kavain, Piper methysticum, and Rauschpfeffer (German term for Piper methysticum). Experts on the subject were contacted to provide further information. There were no restrictions regarding the language of publication. Double-blind, randomized, placebo-controlled trials of oral kava extract for the treatment of anxiety were included. All publications were blinded before assessment by a person not involved in the study. Data were extracted in a standardized, predefined fashion independently by the two reviewers. The methodologic quality of all trials was assessed. Superiority of kava extract over placebo was suggested by all seven reviewed trials. The meta-analysis of three trials suggests a significant difference in the reduction of the total score on the Hamilton Rating Scale for Anxiety in favor of kava extract (weighted mean difference, 9.69; 95% confidence interval, 3.54-15.83). These data imply that kava extract is superior to placebo as a symptomatic treatment for anxiety. Therefore, kava extract is an herbal treatment option for anxiety that is worthy of consideration.

Coffee and tea intake and the risk of myocardial infarction.

Sesso HD, Gaziano JM, Buring JE, Hennekens CH. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.

Am J Epidemiol 1999 Jan 15;149(2):162-7

The authors investigated the association of caffeinated coffee, decaffeinated coffee, and tea with myocardial infarction in a study of 340 cases and age-, sex-, and community-matched controls. The odds ratio for drinking < or = 4 cups/day of caffeinated coffee versus drinking < or = 1 cup/week was 0.84 (95% confidence interval (CI) 0.49-1.42) after adjustment for coronary risk factors (1 cup = 237 ml). The odds ratio for drinking < 1 cup/day of decaffeinated coffee versus nondrinkers was 1.25 (95% CI 0.76-2.04). For tea, the odds ratio for drinking < or = 1 cup/day versus nondrinkers was 0.56 (95% CI 0.35-0.90). In these data, only tea was associated with a lower risk of myocardial infarction.

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes.

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Int J Gynaecol Obstet 1999 Dec;67(3):169-74

OBJECTIVE: To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them.

METHODS: ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG.

RESULTS: CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG.

CONCLUSIONS: Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio.

[Psychosomatic dysfunctions in the female climacteric. Clinical effectiveness and tolerance of Kava Extract WS 1490] [Article in German]

Warnecke G. Gynakologe, Wuppertal.

Fortschr Med 1991 Feb 10;109(4):119-22

Within the framework of a randomized, placebo-controlled double-blind study, two groups each containing 20 patients with climacteric-related symptomatology were treated for a period of 8 weeks with kava WS 1490 extract 3 X 100 mg/day or a placebo preparation. The target variable - the HAMA overall score of anxiety symptomatology - revealed a significant difference in the drug-receiving group vis-a-vis the placebo group already after only 1 week of treatment. The course of such further parameters as depressive mood (DSI), subjective well-being (patient diary), severity of the disease (CGI), and the climacteric symptomatology (Kuppermann Index and Schneider scale) over the overall period of treatment demonstrate a high level of efficacy of kava extract WS 1490 in neurovegetative

and psychosomatic dysfunctions in the climacteric, associated with very good tolerance of the preparation.

Treatment of anxiety patients. Double-blind study: Kava special extract WS 1490 versus benzodiazepine

Woelk H.; Kapoula O.; Lehrl S.; Schroter K.; Weinholz P. Psych./Akademisches Lehrkrankenhaus, Universitat Giessen, Licher Strasse 106,6300 Giessen Germany

Zeitschrift fur Allgemeinmedizin (Z. ALLG.MED.) (Germany) 1993, 69/10 (271-277)

No Abstract Available.

Reduction effect of theanine on blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats.

Yokogoshi H, Kato Y, Sagesaka YM, Takihara-Matsuura T, Kakuda T, Takeuchi N. School of Food and Nutritional Sciences, University of Shizuoka, Japan.

Biosci Biotechnol Biochem 1995 Apr;59(4):615-8

The effect of theanine, one of the components of green tea, on the blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY) was investigated by intraperitoneally administering theanine. The effect of glutamine, which is structurally similar to theanine, was also examined. When SHR were injected with various amounts of theanine (0, 500, 1000, 1500, and 2000 mg/kg), the change was dose-dependent, and a significant decrease in blood pressure was observed with the high doses (1500 and 2000 mg/kg). A dose of 2000 mg/kg of theanine did not alter the blood pressure of WKY, while the same dose to SHR decreased it significantly. On the other hand, glutamine administration to SHR did not change either the blood pressure or the heart rate. The brain 5-hydroxyindole level was significantly decreased by theanine administration to both WKY and SHR, the decrease being dose-dependent.

Effect of theanine, r-glutamylethylamide, on brain monoamines and striatal dopamine release in conscious rats.

Yokogoshi H, Kobayashi M, Mochizuki M, Terashima T. School of Food and Nutritional Sciences, The University of Shizuoka, Yada, Shizuoka, Japan. yokogosi@fns1.u-shizuoka-ken.ac.jp

Neurochem Res 1998 May;23(5):667-73

Theanine, r-glutamylethylamide, is one of the major components of amino acids in Japanese green tea. Effect of theanine on brain amino acids and monoamines, and the striatal release of dopamine (DA) was investigated. Determination of amino acids in the brain after the intragastric administration of theanine showed

that theanine was incorporated into brain through blood-brain barrier via leucine-preferring transport system. The concentrations of norepinephrine, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole acetic acid (5HIAA) in the brain regions were unaffected by the theanine administration except in striatum. Theanine administration caused significant increases in serotonin and/or DA concentrations in the brain, especially in striatum, hypothalamus and hippocampus. Direct administration of theanine into brain striatum by microinjection caused a significant increase of DA release in a dose-dependent manner. Microdialysis of brain with calcium-free Ringer buffer attenuated the theanine-induced DA release. Pretreatment with the Ringer buffer containing an antagonist of non-NMDA (N-methyl-D-aspartate) glutamate receptor, MK-801, for 1 hr did not change the significant increase of DA release induced by theanine. However, in the case of pretreatment with AP-5, (+/-)-2-amino-5-phosphonopentanoic acid; antagonist of NMDA glutamate receptor, the theanine-induced DA release from striatum was significantly inhibited. These results suggest that theanine might affect the metabolism and/or the release of some neurotransmitters in the brain, such as DA.

Cardiovascular risk factors among Japanese and American telephone executives.

Anon.

Int J Epidemiol 1977 Mar;6(1):7-15

Cardiovascular risk factors were determined among two similar groups of telephone executives in Tokyo, Japan and New York City, USA. Both historical and electrocardiographic evidence pointed to a marked excess of coronary heart disease among American executives compared with their Japanese counterparts. In keeping with this finding, the Americans ate diets higher in animal fat, were fatter, and had higher serum cholesterol values but lower triglyceride levels. Mean blood pressures were slightly higher among the Japanese, and showed a greater increase with age. Urinary sodium/creatinine ratios were much higher among the Japanese, suggesting a higher salt intake. Cigarette smoking was more common among the Japanese. A review of other comparative studies between Japanese and Americans indicated that the only risk factors uniformly consistent with the frequency of coronary heart disease in the two countries were dietary fat, obesity, and serum cholesterol.

Cardiovascular risk factors in American and Japanese executives. Telecom Health Research Group.

Comstock GW, Suzuki T, Stone RW, Crumrine JL, Johnson DH, Sakai Y, Matsuya T, Sasaki S.

J R Soc Med 1985 Jul;78(7):536-45

A standardized cardiovascular risk factor examination was given to executives in the headquarters of the American Telephone and Telegraph Company and the

Nippon Telegraph and Telephone Public Corporation. As expected from the national mortality data, evidence of ischaemic heart disease was more common among American than Japanese executives. The frequency of some but not all risk factors was consistent with the observed differences in ischaemic heart disease. Americans were fatter than their Japanese counterparts, obtained a higher proportion of their caloric intake from animal fats, had higher serum cholesterol levels, and more of them felt that their lives were highly stressful. On the other hand, Japanese executives were much more likely to be cigarette smokers and showed a greater increase in blood pressure with age. Serum high-density lipoprotein cholesterol levels and the ratio of saturated to unsaturated fatty acids in the serum were similar in the two groups.

L theanine-a unique amino acid of green tea and its relaxation effect in humans.

Juneja LR, et al. 1999.

Trends Food Sci Tech 10:199 204.

No abstract available.

Protective effect of gamma-glutamylethylamide (theanine) on ischemic delayed neuronal death in gerbils.

Kakuda T, Yanase H, Utsunomiya K, Nozawa A, Unno T, Kataoka K. Central Research Institute, Itoen, Ltd., Shizuoka, Japan. itn00527@nifty.ne.jp

Neurosci Lett 2000 Aug 11;289(3):189-92

We examined the protective effect of gamma-glutamylethylamide (theanine) on ischemic delayed neuronal death in field CA1 of the gerbil hippocampus. One microliter of theanine from each three concentrations (50, 125 and 500 microM) was administered through the lateral ventricle 30 min before ischemia. Transient forebrain ischemia was induced by bilateral occlusion of the common carotid arteries for 3 min under careful control of brain temperature at approximately 37 degrees C. Seven days after ischemia, the number of intact CA1 neurons in the hippocampus was assessed. Ischemia-induced neuronal death in hippocampal CA1 region was significantly prevented in a dose-dependent manner in the theanine-pretreated groups. These findings indicate that theanine might be useful clinically for preventing ischemic neuronal damage.

Mortality among female practitioners of Chanoyu (Japanese "tea-ceremony").

Sadakata S, Fukao A, Hisamichi S. Washiya Hospital, Utsunomiya.

Tohoku J Exp Med 1992 Apr;166(4):475-7

A cohort study aimed to evaluate the effect of drinking green tea on longevity was performed. Three thousand three hundred and eighty female practitioners of chanoyu (Japanese tea-ceremony), living in Tokyo, were followed from 1980 to 1988, and 280 were dead during this period. Standardized mortality ratios were estimated 0.55 when all Japanese women was used as standard population and 0.57 when women living in Tokyo was used, indicating the possibility that green tea is a protective factor for several fatal diseases.

Health status and lifestyle in elderly Hawaii Japanese and Australian men. Exploring known differences in longevity.

Simons LA, McCallum J, Simons J, Friedlander Y. University of NSW School of Medicine, Darlinghurst.

Med J Aust 1992 Aug 3;157(3):188-90

OBJECTIVE: To contrast health status and lifestyle in two elderly populations with differing longevity. DESIGN: Comparison of two cross-sectional data sets. SETTING: Non-institutionalised subjects. SUBJECTS: Men aged 60-81 years resident in Dubbo, New South Wales (n = 1183, 1988-1989) and Japanese men of the same ages resident in Hawaii (n = 1376, 1980-1982). MAIN OUTCOME MEASURES: Cardiovascular and non-cardiovascular disease prevalence, risk factors, social and health status.

RESULTS: A history of heart attack, angina and stroke was twice as prevalent in Dubbo men as in Hawaii Japanese. Other diseases were many times more prevalent in Dubbo--liver disease sixfold, prostate and renal disease twofold, and arthritis 1.5-fold. Hypercholesterolaemia and untreated hypertension were more prevalent in Dubbo (threefold and 1.5-fold respectively). Current smoking was similar in both groups, while diabetes was twice as prevalent in the Hawaii Japanese. More Dubbo men were widowed or lived alone, and fewer remained in paid employment. Dubbo men had more limited physical mobility.

CONCLUSIONS: Elderly Dubbo men have an excess of cardiovascular disease and associated risk factors, as well as an excess of non-cardiovascular disease, compared with Hawaii Japanese. This may account, in part, for a higher total mortality rate in elderly Australians compared with Japanese. Some of this disease burden may be amenable to risk factor intervention.

6. Arrhythmia (Cardiac)

Preventative and curative options include:

CoQ10, Perilla oil, flax oil, fish oil, Magnesium citrate, Potassium, Selenium, Acetyl-L-carnitine, Vitamin D3, Vitamin E, Calcium, Garlic, Ginkgo biloba, Olive leaf extract, Taurine, Thiamine, Tocotrienols, Vitamin E.

Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action

Nair S.S.D.; Leitch J.W.; Falconer J.; Garg M.L.
Australia
Journal of Nutrition (USA), 1997, 127/3 (383-393)

The role of marine fish oil (n-3) polyunsaturated fatty acids in the prevention of fatal ventricular arrhythmia has been established in experimental animals. Prevention of arrhythmias arising at the onset of ischemia and reperfusion is important because if untreated, they result in sudden cardiac death. Animals supplemented with fish oils in their diet developed little or no ventricular fibrillation after ischemia was induced. Similar effects have also been observed in cultured neonatal cardiomyocytes. Several mechanisms have been proposed and studied to explain the antiarrhythmic effects of fish oil polyunsaturated fatty acids, but to date, no definite mechanism has been validated. The sequence of action of these mechanisms and whether more than one mechanism is involved is also not clear. Some of the mechanisms suggested to explain the antiarrhythmic action of fish oils include the incorporation and modification of cell membrane structure by (n-3) polyunsaturated fatty acids, their direct effect on calcium channels and cardiomyocytes and their role in eicosanoid metabolism. Other mechanisms that are currently being investigated include the role of (n-3) polyunsaturated fatty acids in cell signalling mediated through phosphoinositides and their effect on various enzymes and receptors. This article reviews these mechanisms and the antiarrhythmic studies using (n-3) polyunsaturated fatty acids.

Fatty acids suppress voltage-gated Na+ currents in HEK293t cells transfected with the alpha-subunit of the human cardiac Na+ channel

Xiao Y.-F.; Wright S.N.; Ging Kuo Wang; Morgan J.P.; Leaf A.
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Proceedings of the National Academy of Sciences of the United States of America (United States), 1998, 95/5 (2680-2685)

Studies have shown that fish oils, containing n-3 fatty acids, have protective effects against ischemia-induced, fatal cardiac arrhythmias in animals and perhaps in humans. In this study we used the whole-cell voltage- clamp technique to assess the effects of dietary, free long-chain fatty acids on the Na+ current (I(Na,alpha)) in human embryonic kidney (HEK293t) cells transfected with the alpha-subunit of the human cardiac Na+ channel (hH1(alpha)). Extracellular application of 0.01 to 30 microM eicosapentaenoic acid (EPA, C20:5n-3) significantly reduced I(Na,alpha) with an IC50 of 0.51 plus or minus 0.06 microM. The EPA-induced suppression of I(Na,alpha) was concentration- and voltage- dependent. EPA at 5 microM significantly shifted the steady-state inactivation relationship by -27.8 plus or minus 1.2 mV ($n = 6$, $P < 0.0001$) at the V(one-quarter) point. In addition, EPA blocked I(Na,alpha) with a higher 'binding affinity' to hH1(alpha) channels in the inactivated state than in the resting state. The transition from the resting state to the inactivated state was markedly accelerated in the presence of 5 microM EPA. The time for 50% recovery from the inactivation state was significantly slower in the presence of 5 microM EPA, from 2.1 plus or minus 0.8 ms for control to 34.8 plus or minus 2.1 ms ($n = 5$, $P < 0.001$). The effects of EPA on I(Na,alpha) were reversible. Furthermore, docosahexaenoic acid (C22:6n-3), alpha- linolenic acid (C18:3n-3), conjugated linoleic acid (C18:2n-7), and oleic acid (C18:1n-9) at 5 microM and all-trans-retinoic acid at 10 microM had similar effects on I(Na,alpha) as EPA. Even 5 microM of stearic acid (C18:0) or palmitic acid (C16:0) also significantly inhibited I(Na,alpha). In contrast, 5 *p EPA ethyl ester did not alter I(Na,alpha) (8 plus or minus 4%, $n = 8$, $P > 0.05$). The present data demonstrate that free fatty acids suppress I(Na,alpha) with high 'binding affinity' to hH1(alpha) channels in the inactivated state and prolong the duration of recovery from inactivation.

n-3 Polyunsaturated fatty acids, heart rate variability and ventricular arrhythmias in patients with previous myocardial infarcts

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Ugeskrift for Laeger (Denmark), 1997, 159/37 (5525-5529)

There is evidence for an antiarrhythmic effect of n-3 polyunsaturated fatty acids (n-3 PUFA) in animals. The aim of the present study was to investigate the effect of dietary n-3 PUFA on ventricular arrhythmias and heart rate variability (HRV) in patients with a previous myocardial infarction. Fifty-five patients were randomized to receive either 5.2 g of n-3 PUFA daily for 12 weeks or placebo in a double blind, placebo-controlled study. Prior to randomization a 24-hour Holter recording was obtained, and this was repeated at the end of the study. The major end-points were the number of ventricular extrasystoles (VE)/24 hours and the 24-hour HRV. A non-significant decrease in VE/24 hours was found in both the n-3 PUFA group and among controls after dietary supplementation, whereas HRV significantly increased after n-3 PUFA compared to both baseline values (p =

0,04) and to controls (p = 0,01). The present study therefore supports the hypothesis that n-3 PUFA may have an antiarrhythmic effect in humans.

Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarct survival - 4

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In a randomized, placebo-controlled trial, the effects of treatment with fish oil (eicosapentaenoic acid, 1.08 g/day) and mustard oil (alpha-linolenic acid, 2.9 g/day) mere compared for 1 year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with suspected acute myocardial infarction (AMI). Treatments were administered about (mean) 18 hours after the symptoms of AMI in all three groups. The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study. After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.

omega3 fatty acids in the prevention-management of cardiovascular disease

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Epidemiologic studies show that populations who eat fish versus those who do not have a reduced death rate from cardiovascular disease. Experimental studies have shown that omega-3 fatty acids affect the function of cells involved in atherothrombosis in numerous ways, including the modification of eicosanoid products in the cyclooxygenase and lipoxygenase pathways, the reduced synthesis of cytokines and platelet-derived growth factor, and alterations of leukocyte and endothelial cell properties. Intervention studies in patients with restenosis, myocardial infarction, and cardiac arrhythmias with omega-3 fatty acid supplementation have been addressed in several clinical studies. The ingestion of omega-3 fatty acids following one episode of myocardial infarction appears to decrease the rate of cardiac death. These effects of omega-3 fatty acids appear to be due to their antiarrhythmic properties. In fact, fish oil has been shown to reduce ventricular arrhythmias and to be more beneficial than currently used pharmacologic agents. The dose, duration, and mechanisms involved in the prevention and management of cardiovascular disease following omega-3 fatty acid ingestion or supplementation need to be investigated by double blind controlled clinical trials.

Omega-3 fatty acids and prevention of cardiovascular disease

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Cahiers de Nutrition et de Dietetique (France), 1997, 32/2 (107-114)

Most of the cardio-vascular disease (CVD) risk factors may be controlled by nutrition. Polyunsaturated fatty acids (PUFA) of the omega3 series are known for their beneficial effect on risk, but could also influence the CVD severity through their action on the heart, very sensitive to diet-induced alterations of membrane composition. Introducing omega3 PUFA in the diet results in an inversion of the AA/DHA ratio, mainly due to an increase in DHA content. In several experimental models, such structural changes were reported to affect cardiac functions. Arrhythmia which occurs during ischemia and reperfusion, is largely reduced when the membrane contains 20% DHA. Moreover, the membrane omega3 PUFA appear to increase energy utilization efficiency. This may be related to the positive effect of fish oil on the decrease of heart rate in rat in vivo, and on the recovery of mitochondrial function in the post-ischemic heart. At a more cellular level, the omega3 PUFAs (particularly DHA) can influence the activity of phospholipase A2, which contributes to membrane homeostasis, the prostaglandin production or the function of adrenergic receptors, a key system in the regulation of cardiac activity. Quite similar effects were reported in pathological conditions since the presence of omega3 PUFAs in the membranes enhances the cellular recovery after hypoxia and blocks the stimulation of prostacycline synthesis induced by post-hypoxic reoxygenation. However, much research remains to be done, in order to understand the interactions between diet-induced membrane alterations and cardiac physiology, pathology, and pharmacology.

Vitamin E analogues reduce the incidence of ventricular fibrillations and scavenge free radicals

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Fundamental and Clinical Pharmacology (France), 1998, 12/2 (164-172)

The aim of our study was to analyse the protective effects of different alpha-tocopherol analogues 1) against fibrillations induced by an ischemia-reperfusion sequence, and 2) to further investigate in vitro the radical scavenging properties of these analogues by two sensitive methods. Concerning 1: isolated rat hearts underwent 10 min of coronary ligation followed by reperfusion and the alpha-tocopherol analogues were infused 15 min before occlusion. Functional parameters including heart rate and fibrillations were recorded. Concerning 2: the beta-phycoerythrin assay was utilised to determine the oxygen radical absorbing capacity: (ORAC) of these vitamin E analogues against peroxyl radicals. Electron paramagnetic resonance (EPR) was used to measure their scavenger abilities on hydroxyl radical and superoxide anion production. Concerning 1: ventricular fibrillation times were reduced for all analogues treated hearts at concentrations of 1 microM and 5 microM, with Trolox being the most efficacious. Concerning 2: in our experimental conditions of intense production of free radicals, scavenging IC50 values for hydroxyl radical were 1.15, 2.17 and 4.04 mM for Trolox, MDL 74270 and MDL 74366 respectively. Superoxide anion IC50 values were 1.0 and 6.75 mM for Trolox and MDL 74270. Our results show that water-soluble analogues of vitamin E are effective in the prevention of coronary ligation induced reperfusion arrhythmia under our experimental conditions. Moreover, our data demonstrate that these vitamin E analogues are effective scavengers for a variety of radicals. Our studies support the view that compounds that can either inhibit the formation or scavenge free radicals can protect the heart against arrhythmia associated with ischemia-reperfusion.

Antioxidant activity of U-83836E, a second generation lazaroid, during myocardial Ischemia/Reperfusion injury

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Free Radical Research (United Kingdom), 1997, 27/6 (577-590)

The 21-aminosteroid compounds are potent lipid per oxidation inhibitors belonging to a new class of antioxidants given the collective name of 'lazaroids'. They protect cells from oxidative damage induced by oxygen-based free radicals in a variety of in vitro and in vivo test systems. U-83836E is one of the second-

generation lazaroids that are based on a non steroidal structure characterized by a ring portion of alpha-tocopherol bonded with various amine groups. We investigated the ability of U-83836E to reduce myocardial damage in rats undergoing left coronary artery occlusion for 60 min followed by 6 hours of reperfusion. This ischemia/reperfusion model produced wide heart necrosis, membrane lipid peroxidation, ventricular arrhythmias, tissue neutrophil infiltration and a marked decrease in endogenous antioxidants. Intravenous administration of U-83836E, (7.5, 15 and 30 mg/kg) at onset of reperfusion, reduced myocardial necrosis, expressed as a percentage of either the area at risk or the total left ventricle ($p < 0.001$), improved haemodynamic conditions by decreasing ventricular arrhythmias ($p < 0.005$), limited membrane lipid peroxidation (evaluated by assessing conjugated dienes, $p < 0.001$; and 4-hydroxy-nonenal, $p < 0.001$) restored the endogenous antioxidants vitamin E ($p < 0.001$), and superoxide dismutase ($pt < 0.001$). Furthermore, the lazaroid inhibited the derimental hydroxyl radical formation ($p < 0.001$), evaluated indirectly by a trapping agent and reduced heart neutrophil infiltration, measured by testing cardiac tissue elastase ($p < 0.001$) that is released from the stimulated granulocytes at the site of injury. These data suggest that this compound could be a new useful tool to study the mechanisms of oxidative damage during myocardial infarction.

Trace elements and cardioprotection: Increasing endogenous glutathione peroxidase activity by oral selenium supplementation in rats limits reperfusion-induced arrhythmias

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Journal of Trace Elements in Medicine and Biology (Germany), 1998, 12/1 (28-38)

Oxyradicals have been implicated as a possible cause of reperfusion- arrhythmias (RA). However, the use of diverse exogenous oxyradical scavengers designed to reduce RA has given contradictory results. The aim of the present study was to determine whether enhancing the activity of the main endogenous enzyme involved in peroxide elimination in cardiac cells, namely glutathione peroxidase, may limit RA in isolated heart preparations by increasing their antioxidant status. For this purpose, a group of 15 male Wistar rats received a selenium enriched diet for ten weeks (1.5 mg Se/kg diet). Control animals (n=15) received a standard diet containing 0.05 mg Se/kg diet. The incidence of early ventricular arrhythmias was investigated during the reperfusion period following 10 min regional ischemia induced ex-vivo by left coronary artery ligation. Our results show that selenium-supplementation significantly increased the global selenium status of the animals. In the isolated heart preparations, the selenium supplementation induced a significant reduction of the severity of RA as assessed by the arrhythmia score and the limitation of the incidence of both ventricular tachycardia (control: 91% vs, selenium: 36%, $p<0.05$) and irreversible ventricular fibrillation (control: 45%

vs selenium: 0%, p<0.05). These effects were associated with a significant increase in cardiac mitochondrial and cytosolic glutathione peroxidase activities in both the left and the right ventricles. These results illustrate the potential protective effect of selenium against ischemia- reperfusion injury and suggest that peroxides might play a key role in the genesis of some aspects of the reperfusion syndrome.

Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction

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Cardiovascular Drugs and Therapy (United States), 1998, 12/4 (347-353)

The effects of oral treatment with coenzyme Q10 (120 mg/d) were compared for 28 days in 73 (intervention group A) and 71 (placebo group B) patients with acute myocardial infarction (AMI). After treatment, angina pectoris (9.5 vs. 28.1), total arrhythmias (9.5% vs. 25.3%), and poor left ventricular function (8.2% vs. 22.5%) were significantly ($P < 0.05$) reduced in the coenzyme and group than placebo group. Total cardiac events, including cardiac deaths and nonfatal infarction, were also significantly reduced in the coenzyme Q10 group compared with the placebo group (15.0% vs. 30.9%, $P < 0.02$). The extent of cardiac disease, elevation in cardiac enzymes, and oxidative stress at entry to the study were comparable between the two groups. Lipid peroxides, diene conjugates, and malondialdehyde, which are indicators of oxidative stress, showed a greater reduction in the treatment group than in the placebo group. The antioxidants vitamin A, E, and C and beta-carotene, which were lower initially after AMI, increased more in the coenzyme Q10 group than in the placebo group. These findings suggest that coenzyme Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of the onset of symptoms. More studies in a larger number of patients and long-term follow-up are needed to confirm our results.

Effect of coenzyme Q10 therapy in patients with congestive heart failure: A long-term multicenter randomized study

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The improved cardiac function in patients with congestive heart failure treated with coenzyme Q10 supports the hypothesis that this condition is characterized by mitochondrial dysfunction and energy starvation, so that it may be ameliorated by coenzyme Q10 supplementation. However, the main clinical problems in patients with congestive heart failure are the frequent need of hospitalization and the high

incidence of life-threatening arrhythmias, pulmonary edema, and other serious complications. Thus, we studied the influence of coenzyme Q10 long-term treatment on these events in patients with chronic congestive heart failure (New York Heart Association functional class III and IV) receiving conventional treatment for heart failure. They were randomly assigned to receive either placebo (n = 322, mean age 67 years, range 30-88 years) or coenzyme Q10 (n = 319, mean age 67 years, range 26-89 years) at the dosage of 2 mg/kg per day in a 1-year double-blind trial. The number of patients who required hospitalization for worsening heart failure was smaller in the coenzyme Q10 treated group (n = 73) than in the control group (n = 118, $P < 0.001$). Similarly, the episodes of pulmonary edema or cardiac asthma were reduced in the control group (20 versus 51 and 97 versus 198, respectively; both $P < 0.001$) as compared to the placebo group. Our results demonstrate that the addition of coenzyme Q10 to conventional therapy significantly reduces hospitalization for worsening of heart failure and the incidence of serious complications in patients with chronic congestive heart failure.

Serum concentration of lipoprotein(a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role.

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Int J Cardiol 1999 Jan;68(1):23-9

OBJECTIVE: To examine the effect of coenzyme Q10 supplementation on serum lipoprotein(a) in patients with acute coronary disease.

STUDY DESIGN: Randomized double blind placebo controlled trial.

SUBJECTS AND METHODS: Subjects with clinical diagnosis of acute myocardial infarction, unstable angina, angina pectoris (based on WHO criteria) with moderately raised lipoprotein(a) were randomized to either coenzyme Q10 as Q-Gel (60 mg twice daily) (coenzyme Q10 group, n=25) or placebo (placebo group, n=22) for a period of 28 days.

RESULTS: Serum lipoprotein(a) showed significant reduction in the coenzyme Q10 group compared with the placebo group (31.0% vs 8.2% $P<0.001$) with a net reduction of 22.6% attributed to coenzyme Q10. HDL cholesterol showed a significant increase in the intervention group without affecting total cholesterol, LDL cholesterol, and blood glucose showed a significant reduction in the coenzyme Q10 group. Coenzyme Q10 supplementation was also associated with significant reductions in thiobarbituric acid reactive substances, malon/dialdehyde and diene conjugates, indicating an overall decrease in oxidative stress.

CONCLUSION: Supplementation with hydrosoluble coenzyme Q10 (Q-Gel) decreases lipoprotein(a) concentration in patients with acute coronary disease.

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects.

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Proc Natl Acad Sci U S A 1998 Jul 21;95(15):8892-7

Coenzyme Q10 is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Feeding with coenzyme Q10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of coenzyme Q10 resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q10 increases both brain and brain mitochondrial concentrations. They provide further evidence that coenzyme Q10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.

Magnesium in supraventricular and ventricular arrhythmias

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The use of magnesium as an antiarrhythmic agent in ventricular and supraventricular arrhythmias is a matter of an increasing but still controversial discussion during recent years. With regard to the well established importance of magnesium in experimental studies for preserving electrical stability and function of myocardial cells and tissue, the use of magnesium for treating one or the other arrhythmia seems to be a valid concept. In addition, magnesium application represents a physiologic approach, and by this, is simple, cost-effective and safe for the patient. However, when one reviews the available data from controlled studies on the antiarrhythmic effects of magnesium, there are only a few types of diac arrhythmias, such as torsade de pointes, digitalis-induced ventricular arrhythmias and ventricular arrhythmias occurring in the presence of heart failure or during the perioperative state, in which the antiarrhythmic benefit of magnesium has been shown and/or established. Particularly in patients with one of these types of cardiac arrhythmias, however, it should be realized that preventing the patient from a magnesium deficit is the first, and the application of magnesium the second best strategy to keep the patient free from cardiac arrhythmias.

Effect of intravenous magnesium sulfate on cardiac arrhythmias in critically III patients with low serum ionized magnesium

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Magnesium affects cardiac function, although until the recent development of a new ion selective electrode no method existed for measuring the physiologically active form of magnesium, free ions (iMg2+), in the blood. We investigated the antiarrhythmic effect of magnesium sulfate administered to critically ill patients with cardiac arrhythmias and reduced iMg2+ as determined using the ion-selective electrode. Eight patients with a low iMg2+ level (less than 0.40 mmol/L) were given intravenous magnesium sulfate (group L). Magnesium sulfate was also administered to patients with a normal iMg2+ level (more than 0.40 mmol/L) but who did not respond to conventional antiarrhythmic drugs (group N). Intravenous magnesium sulfate significantly increased the iMg2+ level in patients in group L from 0.35plus or minus0.06 mmol/L (mean plus or minus SD) to 0.54 plus or minus 0.09 mmol/L ($p<0.01$), and had an antiarrhythmic effect in 7 of the 8 patients (88%). However, in group N patients, intravenous magnesium sulfate had an antiarrhythmic effect in only 1 of the 6 patients (17%) ($p<0.05$ vs group L). These results suggest that intravenous magnesium sulfate may be effective in the acute management of cardiac arrhythmias in patients with a low serum iMg2+ level.

Prophylactic effects of taurine and diltiazem, alone or combined, on reperfusion arrhythmias in rats

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Acta Pharmacologica Sinica (China), 1996, 17/2 (122-124)

Aim: To study the effects of taurine (Tau) and diltiazem (Dil), alone or in combination, on reperfusion arrhythmias in anesthetized rats.

Methods: The arrhythmias were produced by coronary artery ligation for 15 min followed by reperfusion. Malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were measured by thiobarbituric acid fluorescence assay and colorimetric determination.

Results: Taurine 70 mg . kg-1 in combination with Dil 1 mg . kg-1 were more effective on prevention of the reperfusion arrhythmias than each drug alone. The combination of both drugs not only decreased the content of MDA, but also increased the activity of SOD in reperfusion myocardium.

Conclusion: The inhibition of lipoperoxides formation as well as the inhibition of the calcium influx was involved in the anti-arrhythmic effect of both taurine and diltiazem.

The cardiovascular protective role of docosahexaenoic acid

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Dietary fish oils rich in n-3 polyunsaturated fatty acids can modulate a diverse range of factors contributing to cardiovascular disease. This study examined the relative roles of eicosapentaenoic acid (20:5 n-3; EPA) and docosahexaenoic acid (22:6 n-3; DHA) which are the principal n-3 polyunsaturated fatty acids regarded as candidates for cardioprotective actions. At low dietary intakes (0.4-1.1% of energy (%en)), docosahexaenoic acid but not eicosapentaenoic acid inhibited ischaemia-induced cardiac a rrhythmias. At intakes of 3.9-10.0%en, docosahexaenoic acid was more effective than eicosapentaenoic acid at retarding hypertension development in spontaneously hypertensive rats (SHR) and inhibiting thromboxane-like vasoconstrictor responses in aortas from SHR. In stroke-prone SHR with established hypertension, docosahexaenoic acid (3.9-10.0%en) retarded the development of salt-loading induced proteinuria but eicosapentaenoic acid alone was ineffective. The results demonstrate that purified n-3 polyunsaturated fatty acids mimic the cardiovascular actions of fish oils and imply that docosahexaenoic acid may be the principal active component conferring cardiovascular protection.

Trace elements in prognosis of myocardial infarction and sudden coronary death

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Ca, Cu, Mg, Mn, and Zn concentrates were measured in plasma, RBC, and hair of 350 men aged 40-59 years with myocardial infarction (MI) and/or who died from sudden cardiac death (SCD), as compared with normal controls. Analyses were done by flame atomic absorption spectrophotometry. Cu in plasma of MI patients was significantly higher than the controls'. Plasma Mn was significantly lower in SCD than in MI subjects. No other consistent and significant changes were observed. Past and present evidence indicates that high plasma Cu levels may be associated with heart failure and rhythm disorders. The low plasma Mn levels may be an indicator of decreased parasympathetic tonus thus favouring

myocardial desynchronization and A-V block. Cu inhibits phosphodiesterase activity and Mn inhibits andenylate cyclase activity thus exerting an influence on the contractility of cardiomyocites and of smooth muscle cells in coronary arteries. Cu and Mn analyses may thus have a prognostic significance for MI and SCD.

Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action

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Journal of Nutrition (USA), 1997, 127/3 (383-393)

The role of marine fish oil (n-3) polyunsaturated fatty acids in the prevention of fatal ventricular arrhythmia has been established in experimental animals. Prevention of arrhythmias arising at the onset of ischemia and reperfusion is important because if untreated, they result in sudden cardiac death. Animals supplemented with fish oils in their diet developed little or no ventricular fibrillation after ischemia was induced. Similar effects have also been observed in cultured neonatal cardiomyocytes. Several mechanisms have been proposed and studied to explain the antiarrhythmic effects of fish oil polyunsaturated fatty acids, but to date, no definite mechanism has been validated. The sequence of action of these mechanisms and whether more than one mechanism is involved is also not clear. Some of the mechanisms suggested to explain the antiarrhythmic action of fish oils include the incorporation and modification of cell membrane structure by (n-3) polyunsaturated fatty acids, their direct effect on calcium channels and cardiomyocytes and their role in eicosanoid metabolism. Other mechanisms that are currently being investigated include the role of (n-3) polyunsaturated fatty acids in cell signalling mediated through phosphoinositides and their effect on various enzymes and receptors. This article reviews these mechanisms and the antiarrhythmic studies using (n-3) polyunsaturated fatty acids.

Exposure to the n-3 polyunsaturated fatty acid docosahexaenoic acid impairs alpha1-adrenoceptor-mediated contractile responses and inositol phosphate formation in rat cardiomyocytes

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Naunyn-Schmiedeberg's Archives of Pharmacology (Germany), 1996, 354/2 (109-119)

The beneficial effects of n-3 polyunsaturated fatty acids of fish oil in the prevention of fatal arrhythmias in myocardial ischemia were suggested to be at

least in part mediated by a modulation of dihydropyridine-sensitive L-type calcium channels. As cardiac alpha1-adrenoceptor stimulation has been suggested to have no significant effect on L-type calcium channels, the aim of this study using cultured neonatal rat cardiomyocytes was to investigate whether chronic n-3 polyunsaturated fatty acid exposure may have an influence on alpha1-adrenoceptor-induced positive inotropic effects and induction of arrhythmias. Pretreatment of the rat cardiomyocytes for 3 days in the presence of the n-3 polyunsaturated fish oil-derived fatty acid docosahexaenoic acid (60 micromol/l) markedly decreased alpha1-adrenoceptor-stimulated increase in contraction velocity and induction of arrhythmias. The increase in contraction velocity of the cardiomyocytes induced by the beta-adrenoceptor agonist isoprenaline was also markedly reduced by the n-3 fatty acid pretreatment. Basal contractile amplitude and spontaneous beating frequency of the cardiomyocytes were not significantly altered by the docosahexaenoic acid exposure. The pretreatment of the rat cardiomyocytes for 3 days in the presence of docosahexaenoic acid (60 micromol/l) decreased alpha1-adrenoceptor-stimulat ed formation of the calcium-mobilizing second messenger IP3 and its metabolites IP2 and IP1 by 55%. The depression of IP3 formation by docosahexaenoic acid treatment was not mediated by a decreased uptake of myo-inositol into the cardiomyocytes nor by a decreased synthesis of phosphatidylinositol bisphosphate (PIP2), the substrate of phospholipase C. The level of glycerol-3-phosphate, an important substrate of the phosphoinositide cycle, was unaltered by the docosahexaenoic acid pretreatment. Receptor binding studies revealed that the dissociation constant and maximal binding capacity of the alpha1-adrenoceptor antagonist (3H)prazosin was unchanged by the n-3 polyunsaturated fatty acid exposure. beta-Adrenoceptor- and forskolin-stimulated adenylyl cyclase activities were not diminished by the docosahexaenoic acid pretreatment. Chronic exposure of the cardiomyocytes to the n-6 polyunsaturated fatty acid arachidon ic acid (60 micromol/l) did neither significantly alter alpha1-adrenoceptor-induced inositol phosphate formation nor alpha1-adrenoceptor-stimulated increase in contraction velocity. The results presented show that chronic n-3 polyunsaturated fatty acid pretreatment of rat cardiomyocytes leads to a marked impairment of alpha1-adrenoceptor-induced positive inotropic effects and induction of arrhythmias concomitant with a n-3 fatty acid-induced decrease in IP3 formation. This derangement of the phosphoinositide pathway by chronic n-3 fatty acid exposure may, thus, contribute to the beneficial effects of fish oil-derived fatty acids in the prevention of fatal arrhythmias in myocardial ischemia.

Selenium deficiency associated with cardiac dysfunction in three patients with chronic respiratory failure

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Japanese Journal of Thoracic Diseases (Japan), 1996, 34/12 (1406-1410)

We encountered three patients with chronic respiratory failure who had heart failure of cardiac arrhythmias and low levels of serum selenium. All three had

tracheostomies and had received long-term parenteral nutrition that had not included selenium. All three also had refractory cardiac dysfunction, which was manifested in edema, heart failure, and various tachycardias. We suspected that selenium deficiency had caused their cardiac dysfunction. Serum selenium concentrations were found to be much lower than normal in all three, so 100 microg/day of selenium was administered in addition to their tube feedings. Cardiac function improved after replacement of selenium. These cases show the need for preventing selenium deficiency in patients with chronic respiratory failure during long-term administration of parenteral nutrition.

Fish oil and other nutritional adjuvants for treatment of congestive heart failure

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Medical Hypotheses (United Kingdom), 1996, 46/4 (400-406)

Published clinical research, as well as various theoretical considerations, suggest that supplemental intakes of the 'metavitamins' taurine, coenzyme Q10, and L-carnitine, as well as of the minerals magnesium, potassium, and chromium, may be of therapeutic benefit in congestive heart failure. High intakes of fish oil may likewise be beneficial in this syndrome. Fish oil may decrease cardiac afterload by an antivasopressor action and by reducing blood viscosity, may reduce arrhythmic risk despite supporting the heart's beta-adrenergic responsiveness, may decrease fibrotic cardiac remodeling by impeding the action of angiotensin II and, in patients with coronary disease, may reduce the risk of atherothrombotic ischemic complications. Since the measures recommended here are nutritional and carry little if any toxic risk, there is no reason why their joint application should not be studied as a comprehensive nutritional therapy for congestive heart failure.

Evidence on the participation of the 3',5'-cyclic AMP pathway in the non-genomic action of 1,25-dihydroxy-vitamin D3 in cardiac muscle.

Selles J; Boland R
Mol Cell Endocrinol (Netherlands) Dec 1991, 82 (2-3) p229-35

Several studies have suggested that vitamin D plays a role in cardiovascular function. It has been recently shown that in vitro treatment of vitamin D-deficient chick cardiac muscle with physiological concentrations of 1,25-dihydroxy-vitamin D3 (1,25(OH)2D3) induces a rapid (1-10 min) increase of tissue 45Ca uptake which can be suppressed by Ca channel blockers. The hormone simultaneously stimulated heart microsomal membrane protein phosphorylation. Experiments were performed to investigate the existence of a relationship between these changes and to obtain information about the mechanism involved in 1,25(OH)2D3-induced modifications in cardiac protein phosphorylation.

Dibutyryl cyclic AMP (10 microM) and forskolin (10 microM), known activators of the cAMP pathway, produced time courses of changes in 45Ca uptake by chick heart tissue similar to 1,25(OH)2D3 (10(-10) M). Analogously to the hormone, the effects of both compounds were abolished by nifedipine (30 microM) and verapamil (10 microM). In agreement with these observations, 1,25(OH)2D3 significantly increased (34-70%) heart muscle cAMP levels within 1-10 min of treatment. In addition, 1,25(OH)2D3 and forskolin caused similar changes in cardiac microsomal membrane protein phosphorylation (e.g. stimulation in 43 kDa and 55 kDa proteins). These changes were also evidenced by direct exposure of isolated heart microsomes to 1,25(OH)2D3, suggesting a direct membrane action of the hormone. The fast effects of 1,25(OH)2D3 on dihydropyridine-sensitive cardiac muscle Ca uptake could be reproduced in primary-cultured myocytes isolated from chick embryonic heart. Furthermore, the effects of the hormone could be suppressed by a specific protein kinase A inhibitor. These results suggest that 1,25(OH)2D3 affect s heart cell calcium metabolism through regulation of Ca channel activity mediated by the cAMP pathway.

1,25(OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes.

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J Clin Invest (United States) Apr 1 1996, 97 (7) p1577-88

1,25(OH)2 Vitamin D3 (VD3) and retinoic acid (RA) function as ligands for nuclear receptors which regulate transcription. Though the cardiovascular system is not thought to represent a classical target for these ligands, it is clear that both cardiac myocytes and vascular smooth muscle cells respond to these agents with changes in growth characteristics and gene expression. In this study we demonstrate that each of these ligands suppresses many of the phenotypic correlates of endothelin-induced hypertrophy in a cultured neonatal rat cardiac ventriculocyte model. Each of these agents reduced endothelin-stimulated ANP secretion in a dose-dependent fashion and the two in combination proved to be more effective than either agent used alone (VD3: 49%; RA:52%; VD3 + RA:80% inhibition). RA, at concentrations known to activate the retinoid X receptor, and, to a lesser extent, VD3 effected a reduction in atrial natriuretic peptide, brain natriuretic peptide, and alpha-skeletal actin mRNA levels. Similar inhibition (VD3:30%; RA:33%; VD3 + RA:59% inhibition) was demonstrated when cells transfected with reporter constructs harboring the relevant promoter sequences were treated with VD3 and/or RA for 48 h. These effects were not accompanied by alterations in endothelin-induced c-fos, c-jun, or c-myc gene expression, suggesting either that the inhibitory locus responsible for the reduction in the mRNA levels lies distal to the activation of the immediate early gene response or that the two are not mechanistically coupled. Both VD3 and RA also reduced [3H]leucine incorporation (VD3:30%; RA:33%; VD3 + RA:45% inhibition) in endothelin-stimulated ventriculocytes and, once again, the combination of the two was more effective than either agent used in isolation.

Finally, 1,25(OH)2 vitamin D3 abrogated the increase in cell size seen after endothelin treatment. These findings suggest that the liganded vitamin D and retinoid receptors are capable of modulating the hypertrophic process in vitro and that agents acting through these or similar signaling pathways may be of value in probing the molecular mechanisms underlying hypertrophy.

[Effect of vitamin E deficiency on the development of cardiac arrhythmias as affected by acute ischemia]

Belkina LM; Arkhipenko IuV; Dzhaparidze LM; Saltykova VA; Meerson FZ
Biull Eksp Biol Med (USSR) Nov 1986, 102 (11) p530-2

Malonic dialdehyde content was increased by 53% in the myocardium of male Wistar rats (250-300 g) devoid of vitamin E for 2 months, as compared to the control rats (animals receiving an optimal amount of vitamin E). Transitory ischemia (10 min) with subsequent reoxygenation (5 min) was induced during open heart surgery under urethan anesthesia. Ischemia was induced by the occlusion of the descending branch of the left coronary artery. In ischemic rats with vitamin E deficiency the incidence of ventricular fibrillation, tachycardia, extrasystoles and the additive duration of arrhythmias were significantly increased as compared to the control.

Antioxidant protection against adrenaline-induced arrhythmias in rats with chronic heart hypertrophy.

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Can J Cardiol (Canada) Mar 1990, 6 (2) p71-4

Effects of vitamin E on adrenaline-induced arrhythmias were examined in rats with chronic heart hypertrophy subsequent to narrowing of the abdominal aorta. After 60 weeks of pressure overload, the rats showed an increase of about 21% in heart/body weight ratio and a small but significant rise in left ventricular end diastolic pressure (LVEDP) (sham control 1.7 +/- 0.67 mmHg; hypertrophy 7.1 +/- 2.7 mmHg) without any change in left ventricular peak systolic pressure (LVSP). Intravenous infusion of adrenaline caused rhythm disorders in a dose-dependent manner and pathological arrhythmias (occurrence of six premature ventricular complexes/min) were observed at doses of 2.9 +/- 0.6 and 3.8 +/- 1.0 micrograms/kg of the drug in control and hypertrophy animals, respectively. Administration of two doses of vitamin E (50 mg/kg intraperitoneally), given 24 h and 1 h before adrenaline infusion, significantly increased the amount of adrenaline required to produce pathological arrhythmias (control 8.0 +/- 3.0; hypertrophy 7.7 +/- 2.0 micrograms/kg). Vitamin E pretreatment did not have any detrimental effect on the pressure readings nor did it have any influence on

adrenaline-induced pressure changes. The data suggest that a combination therapy with vitamin E may allow therapeutic use of higher concentrations of adrenaline required to improve function in failing hearts with a reduced risk of arrhythmias

The antiarrhythmic effects of taurine alone and in combination with magnesium sulfate on ischemia/reperfusion arrhythmia

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Chinese Pharmacological Bulletin (China), 1994, 10/5 (358-362)

The effect of tauring (Taur) alone and in combination with magnesium sulfate (MgSO4) on ischemia/reperfusion arrhythmia was investigated. The arrhythmia as produced by coronary artery occlusion for 10 min followed by reperfusion. In addition, the present study also observed the effect of MgSO4 alone and in combination with Taur on hemodynamics. The results showed that Taur (50 mg . kg-1) and MgSO4 (25 mg . kg-1) had partly antiarrhythmic effect. Taur (100, 150mg. kg-1) MgSO4 (50, 100mg. kg-1) had significantly antiarrhythmic effect. Taur (50 mg. kg-1) combined with MgSO4 (25 mg. kg-1) shortened the duration of ventricular tachycardia (VT) more than that either drug did alone. The hypotensive effect of MgSO4 (25 mg. kg-1) was not increased by coadministration of Taur, but the myocardial oxygen consumption was reduced. These findings indicate that Taur in combination with MgSO4 is more effect on reperfusion arrhythmia, and that the mechanism of antiarrhythmic effect of Taur and MgSO4 may be involved in the effect of defence on myocardium.

The effects of antioxidants on reperfusion dysrhythmias

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Ceska a Slovenska Farmacie (Czech Republic), 1995, 44/5 (257-260)

The present study aims to investigate the effects of the lipophilic antioxidant Trolox C (a vitamin E analogue) and stobadine, a scavenger of free oxygen radicals, on reperfusion dysrhythmias. Experiments were performed on isolated perfused rat hearts subjected to global stop-flow ischaemia followed by reperfusion. Trolox C (10-4 mol.l-1) and stobadine (10-5 mol.l-1) were infused immediately prior to ischaemia. Trolox C (10-4 mol.l-1) and stobadine (10-5 mol.l-1) decreased the incidence and duration of reperfusion-induced dysrhythmias (quantified by the dysrhythmia score) in comparison to the ischaemic-reperfusion damaged hearts. There was an improvement in the recovery of contraction force and left ventricular diastolic pressure in Trolox or stobadine pretreated hearts. No significant changes in coronary flow resistance were observed. The results suggest that both substances protect the myocardium

during ischaemic-reperfusion injury probably by affecting the generation and activity of reactive oxygen species.

Protective effects of all-trans-retinoic acid against cardiac arrhythmias induced by isoproterenol, lysophosphatidylcholine or ischemia and reperfusion

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J Cardiovasc Pharmacol (United States) Dec 1995, 26 (6) p943-8

Previous studies have shown that free polyunsaturated fatty acids (PUFA) reduce the excitability of cardiac myocytes and exert antiarrhythmic effects. Therefore, we hypothesized that retinoic acid (RA, vitamin A acid), which has structural characteristics similar to those of PUFA, may have similar antiarrhythmic effects. To test this hypothesis, we used an isolated, spontaneously beating, neonatal rat cardiac myocyte preparation to examine the effects of RA, added to the perfusion solution, on the cell contraction and arrhythmias induced by isoproterenol (ISO) or lysophosphatidylcholine (LPC). All-trans-RA (10-20 microM) induced a marked and reversible reduction in the contraction rate of the cell in 2-5 min without changing the amplitude of the contractions. Superfusion of the myocytes with either ISO (3 microM) or LPC (5 microM) induced sustained tachyarrhythmias characterized by spasmodic contractures and fibrillation. Addition of 15-20 microM all-trans-RA to the perfusion solution effectively prevented as well as terminated the arrhythmias induced by ISO and LPC. Furthermore, in a whole-animal model of arrhythmia in which the left anterior descending coronary artery (LAD) of the anesthetized rat was occluded for 15 min followed by reperfusion, both the incidence and severity of ventricular tachycardia and fibrillation (VT, VF) were significantly reduced during the ischemic and reperfusion periods by intravenous infusion of all-trans-RA. In contrast, other analogues, including retinol and retinal, and other fat-soluble vitamins, including vitamin D, E, and K, did not have such effects. Our results demonstrate that all-trans-RA can produce antiarrhythmic effects similar to those of PUFA, suggesting a novel role of RA as a potential antiarrhythmic agent.

Effects of dietary supplementation with alpha-tocopherol on myocardial infarct size and ventricular arrhythmias in a dog model of ischemia-reperfusion

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J. Am. Coll. Cardiol. (USA), 1994, 24/6 (1580-1585)

Objectives. We investigated whether dietary supplementation with the antioxidant vitamin alpha-tocopherol (500 mg daily) might reduce lethal ventricular arrhythmias and infarct size.

Background. Previous studies suggested that dietary supplementation with alpha-tocopherol may be associated with a reduced risk of ischemic heart disease. However, the mechanism of this protection remains unknown.

Methods. Beagle dogs were randomized to either a supplemented or a control group. Because of the low mortality rate in the supplemented group, five dogs were added to the control group. After 2 months, dogs were anesthetized and underwent a 2-h coronary artery occlusion and 6-h reperfusion. Plasma vitamin E, retinol and malondialdehyde concentrations were assessed in all dogs.

Results. Fourteen dogs (11 of 25 control vs. 3 of 19 supplemented dogs, $p < 0.05$) developed ventricular fibrillation during either ischemia or reperfusion. Malondialdehyde concentrations were higher in dogs that subsequently developed arrhythmias (2.7 plus or minus 0.2 micromol/liter, mean plus or minus SEM) compared with dogs that did not (2.1 plus or minus 0.2 micromol/liter, $p = 0.03$). Among survivors with significant ischemia, infarct size was larger in supplemented ($n = 12$, 58.5 plus or minus 3.3% of area at risk) than in control ($n = 11$, 41.9 plus or minus 6.5%, $p < 0.04$) dogs. In addition, for a given collateral flow, supplemented dogs ($n = 16$) developed larger infarct size than control dogs ($n = 15$, $p < 0.001$, analysis of covariance).

Conclusions. The data suggest that dietary alpha-tocopherol supplementation prevented lethal ventricular arrhythmias associated with ischemia and reperfusion. However, its influence on infarct size and long-term prognosis warrants further inve stigation.

Magnesium flux during and after open heart operations in children.

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Ann Thorac Surg (United States) Apr 1995, 59 (4) p921-7

Hypomagnesemia and depletion of the body's magnesium stores is known to be associated with an increased incidence of both cardiac arrhythmias and neurological irritability. In a two-part prospective study we have evaluated whether magnesium deficiency is a significant occurrence in children treated in the intensive care unit after open heart operations, and subsequently have sought to identify how intraoperative metabolic changes were related to the resultant findings. In 41 children studied after operation the plasma magnesium concentration showed a significant decrease from 0.92 mmol/L (10th to 90th centile, 0.71 to 1.15 mmol/L) immediately after operation to 0.77 mmol/L (0.65 to

0.91 mmol/L) on the following morning. The subsequent change in grouped values was not significant but 14 (34.2%) and 7 (17.1%) possessed values of less than 0.7 mmol/L and 0.6 mmol/L, respectively. The occurrence of cardiac arrhythmias was not statistically related to the occurrence of hypomagnesemia. In 21 children perioperative changes in extracellular and tissue magnesium, potassium, and calcium content were measured. It was found that hemodilution with a prime low in magnesium caused a reduction from a median of 0.81 mmol/L to 0.61 mmol/L ($p < 0.01$). Plasma potassium level, however, was elevated from 3.7 mmol/L to 4.15 mmol/L ($p < 0.05$) and the ionized calcium content from 1.17 mmol/L (1.07 to 1.25 mmol/L) to 1.49 mmol/L (1.25 to 2.56 mmol/L) ($p = 0.0009$). The myocardial content of magnesium did not change significantly but skeletal muscle content was depleted from 6.75 mumol/g (2.85 to 8.35 mumol/g) to 5.65 mumol/g (2.45 to 7.2 mumol/g) ($p < 0.01$)

Sino-atrial Wenckebach conduction in thyrotoxic periodic paralysis: a case report.

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Int J Cardiol (Ireland) Jan 6 1995, 47 (3) p285-9

A 28-year-old male presented with thyrotoxic periodic paralysis. On admission to hospital the serum potassium level was 1.4 mmol/l. The ECG showed classical features of hypokalaemia. In addition, sino-atrial block with Wenckebach conduction was also present. With the normalization of the serum potassium, the ECG became completely normal and showed no evidence of any arrhythmia .

A possible beneficial effect of selenium administration in antiarrhythmic therapy.

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J Am Coll Nutr (United States) Oct 1994, 13 (5) p496-8

OBJECTIVE: The following review of the literature on the importance of Selenium (Se) in myocardial homeostasis and of the pharmacology of this trace metal, represents an attempt to search, without prejudice to other possible explanations, for a rationale of a beneficial effect of Se substitution as an adjuvant to antiarrhythmic therapy.

BACKGROUND: For several years, in the early 1980s, I had to deal with the problem of a serious ventricular arrhythmia (non-sustained and sustained ventricular tachycardia) which was remarkably resistant to a battery of the most potent antiarrhythmic agents. Eventually, dramatic improvement, lasting for a

period of 8 years, was achieved with Flecainide, which, however, left unsolved the episodic occurrence of disabling ventricular bigemini. Over the most recent period of 1 year and 8 months, there was a sudden and unexplained return to unbroken normal sinus rhythm. Among the multiplicity of possible reasons for this fortunate development, the concurrent introduction of Se substitution appeared as the most obvious, though very tentative explanation. Substitution of this trace metal preceded the extinction of ventricular bigemini by 1 week and actually represented the sole modification of otherwise reasonably standardized conditions of antiarrhythmic therapy, life style and diet. (25 Refs.)

Omega-3 fatty acids and prevention of ventricular fibrillation.

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Prostaglandins Leukot Essent Fatty Acids 1995 Feb-Mar;52(2-3):197-8

Interest in the potential cardiovascular benefits of omega-3 long chain polyunsaturated fatty acids has been largely focused on possible antiatherothrombotic effects. In addition, however, definitive antiarrhythmic effects of these dietary omega-3 fatty acids have been reported by Charnock & McLennan. Our studies commenced with the observation that two of these fatty acids, eicosapentaenoic (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA) prevented contracture and fibrillation of isolated neonatal cardiac myocytes when exposed to toxic levels of ouabain (0.1 mM). This protection was associated with prevention of excessively high intracellular calcium concentrations in the myocyte. Further, it was shown that these fatty acids modulate calcium currents through L-type calcium channels and that the effect occurs within a few minutes of adding EPA or DHA to the medium perfusing the cultured cardiac myocytes. Infusing an emulsion of the omega-3 fatty acids intravenously just prior to compression of a coronary artery in a conscious, prepared dog will prevent the expected subsequent ischemia-induced ventricular fibrillation. (9 Refs.)

An expanded concept of "insurance" supplementation--broad-spectrum protection from cardiovascular disease.

McCarty MF
Med Hypotheses (England) Oct 1981, 7 (10) p1287-1302

The preventive merits of "nutritional insurance" supplementation can be considerably broadened if meaningful doses of nutrients such as mitochondrial "metavitamins" (coenzyme Q, lipoic acid, carnitine), lipotropes, and key essential fatty acids, are included in insurance supplements. From the standpoint of cardiovascular protection, these nutrients, as well as magnesium, selenium, and GTF-chromium, appear to have particular value. Sophisticated insurance

supplementation would likely have a favorable impact on many parameters which govern cardiovascular risk--serum lipid profiles, blood pressure, platelet stability, glucose tolerance, bioenergetics, action potential regulation--and as a life-long preventive health strategy might confer substantial benefit. (111 Refs.)

Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure (interim analysis)

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Clin Investig (Germany) 1993, 71 (8 Suppl) pS145-9

Digitalis, diuretics, and vasodilators are considered standard therapy for patients with congestive heart failure, for which treatment is tailored according to the severity of the syndrome and the patient profile. Apart from the clinical seriousness, heart failure is always characterized by an energy depletion status, as indicated by low intramyocardial ATP and coenzyme Q10 levels. We investigated safety and clinical efficacy of coenzyme Q10 (CoQ10) adjunctive treatment in congestive heart failure, whi ch had been diagnosed at least 6 months previously and treated with standard therapy. A total of 2500 patients in NYHA classes II and III were enrolled in this open noncomparative 3-month postmarketing drug surveillance study in 173 Italian centers. The daily dose of CoQ10 was 50-150 mg orally, with the majority of patients (78%) receiving 100 mg/day. Clinical and laboratory parameters were evaluated at the entry into the study and on day 90; the assessment of clinical signs and symptoms was made using from two- to seven-point scales. Preliminary results on 1113 patients (mean age 69.5 years) show a low incidence of side effects: 10 adverse reactions were reported in 8 (0.8%) patients, of which only 5 reactions were considered as correlated to the test treatment. After 3 months of test treatment the proportions of patients with improvement in clinical signs and symptoms were as follows: cyanosis 81%, edema 76.9%, pulmonary rales 78.4%, enlargement of the liver area 49.3%, jugular reflux 81.5%, dyspnea 54.2%, palpitations 75.7%, sweating 82.4%, arrhythmia 62%, insomnia 60.2%, vertigo 73%, and nocturia 50.7%.

Isolated diastolic dysfunction of the myocardium and its response to CoQ10 treatment.

Langsjoen PH, Langsjoen PH, Folkers K
Clin Investig (Germany) 1993, 71 (8 Suppl) pS140-4

Symptoms of fatigue and activity impairment, atypical precordial pain, and cardiac arrhythmia frequently precede by years the development of congestive heart failure. Of 115 patients with these symptoms, 60 were diagnosed as having hypertensive cardiovascular disease, 27 mitral valve prolapse syndrome, and 28 chronic fatigue syndrome. These symptoms are common with diastolic

dysfunction, and diastolic function is energy dependent. All patients had blood pressure, clinical status, coenzyme Q10 (CoQ10) blood levels and echocardiographic measurement of diastolic function, systolic function, and myocardial thickness recorded before and after CoQ10 replacement. At control, 63 patients were functional class III and 54 class II; all showed diastolic dysfunction; the mean CoQ10 blood level was 0.855 micrograms/ml; 65%, 15%, and 7% showed significant myocardial hypertrophy, and 87%, 30%, and 11% had elevated blood pressure readings in hypertensive disease, mitral valve prolapse and chronic fatigue syndrome respectively. Except for higher blood pressure levels and more myocardial thickening in the hypertensive patients, there was little difference between the three groups. CoQ10 administration resulted in improvement in all; reduction in high blood pressure in 80%, and improvement in diastolic function in all patients with follow-up echocardiograms to date; a reduction in myocardial thickness in 53% of hypertensives and 36% of the combined prolapse and fatigue syndrome groups; and a reduced fractional shortening in those high at control and an increase in those initially low.(ABSTRACT TRUNCATED AT 250 WORDS)

Protective effects of propionyl-L-carnitine during ischemia and reperfusion.

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Cardiovasc Drugs Ther (United States) Feb 1991, 5 Suppl 1 p77-83

When cardiac function in isolated rat hearts was impaired by subjecting them to ischemia, subsequent perfusion with propionyl-L-carnitine and related compounds increased their rate of recovery. Thus at 11 mM, both propionyl-L-carnitine and, to a lesser extent, its taurine amide, and also acetyl-L-carnitine, significantly restored cardiac function in 15 minutes after 90 minutes of either low-flow or intermittent no-flow ischemia. Carnitine itself was ineffective. Propionyl-L-carnitine also increased tis sue ATP and creatine phosphate compared with controls, but did not affect the levels of long-chain acyl carnitine and coenzyme. These esters also depleted fatty acid peroxidation, as shown with malonaldehyde, and were more effective than carnitine in preventing the production of superoxide. In myocytes, propionyl-L-carnitine alone stimulated palmitate oxidation, but in rat heart homogenates, both L-carnitine and propionyl-L-carnitine did so, while acetyl-L-carnitine was actually inhibitory. Possible mechanisms for the protective action of propionyl-L-carnitine against ischemia include an increased rate of cellular transport, stimulation of fatty acid oxidation, and a reduction of free radical formation.

Community-based prevention of stroke: nutritional improvement in Japan

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Health Rep 1994;6(1):181-8

OBJECTIVES: (1) To demonstrate the importance of nutrition, especially sodium restriction and increased potassium and protein intakes, in the prevention of hypertension and stroke in a pilot study involving senior citizens. (2) To design a population-based intervention in the Shimane Prefecture of Japan concerning dietary factors such as low sodium and high potassium, protein, magnesium, calcium and dietary fibre in the prevention of stroke.

DESIGN AND METHODS: The intervention study was carried out at a senior citizens' residence and included general health education along with a reduction of dietary salt intake and increases in vegetable and protein, especially from seafood. Sixty-three healthy senior citizens (average age: 74.8 +/- 7.7 years) had their daily meals modified to a low sodium/potassium ratio for four weeks without their knowledge by the use of a potassium chloride substitute for salt, soy sauce and bean paste, which contains much less sodium and more potassium. Monosodium L-glutamate monohydrate used for cooking was changed to monopotassium L-glutamate monohydrate. Blood pressure was measured with the patient in the sitting position. Daily dietary sodium and potassium intakes were assessed by flame photometry from 24-hour urine specimens. Extensive intervention programs were introduced into the Shimane Prefecture, which has a population of 750,000, through health education classes for housewives, home visits by health nurses and an educational TV program for dietary improvement. The mortality from stroke was monitored for 10 years and compared with the average in Japan.

RESULTS: The blood pressure lowering effect of reducing the dietary sodium/potassium ratio was confirmed through a pilot intervention study at the senior citizens' resid ence. The mortality rates for stroke in the middle-aged population from the Shimane Prefecture during the 10 years after the introduction of dietary improvement had a steeper decline in hemorrhagic, ischemic and all strokes than the average for Japan.

Effect of dietary magnesium supplementation on intralymphocytic free calcium and magnesium in stroke-prone spontaneously hypertensive rats.

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Clin Exp Hypertens 1994 May;16(3):317-26

The effects of dietary magnesium (Mg) supplementation on intralymphocytic free Ca2+ ([Ca2+]i) and Mg2+ ([Mg2+]i) were examined in the stroke-prone spontaneously hypertensive rats (SHRSP) at the age of 10 weeks. After 40 day Mg supplementation (0.8% Mg in the diet), systolic blood pressure (SBP) was significantly lower in Mg supplemented group (Mg group) than the control group (0.2% Mg). [Ca2+]i was significantly lower and [Mg2+]i was significantly higher in Mg group than in the control group. Further, [Ca2+]i was positively and [Mg2+]i was negatively correlated with SBP. These results suggest that dietary Mg supplementation modifies [Ca2+]i and [Mg2+]i, and modulates the development of hypertension.

Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report)--antiarrhythmic action of coenzyme Q10 in diabetics.

Fujioka T, Sakamoto Y, Mimura G
Tohoku J Exp Med (Japan) Dec 1983, 141 Suppl p453-63

An investigation was undertaken to evaluate the antiarrhythmic effect of CoQ10 on VPBs using the Holter ECG, in 27 patients with no clinical findings of organic cardiopathies. As a result, the effect of CoQ10 on VPBs was considered beneficial in 6 (22%) of 27 cases, consisting of 1 patient with hypertension and 5 patients with DM. Even in the remaining 2 patients with DM, the frequency of VPBs was reduced by 50% or more during treatment with CoQ10. The mean reduction of VPBs frequency in the 5 responders plus these 2 patients with DM was 85.7%. These findings suggest that CoQ10 exhibits an effective antiarrhythmic action not merely on organic heart disease but also on VPBs supervening on DM.

Usefulness of coenzyme Q10 in clinical cardiology: a long-term study.

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Mol Aspects Med 1994;15 Suppl:s165-75

Over an eight year period (1985-1993), we treated 424 patients with various forms of cardiovascular disease by adding coenzyme Q10 (CoQ10) to their medical regimens. Doses of CoQ10 ranged from 75 to 600 mg/day by mouth (average 242 mg). Treatment was primarily guided by the patient's clinical response. In many instances, CoQ10 levels were employed with the aim of producing a whole blood level greater than or equal to 2.10 micrograms/ml (average 2.92 micrograms/ml, n = 297). Patients were followed for an average of 17.8 months, with a total accumulation of 632 patient years. Eleven patients were omitted from this study: 10 due to non-compliance and one who experienced nausea. Eighteen deaths occurred during the study period with 10 attributable to cardiac causes. Patients were divided into six diagnostic categories: ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), primary diastolic dysfunction (PDD), hypertension (HTN), mitral valve prolapse (MVP) and valvular heart disease (VHD). For the entire group and for each diagnostic category, we evaluated clinical response according to the New York Heart Association (NYHA) functional scale, and found significant improvement. Of 424 patients, 58 per cent improved by one NYHA class, 28% by two classes and 1.2% by three classes. A statistically significant improvement in myocardial function was documented using the following echocardiographic parameters: left ventricular wall thickness, mitral valve inflow slope and fractional shortening. Before treatment with CoQ10, most patients were taking from one to five cardiac medications. During this study, overall medication requirements dropped

considerably: 43% stopped between one and three drugs. Only 6% of the patients required the addition of one drug. No apparent side effects from CoQ10 treatment were noted other than a single case of transient nausea. In conclusion, CoQ10 is a safe and effective adjunctive treatment for a broad range of cardiovascular diseases, producing gratifying clinical responses while easing the medical and financial burden of multidrug therapy.

Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats.

Okamoto H, Kawaguchi H, Togashi H, Minami M, Saito H, Yasuda H
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Biochem Med Metab Biol 1991 Apr;45(2):216-26

To test the hypothesis that structural abnormalities exist in the kidney membrane of spontaneously hypertensive rats, we examined the effect of long-term administration of coenzyme Q10 on membrane lipid alterations in the kidney of stroke-prone spontaneously hypertensive rats (SHRSP). As compared with normotensive Wistar-Kyoto rats, renal membrane phospholipids, especially phosphatidylcholine and phosphatidylethanolamine, decreased and renal phospholipase A2 activity was enhanced with age in untreated SHRSP. Treatment with coenzyme Q10 attenuated the elevation of blood pressure, the membranous phospholipid degradation, and the enhanced phospholipase A2 activity. These results suggest that one factor contributing to the progress of hypertension is a structural membrane abnormality that alters the physical and functional properties of the cell membrane, and coenzyme Q10 might protect the renal membrane from damage due to hypertension in SHRSP.

Co-enzyme Q10: a new drug for cardiovascular disease.

Greenberg S, Frishman WH
Department of Medicine, Mt. Sinai Hospital and Medical Center, New York, New York.
J Clin Pharmacol 1990 Jul;30(7):596-608

Co-enzyme Q10 (ubiquinone) is a naturally occurring substance which has properties potentially beneficial for preventing cellular damage during myocardial ischemia and reperfusion. It plays a role in oxidative phosphorylation and has membrane stabilizing activity. The substance has been used in oral form to treat various cardiovascular disorders including angina pectoris, hypertension, and congestive heart failure. Its clinical importance is now being established in clinical trails worldwide.

[Effects of 2,3-dimethoxy-5-methyl-6-(10'-hydroxydecyl)-1,4-benzoquinone (CV-2619) on adriamycin-induced ECG abnormalities and myocardial energy metabolism in spontaneously hypertensive rats]

Shimamoto N, Tanabe M, Hirata M
Nippon Yakurigaku Zasshi 1982 Oct;80(4):307-15

Antidote actions of CV-2619 and ubiquinone-10 (Q-10) against adriamycin (ADM) cardiotoxicity were studied in spontaneously hypertensive rats. ADM (1 mg/kg/day, i.p.) elicited widening of the QRS complex in the ECG. The widening of the QRS complex was counteracted by a 10-day treatment with CV-2619 (10 and 30 mg/kg/day, p.o.) or Q-10 (10 mg/kg/day, p.o.), which was started on the 15th day of the ADM treatment. CV-2619 or Q-10, however, did not influence ADM-induced decrease in body and heart ventricular weights. Systemic hypotension caused by adriamycin was accelerated by CV-2619 or Q-10. The ADM treatment significantly decreased myocardial glycogen and glucose contents, while it did not affect the lactate content. Furthermore, ADM did not affect the myocardial content of adenine nucleotides, but significantly increased that of creatine phosphate. CV-2619 or Q-10 medication did not counteract changes in these contents by ADM. On the contrary, both agents decreased the lactate content and increased the phosphorylation potential, an index of myocardial energy state. In conclusion, CV-2619 might be as effective as Q-10 to protect the heart against ADM cardiotoxicity, and both test agents improved the myocardial energy state.

Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs.

Kishi H, Kishi T, Folkers K
Res Commun Chem Pathol Pharmacol 1975 Nov;12(3):533-40

Background data revealed that some American and Japanese patients with essential hypertension, including many who were not being treated with any anti-hypertensive drug, had a deficiency of coenzyme Q10. Eight clinically used anti-hypertensive drugs have now been tested for inhibition of two mitochondrial coenzyme Q10-enzymes of heart tissue, succinoxidase and NADH-oxidase. Diazoxide and propranolol significantly inhibited the CoQ10-succinoxidase and CoQ10-NADH-oxidase, respectively. Metoprolol did not inhibit succinoxidase, and was one-fourth as active as propranolol for inhibition of NADH-oxidase. Hydrochlorothiazide, hydralazine, ans clonidine also inhibited CoQ10-NADH-oxidase. Reserpine did not inhibit either CoQ10-enzyme, and methyldopa was a very eak inhibitor of succinoxidase. The internationally recognized clinical side-effects of propranolol may be due, in part, to inhibition of CoQ10-enzymes which are indispensable in the bioenergetics of cardiac function. A pre-existing deficiency of coenzyme Q10 in the myocardium of hypertensive patients could be augmented by subsequent treatment with propranolol, possibly to the "life-threatening" state described by others.

Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension.

Yamagami T, Shibata N, Folkers K
Res Commun Chem Pathol Pharmacol 1975 Jun;11(2):273-88

The specific activities (S.A.) of the succinate dehydrogenase-coenzyme Q10 (CoQ10) reductase of a control group of 65 Japanese adults and 59 patients having essential hypertension were determined. The mean S.A. of the hypertensive group was significantly lower (p less than 0.001) and the mean % deficiency of enzyme activity was significantly higher (p less than 0.001) than the values for the control group. These data on Japanese in Osaka agree with data on Americans in Dallas. Some patients showed no CoQ10-deficiency, and others showed definite deficiencies. Emphasizing the CoQ10-enzyme for patient selection, CoQ10 was administered to hypertensive patients. Four individuals showed significant but partial reductions of blood pressure. Monitoring the CoQ10-enzyme before, during, and after administration of CoQ10 indicated responses. The maintenance of high blood pressure could be primarily due to contraction of the arterial wall. Contraction or relaxation of an arterial wall is dependent upon bioenergetics, which also provide the energy for biosynthesis of angiotensin II, renin, aldosterone, and the energy for sodium and potassium transport. A clinical benefit from administration of CoQ10 to patients with essential hypertension could be based upon correcting a deficiency in bioenergetics, and point to possible combination treatments with a form of CoQ and anti-hypertensive drugs.

[Prevention of cerebrovascular insults]

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Schweiz Med Wochenschr 1994 Nov 12;124(45):1995-2004

Cerebrovascular infarction is the third leading cause of mortality following coronary heart disease and malignancies. WHO studies show that more than half of patients admitted for cerebrovascular infarction were not treated for hypertension. The risk factors for coronary heart disease and cerebrovascular infarction are not identical. Patients with systolic and diastolic hypertension, atrial fibrillation, stenosis of the carotid artery, and smoking, have a significantly elevated risk for cerebrovascular accidents. Hypercholesterolemia and diabetes are less important risk factors. Risk factors amendable by adequate nutritional intake are low supply of carotene and vitamin C. Homocysteineemia appears to be a risk factor that may be influenced by appropriate nutrition. Antihypertensive therapy is the most important primary and secondary preventive measure. No smoking and adequate dietary intake are also important. Primary prevention with low dose salicylic acid (ASA) is recommended in the presence of additional

cardiovascular risk factors. The benefit of low dose anticoagulant therapy in atrial fibrillation without symptoms is not fully established. In subjects with atrial fibrillation with cerebrovascular events anticoagulants are superior to ASA. Surgical treatment of significant stenosis of the carotid artery is indicated. In secondary prevention of thromboembolic events, low dose ASA is recommended. A valuable alternative in case of side effects is available in ticlopidine.

[Essential antioxidants in cardiovascular diseases--lessons for Europe]

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Ther Umsch 1994 Jul;51(7):475-82

Complementary epidemiological studies consistently reveal a substantially increased risk of cardiovascular disease (CVD) at suboptimal plasma levels of essential antioxidants in comparison with optimum ranges of vitamin C (> 50 mumol/l), of lipid-standardized vitamin E (> 30 mumol/l or a tocopherol/cholesterol ratio > 5.2 mumol/mmol), beta-carotene (> 0.4 mumol/l). The poor level of any single essential antioxidant can increase the risk, and the combination of suboptimal levels has additive or even overmultiplicative effects on the risk for CVD. Suboptimal antioxidant levels are stronger predictors of the severalfold regional differences of CVD in Europe than classical risk factor such as hypercholesterolemia, hypertension, etc. Scotsmen and Fins tend to suboptimal levels of essential antioxidants, whereas German-speaking regions may mostly reveal a fair vitamin E status, but at least one out of four subjects can reveal suboptimal levels of vitamin C and carotene, particularly in smokers. This deficit can be avoided by 'prudent diets' rich in fruits and vegetables as practiced by Frenchmen, Italians and Spaniards. The simultaneous correction of all suboptimal antioxidant levels appears to be a promising new means for CVD prevention, particularly in the northern parts of Europe. In the USA the risk of CVD could substantially be reduced without dietary modifications by voluntary daily supplements as follows: vitamin C > 140 mg, vitamin E > 100 IU (100 mg d,l- or 74 mg d-alpha-tocopherylacetate), and in current smokers by gamma-carotene > 8.6 mg. Hence, these antioxidants may be crucial constituents of diets rich in fruits and vegetables, which are by consensus associated with a lower risk of premature death from CVD (and cancer as well).

Antioxidant vitamin intake and coronary mortality in a longitudinal population study.

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Social Insurance Institution, Helsinki, Finland.
Am J Epidemiol 1994 Jun 15;139(12):1180-9

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of vitamin C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection.

The decline in stroke mortality. An epidemiologic perspective.

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Ann Epidemiol 1993 Sep;3(5):571-5

The evidence that treatment of hypertension prevents stroke is incontrovertible. Several observations, however, suggest that improvements in the prevalence of antihypertensive treatment cannot explain all of the recent decline in stroke mortality. Changes in nutritional patterns may explain some of the observed decline. Prospective studies have demonstrated conclusively an independent, increasing risk of hemorrhagic, but not thrombotic, stroke at higher levels of alcohol use. Stroke mortality is associated inversely with fat and protein intake. Dietary sodium has been linked to stroke in ecologic studies but not in prospective studies. Ecologic studies have suggested that foods high in vitamin C and potassium protect against stroke; an inverse association of potassium intake with fatal stroke has been demonstrated in cohort studies. Two studies in humans also suggest a protective effect of serum selenium against subsequent stroke. Determination of the influence of nutrients on stroke incidence offers tantalizing opportunities for future research and possibly, intervention.

Can antioxidants prevent ischemic heart disease?

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J Clin Pharm Ther 1993 Apr;18(2):85-95

Ischemic heart disease remains a major cause of mortality in developed countries. A number of important risk factors for the development of coronary atherosclerosis have been identified including hypertension, hypercholesterolaemia, insulin resistance and smoking. However, these factors can only partly explain variations in the incidence of ischaemic heart disease either between populations or within populations over time. In addition, population interventions based upon these factors have had little impact in the primary prevention of heart disease. Recent evidence suggests that one of the important mechanisms predisposing to the development of atherosclerosis is oxidation of the cholesterol-rich low-density lipoprotein particle. This modification accelerates its uptake into macrophages, thereby leading to the formation of the cholesterol-laden 'foam cell'. In vitro, low-density lipoprotein oxidation can be prevented by naturally occurring antioxidants such as vitamin C, vitamin E and beta-carotene. This article explores the evidence that these dietary anti-oxidants may influence the rate of progression of coronary atherosclerosis in vivo and discusses the need for formal clinical trials of antioxidant therapy.

Antioxidant therapy in the aging process.

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EXS 1992;62:428-37

A total of 1,265 patients with age-related diseases such as diabetes, arthritis, vascular disease and hypertension as well as 1,100 persons in diminished health without apparent disease, were treated with the metal chelator EDTA and antioxidants such as vitamin C, E, beta-carotene, selenium, zinc and chromium. Good results were observed in the majority of patients. This is encouraging for the initiation of controlled clinical trials.

7. Atherosclerosis

Preventative and curative options include:

- Vitamin E, vitamin C, folic acid, B vitamins, zinc, selenium, coenzyme Q10, green tea, ginkgo biloba, ginseng, bilberry, grape seed-skin, vitamin B12, vitamin B6, trimethylglycine (TMG), omega 3 fatty acids, garlic, chromium, copper, artichoke extract, niacin, ginger, curcumin, soy protein, pectins, guar, psyllium, taurine, DHEA.

The role of homocysteine, folate and other B-vitamins in the development of atherosclerosis.

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Arch Latinoam Nutr (Venezuela) Jun 1997, 47 (2 Suppl 1) p9-12

Recently, elevated homocysteine blood concentrations have been identified as an independent risk factor for the development of atherosclerotic lesions. The amino acid homocysteine is metabolized in the human body involving the vitamins folic acid, B12 and B6 as essential cofactors and coenzymes, respectively. There is an inverse relationship between the status of the relevant B-vitamins and the homocysteine blood concentration. Supplementation of these vitamins results in a significant reduction of the homocysteine level. Nutritive amounts seem to be sufficient to obtain this reduction, even in the case of elevated homocysteine levels. (18 Refs.)

Erythrocyte selenium-glutathione peroxidase activity is lower in patients with coronary atherosclerosis.

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Department of Biochemistry, School of Medicine, Akdeniz University, Arapsuyu, Antalya, Turkey.
Jpn Heart J (Japan) Nov 1997, 38 (6) p793-8

To obtain further insight into the role of erythrocyte antioxidant systems in the development of atherosclerosis, intraerythrocyte enzyme activities and selenium levels in erythrocytes were determined in 37 patients with angiographically proved coronary artery stenosis and 15 subjects with normal coronary angiograms as controls. In a preliminary study, the enzymatic activities of glucose-6-phosphate dehydrogenase (G6PD), glutathione reductase (GR) and selenium-dependent glutathione peroxidase (Se-GPx) were measured in both venous and arterial blood samples obtained from patients before angiography. The data of the preliminary study, which showed that only the Se-GPx decreased in the patients, led us to concentrate on the Se-GPx and Se levels to determine the changes in these variables. Our results showed that there was a decrease in both the activity of Se-GPx and Se levels in erythrocytes parallel to the increase in the severity of

coronary artery disease. It was concluded that these parameters might be used as determinants in the assessment of the severity of the disease.

Insulin sensitivity and intake of vitamins E and C in African American, Hispanic, and non-Hispanic white men and women: the Insulin Resistance and Atherosclerosis Study (IRAS).

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Am J Clin Nutr (United States) Nov 1997, 66 (5) p1224-31

Elevated fasting insulin concentrations and insulin resistance have been associated with non-insulin-dependent diabetes mellitus (NIDDM), obesity, atherosclerosis, and hypertension. Vitamin E supplementation in persons with and without NIDDM may be related to greater insulin sensitivity (SI). The cross-sectional associations of the intake of vitamins E and C with SI and insulin concentrations were evaluated among African American, Hispanic, and non-Hispanic white men and women with a wide spectrum of glucose tolerance included in the Insulin Resistance and Atherosclerosis Study (IRAS) (n = 1151). Insulin sensitivity was measured by minimal model analysis of a 12-sample, insulin-modified, frequently sampled intravenous glucose tolerance test. Nutrient intake (including vitamin supplement use) was assessed with a food-frequency questionnaire modified to include foods consumed by the three ethnic groups. Linear-regression models were used, including rank of SI and the log of fasting insulin as the outcome variables. Pearson correlation coefficients for vitamins E and C in relation to rank SI were r = 0.07 (P = 0.01) and r = 0.07 (P = 0.02), respectively. After adjustment for total energy and BMI these associations were no longer statistically significant and did not differ between ethnic groups. Results were similar when vitamins E and C were combined in categories of low and high antioxidant intake. Models replicated with log of fasting insulin as the outcome variable also did not produce significant associations with vitamins E or C. Thus, these cross-sectional analyses do not support the hypothesis of improved SI with increased intake of vitamins E and C.

Effects of malnutrition and atherosclerosis on the fatty acid composition of plasma phospholipids in the elderly.

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Ann Nutr Metab (Switzerland) 1997, 41 (3) p166-72

The fatty acid profiles of plasma phospholipids have been compared in 53 elderly subjects suffering from malnutrition (group U, 17 subjects) or from atherosclerosis (group A, 15 subjects). A control group was also included in the

study (group C, 21 subjects). Main differences were observed in phosphatidylcholine (PC). In group U, the proportion of monounsaturated fatty acids increased in PC, which was reflected by an increase in unsaturated fatty acids without significant modification of essential fatty acids. In group A, no major modification has been observed statistically, although the proportion of saturated fatty acids tended to increase.

The effect of dietary fat, antioxidants, and pro-oxidants on blood lipids, lipoproteins, and atherosclerosis

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Journal of the American Dietetic Association (USA), 1997, 97/7 Suppl. (S31-S41)

A number of primary and secondary prevention trials, including angiographic studies, have indicated that a decrease in dietary saturated fat and cholesterol produces a decrease in the blood levels of cholesterol and low-density lipoprotein (LDL) cholesterol, leading to a decrease in coronary artery disease (CAD). Increasing evidence indicates that the oxidation of LDL in human beings is atherogenic. Of the three major antioxidants, vitamin E, beta carotene, and vitamin C, the evidence is strongest that vitamin E (at a minimum dose of 100 IU/day) has a strong and independent inverse association with CAD. Selenium and flavonoids also have antioxidant properties, but their association with CAD in human beings is equivocal. Two prooxidants, homocysteine and iron, have been found to be associated with CAD. Blood homocysteine levels can be lowered significantly by an increase in dietary folic acid . Clinical trials are needed to assess expeditiously the effect of antioxidants, particularly vitamin E, and of folio acid on CAD and atherosclerosis. The substitution of monounsaturated fat for saturated fat lowers LDL and makes it less susceptible to oxidation without decreasing high-density lipoprotein (HDL) cholesterol. Studies in transgenic mice indicate that apolipoprotein A-I, the major protein of HDL, may inhibit the oxidation of LDL. Dietary trans fatty acids at the level consumed by many Americans can increase LDL cholesterol and may decrease HDL cholesterol. Individuals who have CAD or have family members who have premature CAD have delayed clearance of dietary fat, as judged by studies of postprandial triglyceride metabolism. The importance of decreasing dietary saturated fat and cholesterol is well established, but a number of other factors appear to influence the risk of CAD significantly and provide important areas nutrition for future investigation to improve prevention and treatment through better .

Role of the natural antioxidants in the prevention of atherosclerosis

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Farmacia Clinica (Spain), 1997, 14/1 (43-48)

Many chronic pathologies, including atherosclerotic disease, are connected physiopathologically with an increase in oxidative activity. Various studies have suggested that oxidative modification of the low density lipoproteins (LDL) is fundamental in atherogenesis. If we accept that some human diseases are associated with an imbalance between oxidative stress and antioxidant defence, it is possible, at least in theory, to limit this damage and retard development of the disease by supplementing the antioxidant mechanisms. Possible therapeutic interventions may include natural antioxidants or synthetic pharmacological agents. In this article we review the scientific evidence supporting the oxidative hypothesis of atherosclerosis and examine the results of the use of dietetic antioxidants to prevent and/or retard the atherosclerotic process.

Antioxidant content in low density lipoprotein and lipoprotein oxidation in vivo and in vitro

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Free Radical Research (United Kingdom), 1998, 29/2 (165-173)

Human blood contains naturally occurring multiple-modified low density Lipoprotein (nomLDL) capable of inducing the accumulation of cholesteryl esters in the cells of human aortic intima. NomLDL is desialylated particles of small size with an increased electronegative charge which can be separated from native low density lipoprotein (LDL) by lectin chromatography. The purpose of this study was to determine the content of antioxidants in native and nomLDL obtained from healthy subjects and from patients with coronary heart disease as well as to elucidate a possible relationship between the level of antioxidants and the degree of in vivo and in vitro LDL oxidizability. The apoB-bound cholesterol level in native and nomLDL of healthy subjects was 0.25 plus or minus 0.08 and 0.28 plus or minus 0.05 mol/mol apoB, respectively. The level of apoB-bound cholesterol in native LDL of coronary atherosclerosis patients showed no significant difference from that in healthy subjects' native lipoprotein. At the same time, the level of apoB-bound cholesterol in patients' nomLDL was 7-fold higher than in native LDL. The average duration of the lag phase of native LDL oxidation did not show a significant difference between the lipoprotein of healthy subjects and coronary atherosclerosis patients. The lag phase of nomLDL obtained from healthy subjects and patients was significantly shorter (3- and G-fold, respectively) than for their native LDL. The latter finding points to their increased susceptibility to in vitro oxidation. Oxidizability of total LDL preparations correlated positively with their nomLDL content. The content of all the antioxidants studied (coenzyme-Q10, alpha- and gamma-tocopherols, beta-carotene and lycopene) in nomLDL was 1.5- to 2-fold lower than in native LDL.

The level of apoB-bound cholesterol in nomLDL, correlated positively with the ubiquinone-l0 content and showed negative correlation with ubiquinol-l0 and beta-carotene levels. On the other hand, the content of apoB-bound cholesterol in native LDL correlated positively with the ubiquinol-l0 level. Susceptibility of nomLDL to in vitro oxidation exhibited negative correlation with alpha-tocopherol and beta-carotene levels and a positive correlation with the ubiquinone-l0 content. On the contrary, oxidizability of native LDL correlated positively with the ubiquinone-l0 level. Conclusions: (a) elevated apoB-bound cholesterol level in nomLDL of coronary atherosclerosis patients indicates that peroxidation of lipids occurs in vivo; (b) in vivo lipoperoxidation in nomLDL is corroborated by increased proportion of oxidized form of coenzyme-Q10; (c) content of lipid-soluble antioxidants in nomLDL is lower than in native lipoprotein; (d) nomLDL has a higher susceptibility to in vivtro oxidation than native LDL; (e) it is necessary to use isolated subfractions of native LDL and nomLDL, but not total lipoprotein preparations, to study the mechanisms of lipid peroxidation.

Are there protective environmental factors?

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Protective factors against atherosclerosis are a group of different elements which include the fatty acids, alcohol, antioxidant vitamins, dietary fibres and physical exercise. Unsaturated fatty acids, especially alpha-linolenicacid have a beneficial effect on the coronary vessels. Alpha-linolenic acid is associated with low coronary mortality both in cohort studies (the Seven Countries Study) and in secondary prevention (Lyon Diet Heart Study). There is an inverse relationship between moderate alcohol consumption and coronary artery disease with a reduction of risk of about 30% in all prospective studies. High dietary intake of vitamin E was found to be associated with a decreased coronary risk. On the other hand, dietary supplements of vitamin E in primary and secondary prevention were associated with increased cardiovascular mortality. Folates have a protective effect by their action on homocysteine metabolism. There is no formal proof at present in favour of the systematic introduction of the B vitamins in primary or secondary prevention. Fresh fruit and vegetables seem to be protective by their fibre and vitamin B content. Moderate endurance physical exercise is a protective factor in all studies. Its beneficial effects in function and rehabilitation are well documented. In primary prevention studies, exercise has a beneficial effect but criteria of duration and frequency remain vague. Therefore, there are environmental protective factors against atherosclerosis which allow physicians to introduce a positive note in these recommendations.

Functional food science and the cardiovascular system

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British Journal of Nutrition (United Kingdom), 1998, 80/Suppl. 1 (S113-S146)

Cardiovascular disease has a multifactorial aetiology, as is illustrated by the existence of numerous risk indicators, many of which can be influenced by dietary means. It should be recalled, however, that only after a cause-and-effect relationship has been established between the disease and a given risk indicator (called a risk factor in that case), can modifying this factor be expected to affect disease morbidity and mortality. In this paper, effects of diet on cardiovascular risk are reviewed, with special emphasis on modification of the plasma lipoprotein profile and of hypertension. In addition, dietary influences on arterial thrombotic processes, immunological interactions, insulin resistance and hyperhomocysteinaemia are discussed. Dietary lipids are able to affect lipoprotein metabolism in a significant way, thereby modifying the risk of cardiovascular disease. However, more research is required concerning the possible interactions between the various dietary fatty acids, and between fatty acids and dietary cholesterol. In addition, more studies are needed with respect to the possible importance of the postprandial state. Although in the aetiology of hypertension the genetic component is definitely stronger than environmental factors, some benefit in terms of the development and coronary complications of atherosclerosis in hypertensive patients can be expected from fatty acids such as alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. This particularly holds for those subjects where the hypertensive mechanism involves the formation of thromboxane A2 and/or alpha1-adrenergic activities. However, large-scale trials are required to test this contention. Certain aspects of blood platelet function, blood coagulability, and fibrinolytic activity are associated with cardiovascular risk, but causality has been insufficiently proven. Nonetheless, well-designed intervention studies should be initiated to further evaluate such promising dietary components as the various n-3 and n-6 fatty acids and their combination, antioxidants, fibre, etc. for their effect on processes participating in arterial thrombus formation. Long-chain polyenes of the n-3 family and antioxidants can modify the activity of immunocompetent cells, but we are at an early stage of examining the role of immune function on the development of atherosclerotic plaques. Actually, there is little, if any, evidence that dietary modulation of immune system responses of cells participating in atherogenesis exerts beneficial effects. Although it seems feasible to modulate insulin sensitivity and subsequent cardiovascular risk factors by decreasing the total amount of dietary fat and increasing the proportion of polyunsaturated fatty acids, additional studies on the efficacy of specific fatty acids, dietary fibre, and low-energy diets, as well as on the mechanisms involved are required to understand the real function of these dietary components. Finally, dietary supplements containing folate and vitamins

B6 and/or B12 should be tested for their potential to reduce cardiovascular risk by lowering the plasma level of homocysteine.

Folate deficiencies and cardiovascular pathologies

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Clinical Chemistry and Laboratory Medicine (Germany), 1998, 36/7 (419-429)

Although folates are widely distributed in foods, folate deficiencies may be more frequent than expected because their true availability may be impaired due to their lability under various food cooking and processing conditions. Folate deficiency is frequently observed in elderly people, smokers, alcoholics and oral contraceptive users. It is also associated with the mutation leading to the thermolabile variant of N5,10-methylenetetrahydrofolate reductase which is observed in about 10% of the population. In addition to the essential role of the intracellular pool of polyglutamates in de novo biosynthesis of deoxyribonucleotides which allow cell growth and division, the reduced and methylated form of folate, N5-methyltetrahydrofolate, is required for the remethylation of homocysteine to methionine. By inhibiting this remethylation pathway, folate deficiency induces homocysteine efflux into the circulation. Many studies have shown a negative correlation between plasma folate, particularly N5-methyltetrahydrofolate, and circulating homocysteine levels. In addition, folate deficiency is a major cause of hyperhomocysteinemia which is fully recognised as an independent risk factor for atherothrombosis. Epidemiological and recent experimental studies have demonstrated that folate deficiency might increase the risk of cardiovascular disease by increasing circulating homocysteine levels. Thus, the clinical efficiency of folate supplementation, especially N5-methyltetrahydrofolate, in reducing homocysteine-dependent cardiovascular risk should be evaluated.

Homocysteine vs cholesterol: Competing views, or a unifying explanation of arteriosclerotic cardiovascular disease?

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Laboratory Medicine (United States), 1998, 29/7 (410-417)

The amino acid homocysteine is getting increased recognition as cholesterol's partner in causing heart attacks and strokes. The mounting clinical evidence makes it likely that screening tests for this factor will be part of routine laboratory workups. Learn what homocysteine does to arteries and how to lower your risk of developing coronary artery disease.

Hyperhomocysteinemia and atherosclerotic vascular disease: Pathophysiology, screening, and treatment

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Archives of Internal Medicine (United States), 1998, 158/12 (1301-1306)

Hyperhomocysteinemia has recently been identified as an important risk factor for atherosclerotic vascular disease. This article reviews homocysteine metabolism, causes of hyperhomocysteinemia, the pathophysiological findings of this disorder, and epidemiological studies of homocysteine and vascular disease. Screening for hyperhomocysteinemia should be considered for patients at high risk for vascular disease or abnormalities of homocysteine metabolism. For primary prevention of vascular disease, treatment of patients with homocysteine levels of 14 micromol/L or higher should be considered. For secondary prevention, treatment of patients with homocysteine levels of 11 micromol/L or higher should be considered. Treatment is most conveniently administered as a folic acid supplement (400-1000 microg) and a high-potency multivitamin that contains at least 400 microg of folate. Higher doses of folic acid and cyanocobalamin supplements may be required in some patients. Until prospective clinical trial data become available, these conservative recommendations provide a safe, effective, and evidence-based approach to the diagnosis, evaluation, and management of patients with hyperhomocysteinemia.

Emerging approaches in the prevention of atherosclerotic cardiovascular diseases

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International Journal of Clinical Practice, Supplement (United Kingdom), 1998, -/94 (7-19)

This presentation reviews data from epidemiologic and clinical trials on antioxidant vitamins, angiotensin-converting enzyme inhibitors, and homocysteine and their effect on atherosclerotic cardiovascular disease. Each of these areas seems promising, but the results of large, on-going studies must be determined before definitive conclusions can be made as to the effectiveness of these therapies.

Homocyst(e)inemia and risk of atherosclerosis: A clinical approach to evaluation and management

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Elevated plasma concentrations of total homocysteine (homocyst(e)ine) are associated with increased risk of coronary artery disease, cerebrovascular disease, peripheral vascular disease, and thrombosis. The relationship between plasma homocyst(e)ine concentrations and risk of atherosclerosis is independent and is graded even for values between the 50th and 95th percentiles. Hyperhomocyst(e)inemia has been detected in 10 to 40% of subjects with myocardial infarction, and it appears to be most prevalent among such individuals with normal or low plasma cholesterol levels. Although a cause and effect link between homocyst(e)ine and atherosclerosis has not been established, several lines of evidence suggest that homocysteine is atherogenic and not merely a marker for increased risk. Potential mechanisms by which homocyst(e)ine might contribute to atherogenesis include direct cytotoxic effects, generation of reactive oxygen species, diminished release of nitric oxide (a primary mediator of endothelium-dependent vasodilation), endothelial dysfunction, potentiation of LDL oxidation, stimulation of smooth muscle cell proliferation, and possible abnormalities in platelet function. Screening for hyperhomocyst(e)inemia is indicated in all individuals with atherosclerosis or a strong family history of arterial occlusive disease. Folic acid deficiency is a common cause of elevated plasm homocyst(e)ine concentrations, particularly among subjects with mutations in the gene for methylenetetrahydrofolate reductase. Deficiencies of vitamins B6 and B12 also can contribute to hyperhomocyst(e)inemia. Successful treatment of hyperhomocyst(e)inemia usually is accomplished by increasing intake of folic acid above 400 to 800 microg daily, with the addition of vitamins B6 and B12 if indicated. Although lowering of plasma homocyst(e)ine levels has not been proven to reduce risk of atherosclerosis, the treatment is relatively safe and inexpensive and is expected to provide benefit. Thus, there are not compelling reasons not to provide therapy. Within the next few years, the results of intervention trials are expected to become available that will help substantiate the anticipated effects of treatment on atherosclerotic risk.

High homocysteine, low folate, and low vitamin B6 concentrations

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Transplantation (United States), 1998, 65/4 (544-550)

Background: A high plasma homocysteine concentration is a risk factor for atherosclerosis and thrombosis, which are major causes of morbidity and mortality in heart transplant patients. High homocysteine concentrations may be

caused by lower folate and vitamin B6 levels. We hypothesized that these patients might have high homocysteine concentrations and low levels of folate and vitamin B6, which could contribute to the development of vascular complications.

Methods: Total fasting plasma homocysteine was measured in 189 cardiac transplant recipients and in healthy controls, as were concentrations of folate, vitamin B12, vitamin B6, and creatinine.

Results: Homocysteine concentrations were higher in recipients than controls (19.1plus or minus13.0 vs. 11.0plus or minus3.0 micromol/L, P<0.01), and hyperhomocysteinemia (>90th percentile for controls, 14.6 micromol/L) was seen in 68% of recipients (P<0.01). Folate and vitamin B6 concentrations were lower (5.9plus or minus4.2 vs. 7.9plus or minus4.2 pmol/L and 40plus or minus25 vs. 84plus or minus77 nmol/L, respectively; P<0.01 for both). Folate and vitamin B6 deficiencies were seen in 10.8% and 17.9% of recipients, respectively (P<0.01). Hyperhomocysteinemia was more frequent in patients with vascular complications after transplantation than in those without (79.2% vs. 63.8%, P<0.05).

Conclusions: Elevated plasma homocysteine and deficiencies of folate and vitamin B6 are common in transplant recipients. A high homocysteine concentration was more common in patients with vascular complications. Prospective studies are now required to evaluate the role of these abnormalities as risk factors for the atherothrombotic complications of transplantation.

Recommended dietary allowance of folic acid sufficient for low homocysteine level

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Nederlands Tijdschrift voor Geneeskunde (Netherlands), 1998, 142/14 (782-786)

Objective. To determine the effect of short term supplementation of vitamin B6 (pyridoxine) followed by folic acid in apparently healthy volunteers on the fasting plasma homocysteine concentrations (hyperhomocysteinaemia is an independent risk factor for premature atherosclerosis).

Design. Prospective, descriptive.

Setting. Academic Hospital Groningen, the Netherlands.

Methods. Apparently healthy Dutch volunteers, aged 20-75 years, were supplemented with vitamin B6 1 mg/kg/day during 7 days followed by folic acid 5 mg/day during another 7 days. On days 0, 7 and 14 the fasting plasma homocysteine concentrations were measured. A change of an individual's plasma

homocysteine level was considered statistically significant if the change in percentage exceeded 2.8 times the sum of the analytical and the intraindividual biological variation.

Results. There were 103 participants, 45 males and 58 females, with average ages of 43 and 44 years, respectively (on day 7, data were available on 101 participants). Baseline folic acid concentration of all participants were above the lower limit of the reference range. Eight and two of the them had vitamin B6 and vitamin B12 concentrations below the reference range, respectively. Plasma homocysteine was inversely related to plasma levels of folic acid and vitamin B12 at that moment. During vitamin B6 supplementation the mean plasma homocysteine level did not change; one participant exhibited a significant plasma homocysteine decrease. During folic acid supplementation the mean plasma homocysteine decreased from 11.7 micromol/l (SD: 5.6) to 9.1 (SD: 3.4); 40 participants (40%) exhibited significant plasma homocysteine decreases. At the end of the study plasma homocysteine was still related to plasma vitamin B12.

Conclusion. The folic acid status of the participants at baseline was not associated with the lowest plasma homocysteine levels. Since atherosclerosis risk may increase continuously with decreasing plasma homocysteine, it may be wise to keep plasma homocysteine levels as low as possible. To reach this goal, the recommended dietary allowance of folic acid may have to be increased.

Homocysteine and cardiovascular disease

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Annual Review of Medicine (United States), 1998, 49/- (31-62)

An elevated level of total homocysteine (tHcy) in blood, denoted hyperhomocysteinemia, is emerging as a prevalent and strong risk factor for atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels, and for arterial and venous thromboembolism. The basis for these conclusions is data from about 80 clinical and epidemiological studies including more than 10,000 patients. Elevated tHcy confers a graded risk with no threshold, is independent of but may enhance the effect of the conventional risk factors, and seems to be a particularly strong predictor of cardiovascular mortality. Hyperhomocysteinemia is attributed to commonly occurring genetic and acquired factors including deficiencies of folate and vitamin B12. Supplementation with B-vitamins, in particular with folic acid, is an efficient, safe, and inexpensive means to reduce an elevated tHcy level. Studies are now in progress to establish whether such therapy will reduce cardiovascular risk.

Vitamin supplementation reduces blood homocysteine levels: A controlled trial in patients with venous thrombosis and healthy volunteers

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Arteriosclerosis, Thrombosis, and Vascular Biology (United States), 1998, 18/3 (356-361)

Hyperhomocysteinemia is a risk factor for atherosclerosis and thrombosis and is inversely related to plasma folate and vitamin B12 levels. We assessed the effects of vitamin supplementation on plasma homocysteine levels in 89 patients with a history of recurrent venous thrombosis and 227 healthy volunteers. Patients and hyperhomocysteinemic (homocysteine level >16 micromol/L) volunteers were randomized to placebo or high-dose multivitamin supplements containing 5 mg folic acid, 0.4 mg hydroxycobalamin, and 50 mg pyridoxine. A subgroup of volunteers without hyperhomocysteinemia was also randomized into three additional regimens of 5 mg folic acid, 0.5 mg folic acid, or 0.4 mg hydroxycobalamin. Before and after the intervention period, blood samples were taken for measurements of homocysteine, folate, cobalamin, and pyridoxal-5'-phosphate levels. Supplementation with high-dose multivitamin preparations normalized plasma homocysteine levels (less than or equal to 16micromol/L) in 26 of 30 individuals compared with 7 of 30 in the placebo group. Also in normohomocysteinemic subjects, multivitamin supplementation strongly reduced homocysteine levels (median reduction, 30%; range, -22% to 55%). In this subgroup the effect of folic acid alone was similar to that of multivitamin: median reduction, 26%; range, -2% to 52% for 5 mg folic acid and 25%; range, -54% to 40% for 0.5 mg folic acid. Cobalamin supplementation had only a slight effect on homocysteine lowering (median reduction, 10%; range, -21% to 41%). Our study shows that combined vitamin supplementation reduces homocysteine levels effectively in patients with venous thrombosis and in healthy volunteers, either with or without hyperhomocysteinemia. Even supplementation with 0.5 mg of folic acid led to a substantial reduction of blood homocysteine levels.

Hyperhomocysteinaemia - A new risk factor for atherosclerosis

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Klinikarzt (Germany), 1998, 27/3 (64-71)

Prospective and case control studies have shown that a mile elevation of plasma homocysteine represents a risk factor for coronary, cerebrovascular and peripheral arterial disease. Hyperhomocysteinemia is a result of a combination of genetic and dietary factors. The mechanisms by means of which raised plasma

homocysteine leads to vascular disease are not fully understood, and are presently undergoing intensive investigation. It appears that homocysteine has an effect on endothelial cells, smooth muscle cells in the vessel wall, the connective tissue matrix of atherosclerotic plaques, blood platelets and coagulation factors, and also plays a role in the oxidative modification of lipids and lipoproteins. Folic acid supplementation, either alone or in combination with vitamin B6 reduces or normalises increased homocysteine levels. The optimal dosage and combination of the B vitamins is, however not yet known. Ongoing long-term prospective, randomized and placebo-controlled studies are presently investigating the question whether this treatment can also exert a positive influence on the incidence and progression of atherosclerotic vascular disease, possibly even reducing the morbidity and mortality of these diseases. In clinical practice, however, mild hyperhomocysteinaemia should already be included in she differential diagnostic consideration of atherosclerotic risk factors. In view of its low level of side-effects treatment of patients with mild hyperhomocysteinaemia with folic acid and pyridoxal phosphate, would, however already appeal justified, even though no information is presently available as to its longterm effects.

Homocysteine and vascular diseases

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Hematologie (France), 1998, 4/1 (7-16)

Homocysteine is metabolized through 2 pathways: transsulfuration leading to the formation of cystathionine via cystathionine beta synthase (CbetaS) and its co-factor, pyridoxal 5' phosphate (vitamin B6); remethylation forming methionine via methionine synthase and its coenzyme methylcobalamin, the methyl donor being methyltetrahydrofolate (methylTHF) derived from the reduction of methylene THF via methylenetetrahydrofolate reductase (MTHFR). The increase of homocysteine is an independent risk factor for vascular diseases; indeed hyperhomocysteinemia is toxic for the endothelial cell. The increase of homocysteine is due - to genetic factors: CbetaS or MTHFR deficiency, defective synthesis of active forms of cobalamins - nutritional factors such as folate, vitamin B12 or B6 deficiencies; - some diseases mainly chronic renal insufficiency. In congenital diseases associated with severe hyperhomocysteinemia and huge homocystinuria, the vascular lesion is characterized by precocious atherosclerosis associated to arterial and venous thromboembolism. Besides, numerous epidemiological studies have shown the relationship between moderate hyperhomocysteinemia and the occurrence of vascular diseases, cerebral, coronary, peripheral artery diseases, venous thrombosis. In addition, hyperhomocysteinemia is a predictive risk factor of vascular diseases or even of mortality. There is a relation between plasma homocysteine levels and folate, vitamin B6 and B12 levels from one part, and plasma homocysteine levels and a mutation on the gene of MTHFR C677 right arrow T, which in an homozygous state, usually induces an increase of plasma

homocysteine levels. Folic acid alone or in association with vitamin B12 and B6 decreases and often normalizes homocysteine levels. Folic acid supplementation could be an effective treatment, inexpensive and not toxic for the prevention of some vascular diseases.

Effects of folic acid supplementation on hyperhomocysteinemia in CAPD patients: Effects on unsaturated fatty acids

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Hyperhomocysteinemia has been recognized as one of the risk factors for atherosclerosis and premature vascular disease. Patients on dialysis and end- stage renal disease also manifest high plasma concentrations of homocysteine. We performed this study to evaluate the effects of folic acid supplementation on hyperhomocysteinemia in CAPD patients. Twenty-three CAPD patients (8 males, 15 females, 49.1 plus or minus 14.2-years-old) dialyzed for 22.7 plus or minus 19.2 months participated in the study. Daily 5-mg doses of folic acid supplementation for 4 weeks significantly reduced plasma concentrations of total homocysteine ($p < 0.01$) and serine ($p < 0.001$). This observation suggests that the reduction of plasma concentrations of total homocysteine results from activation of homocysteine remethylation to methionine. On the other hand, folic acid supplementation also revealed significant correlations between changes in serum concentrations of both dihomo-gamma-linolenic acid and arachidonic acid and changes in plasma concentrations of total homocysteine ($r = -0.517$, $p < 0.05$, $r = -0.451$, $p < 0.05$, respectively). In addition, serum concentrations of both dihomo-gamma-linolenic acid and arachidonic acid in 11 CAPD patients with hyperhomocysteinemia (less than or equal to35 micromol/litter) were significantly lower than those of 12 CAPD patients with normohomocysteinemia (<35 micromol/litter) ($p < 0.05$, respectively). Serum concentrations of both dihomo-gamma-linolenic acid and arachidonic acid in CAPD patients with hyperhomocysteinemia increased significantly ($p < 0.01$, $p < 0.05$, respectively) and reached similar levels of CAPD patients with normohomocysteinemia, while plasma concentrations of total homocysteine decreased after folic acid supplementation. These findings suggest that correction of hyperhomocysteinemia in patients on dialysis produces an increase in unsaturated fatty acids.

Low circulating folate and vitamin B6 concentrations risk factors forstroke, peripheral vascular disease, and coronary artery disease

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Background- A high plasma homocysteine concentration is a risk factor for atherosclerosis, and circulating concentrations of homocysteine are related to levels of folate and vitamin B6. This study was performed to explore the interrelationships between homocysteine, B vitamins, and vascular diseases and to evaluate the role of these vitamins as risk factors for atherosclerosis.

Methods-In a multicenter case-control study in Europe, 750 patients with documented vascular disease and 800 control subjects frequency- matched for age and sex were compared. Plasma levels of total homocysteine (before and after methionine loading) were determined, as were those of red cell folate, vitamin B12, and vitamin B6.

Results- In a conditional logistic regression model, homocysteine concentrations greater than the 80th percentile for control subjects either fasting (12.1 micromol/L) or after a methionine load (38.0 micromol/L) were associated with an elevated risk of vascular disease independent of all traditional risk factors. In addition, concentrations of red cell folate below the lowest 10th percentile (<513 nmol/L) and concentrations of vitamin B6 below the lowest 20th percentile (<23.3 nmol/L) for control subjects were also associated with increased risk. This risk was independent of conventional risk factors and for folate was explained in part by increased homocysteine levels. In contrast, the relationship between vitamin B6 and atherosclerosis was independent of homocysteine levels both before and after methionine loading.

Conclusions- Lower levels of folate and vitamin B6 confer an increased risk of atherosclerosis. Clinical trials are now required to evaluate the effect of treatment with these vitamins in the primary and secondary prevention of vascular diseases.

Vitamins B6, B12, and folate: Association with plasma total homocysteine and risk of coronary atherosclerosis

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Journal of the American College of Nutrition (United States), 1998, 17/5 (435-441)

Objectives: To investigate the association of status of vitamins B6, B12 and folate with plasma fasting total homocysteine (tHcy) and with risk of coronary atherosclerosis; and to establish whether associations between vitamins and risk of coronary atherosclerosis are mediated by tHcy.

Methods: The study population consisted of 131 patients with angiographically-defined severe coronary atherosclerosis and 88 referents with no or minor

coronary stenosis. Previous analyses in this study population have shown that fasting tHcy is an independent risk factor for coronary atherosclerosis. In the present analyses, using multiple linear regression, we estimated differences in tHcy concentrations between subjects in the lowest and highest quartiles of concentrations of each of the vitamins, adjusting for age, gender, total:HDL cholesterol ratio, smoking habits, alcohol intake, blood pressure, serum creatinine, body mass index and the two other vitamins. We used logistic regression analysis conditional on the set of potential confounders described above to study the association between vitamin concentration and risk of coronary atherosclerosis. By comparing these estimated odds ratios (ORs) with those that were additionally adjusted for fasting tHcy, we determined whether the vitamins exerted their effects on disease risk via homocysteine metabolism.

Results: Cases who were in the upper quartile of serum vitamin B12 and erythrocyte folate concentrations showed statistically significantly lower tHcy concentrations (-4.00 and -4.71 micromol/L, respectively) than those in the lowest quartile. Referents in the upper quartile of plasma B6 showed significantly lower tHcy concentrations (-2.36 micromol/L) than referents in the lowest quartile. Subjects in the lowest quartile of vitamin B12 concentration had higher risk of coronary atherosclerosis (OR: 2.91; 95% CI: 1.10, 7.71) compared to those in the highest quartile. The ORs and 95% CIs for low B6 and low folate were 0.86 (95% CI: 0.33, 2.22) and 0.58 (95% CI: 0.23, 1.48), respectively. Additional adjustment for fasting tHcy weakened associations, although data indicated that low vitamin B12 concentration is a risk factor for coronary atherosclerosis, independently of tHcy.

Conclusion: The presently accepted view that vitamin B6 mainly affects tHcy after methionine loading, and not fasting tHcy, is contradicted by our findings in referents. Low vitamin B12 concentrations were associated with an increased risk of coronary atherosclerosis, partly independently of tHcy. Although low folate status was a strong determinant of elevated tHcy concentrations, it was not associated with increased risk of coronary atherosclerosis.

Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: The atherosclerosis risk in communities (ARIC) study

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Background - Elevated plasma total homocysteine (tHcy), low B-vitamin intake, and genetic polymorphisms related to tHcy metabolism may play roles in coronary heart disease (CHD). More prospective studies are needed.

Methods and Results - We used a prospective case-cohort design to determine whether tHcy-related factors are associated with incidence of CHD over an average of 3.3 years of follow-up in a biracial sample of middle-aged men and women. Age-, race-, and field center-adjusted CHD incidence was associated positively ($P<0.05$) with tHcy in women but not men, and CHD was associated negatively ($P<0.05$) with plasma folate (women only), plasma pyridoxal 5'-phosphate (both sexes), and vitamin supplementation (women only). However, after accounting for other risk factors, only plasma pyridoxal 5'-phosphate was associated with CHD incidence; the relative risk for the highest versus lowest quintile of pyridoxal 5'-phosphate was 0.28 (95% CI=0.1 to 0.7). There was no association of CHD with the C677T mutation of the methylenetetrahydrofolate reductase gene or with 3 mutations of the cystathionine beta-synthase gene.

Conclusions - Our prospective findings add uncertainty to conclusions derived mostly from cross-sectional studies that tHcy is a major, independent, causative risk factor for CHD. Our findings point more strongly to the possibility that vitamin B6 offers independent protection. Randomized trials, some of which are under way, are needed to better clarify the interrelationships of tHcy, B vitamins, and cardiovascular disease.

Hypothesis: Cis-unsaturated fatty acids as potential anti-peptic ulcer drugs

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It is now reasonably well established that Helicobacter pylori is the most likely cause for duodenal ulcer. What is not clear is how this infection is related to the excess acid production, why few people with Helicobacter pylori infection have duodenal ulcer and how diet is related to duodenal ulcer. Here it is suggested that a deficiency of cis-unsaturated fatty acids (otherwise called as polyunsaturated fatty acids, PUFAs) especially gamma- linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid and eicosapentaenoic acid may be responsible for duodenal ulcer. Patients with active duodenal ulcer are known to have low concentrations of these PUFAs in their plasma phospholipid fraction and they revert to normal levels after treatment with H2 blockers. In addition, these PUFAs have the ability to inhibit the growth of Helicobacter pylori, suppress acid production and both in experimental animals and humans these PUFAs could heal the ulcer and protect the gastric mucosa from aspirin and steroid-induced damage. Further, PUFAs have other beneficial actions such as capacity to prevent/arrest atherosclerosis, lower plasma cholesterol and triglyceride levels and cytotoxic action on tumour cells. Since PUFAs can be administered over long periods of time and are relatively non-toxic, it is suggested that PUFAs may be exploited as potential anti-ulcer agents.

Influence of long-chain polyunsaturated fatty acids on oxidation of low density lipoprotein

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Enrichment of low density lipoprotein (LDL) with long-chain fatty acids, such as eicosapentaenoic acid (EPA; 20:5 n-8) and docosahexaenoic acid (DHA; 22:6 n-3) found in fish oil, is thought to increase its oxidative susceptibility although such an increase has not been clearly demonstrated. The purpose of this study was to determine the composition and fatty acid concentration of LDL obtained from postmenopausal women given a supplement of fish oil and relate these values to its oxidative susceptibility. Fish oil supplementation significantly increased LDL concentration of EPA (P = 0.0001) and DHA (P = 0.0001) and decreased that of linoleic acid P = 0.006). The concentration of free cholesterol, cholesterol ester, phospholipids and protein was unchanged while triglyceride concentration increased 8% (P = 0.02). Cu2+-mediated oxidation resulted in a shorter lag time, slower oxidation rate and similar concentrations of conjugated dienes of EPA/DHA-enriched LDL than EPA/DHA-unenriched LDL. Stepwise multiple regression indicated that the primary predictor of oxidative susceptibility of LDL was linoleic acid, even after enrichment with EPA and DHA. The oxidation rate of EPA/DHA-unenriched LDL correlated with the cholesteryl ester concentration (P = 0.003) while that of EPA/DHA-enriched correlated with the concentration of phospholipids (P = 0.03). These data suggest that EPA/DHA-enriched LDL have decreased oxidative susceptibility and that surface lipids may mediate its rate of oxidation.

Effects of eicosapentaenoic acids on remnant-like particles, cholesterol concentrations and plasma fatty acid composition in patients with diabetes mellitus

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In Vivo (Greece), 1998, 12/3 (311-314)

Remnant lipoproteins are transient metabolites from chylomicron and/or very low density lipoproteins (VLDL), and remnant hyperlipoproteinemia has recently been reported to be a risk factor for atherosclerosis. Eicosapentaenoic acid (EPA), a major component of fish oil, has the following effects: anti-platelet aggregation, vaso-dilation, anti-inflammation, hypotriglyceridemia, and therefore has potential anti-atherosclerotic effects. We measured serum of remnant-like particle

cholesterol (RLP-C) concentrations, and investigated the effects of EPA on serum RLP-C concentrations in patients with diabetes mellitus. Ten patients with non-insulin dependent diabetes mellitus were treated with 900-1800 mg EPA ethyl-ester daily for 3 months. We investigated serum RLP-C concentrations and plasma fatty acid composition before and after the administration of EPA. Serum RLP-C concentrations were significantly decreased 3 months after the administration of EPA (from 14.5 plus or minus 5.3 mg/dL to 3.3 plus or minus 0.8 mg/dL, $P < 0.01$). Plasma EPA concentrations and the ratios of EPA to arachidonic acids (AA) were significantly increased during the same period (from 86.2 plus or minus 12.4 mg/L to 194.6 plus or minus 27.3 mg/L, $P < 0.01$, from 0.571 plus or minus 0.074 to 1.242 plus or minus 0.163. $P < 0.01$, respectively). Serum RLP-C concentrations were inversely correlated with the ratios of EPA to AA in plasma ($r = -.516$, $P < 0.05$). These results suggested that administration of EPA was effective on remnant hyperlipoprote nemia which was a risk factor for atherosclerosis.

Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients

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Clinical Drug Investigation (New Zealand), 1998, 15/6 (473-482)

This study investigated whether an ethyl ester preparation of fish oil (omega-3) could normalise raised plasma concentrations of triglycerides, apolipoprotein CIII on apolipoprotein B-containing particles (LP CIII:B) found in patients with recent acute myocardial infarction. We also studied the effect of fish oil on antithrombin III levels. Out of 75 patients with a plasma triglyceride value less than or equal to 2.0 mmol/L, 22 normalised their triglycerides during diet and were therefore not randomised. The remaining patients were randomly assigned to 12 weeks' treatment with a daily dose of 4g omega-3 or placebo. Mean plasma triglyceride concentrations were reduced by 24% from 3.10 plus or minus 1.15 (SD) to 2.53 plus or minus 0.94 mmol/L ($p < 0.001$) on omega-3 ($p < 0.001$ vs placebo). The reduction was due to decreases in very low density lipoprotein concentrations. Total apolipoprotein CIII decreased significantly. This was due to reductions in LP CIII:non B concentrations, but the ratio LP CIII:non B/LP CIII:B was unaffected because of a slight insignificant decrease in LP CIII:B. The plasma triglyceride decreasing effect of omega-3 could therefore not be due to redistribution of CIII between lipoproteins. Low density lipoprotein (LDL) cholesterol increased significantly with omega-3 by 7%, and antithrombin III increased significantly with fish oil. In conclusion, omega-3 had a moderate plasma triglyceride lowering effect and increased LDL cholesterol slightly, while antithrombin III increased in patients with hypertriglyceridaemia who had recently experienced a myocardial infarction. Myocardial infarction starts via a thrombotic process at an atherosclerotic lesion in a coronary artery. Most patients developing this disease have an abnormal plasma lipoprotein pattern consisting of

slightly raised triglycerides (TGs), moderately elevated total cholesterol, and low high density lipoprotein (HDL) cholesterol values predisposing to atherosclerosis. Hypertriglyceridaemia may be associated with a greater risk for thrombosis in postmyocardial infarction patients because of a reduced fibrinolytic capacity. The dyslipidaemia may also indicate an unfavourable distribution of plasma lipoprotein particles in patients with myocardial infarction. Dietary changes normalise the dyslipidaemia in some patients but are inadequate in others. In these latter patients pharmacological lipid-lowering treatment is necessary. The myocardial infarction patient with an athero-thrombogenic syndrome could theoretically therefore benefit from a pharmacological agent acting on both the thrombotic and lipidaemic pathophysiological pathways. The pharmacological potency of the omega-3-fatty acids allows for this possibility. It has been known since the mid 1970s that omega-3-fatty acids are effective in lowering plasma triglyceride concentrations. They also increase the concentration of HDL cholesterol slightly. Their effects on cholesterol have varied, with some studies showing increases and others decreases. These fatty acids also inhibit platelet aggregation. It was therefore of interest to expand the experience of this type of treatment to effects on plasma lipoprotein particle distribution. We also studied parameters of fibrinolysis since the literature shows diverging results of omega-3-fatty acids on these parameters. In the present study we tested a new compound, omega-3, an oil consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with the aim of normalising dyslipidaemia, and reducing the thrombotic tendency in a potentially important target population for such treatment, postmyocardial infarction patients. The high EPA and DHA concentration in omega-3 made a convenient intake of only four capsules daily possible. The design of the study followed the current guidelines for secondary prevention of ischaemic heart disease.

A central role for protein kinase c overactivity in diabetic glomerulosclerosis: Implications for prevention with antioxidants, fish oil, and ACE inhibitors

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The primary etiologic factor in diabetic glomerulosclerosis appears to be an overproduction of transforming growth factor-beta by mesangial cells, which in turn reflects a hyperglycemically mediated overactivation of protein kinase C (PKC) throughout the glomerulus. Membrane-active antioxidants, fish oil, and angiotensin-converting enzyme inhibitors can act to down-regulate glomerular PKC activity, via a variety of mechanisms that may include activation of diacylglycerol kinase and suppression of phosphatidate phosphohydrolase, support of endothelial nitric oxide and heparan sulfate production, inhibition of thromboxane and angiotensin synthesis/activity, and correction of glomerular hypertension. The beneficial impact of these measures on vascular endothelial function may be of more general utility in the prevention of diabetic

complications such as retinopathy, neuropathy, and atherosclerosis. Adjunctive use of gamma-linolenic acid is indicated for prevention of neuropathy, and it is conceivable that bioactive chromium will have protective activity not solely attributable to improved glycemic control. Re-establishing euglycemia must clearly remain the core strategy for preventing diabetic complications, but when glycemic control remains suboptimal, practical, safe measures are at hand for decreasing risk.

Taurine in management of diffuse cerebral arteriopathy. Clinical and electroencephalographic observations, and mental test results

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Clin.Ter. (Italy), 1974, 71/5 (427-436)

Following previous work on the subject, a number of patients suffering from cerebral arteriopathy were treated with Taurine by mouth (3-4 g a day, for some weeks). The patients were subdivided into 3 groups, according to the main presenting symptom. The treatment was in every case well tolerated. Noticeable improvement, of statistical significance, was obtained in the power of concentration, of memory and of orientation. The best results were obtained in those patients who presented intermittent confusional episodes, while least success was obtained in those with severe intellectual deterioration and in the most elderly.

Effect of taurine on incipient senile involution of the brain

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Clin.Ter. (Italy), 1974, 70/5 (425-433)

The use of taurine was investigated in the treatment of early mental deterioration from senile involution (so called cerebral arteriosclerosis). It was carried out as a double blind trial using a placebo. Psychometric tests were used to evaluate its effects objectively. Statistical evaluation showed that taurine can produce amelioration of the early symptoms of senile mental deterioration, suggesting that it can be used to treat, or as a prophylactic for, mental involution in the pre senile and senile age groups.

Ginkgo - Myth and reality

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Ginkgo biloba is one of the oldest, still existing plants. Extracts from its leaves were already used in ancient China whereas in the Western World, they have been utilized only since the Sixties when it became technically possible and feasible to isolate the essential substances of Ginkgo biloba. Pharmacologically, there are two groups of substances which are of some significance: the flavonoids, effective as oxygen-free radical scavengers, and the terpenes (i.e. the ginkgolides) with their highly specific action as platelet activating factor (PAF) inhibitors. Clinically important indications for Ginkgo biloba extracts are cerebral insufficiency and atherosclerotic disease of peripheral arteries of intermediate severity. In several placebo-controlled clinical studies, symptoms of cerebral insufficiency have been effectively and significantly influenced. Most of these investigations have examined the efficacy of Ginkgo biloba extracts such as EGb 761 and LI 1370.

Phytotherapy in cardiovascular diseases. Supportive therapy in early stages

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Circulatory effective herbs such as haw-thorn, ginkgo and garlic have a very important share in the entire phytotherapy. Due to their good tolerance they are used in less severe classes of the frequent circulatory sytem's diseases as arterio-sclerosis and consequent symptoms, heart failure, orthostatic dysfunction.

Evaluation of the evidence on the role of tomato products in disease prevention

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During the last 30 years, research in the field of nutrition and chronic disease causation has led to exciting, significant progress in providing an understanding of specific risk factors and chemopreventive agents. The major health problems considered are cardiovascular diseases and the nutritionally linked cancers, including those in the stomach, colon, breast, prostate, ovary, and endometrium. The major elements considered were salt, type and amount of fat, and heterocyclic amines formed during cooking. Bran cereal fiber, as well as vegetables, fruits, and

tea have been shown to inhibit the complex processes of initiation and development of these diseases. One aspect involved in initiation and development of both cardiovascular diseases and the cancers noted are abnormal oxidative processes leading to the generation of hydroxy radicals and peroxy compounds. In part, the protective role of vegetables, fruits, and tea is to provide antioxidant vitamins and specific polyphenols that display a powerful inhibition in oxidative reactions. Epidemiological studies as well as laboratory experimentation have yielded sound data and evidence in support of the fact that vegetables, fruits, and tea and specific antioxidants therein account mechanistically for inhibition. Geographic pathology has provided important data that populations with a regular intake of tomato products, such as in the Mediterranean region, have a lower incidence of the chronic diseases noted. The current Symposium is considering the varied mechanisms of action of tomato products in general, and one of the active principles, lycopene. Cooking is a factor in releasing the desirable antioxidants from tomatoes. Cooked tomato products may be preferable to the raw vegetable or juices derived from tomatoes bearing on absorption of the active principles. Optimally, absorption of lycopene, a highly lipid-soluble chemical, is improved in the presence of a small, but essential amount of oil or fat. Research in the field of nutrition and health has shown that monounsaturated oils such as olive oil or canola oil are most desirable, since such oils do not increase the risk of atherosclerosis, coronary heart disease, or the nutritionally linked cancers. The International Symposium on tea conducted in 1991 has provided worldwide interest in research on the beneficial effects of tea. It is now hoped that the present Symposium, dealing with another inexpensive and readily available food, tomatoes, will enhance interest in and funding for additional research, to underwrite future recommendations for possibly enhanced production and use of tomato-derived nutritional elements, with the goal of application to the prevention of major chronic diseases, the treatment of which is costly and often ineffective.

Copper: An antioxidant nutrient for cardiovascular health

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Dietary copper often is low in the Western diet; low intakes may affect all stages of atherosclerosis adversely. Impaired oxidative defense in copper deficiency contributes to hypercholesterolemia, hypertension, and impaired prostaglandin metabolism. Free copper ion does not exist in vivo; some in-vitro experiments are conducted with millions-fold excesses.

Trace elements and cardiovascular diseases

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Evidence linking marginal intakes of the trace elements, chromium, copper, zinc and selenium, with abnormal lipid metabolism and ultimately cardiovascular diseases is accumulating from both animal and human studies. Chromium supplementation of normal adult men, as well as diabetics, has been reported to increase high density lipoprotein cholesterol and decrease triglycerides and total cholesterol. Subjects with the highest total cholesterol and triglycerides usually respond the most to supplemental chromium. Improvements in lipid metabolism, as well as those in glucose metabolism, appear to be related to improvements in insulin efficiency due likely to increased receptor number. Animal studies also indicate that improvements in serum cholesterol, aortic lipids and plaque formations due to supplemental chromium are associated with decreased circulating insulin. Insufficient dietary copper also leads to elevated lipid levels and impaired heart function. Animal studies indicate an obvious degradation of the heart muscles. Zinc appears to function in cardiovascular diseases primarily via its antagonism with copper. Selenium may also affect cardiovascular diseases since selenium is postulated to be involved in platelet aggregation. These data demonstrate that the trace elements, chromium, copper, and selenium, have beneficial effects on risk factors associated with cardiovascular diseases suggesting that a decreased risk of cardiovascular disease may be achieved by adequate intake of trace elements.

Increased cholesterol in plasma in a young man during experimental copper depletion

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Signs of copper depletion were produced in a healthy man by an amount of dietary copper (0.83 mg/day) similar to that in some contemporary diets. Urinary and fecal loss of copper exceeded intake. Plasma copper, ceruloplasmin and superoxide dismutase activity in erythrocytes decreased. Cholesterol in plasma increased, and hematologic indices were unchanged. Lipid metabolism may be a more sensitive index of copper nutriture than are changes in hematology. The findings support the hypothesis that inadequate copper nutriture or altered copper metabolism contributes to the occurrence of ischemic heart disease.

Antioxidant vitamin levels in plasma and low density lipoprotein of obese girls

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To investigate the antioxidant status of obese children, we analyzed beta-carotene and alpha-tocopherol levels in plasma and low density lipoprotein (LDL). We also analyzed the fatty acid composition of LDL as a substrate for oxidative stress. The plasma beta-carotene and alpha-tocopherol levels were relatively lower in obese girls than in normal controls. However, the plasma alpha-tocopherol/lipids ratio was significantly lower in obese girls than in normal controls. Both LDL beta-carotene and LDL alpha-tocopherol levels were significantly lower in obese girls than in normal controls, although no obvious differences were observed in plasma levels. In obese girls LDL contained more polyunsaturated fatty acid (PUFA) compared with normal controls. When the peroxidizability Index (PI) was calculated to estimate the susceptibility of lipids to oxidative stress, obese girls had significantly higher PI values than normal controls. Both the LDL beta-carotene/PI ratio and the LDL alpha-tocopherol/PI ratio were significantly lower in obese girls than in normal controls. These results indicate the increased susceptibility of LDL to oxidative stress in obese girls which may promote atherosclerosis later in life.

Dietary iron concentration alters LDL oxidatively the effect of antioxidants

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Low-density lipoprotein (LDL) cholesterol participates in the atherosclerotic process only after oxidative modification (o-LDL). Persons with elevated body iron concentrations are at higher risk of atherosclerosis. Iron in vitro is capable of oxidizing LDL, but it is unknown whether or not high dietary iron concentrations alter LDL in vivo. The aim of this study was, therefore, to investigate (i) whether dietary iron concentrations cause LDL-cholesterol oxidation and (ii) whether antioxidants can prevent such changes. Rats received diets differing only in iron concentration: 35 mg/kg, 150 mg/kg or 300 mg/kg diet. A LDL-VLDL particle was isolated and the following parameters measured: malondialdehyde and lipid hydroperoxide concentrations (as an indication for lipid peroxidation); alpha-tocepherol and retinol concentrations (as antioxidants); protein sulfhydryl and carbonyl concentrations (as an indication of protein modification); agarose gel electrophoresis and cholesterol/protein ratio. Dietary iron increased LDL- VLDL lipid peroxidation (malondialdehyde and lipid hydroperoxide concentrations), protein modification (sulfhydryl concentration), agarose migration distance and band width as well as cholesterol/protein ratio. Increased quantities of dietary iron led to a higher degree of oxidative change in LDL-VLDL. Lipid peroxidation, as

well as protein modification, occurred, suggesting apoB changes. This was probably due to diminished antioxidant concentrations of alpha-tocopherol and beta-carotene. Antioxidant supplementation (alpha-tocopherol and beta-carotene), however, prevented all the above changes and could be helpful in the prevention of atherosclerosis.

Plasma antioxidant and trace element status in familial hypercholesterolemic patients treated with LDL-apheresis

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Oxidation of low density lipoprotein is involved in the pathogenesis of atherosclerosis. Epidemiological studies suggest a negative correlation between the occurrence of cardiovascular diseases and blood concentrations of lipophilic antioxidants such as vitamin A and E and beta-carotene. Trace elements such as selenium, zinc and copper are involved in the activity of antioxidant enzymes: glutathione peroxidase and superoxide dismutase. The aim of this work was to determine the antioxidant and trace elements status of patients with very severe hypercholesterolemia and who were treated by dextran sulphate low density lipoprotein apheresis, in comparison with two control populations: one constituted by normocholesterolemic subjects and the other by hypercholesterolemic patients before treatment. Our results showed that, as compared with normocholesterolemic subjects, patients treated by LDL-apheresis were not deficient in vitamin E, beta-carotene and copper but had low plasma levels of selenium, zinc and vitamin A. The low selenium and vitamin A levels were due to the treatment by LDL-apheresis by itself, while the hypercholesterolemia of these patients might have provoked the low plasma levels of zinc. This study pointed out the interest of a supplement of selenium, zinc and vitamin A in patients treated by LDL-apheresis.

Ascorbic acid clearance in diabetic nephropathy

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The incidence of cardiovascular disease is increased in diabetic nephropathy. Increased oxidative stress in diabetes is believed to play an important role in the pathogenesis of atherosclerosis in diabetes. Since antioxidant vitamins, such as ascorbic acid, often are reduced in diabetes, we hypothesized that the renal

clearance of ascorbic acid is increased in patients with diabetic nephropathy. Thirty-seven subjects with diabetic nephropathy were studies: 18 had microalbuminuria (30-300 mg/day albuminuria); the remainder had clinical nephropathy (> 300 mg/day albuminuria). Indices of glycemic control (glucose, hemoglobin A(1C)) and renal function (albuminuria and creatinine clearance) were measured in addition to serum and urinary ascorbic acid levels. Results showed that subjects with clinical nephropathy had lower mean plasma ascorbic acid ($p = 0.0009$) and higher renal clearance of ascorbic acid ($p = 0.005$) than those with microalbuminuria. Bivariate analysis revealed an inverse correlation between creatinine clearance and AA clearance ($r = -0.42$, $p = 0.009$). There was a significant linear association between the quantity of albuminuria and ascorbic acid clearance ($r = 0.49$, $p = 0.002$). Thus, patients with diabetic nephropathy have reduced ascorbic acid levels due to increased ascorbic acid clearance. The decrease in antioxidant defense that arises from the low levels of vitamin C may contribute to the increased cardiovascular morbidity and mortality observed in this population.

Vascular damage from smoking: Disease mechanisms at the arterial wall

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Vascular Medicine (United Kingdom), 1998, 3/1 (21-28)

The products of tobacco combustion are absorbed into the systemic circulation. Absorbed nicotine stimulates the release of catecholamines, whilst other products (perhaps including nicotine) injure the arterial endothelium and promote atherogenesis. Free radicals and aromatic compounds diminish the endothelial synthesis of nitric oxide, causing impaired endothelium-dependent relaxation of arteries, the earliest clinical sign of endothelial dysfunction. Smoking alters the shear forces and rheology at the endothelial surface and these changes enhance the effects of products of tobacco combustion to upregulate leucocyte adhesion molecules on the endothelial surface. The increased oxidation of low density lipoprotein (LDL) in smokers has synergistic effects to promote monocyte adhesion and monocyte migration into the subintimal space. Continued stimulation of intimal cells by oxidized LDL leads to the development of atherosclerosis. Many of these effects are ameliorated by high concentrations of vitamin C. Smoking also potentiates thrombosis at the dysfunctional endothelium by increasing the concentration of plasma fibrinogen and altering the activity of platelets. All these pro-atherogenic effects of smoking to injure the endothelium also are observed, albeit to lesser extent, in passive smokers.

Dynamics of vitamin E action against LDL oxidation

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Vitamin E acts as an important antioxidant against oxidative modification of low density lipoprotein (LDL) which is accepted as an initial event in the pathogenesis of atherosclerosis. In spite of the numerous studies and reports, the action and role of vitamin E have not been fully elucidated yet. In this brief overview, the dynamics of action of vitamin E as an antioxidant have been discussed and it is emphasized that the total antioxidant potency is determined by the relative importance of many competing reactions which is determined by the reactivities and concentrations of substrates, radicals and antioxidant and by physical factors of the environment.

Cost-effectiveness of vitamin E therapy in the treatment of patients with angiographically proven coronary narrowing (CHAOS trial)

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Epidemiologic studies have suggested that vitamin E (alpha-tocopherol) may play a preventive role in reducing the incidence of atherosclerosis. The aim of this paper was to conduct a cost-effectiveness analysis of vitamin E supplementation in patients with coronary artery disease using data from the Cambridge Heart Antioxidant Study (CHAOS). The study compared cost- effectiveness in the context of Australian and United States (US) health care utilization. The main clinical outcome used in the economic evaluation was the incidence of acute myocardial infarction (AMI) which was nonfatal. Utilization of health care resources was estimated by conducting a survey of Australian clinicians and published Australian and US cost data. Cost savings of $127 (A$181) and $578/patient randomized to vitamin E therapy compared with patients receiving placebo were found for Australian and US settings, respectively. Savings in the vitamin E group were due primarily to reduction in hospital admissions for AMI. This occurred because the vitamin E group had a 4.4% lower absolute risk of AMI than did the placebo group. Less than 10% of health care costs in the Australian evaluation was due to vitamin E ($150 [A$214/patient]). Our economic evaluation indicates that vitamin E therapy in patients with angiographically proven atherosclerosis is cost-effective in the Australian and US settings.

Alpha-Tocopherol induces oxidative damage to DNA in the presence of copper(II) ions

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There is currently much interest in the possibility that dietary antioxidants may confer protection from certain diseases, such as atherosclerosis and cancer. The importance of alpha-tocopherol (vitamin E) as a biological antioxidant is widely recognized. However, pro-oxidant properties of alpha-tocopherol have been observed in chemical systems, and it has been reported that the vitamin can induce tumor formation and act as a complete tumor promotor in laboratory animals. In the present communication, we find that alpha-tocopherol can act as a potent DNA-damaging agent in the presence of copper(II) ions, using a simplified, in vitro model. alpha-Tocopherol was found to promote copper-dependent reactive oxygen species formation from molecular oxygen, resulting in DNA base oxidation and backbone cleavage. Neither alpha- tocopherol nor Cu(II) alone induced DNA damage. Bathocuproine, a Cu(I)- specific chelator, and catalase inhibited the DNA damage, whereas free hydroxyl radical scavengers did not. The order of DNA cleavage sites was thymine, cytosine > guanine residues. Examinations using an oxygen electrode and cytochrome c indicate that molecular oxygen was consumed in the reaction of alpha-tocopherol and Cu(II) and that superoxide was formed. Stoichiometry studies showed that two Cu(II) ions could be reduced by each alpha-tocopherol molecule. Electron spin resonance spin-trapping investigations were then used to demonstrate that hydrogen peroxide interacts with Cu(I) to generate the reactive species responsible for DNA damage, which is either the hydroxyl radical or a species of similar reactivity. These findings may be of relevance to the tumorigenic properties of the vitamin reported in the literature. However, further studies are required to establish the significance of these reactions under in vivo conditions.

Erythrocyte antioxidant status in asymptomatic hypercholesterolemic men

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An imbalance between antioxidant and oxidant-generating systems leading to an oxidative stress has already been proposed in the pathogenesis of atherosclerosis. In the present study we investigated the antioxidant status in 60 asymptomatic hypercholesterolemic (HC) men compared with 48 normocholesterolemic (NC) men. Hypercholesterolemic subjects had a significantly lower red blood cell vitamin E (vit E-RBC) content in spite of their normal total plasma and HDL vitamin E concentrations. Activities of erythrocyte superoxide dismutase and glutathione peroxidase were not significantly different between groups. We also determined the resistance of RBCs to an oxidative stress by determining the extent of hemolysis induced by a water-soluble azo-compound. This resistance

was significantly decreased in HC men compared with NC subjects. These results demonstrate an altered antioxidant status of RBC in asymptomatic HC men associated with an increased erythrocyte susceptibility to an oxidative stress. The measure of the vitamin E content in RBC might be the most sensitive parameter for evidencing early oxidative stress which does not need an adaptation of enzymatic protective systems.

Monocyte superoxide production is inversely related to normal content of alpha-tocopherol in low-density lipoprotein

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Vitamin E (alpha-tocopherol) is a potent peroxyl radical scavenger. According to the oxidative theory of atherosclerosis, it prevents oxidation of low-density lipoprotein (LDL) and thereby lowers the risk of cardiovascular disease. It also mediates cell actions, and specifically decreases monocyte superoxide anion-production (O2-production), which is involved in LDL oxidation. We investigated whether alpha-tocopherol-containing LDL decreases this production in a manner dependent on the LDL alpha-tocopherol content (the alpha-tocopherol/apB molar ratio) in human, phorbol ester- stimulated, adherent monocytes. We found that O./-/2-production was inhibited by native LDL (n-LDL) in a manner highly sensitive to the increasing alpha-tocopherol content (range 4.5-8). In addition: (1) inhibition was greater when alpha-tocopherol was associated to acetylated LDL (ac-LDL), the maximal percentage of inhibition being 80% as opposed to 355 for n-LDL; (2) the alpha-tocopherol overloading of either form of LDL did not produce further inhibition; (3) the free form of alpha-tocopherol produced lower inhibition compared with the lipoprotein-associated forms; (4) inhibition was not related to the cell content of alpha-tocopherol. We propose that the cell targeting of alpha-tocopherol is crucial to the inhibition of monocyte O./- /2-production, and thus that the role of normal LDL-alpha-tocopherol contents (range 6-8) in the prevention of atherogenic processes needs to be reexamined.

Dehydroepiandrosterone protects low density lipoproteins against peroxidation by free radicals produced by gamma-radiolysis of ethanol-water mixtures

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Oxidized low density lipoproteins (LDL) are believed to play a central role in the events that initiate atherosclerosis. Antioxidants have been shown to decrease the oxidation of LDL, leading to the diminution of atherosclerosis. Since it is well-known that decreased levels of dehydroepiandrosterone (DHEA) are linked to the development of atherosclerosis, we studied the modulation of the oxidation of LDL by DHEA. LDL were obtained from 10 healthy subjects and oxidized by free radicals produced by gamma-radiolysis of ethanol-water mixtures. The formation of conjugated dienes and thiobarbituric acid-reactive substances (TBARS), the vitamin E content, as well as the incorporation of 4-[14C]DHEA in LDL and the chemotactic effect of oxidized LDL in the presence of DHEA towards monocytes, were investigated. It was found that DHEA was able to inhibit the oxidation of LDL by reducing over 90% of the conjugated dienes and TBARS formation, as well as by reducing the vitamin E disappearance and significantly decreasing the chemotactic activity towards monocytes. Our results suggest that DHEA exerts its antioxidative effect by protecting the endogenous vitamin E of LDL.

Oxidation of low density lipoproteins in the pathogenesis of atherosclerosis

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Malondialdehyde (MDA)-modified and oxidized low density lipoproteins (LDL) have been demonstrated in atherosclerotic lesions. Elevated titers of autoimmune antibodies specific for MDA-modified LDL predicted the progression of carotid atherosclerosis and of myocardial infarction. Recently, elevated levels of MDA-modified LDL were detected in the plasma of patients with ischemic heart disease, whereas, elevated levels of oxidized LDL were detected in the plasma of patients with ischemic heart disease and of heart transplant patients with post-transplant cardiovascular disease. Although increased levels of autoimmune antibodies against oxidatively modified LDL and increased levels of oxidized LDL antigen appear to be associated with atherosclerotic cardiovascular disease, there is to date no direct proof of the causal role of oxidized LDL in atherothrombosis. However, the decreased risk of cardiovascular disease associated with the administration of antioxidants (e.g. vitamin E), estrogen supplementation and increased levels of high density lipoproteins (HDL) may, at least partially, be due to the inhibition of oxidation of LDL or to the reversal of the atherothrombotic effects of oxidized LDL.

Vitamin E in diabetes mellitus

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There is growing evidence that supplementation with vitamin E in higher doses has a protective role in prevention of atherosclerosis. Patients with diabetes mellitus have an increased risk of cardiovascular complications and oxidative stress plays a promoting role in developing of long-term diabetic late complications. Low vitamin E status is a risk factor for diabetes mellitus. Therefore, an increased need for antioxidative substances, especially vitamin E, is given. The results prove that a therapy with adjuvant vitamin E in higher doses e.g. Pexan E (R) may leed to a regression of diabetic late complications. Epidemiological and prospective clinical studies indicate that high vitamin E levels may be associated with decreased cardiovascular diseases. For patients with diabetes mellitus the supplementation with vitamin E in higher doses is to be recommended in particular.

Metabolic consequences of reduced plasma LDL-C during hypolipidaemic therapy: Assessment of lipoperoxidation activity and vitamin E in lipoprotein fractions

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There is evidence that statins may have other anti-atherogenic effects besides their lipid-lowering activity, including effects on oxidability of lipoproteins. Thus the aim of the present study was to examine consequences of reduced plasma cholesterol during hypolipidaemic therapy, lipoperoxidation activity and the distribution of the antioxidant vitamin E in lipoprotein fractions. A group of 14 patients (8 men, 6 women, age 35-65y) with hypercholesterolaemia was treated using simvastatin (Zocor (R) MSD, 20 mg daily). Blood samples were examined before treatment, after 4 and 8 weeks of therapy. After ultracentrifugation, samples were analyzed for vitamin E content in lipoprotein fractions. Antioxidant status was examined using serum thiobarbituric acid reacting substance (TBARS) activity. Simvastatin reduced both total cholesterol (9.28plus or minus0.56 vs. 6.64plus or minus0.35 mmol/l; $p<0.001$), IDL-C (1.76plus or minus0.15 vs. 1.08plus or minus0.09 mmol/l; $p<0.001$), and LDL-C (3.80plus or minus0.35 vs. 2.63plus or minus0.23 mmol/l; $p<0.001$). Total serum vitamin E was reduced during hypolipidaemic therapy (44.54plus or minus3.62 vs. 36.85plus or minus1.72 micromol/l; $p =0.06$). However, the ratio of serum vitamin E/total serum cholesterol (4.86plus or minus0.31 vs. 5.63plus or minus0.28 micromol/mmol; $p = 0.09$) and the ratio of LDL-C vitamin E/LDL-C (3.57plus or minus0.31 vs. 3.67plus or minus0.31 micromol/mmol; n.s.) did not change, and the ratio of IDL-C vitamin E/IDL-C (4.44plus or minus0.32 vs. 5.40plus or minus0.61 micromol/mmol; $p<0.01$) and HDL- C vitamin E/HDL-C (3.76plus or

minus0.41 vs. 5.83plus or minus0.49 micromol/mmol; p = 0.01) increased significantly. Serum TBARS decreased significantly (6.97plus or minus0.69 vs. 4.72plus or minus0.48 micromol/l; p<0.001). We conclude that effective hypolipidaemic treatment with simvastatin is associated with improved antioxidant status and a proportional increase in the serum content of vitamin E in the HDL- and IDL-cholesterol fraction, and that the content of vitamin E in total and LDL-cholesterol did not change despite the decreased concentration of its lipid carrier. With regard to functions of vitamin E, this may be an additional anti-atherogenic effect of such therapy.

Where are we with vitamin E?

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Oxidative modification of low-density lipoproteins appears to significantly enhance their role in atherogenesis. Inhibition of this process with naturally occurring antioxidants has been proposed as a mechanism to retard the progression of coronary artery disease. Vitamin E has been among those natural antioxidants found to reduce atherosclerotic lesion formation in animal models. Further supported by a substantial accumulation of observational epidemiologic data demonstrating an association between antioxidant vitamin intake and reduced risk of cardiovascular mortality vitamin E has been examined in a number of case-control and prospective cohort studies as a potential agent in the primary and secondary prevention of morbidity and mortality from coronary artery disease. These efforts have generated a large body of evidence suggesting a protective role, but conflict in the data remains. In addition, even with large, well-conducted prospective epidemiologic studies, the potential effects of residual confounding may be on the same order of magnitude as the reported benefit. The several small randomized interventional trials and two larger placebo-controlled studies that have been completed to date leave some key questions unanswered. Currently ongoing are several large randomized interventional trials that will serve to further clarify the role of this promising agent in the primary and secondary prevention of atherosclerotic coronary disease.

The antioxidative effects of the isoflavan glabridin on endogenous constituents of LDL during its oxidation

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The effect of the consumption of glabridin, an isoflavan isolated from Glycyrrhiza glabra (licorice) root, on the susceptibility of low density lipoprotein (LDL) to oxidation was studied in atherosclerotic apolipoprotein E deficient (Edegreemice) and was compared with that of the known flavonoids, quercetin and catechin. Glabridin inhibitory activity on in vitro oxidation of human LDL was also investigated by determining the formation of lipid peroxides and oxysterols and the consumption of LDL-associated lipophilic antioxidants. Determination of the extent of LDL oxidation by measuring the formation of thiobabituric acid reactive substances (TBARS) after 2 h of LDL incubation with CuSO4 (10 microM) or 2,2'-azobis (2-amidino-propane) dihydrochloride (AAPH) (5 mM), revealed that glabridin or quercetin consumption resulted in a 53 and 54% reduction in copper ion induced oxidation, respectively, and a 95 and 83% reduction in AAPH induced LDL oxidation, respectively. No inhibition was obtained with consumption of catechin. About 80% of glabridin was found to bind to the LDL human particle. In the in vitro oxidation of LDL induced by AAPH (5 mM), glabridin inhibited the formation of TBARS, lipid peroxides and cholesteryl linoleate hydroperoxide (CLOOH) at all the concentrations tested (5-60 microM), while in oxidation induced by copper ions (10 microM), glabridin exhibited a pro-oxidant activity at concentrations lower than 20 microM, and a clear antioxidant activity at concentrations greater than 20 microM. Glabridin (30 microM) inhibited the formation of cholest-5-ene-3,7-diol (7-hydroxycholesterol), cholest-5- ene-3-ol-7-one (7-ketocholesterol) and cholestan-5,6-epoxy-3-ol (5,6-epoxycholesterol) after 6 h of AAPH induced LDL oxidation, by 55, 80 and 40%, respectively, and after 6 h of copper ion induced LDL oxidation, by 73, 94 and 52%, respectively. Glabridin also inhibited the consumption of beta- carotene and lycopene by 38 and 52%, respectively, after 0.5 h of LDL oxidation with AAPH, but failed to protect vitamin E. The in vivo and in vitro reduction of the susceptibility of LDL to oxidation obtained with glabridin, may be related to the absorption or binding of glabridin to the LDL particle and subsequent protection of LDL from oxidation by inhibiting the formation of lipid peroxides and oxysterols, and by protecting LDL associated carotenoids.

Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease

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Backgrounds: Oxidized low-density lipoprotein is involved in the pathogenesis of atherosclerosis. In epidemiological studies antioxidants have been inversely related with coronary heart disease. Findings from controlled trials are inconclusive.

Methods: We studied the primary preventive effect of vitamin E (alpha tocopherol) and beta carotene supplementation on major coronary events in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a controlled trial undertaken primarily to examine the effect of these agents 50 to 69 years with no history of myocardial infarction were randomly assigned to receive vitamin E (50 mg), beta carotene (20 mg), both agents, or placebo daily for 5 to 8 years (median, 6.1 years). The end point was the first major coronary event, either nonfatal myocardial infarction (surviving at least 28 days; n=1204) or fatal coronary heart disease (n=907).

Results: The incidence of primary major coronary events decreased 4% (95% confidence interval, -12% to 4%) among recipients of vitamin E and increased 1% (95% confidence interval, -7% to 10%) among recipients of beta carotene compared with the respective nonrecipients. Neither agent affected the incidence of nonfatal myocardial infarction. Supplementation with vitamin E decreased the incidence of fatal coronary heart disease by 8% (95% confidence interval, - 19% to 5%), but beta carotene had no effect on this end point.

Conclusions: Supplementation with small dose of vitamin E has only marginal effect on the incidence of fatal coronary heart disease in male smokers with no history of myocardial infarction, but no influence on nonfatal myocardial infarction. Supplementation with beta carotene has no primary preventive effect on major coronary events.

Low-density lipoprotein oxidation and vitamins E and C in sustained and white-coat hypertension

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Hypertension (United States), 1998, 31/2 (621-626)

Low-density lipoprotein oxidation and antioxidant vitamins E and C were investigated in white-coat hypertension in comparison with sustained hypertension and normotension. We selected 21 sustained hypertensive subjects, 21 white-coat hypertensive subjects, and 21 normotensive subjects matched for gender, age, and body mass index. White-coat hypertension was defined as clinical hypertension and daytime ambulatory blood pressure <139/90 (subjects were also reclassified using 134/90 and 135/85 mm Hg as cutoff points for daytime blood pressure). Blood samples were drawn for lipid profile determination, assessment of fluorescent products of lipid peroxidation in native LDL, evaluation of susceptibility to LDL oxidation in vitro (lag phase and propagation rate), and determination of LDL vitamin E and plasma vitamins E and C contents. Compared with sustained hypertensive subjects, white-coat hypertensives had significantly lower fluorescent products of lipid peroxidation (15.4plus or minus3.4 versus 10.2 plus or minus3 units of relative

fluorescence/mg LDL protein, P<.05), longer lag phase (54plus or minus10 versus 88plus or minus 10 minutes, P<.05), lower propagation rate (8.2plus or minus2.5 versus 5.95plus or minus2.1 nmol diene/min per mg LDL cholesterol, P<.05), higher LDL vitamin E content (8.3plus or minus1.1 versus 10.1plus or minus1.8 nmol/mg LDL cholesterol, P<.05), and plasma vitamin C content (40plus or minus 13 versus 57plus or minus9 micromol/L, P<. 05). No significant difference was observed between white-coat hypertensive and normotensive subjects. The results did not change after reclassification of subjects. Our data show that white-coat hypertensive subjects do not show an enhanced propensity to LDL oxidation or reduction in antioxidant vitamins. Given the role of LDL oxidation in the development of atherosclerosis and that of vitamin E and C in protecting against it, these findings suggest that white- coat hypertension per se carries a low atherogenic risk.

Progress in cardiology

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Medecine et Hygiene (Switzerland), 1998, 56/2191 (16-20)

Coronary angioplasty is new one of the most important techniques in cardiology. Stents represent a partial solution to the frequent problem of restenosis. Hopes for prevention rest on new antiplatelet and antioxidant agents, intracoronary radiotherapy and genic therapy. Efficacy of low- molecular-weight heparin is equivalent to conventional heparin for the treatment of DVT, pulmonary embolism and unstable angina. Moreover it has the advantage of subcutaneous administration and absence of coagulation control. Unstable coronary syndrome are very common. In addition to conventional antiischemic drugs and heparin, IIb/IIa antagonists represent a promising contribution. The role of antioxidants for coronary prevention remains controversial but vitamin E appears to be useful.

Effect of supplementation with vitamin E on LDL oxidizability and prevention of atherosclerosis

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BioFactors (Netherlands), 1998, 7/1-2 (51-54)

Supplementation of LDL with vitamin E is thought to protect LDL from oxidative modification and prevent the development of atherosclerosis. Large epidemiological studies have revealed that vitamin E levels in plasma are inversely correlated to the incidence of coronary heart disease. Double-blind placebo-controlled trials have reported that supplementation with vitamin E

decreases the incidence of coronary events in coronary heart disease (CHD) patients. However, it is not clear how high a dose of vitamin E is needed to prevent formation of atherosclerosis. In animal studies, a diet containing 0.125% vitamin E increased its levels in plasma two-fold and prevented formation of early atherosclerotic lesions in the thoracic aorta of hypercholesterolemic rabbits. Dose-response studies in humans have reported that 400 IU/day vitamin E increased its levels in plasma two-fold and prolonged the lag time before LDL oxidation. It has been reported that oxidizability of LDL was correlated to the atherosclerotic score of coronary angiography in CHD patients. About 400 IU/day vitamin E, which increases its levels two-fold and prolongs sufficiently the lag time before LDL oxidation, might be beneficial in decreasing the individual risk of CHD.

Action of vitamin E as antioxidant against oxidative modification of low density lipoprotein

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BioFactors (Netherlands), 1998, 7/1-2 (41-50)

The hypothesis that the oxidative modification of LDL is a key event for development of atherosclerosis was originally put forward to explain the recruitment of monocytes and the accumulation of lipid-laden macrophage-derived foam cells in the fatty streak lesion (1). Subsequent studies demonstrated a large number of biological properties of oxidized LDL that could make it more atherogenic than native LDL (2). Several kinds of oxidation products in the oxidation of LDL have been identified and purified, and their biological properties investigated (3-9). These oxidation products contribute to the development of atherosclerotic lesions not only directly by inducing expression of binding molecules (10,11), cell growth (8,9) and monocyte chemotaxis (12-14) but also indirectly by inducing the release of several kinds of cytokines (13,15) for which cytotoxicity of oxidized LDL is responsible. Findings which were accumulated through these studies are summarized in Scheme 1. It has been also shown that antioxidants could attenuate the effects of these oxidative modifications of LDL. Although the relative importance of these oxidative modifications in vivo remains to be established, it is well-established in several experimental animal models that the administration of antioxidant can retard the development of early atherosclerotic lesions (16-20). Polyclonal and monoclonal antibodies against oxidized LDL have been established and gave positive reactions in Watanabe heritable hyperlipidemea (WHHL) rabbit and human atherosclerotic lesions (21-27).

Atherogenic lipoproteins support assembly of the prothrombinase complex and thrombin generation: Modulation by oxidation and vitamin E

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Blood (United States), 1998, 91/2 (508-515)

The importance of lipoproteins in the etiology of atherosclerosis is well established. Evidence is now accumulating to implicate thrombin in the pathogenesis of atherosclerosis. We have investigated whether atherogenic lipoproteins can support thrombin generation. In the absence of platelets or endothelial cells, both very low-density lipoprotein (VLDL) and oxidized low-density lipoprotein (LDL) support assembly of the prothrombinase complex and generation of thrombin. Thrombin generation (per microg of apolipoprotein) supported by VLDL was 19.4-fold greater than that supported by high-density lipoprotein (HDL), P < .00001, and 11.7-fold greater than that supported by LDL, P < .00001. Oxidation of LDL increased lipoprotein-supported thrombin generation 12-fold compared to unmodified LDL, P < .0001. We have shown that the phenomenon of lipoprotein-supported thrombin generation is mediated predominantly by specific phospholipids and is enhanced by oxidation of these phospholipids. The addition of vitamin E (alpha-tocopherol) markedly reduced the increase in thrombin generation observed after oxidation of LDL (822 plus or minus 57 v 138 plus or minus 47 nmol/L; P < .0001). These effects suggest that lipoproteins are important in the production of thrombin and that vitamin E may confer protection from the detrimental effects of lipoprotein oxidation by limiting thrombin formation. These results suggest that atherogenic lipoproteins are linked to the development of atherosclerosis in part by their capacity to support thrombin generation.

A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids.

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A double-blind crossover study comparing the effect of aged garlic extract with a placebo on blood lipids was performed in a group of 41 moderately hypercholesterolemic men [cholesterol concentrations 5.7-7.5 mmol/L (220-290 mg/dL)]. After a 4-wk baseline period, during which the subjects were advised to adhere to a National Cholesterol Education Program Step I diet, they were started on 7.2 g aged garlic extract per day or an equivalent amount of placebo as a dietary supplement for a period of 6 mo, then switched to the other supplement for an additional 4 mo. Blood lipids, blood counts, thyroid and liver function measures, body weight, and blood pressure were followed over the entire study period. The major findings were a maximal reduction in total serum cholesterol of 6.1% or 7.0% in comparison with the average concentration during the placebo

administration or baseline evaluation period, respectively. Low-density-lipoprotein cholesterol was also decreased by aged garlic extract, 4% when compared with average baseline values and 4.6% in comparison with placebo period concentrations. In addition, there was a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure in response to aged garlic extract. We conclude that dietary supplementation with aged garlic extract has beneficial effects on the lipid profile and blood pressure of moderately hypercholesterolemic subjects.

Plasma homocysteine levels and mortality in patients with coronary artery disease.

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N Engl J Med 1997 Jul 24;337(4):230-6
Comment in: N Engl J Med 1997 Nov 27;337(22):1631-2; discussion 1632-3

BACKGROUND: Elevated plasma homocysteine levels are a risk factor for coronary heart disease, but the prognostic value of homocysteine levels in patients with established coronary artery disease has not been defined.

METHODS: We prospectively investigated the relation between plasma total homocysteine levels and mortality among 587 patients with angiographically confirmed coronary artery disease. At the time of angiography in 1991 or 1992, risk factors for coronary disease, including homocysteine levels, were evaluated. The majority of the patients subsequently underwent coronary-artery bypass grafting (318 patients) or percutaneous transluminal coronary angioplasty (120 patients); the remaining 149 were treated medically.

RESULTS: After a median follow-up of 4.6 years, 64 patients (10.9 percent) had died. We found a strong, graded relation between plasma homocysteine levels and overall mortality. After four years, 3.8 percent of patients with homocysteine levels below 9 micromol per liter had died, as compared with 24.7 percent of those with homocysteine levels of 15 micromol per liter or higher. Homocysteine levels were only weakly related to the extent of coronary artery disease but were strongly related to the history with respect to myocardial infarction, the left ventricular ejection fraction, and the serum creatinine level. The relation of homocysteine levels to mortality remained strong after adjustment for these and other potential confounders. In an analysis in which the patients with homocysteine levels below 9 micromol per liter were used as the reference group, the mortality ratios were 1.9 for patients with homocysteine levels of 9.0 to 14.9 micromol per liter, 2.8 for those with levels of 15.0 to 19.9 micromol per liter, and 4.5 for those with levels of 20.0 micromol per liter or higher (P for trend=0.02). When death due to cardiovascular disease (which occurred in 50 patients) was used as the end point in the analysis, the relation between homocysteine levels and mortality was slightly strengthened.

CONCLUSIONS: Plasma total homocysteine levels are a strong predictor of mortality in patients with angiographically confirmed coronary artery disease.

The effect of folic acid fortification on plasma folate and total homocysteine concentrations.

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N Engl J Med 1999 May 13;340(19):1449-54

BACKGROUND: In 1996, the Food and Drug Administration issued a regulation requiring all enriched grain products to be fortified with folic acid to reduce the risk of neural-tube defects in newborns. Fortification (140 microg per 100 g) began in 1996, and the process was essentially complete by mid-1997.

METHODS: To assess the effect of folic acid fortification on folate status, we measured plasma folate and total homocysteine concentrations (a sensitive marker of folate status) using blood samples from the fifth examination (January 1991 to December 1994) of the Framingham Offspring Study cohort for baseline values and the sixth examination (January 1995 to August 1998) for follow-up values. We divided the cohort into two groups on the basis of the date of their follow-up examination: the study group consisted of 350 subjects who were seen after fortification (September 1997 to March 1998), and the control group consisted of 756 subjects who were seen before fortification (January 1995 to September 1996).

RESULTS: Among the subjects in the study group who did not use vitamin supplements, the mean folate concentrations increased from 4.6 to 10.0 ng per milliliter (11 to 23 nmol per liter) ($P<0.001$) from the baseline visit to the follow-up visit, and the prevalence of low folate concentrations (<3 ng per milliliter [7 nmol per liter]) decreased from 22.0 to 1.7 percent ($P< 0.001$). The mean total homocysteine concentration decreased from 10.1 to 9.4 micromol per liter during this period ($P<0.001$), and the prevalence of high homocysteine concentrations (>13 micromol per liter) decreased from 18.7 to 9.8 percent ($P<0.001$). In the control group, there were no statistically significant changes in concentrations of folate or homocysteine.

CONCLUSIONS: The fortification of enriched grain products with folic acid was associated with a substantial improvement in folate status in a population of middle-aged and older adults.

Dietary supplement with vitamin C prevents nitrate tolerance.

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J Clin Invest 1998 Jul 1;102(1):67-71

Enhanced formation of superoxide radicals has been proposed to play a major role in the development of nitrate tolerance in humans. We tested the effects of vitamin C (Vit-C) supplementation on glyceroltrinitrate (GTN)-induced hemodynamic effects during 3-d nonintermittent transdermal administration of GTN (0.4 mg/h) in nine healthy subjects. Tolerance development was monitored by changes in arterial pressure, dicrotic digital pulse pressure, and heart rate. Studies with GTN, Vit-C, or GTN/Vit-C were successively carried out at random in three different series in the same subjects. GTN treatment caused an immediate rise in arterial conductivity (a/b ratio of dicrotic pulse), but within 2 d of initiating GTN, the a/b ratio progressively decreased and reached basal levels. In addition, there was a progressive loss of the orthostatic decrease in blood pressure. However, coadministration of Vit-C and GTN fully maintained the GTN-induced changes in the orthostatic blood pressure, and the rise of a/b ratio was augmented by 310% for the duration of the test period. Changes in vascular tolerance in GTN-treated subjects were paralleled by upregulation of the activity of isolated platelets, which was also reversed by Vit-C administration. These findings demonstrate that dietary supplementation with Vit-C eliminates vascular tolerance and concomitant upregulation of ex vivo-washed platelet activity during long-term nonintermittent administration of GTN in humans.

Randomized, double-blind, placebo-controlled study of the preventive effect of supplemental oral vitamin C on attenuation of development of nitrate tolerance.

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OBJECTIVES: This study sought to evaluate the preventive effect of vitamin C, an antioxidant, on the development of nitrate tolerance.

BACKGROUND: Decreased intracellular production of cyclic guanosine monophosphate (cGMP) is a mechanism of nitrate tolerance, and increased superoxide levels and reduced activation of guanylate cyclase have been observed in vitro.

METHODS: In this double-blind, placebo-controlled study, 24 normal volunteers and 24 patients with ischemic heart disease (IHD) were randomized to receive either vitamin C (2 g three times daily [vitamin C group, n=12]) or placebo (placebo group, n=12). The vasodilator response to nitroglycerin was assessed

with forearm plethysmography by measuring the change in FBF before and 5 min after sublingual administration of 0.3 mg of nitroglycerin. Blood samples were simultaneously obtained to measure platelet cGMP levels. FBF was measured, and blood sampling was performed serially at baseline (day 0), 3 days after administration of vitamin C or placebo (day 3) and 3 days after application of a 10-mg/24-h nitroglycerin tape concomitantly with oral vitamin C or placebo (day 6).

RESULTS: There were no differences between the vitamin C and placebo groups in percent increases in FBF (%FBF) or platelet cGMP levels (%cGMP) after administration of sublingual nitroglycerin on day O (%FBF: normal volunteers 31+/-8 vs. 32+/-10; patients with IHD 32+/-9 vs. 32+/-8; %cGMP: normal volunteers 37+/-9 vs. 39+/-10; patients with IHD 38+/-10 vs. 39+/-10 [vitamin C group vs. placebo group]) or day 3 (%FBF: normal volunteers 32+/-9 vs. 33+/-9; patients with IHD 31+/-10 vs. 31+/-10; %cGMP: normal volunteers 36+/-8 vs. 37+/-9; patients with IHD 39+/-11 vs. 38+/-10 [vitamin C group vs. placebo group]). The %FBF and %cGMP in the placebo group were significantly lower on day 6 than in the vitamin C group (%FBF: normal volunteers 30+/-8 vs. 19 4, $p < 0.01$; patients with IHD 29+/-9 vs. 17+/-6, $p < 0.01$; %cGMP: normal volunteers 36 10 vs. 17+/-6, $p < 0.01$; patients with IHD 37+/-11 vs. 15+/-5, $p < 0.01$ [vitamin C group vs. placebo group]).

CONCLUSIONS: These results indicate that combination therapy with vitamin C is potentially useful for preventing the development of nitrate tolerance.

Co-enzyme Q10: a new drug for cardiovascular disease.

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J Clin Pharmacol 1990 Jul;30(7):596-608

Co-enzyme Q10 (ubiquinone) is a naturally occurring substance which has properties potentially beneficial for preventing cellular damage during myocardial ischemia and reperfusion. It plays a role in oxidative phosphorylation and has membrane stabilizing activity. The substance has been used in oral form to treat various cardiovascular disorders including angina pectoris, hypertension, and congestive heart failure. Its clinical importance is now being established in clinical trails worldwide.

Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. CoQ10 Drug Surveillance Investigators.

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Mol Aspects Med 1994;15 Suppl:s287-94

Digitalis, diuretics and vasodilators are considered the standard therapy for patients with congestive heart failure, for which treatment is tailored according to the severity of the syndrome and the patient profile. Apart from the clinical seriousness, heart failure is always characterized by an energy depletion status, as indicated by low intramyocardial ATP and coenzyme Q10 levels. We investigated safety and clinical efficacy of Coenzyme Q10 (CoQ10) adjunctive treatment in congestive heart failure which had been diagnosed at least 6 months previously and treated with standard therapy. A total of 2664 patients in NYHA classes II and III were enrolled in this open noncomparative 3-month postmarketing study in 173 Italian centers. The daily dosage of CoQ10 was 50-150 mg orally, with the majority of patients (78%) receiving 100 mg/day. Clinical and laboratory parameters were evaluated at the entry into the study and on day 90; the assessment of clinical signs and symptoms was made using from two-to seven-point scales. The results show a low incidence of side effects: 38 adverse effects were reported in 36 patients (1.5%) of which 22 events were considered as correlated to the test treatment. After three months of test treatment the proportions of patients with improvement in clinical signs and symptoms were as follows: cyanosis 78.1%, oedema 78.6%, pulmonary rales 77.8%, enlargement of liver area 49.3%, jugular reflux 71.81%, dyspnoea 52.7%, palpitations 75.4%, sweating 79.8%, subjective arrhytmia 63.4%, insomnia 662.8%, vertigo 73.1% and nocturia 53.6%. Moreover we observed a contemporary improvement of at least three symptoms in 54% of patients; this could be interpreted as an index of improved quality of life.

Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure (interim analysis). The CoQ10 Drug Surveillance Investigators.

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Clin Investig 1993;71(8 Suppl):S145-9

Digitalis, diuretics, and vasodilators are considered standard therapy for patients with congestive heart failure, for which treatment is tailored according to the severity of the syndrome and the patient profile. Apart from the clinical seriousness, heart failure is always characterized by an energy depletion status, as indicated by low intramyocardial ATP and coenzyme Q10 levels. We investigated safety and clinical efficacy of coenzyme Q10 (CoQ10) adjunctive treatment in congestive heart failure, which had been diagnosed at least 6 months previously and treated with standard therapy. A total of 2500 patients in NYHA classes II and III were enrolled in this open noncomparative 3-month postmarketing drug surveillance study in 173 Italian centers. The daily dose of CoQ10 was 50-150 mg orally, with the majority of patients (78%) receiving 100 mg/day. Clinical and

laboratory parameters were evaluated at the entry into the study and on day 90; the assessment of clinical signs and symptoms was made using from two- to seven-point scales. Preliminary results on 1113 patients (mean age 69.5 years) show a low incidence of side effects: 10 adverse reactions were reported in 8 (0.8%) patients, of which only 5 reactions were considered as correlated to the test treatment. After 3 months of test treatment the proportions of patients with improvement in clinical signs and symptoms were as follows: cyanosis 81%, edema 76.9%, pulmonary rales 78.4%, enlargement of the liver area 49.3%, jugular reflux 81.5%, dyspnea 54.2%, palpitations 75.7%, sweating 82.4%, arrhythmia 62%, insomnia 60.2%, vertigo 73%, and nocturia 50.7%.

Clinical experience of coenzyme Q10 to enhance intraoperative myocardial protection in coronary artery revascularization.

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Cardiovasc Drugs Ther 1991 Mar;5 Suppl 2:297-300

Seventy-eight patients undergoing coronary artery bypass grafting (CABG) were compared retrospectively to evaluate whether pretreatment with coenzyme Q10 (CoQ) is effective in preventing left ventricular depression in early reperfusion following CABG. CoQ (5 mg/kg, intravenously) was given to 60 patients, 2 hours prior to the onset of cardiopulmonary bypass (CPB). CABG was performed using saphenous vein under CPB associated with cold cardioplegia in the standard fashion. Heart rate, mean arterial pressure, and cardiac index showed no significant difference between the CoQ and control groups. However, left ventricular stroke work index was significantly elevated at 6 and 10 hours of reperfusion following CABG in the CoQ-treated group compared with the controls. Serum MB-CK was lower at 0 and 6 hours of reperfusion in the CoQ group compared with the controls. These results suggest that pretreatment with intravenous CoQ is effective in preventing left ventricular depression in early reperfusion and in minimizing myocardial cellular injury during CABG followed by reperfusion.

Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis.

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N Engl J Med 1995 Feb 2;332(5):286-91
Comment in: N Engl J Med 1995 Feb 2;332(5):328-9
Comment in: N Engl J Med 1995 Aug 3;333(5):325

BACKGROUND. Epidemiologic studies have identified hyperhomocysteinemia as a possible risk factor for atherosclerosis. We determined the risk of carotid-artery atherosclerosis in relation to both plasma homocysteine concentrations and nutritional determinants of hyperhomocysteinemia.

METHODS. We performed a cross-sectional study of 1041 elderly subjects (418 men and 623 women; age range, 67 to 96 years) from the Framingham Heart Study. We examined the relation between the maximal degree of stenosis of the extracranial carotid arteries (as assessed by ultrasonography) and plasma homocysteine concentrations, as well as plasma concentrations and intakes of vitamins involved in homocysteine metabolism, including folate, vitamin B12, and vitamin B6. The subjects were classified into two categories according to the findings in the more diseased of the two carotid vessels: stenosis of 0 to 24 percent and stenosis of 25 to 100 percent.

RESULTS. The prevalence of carotid stenosis of > or = 25 percent was 43 percent in the men and 34 percent in the women. The odds ratio for stenosis of > or = 25 percent was 2.0 (95 percent confidence interval, 1.4 to 2.9) for subjects with the highest plasma homocysteine concentrations (> or = 14.4 mumol per liter) as compared with those with the lowest concentrations (< or = 9.1 mumol per liter), after adjustment for sex, age, plasma high-density lipoprotein cholesterol concentration, systolic blood pressure, and smoking status ($P < 0.001$ for trend). Plasma concentrations of folate and pyridoxal-5'-phosphate (the coenzyme form of vitamin B6) and the level of folate intake were inversely associated with carotid-artery stenosis after adjustment for age, sex, and other risk factors.

CONCLUSIONS. High plasma homocysteine concentrations and low concentrations of folate and vitamin B6, through their role in homocysteine metabolism, are associated with an increased risk of extracranial carotid-artery stenosis in the elderly.

Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia.

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Am J Clin Nutr 1993 Jan;57(1):47-53

We measured the vitamin B-6, vitamin B-12, and folic acid nutritional status in a group of apparently healthy men (n = 44) with moderate hyperhomocysteinemia (plasma homocysteine concentration > 16.3 mumol/L). Compared with control subjects (n = 274) with normal plasma homocysteine (< or = 16.3 mumol/L) concentrations, significantly lower plasma concentrations of pyridoxal-5'-phosphate ($P < 0.001$), cobalamin ($P < 0.001$), and folic acid ($P = 0.004$) were demonstrated in hyperhomocysteinemic men. The prevalence of suboptimal vitamin B-6, B-12, and folate status in men with hyperhomocysteinemia was

25.0%, 56.8%, and 59.1%, respectively. In a placebo-controlled follow-up study, a daily vitamin supplement (10 mg pyridoxal, 1.0 mg folic acid, 0.4 mg cyanocobalamin) normalized elevated plasma homocysteine concentrations within 6 wk. Because hyperhomocysteinemia is implicated as a risk factor for premature occlusive vascular disease, appropriate vitamin therapy may be both efficient and cost-effective to control elevated plasma homocysteine concentrations.

Carotid and femoral artery wall thickness and stiffness in patients at risk for cardiovascular disease, with special emphasis on hyperhomocysteinemia.

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Arterioscler Thromb Vasc Biol 1998 Dec;18(12):1958-63

Recent developments in ultrasound technology enable the noninvasive measurement of structural and functional vessel wall changes. Until now, the effect of homocysteine on the arterial wall has remained unclear: reports on intima-media thickness (IMT) yield conflicting results, whereas data on vessel wall stiffness are lacking. Because several cardiovascular risk factors result in an increased IMT or stiffness, different groups at risk for atherosclerotic disease, with special emphasis on hyperhomocysteinemia, were studied. Nineteen patients homozygous and 14 subjects heterozygous for cystathionine beta-synthase (CBS) deficiency, 21 patients with familial hypercholesterolemia (FH), 15 patients with essential hypertension, 20 smokers, and 28 control subjects were studied. The IMT values (both right and left) of the common carotid artery (CCA), bulb (BUL), internal carotid artery (ICA), and common femoral artery (CFA) were measured in millimeters by high-resolution ultrasound (Biosound). The distensibility (DC, in 10(-3). kPa-1) and compliance (CC in mm2. kPa-1) coefficients of the CCA (right and left) and CFA (right) were determined by a wall track system (Pie Medical). The mean IMT of the posterior wall in the CCA was 0.70+/-0.09 mm in healthy controls. For patients with vascular disease, FH, and hypertension and in smokers, the mean CCA IMT was larger, whereas no major differences in IMT were observed in patients either homozygous or heterozygous for CBS deficiency. The DC and CC in the right CCA were 23.5+/-6.9 (10(-3). kPa-1) and 0.9+/-0.3 (mm2. kPa-1) in healthy subjects, slightly lower in patients homozygous for CBS deficiency, and clearly lower in patients with vascular disease, FH, and hypertension. No positive correlation was found between plasma homocysteine level and either IMT, CC, or DC. Because smoking was a confounder in each risk group, a stepwise regression analysis was carried out to assess the contribution of each risk factor on IMT and arterial wall stiffness. Age explained most of the variation in IMT of the CCA (coefficient of determination R2 of 0.34), whereas R2 values for serum low density lipoprotein cholesterol, smoking (pack-years), and systolic blood pressure were 0.08, 0.07, and 0.06, respectively. Homocysteine did not contribute to variation in IMT in

both the CCA and CFA. Age and smoking contributed to the variation in IMT in the CFA. The variation in DC and CC in the right CCA and right CFA could in part be explained by age, low density lipoprotein cholesterol, and blood pressure. Plasma homocysteine concentration explained only a small proportion of the variation in DC in the CCA (R2=0.02) and in CC in the CFA (R2=0.04). In this study, no relationship was found between homocysteine level and the thickness of the arterial wall, with only a marginal influence on stiffness.

Serum homocysteine and risk of coronary heart disease and cerebrovascular disease in elderly men: a 10-year follow-up.

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Arterioscler Thromb Vasc Biol 1998 Dec;18(12):1895-901

Hyperhomocysteinemia is an independent risk factor for atherosclerotic disease in the middle-aged. We investigated whether a high serum homocysteine level is a risk factor for vascular disease in 878 elderly men (mean age at baseline, 71.5 years; range, 64 to 84 years) in a population-based, representative cohort followed up for 10 years in Zutphen, the Netherlands. Thirty-one percent had nonfasting homocysteine levels >/=17 micromol/L. After adjustment for other major risk factors, high homocysteine levels at baseline (the third compared with the first tertile) were associated with an increased baseline prevalence of myocardial infarction (odds ratio [OR], 1.81; 95% confidence interval [CI], 1.07 to 3.08; P for trend, 0.03) and with a marginally significant increase in the risk of dying of coronary heart disease (relative risk [RR], 1.58; 95% CI, 0.93 to 2.69; P for trend, 0.09) but not with an increased risk of first-ever myocardial infarction. In addition, high homocysteine levels at baseline were associated with an increased baseline prevalence of stroke (OR, 4.61; 95% CI, 1.79 to 11.89; P for trend, 0.002) and with an increased risk of dying of cerebrovascular disease in subjects without hypertension (RR, 6.18; 95% CI, 2.28 to 16.76) but not in those with hypertension. High homocysteine levels were associated with an increased risk of first-ever stroke among normotensive subjects that was not statistically significant (RR, 1. 77 [95% CI, 0.83 to 3.75; P for trend, 0.14]). In a general population of elderly men, a high homocysteine level is common and is strongly associated with the prevalence of coronary heart disease and cerebrovascular disease. It is a strong predictive factor for fatal cerebrovascular disease in men without hypertension but less so for coronary heart disease.

Vitamin supplementation reduces blood homocysteine levels: a controlled trial in patients with venous thrombosis and healthy volunteers.

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Arterioscler Thromb Vasc Biol 1998 Mar;18(3):356-61

Hyperhomocysteinemia is a risk factor for atherosclerosis and thrombosis and is inversely related to plasma folate and vitamin B12 levels. We assessed the effects of vitamin supplementation on plasma homocysteine levels in 89 patients with a history of recurrent venous thrombosis and 227 healthy volunteers. Patients and hyperhomocysteinemic (homocysteine level >16 micromol/L) volunteers were randomized to placebo or high-dose multivitamin supplements containing 5 mg folic acid, 0.4 mg hydroxycobalamin, and 50 mg pyridoxine. A subgroup of volunteers without hyperhomocysteinemia was also randomized into three additional regimens of 5 mg folic acid, 0.5 mg folic acid, or 0.4 mg hydroxycobalamin. Before and after the intervention period, blood samples were taken for measurements of homocysteine, folate, cobalamin, and pyridoxal-5'-phosphate levels. Supplementation with high-dose multivitamin preparations normalized plasma homocysteine levels (< or = 16 micromol/L) in 26 of 30 individuals compared with 7 of 30 in the placebo group. Also in normohomocysteinemic subjects, multivitamin supplementation strongly reduced homocysteine levels (median reduction, 30%; range, -22% to 55%). In this subgroup the effect of folic acid alone was similar to that of multivitamin: median reduction, 26%; range, -2% to 52% for 5 mg folic acid and 25%; range, -54% to 40% for 0.5 mg folic acid. Cobalamin supplementation had only a slight effect on homocysteine lowering (median reduction, 10%; range, -21% to 41%). Our study shows that combined vitamin supplementation reduces homocysteine levels effectively in patients with venous thrombosis and in healthy volunteers, either with or without hyperhomocysteinemia. Even supplementation with 0.5 mg of folic acid led to a substantial reduction of blood homocysteine levels.

Plasma homocysteine levels related to interactions between folate status and methylenetetrahydrofolate reductase: a study in 52 healthy subjects.

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Metabolism 1998 Nov;47(11):1413-8

Hyperhomocysteinemia, a risk factor for vascular disease, is related to vitamin B12, vitamin B6, and especially folate deficiency, or to genetic factors such as mutations in methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in the remethylation pathway of homocysteine to methionine. Recently, a C677 --> T mutation identified in the MTHFR gene was found to be frequently associated with decreased MTHFR activity and an elevated plasma homocysteine concentration. Since hyperhomocysteinemia seems to be determined by both genetic and environmental factors, we studied the interactions between MTHFR (phenotype and genotype) and folate status, including methyltetrahydrofolate

(methylTHF), the product of MTHFR, on the homocysteine concentration in 52 healthy subjects, (28 women and 24 men; mean age, 32.7 years). MTHFR activity seems to be dependent on folate status, as shown by a lower activity in folate-deficient subjects and a return to normal values after supplementation with folic acid, and also by a decreased enzymatic activity on phytohemagglutinin (PHA)-stimulated lymphocytes grown in a folic acid-deficient medium. Conversely, the C677 --> T mutation seems to influence folate metabolism. Subjects who were homozygous for this mutation (+/+) had significantly higher plasma homocysteine and lower plasma folate and total and methylfolate levels in red blood cells (RBCs) than heterozygous (+/-) and normal (-/-) subjects. The ratio of RBC methylfolate to RBC total folate was, respectively, 0.27 in +/+, 0.66 in +/-, and 0.71 in -/-. This mutation seems to have an impact on methylTHF generation. These data illustrate the interactions between nutritional and genetic factors.

Effectiveness of low-dose crystalline nicotinic acid in men with low high-density lipoprotein cholesterol levels.

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Arch Intern Med 1996 May 27;156(10):1081-8

BACKGROUND: Hypoalphalipoproteinemia (low serum concentration of high-density lipoprotein cholesterol [HDL-C]) is a common pattern of dyslipidemia associated with coronary heart disease. High doses of nicotinic acid effectively raise HDL-C levels in this condition, but they are commonly accompanied by side effects. The efficacy of low doses of nicotinic acid that may produce fewer side effects has not been adequately studied. OBJECTIVE: To determine the effects of low-dose nicotinic acid on HDL-C levels in patients with hypoalphalipoproteinemia.

METHODS: Forty-four men with low HDL-C levels (< 1.03 mmol/L [< 40 mg/dL]) entered the study. Twenty-four patients otherwise had normal lipid levels, and 20 were moderately hypertriglyceridemic (range of plasma triglyceride levels, 2.82 to 5.64 mmol/L 250 to 500 mg/dL). The trial consisted of 3 phases; each phase lasted 8 weeks. The first phase was diet only (30% fat diet); in the second phase, crystalline nicotinic acid was added at 1.5 g/d; and in the third phase, the dose was increased to 3 g/d.

RESULTS: Of the 44 patients who entered the study, 37 completed the low-dose phase (1.5 g/d); the remaining patients were withdrawn because of side effects to nicotinic acid. Four other patients who completed the low-dose phase were excluded from the higher dose phase because of side effects that developed when they were receiving the low dose. Ten other patients withdrew during the high-dose phase because of side effects. In both groups, responses to nicotinic acid therapy tended to be dose-dependent. For both groups, the higher dose generally produced a greater reduction in apolipoprotein B-containing lipoproteins and a

greater rise in HDL-C levels. However, for both groups, the low dose of nicotinic acid gave an average 20% increase in HDL-C levels.

CONCLUSIONS: A low dose (1.5 g/d) of crystalline nicotinic acid causes an average 20% increase in HDL-C levels and significantly lowers triglyceride levels in both normolipidemic and hyperlipidemic patients with low HDL-C levels. Although the changes induced by this dose are less than those that can be achieved by a higher dose, the lower dose is better tolerated. Nicotinic acid may be useful in combined drug therapy for secondary prevention of coronary heart disease, and if higher doses cannot be tolerated, use of a lower dose should still be useful for producing a moderate rise in HDL-C levels in patients with hypoalphalipoproteinemia.

Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study.

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Am J Cardiol 1998 Dec 17;82(12A):35U-38U; discussion 39U-41U

Niacin is a useful lipid-modifying drug because it (1) decreases low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein(a), and (2) raises high-density lipoprotein (HDL) cholesterol. Its use tends to be limited by side effects and inconvenient dosing regimens. The availability of an extended-release preparation (Niaspan-which has safety and efficacy similar to immediate-release niacin but which can be given once a day) provides an opportunity to increase the use of this effective lipid-modifying agent. To study the safety and efficacy of escalating doses of extended-release niacin, hyperlipidemic patients were randomly assigned to placebo or Niaspan. A forced dose-titration was done with the dosage increasing by 500 mg every 4 weeks to a maximum of 3,000 mg/day. Niaspan showed dose-related changes in total, LDL, and HDL cholesterol levels, triglycerides, cholesterol/HDL ratio, and lipoprotein(a). At a dosage of 2,000 mg/day, total cholesterol decreased by 12.1%, LDL cholesterol by 16.7%, triglycerides by 34.5%, and lipoprotein(a) by 23.6%; HDL cholesterol increased by 25.8%. Flushing was the most commonly reported side effect; flushing episodes tended to decrease with time despite an increasing dose of niacin. Of the reported side effects, only pruritus and rash were significantly different between the 2 groups. Aspartate aminotransferase, lactate dehydrogenase, and uric acid increased in a dose-dependent fashion, but fasting blood sugar increased by about 5% across most dosages. Two subjects had aspartate aminotransferase levels greater than twice the upper limit of normal, but there were no subjects in whom transaminases increased to 3 times the upper limit of normal. Women tended to have a greater LDL cholesterol response to the medication and also experienced more side effects, especially at higher dosages. Thus, the use of lower dosages of niacin may be desirable in women. The results of this dose-escalation study show beneficial effects of Niaspan on the entire lipid

profile. At the maximum recommended dosage of 2,000 mg/day, all lipid and lipoprotein levels changed in desirable directions. Side effects (other than flushing) and blood chemistries were comparable to those seen with immediate-release niacin.

Vitamin E and atherosclerosis.

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J Nutr 1998 Oct;128(10):1593-6

Vitamin E was advocated as an effective treatment for heart disease by Dr. Even Shute of London, Ontario more than 50 years ago. His pioneering claims, which were unacceptable to the medical community at large, have been confirmed by recent findings from epidemiologic studies and clinical trials. This review integrates our current knowledge of atherogenesis with the biological functions of vitamin E. The response-to-injury hypothesis explains atherosclerosis as a chronic inflammatory response to injury of the endothelium, which leads to complex cellular and molecular interactions among cells derived from the endothelium, smooth muscle and several blood cell components. Inflammatory and other stimuli trigger an overproduction of free radicals, which promote peroxidation of lipids in LDL trapped in the subendothelial space. Products of LDL oxidation are bioactive, and they induce endothelial expression and secretion of cytokines, growth factors and several cell surface adhesion molecules. The last-mentioned are capable of recruiting circulating monocytes and T lymphocytes into the intima where monocytes are differentiated into macrophages, the precursor of foam cells. In response to the growth factors and cytokines, smooth muscle cells proliferate in the intima, resulting in the narrowing of the lumen. Oxidized LDL can also inhibit endothelial production of prostacyclin and nitric oxide, two potent autacoids that are vasodilators and inhibitors of platelet aggregation. Evidence is presented that vitamin E is protective against the development of atherosclerosis. Vitamin E enrichment has been shown to retard LDL oxidation, inhibit the proliferation of smooth muscle cells, inhibit platelet adhesion and aggregation, inhibit the expression and function of adhesion molecules, attenuate the synthesis of leukotrienes and potentiate the release of prostacyclin through up-regulating the expression of cytosolic phospholipase A2 and cyclooxygenase. Collectively, these biological functions of vitamin E may account for its protection against the development of atherosclerosis.

Dynamics of vitamin E action against LDL oxidation.

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Free Radic Res 1998 Jun;28(6):561-72

Vitamin E acts as an important antioxidant against oxidative modification of low density lipoprotein (LDL) which is accepted as an initial event in the pathogenesis of atherosclerosis. In spite of the numerous studies and reports, the action and role of vitamin E have not been fully elucidated yet. In this brief overview, the dynamics of action of vitamin E as an antioxidant have been discussed and it is emphasized that the total antioxidant potency is determined by the relative importance of many competing reactions which is determined by the reactivities and concentrations of substrates, radicals and antioxidant and by physical factors of the environment.

Cost-effectiveness of vitamin E therapy in the treatment of patients with angiographically proven coronary narrowing (CHAOS trial). Cambridge Heart Antioxidant Study.

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Am J Cardiol 1998 Aug 15;82(4):414-7

Epidemiologic studies have suggested that vitamin E (alpha-tocopherol) may play a preventive role in reducing the incidence of atherosclerosis. The aim of this paper was to conduct a cost-effectiveness analysis of vitamin E supplementation in patients with coronary artery disease using data from the Cambridge Heart Antioxidant Study (CHAOS). The study compared cost-effectiveness in the context of Australian and United States (US) health care utilization. The main clinical outcome used in the economic evaluation was the incidence of acute myocardial infarction (AMI) which was nonfatal. Utilization of health care resources was estimated by conducting a survey of Australian clinicians and published Australian and US cost data. Cost savings of $127 (A$181) and $578/patient randomized to vitamin E therapy compared with patients receiving placebo were found for Australian and US settings, respectively. Savings in the vitamin E group were due primarily to reduction in hospital admissions for AMI. This occurred because the vitamin E group had a 4.4% lower absolute risk of AMI than did the placebo group. Less than 10% of health care costs in the Australian evaluation was due to vitamin E ($150 [A$214/patient]). Our economic evaluation indicates that vitamin E therapy in patients with angiographically proven atherosclerosis is cost-effective in the Australian and US settings.

Antioxidant vitamin intake and coronary mortality in a longitudinal population study.

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Am J Epidemiol 1994 Jun 15;139(12):1180-9

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of vitamin C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection.

Will the 'good fairies' please prove to us that vitamin E lessens human degenerative disease?

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Free Radic Res 1997 Nov;27(5):511-32
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Recent research about the role of free radical derivatives of oxygen and nitrogen in biological systems has highlighted the possibility that antioxidants, such as vitamin E, that prevent these processes in vitro may be capable of carrying out a similar function in living organisms in vivo. There is increasing evidence that free radical reactions are involved in the early stages, or sometimes later on, in the development of human diseases, and it is therefore of particular interest to inquire whether vitamin E and other antioxidants, which are found in the human diets, may be capable of lowering the incidence of these diseases. Put simply, the proposition is that by improving human diets by increasing the quantity in them of antioxidants, it might be possible to reduce the incidence of a number of degenerative diseases. Of particular significance to these considerations is the likely role of the primary fat-soluble dietary antioxidant vitamin E in the prevention of degenerative diseases such as arteriosclerosis, which is frequently

the cause of consequent heart attacks or stroke, and prevention of certain forms of cancer, as well as several other diseases. Substantial evidence for this proposition now exists, and this review is an attempt to give a brief account of the present position. Two kinds of evidence exist; on the one hand there is very substantial basic science evidence which indicates an involvement of free radical events, and a preventive role for vitamin E, in the development of human disease processes. On the other hand, there is also a large body of human epidemiological evidence which suggests that incidence of these diseases is lowered in populations having a high level of antioxidants, such as vitamin E, in their diet, or who have taken steps to enhance their level of intake of the vitamin by taking dietary supplements. There is also some evidence which suggests that intervention with dietary supplements of vitamin E can result in a lowered risk of disease, in particular of cardiovascular disease, which is a major killer disease among the developed nations of the world. The intense interest in this subject recently has as its objective the possibility that, by making some simple alterations to dietary lifestyle, or by enhancing the intake of vitamin E by fortification of foods, or by dietary supplements, it may be possible to reduce substantially the risk of a large amount of common, highly disabling human disease. By this simple means, therefore it may be possible to improve substantially the quality of human life, in particular for people of advancing years.

Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group.

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N Engl J Med 1997 Aug 7;337(6):365-72
Comment in: N Engl J Med 1997 Dec 25;337(26):1918; discussion 1919

BACKGROUND: Oxidizing metabolites generated at the site of coronary angioplasty can induce chain reactions that may lead to restenosis. Antioxidants may counter oxidative stress and modify neointimal formation and vascular remodeling. Experimental data and small clinical studies have suggested that antioxidants may prevent restenosis after angioplasty. In a double-blind, randomized trial, we studied whether drugs with antioxidant properties decrease the incidence and severity of restenosis after angioplasty.

METHODS: One month before angioplasty, 317 patients were randomly assigned to receive one of four treatments: placebo, probucol (500 mg), multivitamins (30,000 IU of beta carotene, 500 mg of vitamin C, and 700 IU of vitamin E), or both probucol and multivitamins-all given twice daily. Patients were treated for four weeks before and six months after angioplasty. Patients received an extra 1000 mg of probucol, 2000 IU of vitamin E, both probucol and vitamin E, or placebo 12 hours before angioplasty, according to their treatment assignments. Base-line and follow-up angiograms were interpreted by blinded investigators using a quantitative approach.

RESULTS: The mean (+/-SD) reduction in luminal diameter six months after angioplasty was 0.12 +/- 0.41 mm in the probucol group, 0.22 +/- 0.46 mm in the combined-treatment group, 0.33 +/- 0.51 in the multivitamin group, and 0.38 +/- 0.50 mm in the placebo group (P = 0.006 for those receiving vs. those not receiving probucol, and P = 0.70 for those receiving vs. those not receiving vitamins. Restenosis rates per segment were 20.7 percent in the probucol group, 28.9 percent in the combined-treatment group, 40.3 percent in the multivitamin group, and 38.9 percent in the placebo group (P = 0.003 for probucol vs. no probucol). The rates of repeat angioplasty were 11.2 percent. 16.2 percent, 24.4 percent, and 26.6 percent, respectively (P = 0.009 for probucol vs. no probucol).

CONCLUSIONS: The antioxidant probucol is effective in reducing the rate of restenosis after balloon coronary angioplasty.

Effects of intravenous perilla oil emulsion on nutritional status, polyunsaturated fatty acid composition of tissue phospholipids, and thromboxane A2 production in streptozotocin-induced diabetic rats.

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Nutrition 1995 Sep-Oct;11(5):450-5

The effects of a perilla oil (PO) emulsion rich in alpha-linolenic acid, administered by intravenous infusion, on nutritional status, fatty acid composition, and thromboxane A2 production were compared with those of a soybean oil (SO) emulsion in streptozotocin-induced diabetic rats given a fat-free diet for 7 days. The PO emulsion improved body weight gain and nitrogen balance compared with the SO emulsion and reduced thromboxane A2 production by platelets. The PO emulsion also increased the proportion of eicosapentaenoic acid, but decreased that of arachidonic acid, in liver and serum phospholipids. Plasma insulin concentrations and blood biochemical indices were similar in the two groups. An intravenously infused PO emulsion effectively reduces thromboxane A2 production through changes in the fatty acid composition of liver and serum phospholipids, as with oral administration, and improves the nutritional status of diabetic rats.

Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate.

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Am J Epidemiol 1996 May 1;143(9):845-59

Elevated plasma homocyst(e)ine levels are an independent risk factor for vascular disease. In a case-control study, the authors studied the associations of fasting plasma homocyst(e)ine and vitamins, which are important cofactors in homocysteine metabolism, with the risk of myocardial infarction. The cases were 130 Boston area patients hospitalized with a first myocardial infarction and 118 population controls, less than 76 years of age, enrolled in 1982 and 1983. Dietary intakes of vitamins B6, B12, and folate were estimated from a food frequency questionnaire. After adjusting for sex and age, the authors found that the geometric mean plasma homocyst(e)ine level was 11% higher in cases compared with controls ($p = 0.006$). There was no clear excess of cases with extremely elevated levels. The age- and sex-adjusted odds ratio for each 3-mumol/liter (approximately 1 standard deviation) increase in plasma homocyst(e)ine was 1.35 (95% confidence interval 1.05-1.75; p trend = 0/007). After further control for several risk factors, the odds ratio was not affected, but the confidence interval was wider and the p value for trend was less significant. Dietary and plasma levels of vitamin B6 and folate were lower in cases than in controls, and these vitamins were inversely associated with the risk of myocardial infarction, independently of other potential risk factors. Vitamin B12 showed no clear association with myocardial infarction, although methylmalonic acid levels were significantly higher in cases. Comparing the mean levels of several homocysteine metabolites among cases and controls, the authors found that impairment of remethylation of homocyst(e)ine (dependent of folate and vitamin B12 rather than on vitamin B6-dependent transsulfuration) was the predominant cause of high homocyst(e)ine levels in cases. Accordingly, plasma folate and, to a lesser extent, plasma vitamin B12, but not vitamin B6, correlated inversely with plasma homocyst(e)ine, even for concentrations at the high end of normal values. These data provide further evidence that plasma homocyst(e)ine is an independent risk factor for myocardial infarction. In this population, folate was the most important determinant of plasma homocyst(e)ine, even in subjects with apparently adequate nutritional status of this vitamin.

Homocysteine and cardiovascular disease.

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Annu Rev Med 1998;49:31-62

An elevated level of total homocysteine (tHcy) in blood, denoted hyperhomocysteinemia, is emerging as a prevalent and strong risk factor for atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels, and for arterial and venous thromboembolism. The basis for these conclusions is data from about 80 clinical and epidemiological studies including more than 10,000 patients. Elevated tHcy confers a graded risk with no threshold, is independent of but may enhance the effect of the conventional risk factors, and seems to be a particularly strong predictor of cardiovascular mortality. Hyperhomocysteinemia is attributed to commonly occurring genetic and acquired

factors including deficiencies of folate and vitamin B12. Supplementation with B-vitamins, in particular with folic acid, is an efficient, safe, and inexpensive means to reduce an elevated tHcy level. Studies are now in progress to establish whether such therapy will reduce cardiovascular risk.

The antiatherosclerotic effect of Allium sativum.

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Atherosclerosis 1999 May;144(1):237-49

In a randomized, double-blind, placebo-controlled clinical trial, the plaque volumes in both carotid and femoral arteries of 152 probationers were determined by B-mode ultrasound. Continuous intake of high-dose garlic powder dragees reduced significantly the increase in arteriosclerotic plaque volume by 5-18% or even effected a slight regression within the observational period of 48 months. Also the age-dependent representation of the plaque volume shows an increase between 50 and 80 years that is diminished under garlic treatment by 6-13% related to 4 years. It seems even more important that with garlic application the plaque volume in the whole collective remained practically constant within the age-span of 50-80 years. These results substantiated that not only a preventive but possibly also a curative role in arteriosclerosis therapy (plaque regression) may be ascribed to garlic remedies.

Dietary soy protein and estrogen replacement therapy improve cardiovascular risk factors and decrease aortic cholesteryl ester content in ovariectomized cynomolgus monkeys.

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Metabolism (United States) Jun 1997, 46 (6) p698-705

Estrogen replacement therapy (ERT) decreases the progression of coronary artery atherosclerosis in monkeys. Dietary soy protein also retards the progression of atherosclerosis relative to animal proteins such as casein. Soy protein contains weakly estrogenic compounds called isoflavones or phytoestrogens that may be responsible for the cardioprotective effects. This study was designed as a 2 x 2 factorial to determine the magnitude of soy protein's effects on cardiovascular risk factors relative to casein and lactalbumin, with or without estradiol treatment. Ovariectomized female monkeys were randomized to four treatment groups based on past dietary cholesterol consumption, their origin, and past reproductive history, and studied for 7 months. The animals were divided into (1) a group fed

casein and lactalbumin as the protein source (n = 14), (2) a group fed casein and lactalbumin as the protein source plus 17 beta-estradiol (E2) (n = 13), (3) a group fed soybean protein isolate as the protein source (n = 11), and (4) a group fed soybean protein isolate as the protein source plus E2 (n = 10). Soy protein compared with casein consumption resulted in a significant improvement in plasma lipid and lipoprotein concentrations, a significant improvement in insulin sensitivity and glucose effectiveness as determined by minimal-model analyses, and a decrease in arterial lipid peroxidation. E2-treated monkeys had a significant reduction in fasting insulin levels and insulin to glucose ratios, total body weight, and amounts of abdominal fat, and had smaller low-density lipoprotein (LDL) particles. In addition, E2 treatment resulted in a significant reduction (P = .001) in aortic cholesteryl ester content. A similar trend (P = .14) was found for soy protein compared with casein. There also was a significant interaction (P = .02) with soy and E2, such that animals consuming soy protein +E2 had the least arterial cholesteryl ester content. These results suggest that both ERT and dietary soybean protein have beneficial effects on cardiovascular risk factors. Interestingly, the two treatments affected different risk factors and together resulted in the greatest reduction in arterial cholesterol content. Further studies are needed to determine the active component of the soy protein and to assess its long-term effects on the cardiovascular system and other organ systems (such as the bones and reproductive system).

Hyperhomocysteinemia and venous thromboembolic disease.

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Haematologica (Italy) Mar-Apr 1997, 82 (2) p211-9

BACKGROUND AND OBJECTIVE: In spite of the large number of reports showing that hyperhomocysteinemia (HHcy) is an independent risk factor for atherosclerosis and arterial occlusive disease, this metabolite of the methionine pathway is measured in relatively few laboratories and its importance is not fully appreciated. Recent data strongly suggest that mild HHcy is also involved in the pathogenesis of venous thromboembolic disease. The aim of this paper is to analyze the most recent advances in this field.

EVIDENCE AND INFORMATION SOURCES: The material examined in the present review includes articles and abstracts published in journals covered by the Science Citation Index and Medline. In addition the authors of the present article have been working in the field of mild HHcy as cause of venous thromboembolic disease.

STATE OF ART AND PERSPECTIVES: The studies examined provide very strong evidence supporting the role of moderate HHcy in the development of premature and/or recurrent venous thromboembolic disease. High plasma homocysteine levels are also a risk factor for deep vein thrombosis in the general population. Folic acid fortification of food has been proposed as a major tool for

reducing coronary artery disease mortality in the United States. Vitamin supplementation may also reduce recurrence of venous thromboembolic disease in patients with HHcy. At the present time, however, the clinical efficacy of this approach has not been tested. In addition, the bulk of evidence indicates that fasting total homocysteine determinations can identify up to 50% of the total population of hyperhomocysteinemic subjects. Patients with isolated methionine intolerance may benefit from vitamin B6 supplementation. Homocysteine-lowering vascular disease prevention trials are urgently needed. Such controlled studies, however, should not focus exclusively on fasting homocysteine determinations and folic acid monotherapy. (127 Refs.)

Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project.

Graham IM; Daly LE; Refsum HM; Robinson K; Brattstrom LE; Ueland PM; Palma-Reis RJ; Boers GH; Sheahan RG; Israelsson B; Uiterwaal CS; Meleady R; McMaster D; Verhoef P; Witteman J; Rubba P; Bellet H; Wautrecht JC; de Valk HW; Sales Luis AC; Parrot-Rouland FM; Tan KS; Higgins I; Garcon D; Andria G ; et al
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JAMA (United States) Jun 11 1997, 277 (22) p1775-81

CONTEXT: Elevated plasma homocysteine is a known risk factor for atherosclerotic vascular disease, but the strength of the relationship and the interaction of plasma homocysteine with other risk factors are unclear.

OBJECTIVE: To establish the magnitude of the vascular disease risk associated with an increased plasma homocysteine level and to examine interaction effects between elevated plasma homocysteine level and conventional risk factors.

DESIGN: Case-control study.

SETTING: Nineteen centers in 9 European countries.

PATIENTS: A total of 750 cases of atherosclerotic vascular disease (cardiac, cerebral, and peripheral) and 800 controls of both sexes younger than 60 years.

MEASUREMENTS: Plasma total homocysteine was measured while subjects were fasting and after a standardized methionine-loading test, which involves the administration of 100 mg of methionine per kilogram and stresses the metabolic pathway responsible for the irreversible degradation of homocysteine. Plasma cobalamin, pyridoxal 5'-phosphate, red blood cell folate, serum cholesterol, smoking, and blood pressure were also measured.

RESULTS: The relative risk for vascular disease in the top fifth compared with the bottom four fifths of the control fasting total homocysteine distribution was 2.2 (95% confidence interval, 1.6-2.9). Methionine loading identified an

additional 27% of at-risk cases. A dose-response effect was noted between total homocysteine level and risk. The risk was similar to and independent of that of other risk factors, but interaction effects were noted between homocysteine and these risk factors; for both sexes combined, an increased fasting homocysteine level showed a more than multiplicative effect on risk in smokers and in hypertensive subjects. Red blood cell folate, cobalamin, and pyridoxal phosphate, all of which modulate homocysteine metabolism, were inversely related to total homocysteine levels. Compared with nonusers of vitamin supplements, the small number of subjects taking such vitamins appeared to have a substantially lower risk of vascular disease, a proportion of which was attributable to lower plasma homocysteine levels.

CONCLUSIONS: An increased plasma total homocysteine level confers an independent risk of vascular disease similar to that of smoking or hyperlipidemia. It powerfully increases the risk associated with smoking and hypertension. It is time to undertake randomized controlled trials of the effect of vitamins that reduce plasma homocysteine levels on vascular disease risk.

Homocyst(e)ine: an important risk factor for atherosclerotic vascular disease.

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Curr Opin Lipidol (United States) Feb 1997, 8 (1) p28-34

Homocysteine is an intermediate compound formed during metabolism of methionine. The results of many recent studies have indicated that elevated plasma levels of homocyst(e)ine are associated with increased risk of coronary atherosclerosis, cerebrovascular disease, peripheral vascular disease, and thrombosis. The plasma level of homocyst(e)ine is dependent on genetically regulated levels of essential enzymes and the intake of folic acid, vitamin B6 (pyridoxine), and vitamin B12 (cobalamin). Impaired renal function, increased age, and pharmacologic agents (e.g. nitrous oxide, methotrexate) can contribute to increased levels of homocyst(e)ine. Plausible mechanisms by which homocyst(e)ine might contribute to atherogenesis include promotion of platelet activation and enhanced coagulability, increased smooth muscle cell proliferation, cytotoxicity, induction of endothelial dysfunction, and stimulation of LDL oxidation. Levels of homocysteine can be reduced with pharmacologic doses of folic acid, pyridoxine, vitamin B12, or betaine, but further research is required to determine the efficacy of this intervention in reducing morbidity and mortality associated with atherosclerotic vascular disease.

[Homocysteine, a risk factor of atherosclerosis]

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Arch Mal Coeur Vaiss (France) Dec 1996, 89 (12) p1667-71

Homocysteine is a sulphurated amino acid which, at high plasma concentrations, predisposes to thrombosis and induces focal arteriosclerosis. These characteristics have been established both in patients with homocystinuria, a genetic disease in which homocysteine accumulates in the blood, and in animals submitted to intravenous infusions of this amino acid. Many recent publications have addressed the problem of whether mild increases in plasma homocysteine predisposed to the development of the usual forms of atherosclerosis. Transverse epidemiological studies have established a correlation between homocysteine levels and atherosclerosis at all its vascular localisations, coronary, carotid and lower limb. Multivariate analysis in several prospective studies have shown plasma homocysteine to be an independent risk factor for cerebrovascular accidents and myocardial infarction. Causes of mild increases in plasma homocysteine are usually dietetic deficiencies in folic acid, vitamin B6 or B12, or genetic by mutation of the methylene-tetrahydrofolate reductase. Renal failure is also associated with a high risk in plasma homocysteine levels. However, the toxicity of homocysteine to the arterial wall at slightly elevated concentration remains speculative.

Comparison between dietary soybean protein and casein of the inhibiting effect on atherogenesis in the thoracic aorta of hypercholesterolemic (ExHC) rats treated with experimental hypervitamin D.

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Biosci Biotechnol Biochem (JAPAN) Mar 1997, 61 (3) p514-9

Atherosclerotic lesions of the thoracic aorta were induced in exogenously hypercholesterolemic (ExHC) rats by treating initially with hypervitamin D2 and subsequently feeding on hypercholesterolemic diets for 180 days. Dietary soybean protein, in comparison with casein, substantially decreased the degree of atherosclerotic lesions, which was evaluated by intimal thickening, although with a similar topographical distribution. The casein-fed rats tended to maintain a high concentration of serum cholesterol, particularly in triacylglycerol-rich lipoproteins. The concentrations of apo A-I and TBARS in the serum was comparable between the dietary protein groups. The data suggest that dietary soybean protein, compared to casein, produced lipoproteins which were less atherosclerotic by partitioning cholesterol in the triacylglycerol-poor lipoproteins.

Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques.

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Fertil Steril (United States) Jan 1997, 67 (1) p148-54

OBJECTIVE: To examine the effects of soy phytoestrogens on coronary vascular reactivity in atherosclerotic male and female rhesus monkeys.

DESIGN: A prospective, randomized, blinded, controlled study.

SETTING:Comparative Medicine Clinical Research Center of an academic medical center.

PATIENT(S): Twenty-two young adult rhesus monkeys with pre-existing diet-induced atherosclerosis.

INTERVENTION(S): Monkeys were fed soy-based diets for 6 months identical in composition, except that the isoflavones were extracted from one flow-isoflavone) and intact in the other (high-isoflavone). Quantitative coronary angiography was performed at the end of the study period. Females in the low-isoflavone group under went a second angiography after an acute IV dose of genistein.

MAIN OUTCOME MEASURE(S): Percent change in diameter of the proximal left circumflex coronary artery in response to intracoronary acetylcholine and nitroglycerin, compared with control diameter.

RESULT(S): Arteries from males constricted in response to acetylcholine. Arteries from females in the low-isoflavone group constricted (-6.2% +/- 2.8%, mean +/- SEM), whereas arteries from females in the high-isoflavone group dilated (6.4% +/- 1.2%, mean +/- SEM). Intravenous administration of genistein caused dilation in the previously constricting low-isoflavone females (3.3% +/- 2.8%).

CONCLUSION(S): Like mammalian estrogens, dietary soy isoflavones enhance the dilator response to acetylcholine of atherosclerotic arteries in female monkeys.

Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations.

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Circulation (United States) Dec 1 1996, 94 (11) p2743-8

BACKGROUND: A high level of total plasma homocysteine is a risk factor for atherosclerosis, which is an important cause of death in renal failure We evaluated the role of this as a risk factor for vascular complications of end-stage renal disease.

METHODS AND RESULTS: Total fasting plasma homocysteine and other risk factors were documented in 176 dialysis patients (97 men, 79 women; mean age, 56.3 +/- 14.8 years). Folate, vitamin B12, and pyridoxal phosphate concentrations were also determined. The prevalence of high total homocysteine values was determined by comparison with a normal reference population, and the risk of associated vascular complications was estimated by multiple logistic regression. Total homocysteine concentration was higher in patients than in the normal population (26.6 +/- 1.5 versus 10.1 +/- 1.7 mumol/L; P < .01). Abnormally high concentrations (> 95th percentile for control subjects, 16.3 mumol/L) were seen in 149 patients (85%) with end-stage renal disease (P < .001). Patients with a homocysteine concentration in the upper two quintiles (> 27.8 mumol/L) had an independent odds ratio of 2.9 (CI, 1.4 to 5.8; P = .007) of vascular complications. B vitamin levels were lower in patients with vascular complications than in those without. Vitamin B6 deficiency was more frequent in patients than in the normal reference population (18% versus 2%; P < .01).

CONCLUSIONS: A high total plasma homocysteine concentration is an independent risk factor for atherosclerotic complications of end-stage renal disease. Such patients may benefit from higher doses of B vitamins than those currently recommended.

High dose-B-vitamin treatment of hyperhomocysteinemia in dialysis patients.

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Kidney Int (United States) Jan 1996, 49 (1) p147-52

Hyperhomocysteinemia, an arteriosclerotic risk factor, persists in 75% of dialysis patients despite routine low dose supplementation with the B-vitamin co-factors/substrates for homocysteine (Hcy) metabolism, and normal or supernormal plasma status of these vitamins (Atherosclerosis 114:93, 1995). We conducted a placebo-controlled eight-week trial of the effect on plasma homocysteine of adding supraphysiologic dose folic acid (15 mg/day), B-6 (100 mg/day), and B-12 (1 mg/day) to the usual daily dosing of 1 mg folic acid, 10 mg B-6, and 12 micrograms B-12, in 27 hyperhomocysteinemic dialysis patients. Total plasma homocysteine was measured at baseline, and after four and eight weeks. Blinded analyses revealed no evidence of toxicity in the group randomized

to supraphysiologic dose B-vitamin supplementation. Plasma homocysteine was significantly reduced after both four weeks (-29.8% vs. -2.0%; P = 0.0024) and eight weeks (-25.8% vs. +0.6%; P = 0.0009) of active versus placebo treatment. Also, 5 of 15 treated versus 0 of 12 placebo group patients had their plasma Hcy reduced to within the normative range (< 15 mumol/liter). Supraphysiologic doses of B-vitamins may be required to correct hyperhomocysteinemia in dialysis patients.

Measurement of the ratio between the reduced and oxidized forms of coenzyme Q10 in human plasma as a possible marker of oxidative stress.

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J Lipid Res (United States) Jan 1996, 37 (1) p67-75

It has been postulated that lipid peroxidation plays a crucial role in the pathogenesis of atherosclerosis. As CoQ10H2 (reduced form of coenzyme Q10) is easily oxidized to CoQ10 (oxidized form of coenzyme Q10), it has been proposed that the CoQ10H2/CoQ10 ratio may be used as a possible marker of in vivo oxidative stress. However, sample preparation has an important effect on the redox status of coenzyme Q10 due to the extreme sensitivity of CoQ10H2 towards oxidation. We now report a rapid, simple isocratic HPLC procedure for the determination of CoQ10H2 and CoQ10 in plasma isopropanol extracts, and we used this method to investigate conditions by which the CoQ10H2/CoQ10 ratio can be reliably measured. Our results indicate that CoQ10H2 is unstable in whole blood, plasma, and isopropanol extracts; subsequently the CoQ10H2/CoQ10 ratio changes considerably soon after a blood sample has been obtained. The time period since blood sampling and HPLC analysis, as well as the sample pretreatment procedure, are two factors that have a profound effect on the pre-analytical variation in the determination of the CoQ10H2/CoQ10 ratio. If these two factors are properly controlled, the CoQ10H2/CoQ10 ratio may be a sensitive and practical way to measure in vivo oxidative stress. Furthermore, this indicator is independent from plasma total cholesterol concentrations, implying that groups who differ with respect to cholesterol levels may be compared directly.

Hyperhomocysteinemia induced by folic acid deficiency and methionine load--applications of a modified HPLC method.

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Clin Chim Acta (Netherlands) Aug 15 1996, 252 (1) p83-93

The increasing possibility that homocysteine might be involved in atherosclerosis in non-homocysteinuric subjects has required the measurement of low concentrations of this aminothiol in biological samples. The procedure described here represents an improvement of different HPLC methods. We utilized an isocratic HPLC system with fluorescence detection of plasma total homocysteine derivatized after reaction with ammonium 7-fluoro-benzo-2-oxa-1,3-diazole-4-sulphonate. With the help of the rapidly eluting internal standard N-acetyl-cysteine, the method ensures very good recovery (approximately 100%), reproducibility and precision (within-assay 2.31%; day-to-day: 2.8%) in the physiological concentration range. This procedure allowed us to validate various animal models of hyperhomocysteinemia such as dietary folic acid deficiency in rat and acute methionine loads in rat and hamster. Using this method, we also confirmed that men have higher plasma total homocysteine levels than women. Due to its simplicity and reliability, our procedure is suitable for routine analysis of total homocysteine and other aminothiols (cysteine, cysteinyl-glycine and glutathione) in biological samples, as required in clinical and research laboratories.

Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys.

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J Nutr (United States) Jan 1996, 126 (1) p43-50

Although the beneficial effects of dietary soybean protein compared with animal proteins on plasma lipids, lipoproteins and atherosclerosis have been known for about 50 years, it has been uncertain whether these effects are due to its amino acid concentrations or other components in soybeans. To assess the effect of soybean protein's alcohol-extractable components (including the isoflavonic phytoestrogens genistein and daidzein) on plasma lipid and lipoprotein concentrations and to establish its lack of effect on the reproductive system, we fed 27 peripubertal male and female rhesus monkeys moderately atherogenic diets in which the source of dietary protein was a soy isolate (20% by weight), either containing phytoestrogens (also termed isoflavones) or with the phytoestrogens removed by alcohol extraction. The study was a crossover design with each period lasting for 6 mo. The phytoestrogen-intact soy protein (compared with the alcohol-extracted soy protein) had favorable effects on plasma lipid and lipoprotein concentrations, specifically by significantly reducing LDL+VLDL cholesterol concentrations in both males and females (approximately 30-40% lower), significantly increasing high density lipoprotein cholesterol (HDLC) concentrations for females (approximately 15% higher) and significantly lowering total plasma cholesterol (TPC):HDLC ratios (approximately 20% lower for males and 50% lower for females). The phytoestrogens had no adverse effects on the reproductive systems of either the males or females, as evaluated by reproductive hormone concentrations and organ weights at necropsy. Thus, the isoflavones in

soy protein improve cardiovascular disease risk factors without apparent deleterious effects on the reproductive system of peripubertal rhesus monkeys.

Therapeutic actions of garlic constituents.

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Med Res Rev (United States) Jan 1996, 16 (1) p111-24

Most studies on garlic during the past 15 years have been primarily in the fields of cardiovascular and cancer research. Cardiovascular studies have been mainly related to atherosclerosis, where effects were examined on serum cholesterol, LDL, HDL, and triglycerides. Although the studies were not consistent in relation to the dosage, standardization of garlic preparations, and period of treatment, most findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. Lowering of serum lipids by garlic ingestion may decrease the atherosclerosis process. The other major beneficial effect of garlic is due to its antithrombotic actions. This field of garlic research has been extensively studied. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents of garlic because of their in vitro effects. Since both allicin and adenosine are rapidly metabolized in human blood and other tissues, it is doubtful that these compounds contribute to any antithrombotic actions in the body. In addition, ajoene also seems not to be an active antiplatelet principle, because it is not naturally present in garlic, garlic powders, or other commercial garlic preparations. Only a small amount of ajoene can be found in garlic oil-macerates; however, ajoene is being developed as a drug for treatment of thromboembolic disorders. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts are interesting, and may have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory, and anticancer actions. Epidemiological studies have suggested that garlic plays a significant role in the reduction of deaths caused by malignant diseases. This had led many investigators to examine garlic and garlic constituents for their antitumor and cytotoxic actions both in vitro and in laboratory animals. The data from these investigations suggest that garlic contains several potentially important agents that possess antitumor and anticarcinogenic properties. In summary, the epidemiological, clinical, and laboratory data have proved that garlic contains many biologically and pharmacologically important compounds, which are beneficial to human health from cardiovascular, neoplastic, and several other diseases. Numerous studies are in progress all over the world to develop effective and odorless garlic preparations, as well as to isolate the active principles that may be therapeutically useful. (132 Refs.)

Prevention of preatheromatous lesions in sand rats by treatment with a nutritional supplement.

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Arzneimittelforschung (Germany) Jun 1996, 46 (6) p610-4

Sand rats fed a hypercholesterolaemic diet containing 0.01% of the anti-thyroid agent 2-mercapto-1-imidazole develop preatheromatous lesions similar to those found in humans, in addition to obesity and insulin resistance. The effects of a nutritional supplement rich in essential fatty acids and garlic extract (Arterodiet) on the appearance and evolution of the lesions were studied. Treatment with this nutritional supplement significantly decreased circulating triglycerides and low-density lipoprotein (LDL)-cholesterol levels but did not alter plasma insulin or glucose levels. Intra-arterial cholesterol levels were also decreased by the treatment which resulted in a normalisation of the atherosclerotic lesions in these animals.

Evaluation of hydroxyl radical-scavenging property of garlic.

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Mol Cell Biochem (Netherlands) Jan 12 1996, 154 (1) p55-63

Garlic has been reported to provide protection against hypercholesterolemic therosclerosis and ischemia-reperfusion-induced arrhythmias and infarction. Oxygen free radicals (OFRs) have been implicated as causative factors in these diseases and antioxidants have been shown to be effective against these conditions. The effectiveness of garlic in these disease states could be due to its ability to scavenge OFRs. However, the OFR-scavenging activity of garlic is not known. Also it is not known if its activity is affected by cooking. We therefore investigated, using high pressure liquid chromatography, the ability of garlic extract (heated or unheated) to scavenge exogenously generated hydroxyl radical (.OH). .OH was generated by photolysis of H2O2 (1.2-10 mumoles/ml) with ultraviolet (UV) light and was trapped with salicylic acid (500 nmoles/ml). H2O2 produced .OH in a concentration-dependent manner as estimated by .OH adduct products 2,3-dihydroxybenzoic acid (DHBA) and 2,5-DHBA. Garlic extract (5-100 microliters/ml) produced an inhibition (30-100%) of 2,3-DHBA and 2,5-DHBA generated by photolysis of H2O2 (5.00 pmoles/ml) in a concentration-dependent manner. Its activity is reduced by 10% approximately when heated to 100 degrees C for 20, 40 or 60 min. The extent of reduction in activity was similar for the three heating periods. Garlic extract prevented the .OH-induced formation of malondialdehyde in the rabbit liver homogenate in a concentration-dependent

manner. It alone did not affect the MDA levels in the absence of .OH. These results indicate that garlic extract is a powerful scavenger of .OH and that heating reduces its activity slightly.

[Hyperhomocysteinemia]

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Cas Lek Cesk (Czech Republic) May 2 1996, 135 (9) p266-9

Similarly as in other inborn metabolic diseases the cause of hyperhomocysteinaemia are interactions between genetically conditioned changes most frequently due to reduced cystathionine-beta synthase activities and negative factors of the external environment. Negative environmental factors include above all a high dietary animal protein consumption which is the main methionine donor and a low intake of protein of plant origin. Another negative factor is a low intake of foods of plant origin. Fruits and vegetables are among others important sources of folic acid and pyridoxine. Substitution therapy with vitamin preparations is essential in homozygotes and in high risk heterozygotes of cystathionine beta-synthase. This treatment is also necessary during the periconception period in hyperhomocysteinaemic fertile women to reduce the risk of neurotubal defects in their future children. So far investigations are lacking which would provide evidence of a reduced risk of ischaemic heart disease and other cardiovascular diseases in isolated treatment of mildly elevated levels of plasma homocysteine. To elucidate the part played by hyperhomocysteinaemia in hastening of the atherogenetic process further studies are essential, focused on the interaction of elevated homocysteine plasma levels, dyslipoproteinaemias, hyperfibrinogenaemia and other metabolic indicators in this process. (31 Refs.)

[Homocysteine, a less well-known risk factor in cardiac and vascular diseases]

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Cas Lek Cesk (Czech Republic) May 2 1996, 135 (9) p263-5

Hyperhomocyst(e)mia (Hcy) negatively influences vascular endothelium and coagulation factors. Association of Hcy with premature arteriosclerosis (rather than atherosclerosis), stroke, myocardial infarction and peripheral arterial and venous disease was proved in clinical and epidemiological studies, even as the association with conventional risk factors like age, male sex, smoking, hypertension and hypercholesterolemia. Vitamin substitution of folates, vitamin B6 and B12 decreases Hcy blood levels, however definite evidence is still lacking, whether it results in lower incidence and mortality from cardiovascular diseases. Therefore clinical and epidemiological studies are necessary. Before the

grant-application we proved in a pilot study significantly higher Hcy levels in 97 patients with manifest ischaemic heart disease than in 37 controls.

Long-term folic acid (but not pyridoxine) supplementation lowers elevated plasma homocysteine level in chronic renal failure.

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Miner Electrolyte Metab (Switzerland) 1996, 22 (1-3) p106-9

Moderate hyperhomocysteinemia, a risk factor for premature atherosclerosis, is present in chronic uremic patients. We prospectively evaluated the effects of sequential supplementation with pyridoxine (70 mg/day) and folic acid (10 mg/day) for two 3-month periods in 37 nondialyzed patients (29 males) with creatinine clearance (Ccr) ranging from 10 to 80 ml/min, whose plasma vitamin B12 and folate level was in the normal range. Mean (+/- SD) baseline plasma total homocysteine (Hcy) was 14.9 +/- 5.2, 16.5 +/- 5.1 and 26.1 +/- 12.1 mumol/l (upper limit in 45 healthy controls 14.1 mumol/l) in patients with CCr 40-80, 20-40 and < 20 ml/min, respectively. Following pyridoxine Hcy did not significantly decrease whereas following folic acid Hcy decreased significantly to 9.9 +/- 2.9 (-33% vs. baseline), 10.3 +/- 3.4 (-37%) and 15.4 +/- 5.5 (-40%), respectively (Student's paired t test, $p < 0.001$) in the 3 groups. We conclude that folate (but not pyridoxine) pharmacologic supplementation is effective in lowering elevated plasma Hcy in chronic renal failure patients, thus suggesting that enhancing the Hcy remethylation pathway may overcome hyperhomocysteinemia in such patients. In view of the potential atherogenic effects of hyperhomocysteinemia, long-term folate supplementation should be considered in uremic patients.

Fish oil supplementation in patients with heterozygous familial hypercholesterolemia.

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Recenti Prog Med (Italy) Mar 1996, 87 (3) p102-5

Familial hypercholesterolemia is associated with premature coronary heart disease. In patients with familial hypercholesterolemia, monotherapy with hydroxymethylglutaril coenzyme. A reductase inhibitors rarely achieves the goal of desirable low-density lipoprotein levels. Epidemiological studies suggest that populations with a high dietary intake of marine n3 fatty acids are protected against coronary heart disease. Hepatic synthesis and secretion of very low density lipoproteins are reduced during fish oil supplementation while other effects on lipid and lipoprotein metabolism are controversial. Fourteen patients affected by familial heterozygous hypercholesterolemia on chronic treatment with simvastatin were enrolled in a double blind, placebo controlled, randomized

crossover trial that evaluated the effect of fish oil ethyl ester (Esapent, 5.1 g/day) on lipid and lipoprotein serum concentrations. Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, apoprotein B, apoprotein AI, lipoprotein (a) did not show any significant variation during the four week treatment period with fish oil ethyl ester. The present data suggest that the possible favourable influence of fish oil on the progression of atherosclerosis in these high-risk patients might involve mechanisms which are different from lipid metabolism.

Homocysteine and coronary atherosclerosis.

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J Am Coll Cardiol (United States) Mar 1 1996, 27 (3) p517-27

Homocysteine is increasingly recognized as a risk factor for coronary artery disease. An understanding of its metabolism and of the importance of vitamins B6 and B12 and folate as well as enzyme levels in its regulation will aid the development of therapeutic strategies that, by lowering circulating concentrations, may also lower risk. Possible mechanisms by which elevated homocysteine levels lead to the development and progression of vascular disease include effects on platelets, clotting factors and endothelium. This review presents the clinical and basic scientific evidence supporting the risk and mechanisms of vascular disease associated with elevated homocysteine concentrations as well as the results of preliminary therapeutic trials.

Association of serum vitamin levels, LDL susceptibility to oxidation, and autoantibodies against MDA-LDL with carotid atherosclerosis. A case-control study. The ARIC Study Investigators. Atherosclerosis Risk in Communities.

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Arterioscler Thromb Vasc Biol (United States) Jun 1997, 17 (6) p1171-7

Oxidative modification of LDL is believed to be a crucial step in atherosclerosis. Thus, antioxidant vitamins may have a role in the prevention of coronary disease. We examined the cross-sectional association of serum vitamin levels, the susceptibility of LDL to hemin-induced oxidation (lag phase to conjugated diene formation), and the malondialdehyde-LDL (MDA-LDL) to native LDL radioactivity binding ratio with carotid intima-media thickness (IMT), a measure of asymptomatic early atherosclerosis. The participants in this observational study were 231 asymptomatic age-, sex-, race-, and field center-matched case-control

pairs selected from the Atherosclerosis Risk in Communities (ARIC) study cohort on the basis of B-mode carotid artery ultrasonograms obtained from 1986 through 1989. Cases exceeded the 90th percentile of IMT, and control subjects were below the 75th percentile of IMT for all arterial segments. Biochemical analyses were performed on fasting frozen (-70 degrees C) serum specimens collected from 1990 through 1992. In conditional logistic regression adjusting for age, blood storage time, total cholesterol, and log-triglyceride concentrations, serum beta-cryptoxanthin and lutein plus zeaxanthin levels were inversely related to the extent of atherosclerosis (odds ratio [OR] per 1-SD increase: 0.75, 95% confidence interval [CI]: 0.59-0.94; and OR per 1-SD increase: 0.76, 95% CI: 0.59-0.95, respectively). Increases in alpha-carotene and lycopene were associated with nonsignificantly lower odds of being a case, whereas beta-carotene, retinol, and alpha-tocopherol were unrelated to IMT. Although not reaching statistical significance, the lag phase and autoantibodies against MDA-LDL were positively associated with asymptomatic atherosclerosis. After adjustment for potential confounders, only the inverse association of lutein plus zeaxanthin with asymptomatic atherosclerosis was maintained. This study supports a modest inverse association between circulating levels of some carotenoids, particularly lutein plus zeaxanthin, and carotid IMT. These findings suggest that these carotenoid compounds (regarded as biomarkers of fruit and vegetable intake) may be important in early stages of atherosclerosis.

Acetylsalicylic acid and vitamin E in prevention of arterial thrombosis.

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Can J Cardiol (Canada) May 1997, 13 (5) p533-5

Both acetylsalicylic acid and vitamin E have been shown to be beneficial in the prevention of stroke and heart attacks. It is implied that their combination in the treatment of thrombotic complications of atherosclerosis may have added benefits. It is suggested that vitamin E may work as a platelet lysosome stabilizing agent.

Alpha-Tocopherol and beta-carotene serum levels in post-menopausal women treated with transdermal estradiol and oral medroxyprogesterone acetate.

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Horm Metab Res (Germany) Oct 1996, 28 (10) p558-61

Estrogens exert a protective effect against atherosclerosis. It is well known that hormone replacement therapy (HRT) can effectively decrease LDL-cholesterol

and increase HDL-cholesterol and Apo-Al serum levels. Some recent studies have suggested that estrogens alone or in association with progestins may exert an antioxidant effect on lipids. Besides sex steroids, also vitamins exert an antioxidant effect on LDL and may preserve the endogenous antioxidants of LDL. The aim of our study was to evaluate whether HRT can improve alpha-tocopherol and beta-carotene serum levels in post-menopausal women. Fifteen postmenopausal women with climacteric symptoms were treated with 50 micrograms/24 h estradiol transdermally applied twice a week for 21 days. A daily dose of 10 mg oral medroxyprogesterone acetate was added for 12 days in each treatment cycle. This therapy lasted 6 months. A significant reduction was found in total cholesterol and LDL-cholesterol after treatment. Besides, our study has shown that alpha-toc/LDL and beta-car/LDL ratios significatively increased after treatment, while alpha-tocopherol and beta-carotene serum levels did not change significantly after therapy. These preliminary findings suggest that HRT can preserve the content of alpha-tocopherol and beta-carotene in LDL particles and keep the LDL in a reduced antioxidant state.

Vitamin E consumption and the risk of coronary disease in women

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Channing Laboratory, Boston, MA 02115.
New Engl. J. Med. (USA), 1993, 328/20 (1444-1449)

Background. Interest in thdocumented 552 cases of major coronary disease (437 nonfatal myocardial infarctions and 115 deaths due to coronary disease).

Results. As compared with women in the lowest fifth of the cohort with respect to vitamin E intake, those in the top fifth had a relative risk of major coronary disease of 0.66 (95 percent confidence interval, 0.50 to 0.87) after adjustment for age and smoking. Further adjustment for a variety of other coronary risk factors and nutrients, including other antioxidants, had little effect on the results. Most of the variability in intake and reduction in risk was attributable to vitamin E consumed as supplements. Women who took vitamin E supplements for short periods had little apparent benefit, but those who took them for more than two years had a relative risk of major coronary disease of 0.59 (95 percent confidence interval, 0.38 to 0.91) after adjustment for age, smoking status, risk factors for coronary disease, and use of other antioxidant nutrients (including multivitamins).

Conclusions. Although these prospective data do not prove a cause-and-effect relation, they suggest that among middle-aged women the use of vitamin E supplements is associated with a reduced risk of coronary heart disease. Randomized trials of vitamin E in the primary and secondary prevention of coronary disease are being conducted; public policy recommendations about the widespread use of vitamin E should await the results of these trials.

The role of free radicals in disease

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Aust N Z J Ophthalmol 1995 Feb;23(1):3-7

Evidence is accumulating that most of the degenerative diseases that afflict humanity have their origin in deleterious free radical reactions. These diseases include atherosclerosis, cancer, inflammatory joint disease, asthma, diabetes, senile dementia and degenerative eye disease. The process of biological ageing might also have a free radical basis. Most free radical damage to cells involves oxygen free radicals or, more generally, activated oxygen species (AOS) which include non-radical species such as singlet oxygen and hydrogen peroxide as well as free radicals. The AOS can damage genetic material, cause lipid peroxidation in cell membranes, and inactivate membrane-bound enzymes. Humans are well endowed with antioxidant defences against AOS; these antioxidants, or free radical scavengers, include ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), beta-carotene, coenzyme Q10, enzymes such as catalase and superoxide dismutase, and trace elements including selenium and zinc. The eye is an organ with intense AOS activity, and it requires high levels of antioxidants to protect its unsaturated fatty acids. The human species is not genetically adapted to survive past middle age, and it appears that antioxidant supplementation of our diet is needed to ensure a more healthy elderly population.

Coenzyme Q10 and coronary artery disease

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Clin Investig 1993;71(8 Suppl):S112-5

It has been postulated that oxidatively modified low-density lipoprotein (LDL) contributes to the genesis of atherosclerosis. Ubiquinone has been suggested to be an important physiological lipid-soluble antioxidant and is found in LDL fractions in the blood. We measured plasma level of ubiquinone using high-performance liquid chromatography and plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in 245 normal subjects (186 males, 59 females) and in 104 patients (55 males, 49 females) who had coronary artery disease not receiving pravastatin and 29 patients (12 males, 17 females) receiving pravastatin. In the normal subjects, the plasma ubiquinone levels did not vary with age. In the patient groups, the plasma total cholesterol and LDL levels were higher and the plasma ubiquinone level lower than in the normal subject group. The LDL/ubiquinone ratio was higher in the patient groups. We found that ubiquinone level, either alone or when expressed in relation to LDL levels, was significantly lower in the patient groups compared with the normal subject group. The 3-hydroxy-3-methylglutaryl coenzyme A (HMC CoA) reductase inhibitor is

thought to prevent atherosclerosis, however, it also inhibits ubiquinone production. The present study revealed that HMG CoA reductase inhibitor decreased plasma cholesterol level, and that it did not improve either the ubiquinone level or the LDL/ubiquinone ratio. From these results, the LDL/ubiquinone ratio is likely to be a risk factor for atherogenesis, and administration of ubiquinone to patients at risk might be needed.

- Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women

New England Journal of Medicine (USA), 1996, 334/18

Background. The role of dietary antioxidant vitamins in preventing coronary heart disease has aroused considerable interest because of the knowledge that oxidative modification of low-density lipoprotein may promote atherosclerosis. Methods. We studied 34,486 postmenopausal women with no cardiovascular disease who in early 1986 completed a questionnaire that assessed, among other factors, their intake of vitamins A, E, and C from food sources and supplements. During approximately seven years of follow-up (ending December 31, 1992), 242 of the women died of coronary heart disease. Results. In analyses adjusted for age and dietary energy intake, vitamin E consumption appeared to be inversely associated with the risk of death from coronary heart disease. This association was particularly striking in the subgroup of 21,809 women who did not consume vitamin supplements (relative risks from lowest to highest quintile of vitamin E intake, 1.0, 0.68, 0.71, 0.42, and 0.42; P for trend = 0.008). After adjustment for possible confounding variables, this inverse association remained (relative risks from lowest to highest quintile, 1.0, 0.70, 0.76, 0.32, and 0.38; P for trend = 0.004). There was little evidence that the intake of vitamin E from supplements was associated with a decreased risk of death from coronary heart disease, but the effects of high-dose supplementation and the duration of supplement use could not be definitively addressed. Intake of vitamins A and C did not appear to be associated with the risk of death from coronary heart disease. Conclusions. These results suggest that in postmenopausal women the intake of vitamin E from food is inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements. By contrast, the intake of vitamins A and C was not associated with lower risks of dying from coronary disease.

Randomized, controlled trial of antioxidant vitamins and cardioprotective diet on hyperlipidemia, oxidative stress, and development of experimental atherosclerosis: The diet and antioxidant trial on atherosclerosis (DATA)

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Cardiovasc Drugs Ther 1995 Dec;9(6):763-71

The effects of administration of guava and papaya fruit (100 g/day), vegetables, and mustard oil (5 g/day) (group A); antioxidant vitamins C (50 mg/day) and E (30 mg/day) plus betacarotene (10 mg/day) (group B); a high-fat (5-10 g/day) (group C); or a low-fat (4-5 g/day) diet (group D) were compared over 24 diet weeks in a randomized fashion, while all groups of rabbits (five in each of four groups) received a hydrogenated fat diet (5-10 g/day) for a period of 36 weeks. After 12 weeks on the high fat diet, each group of rabbits had an increase in blood lipoproteins. The fruit and vegetable-enriched prudent diet (group A) caused a significant decline in blood lipids at 24 and 36 weeks, whereas the lipid levels increased significantly in groups C and D. Group A also had a significant rise in vitamin E (2.1 Umol/l), C (10.5 Umol/l), A (0.66 Umol/l), and carotene (0.08 Umol/l) and a decrease in lipid peroxides (0.34 nmol/ml at 36 weeks, whereas the levels were unchanged in groups C and D. Group B rabbits had a significant and greater increase than group A in plasma vitamins E, C, A, and carotene; a rise in HDL cholesterol; and a greater decrease in lipid peroxides after 24 and 36 weeks of treatment. After stimulation of lipid peroxidation in all rabbits, 3 of 5 group C and 2 of 5 group D rabbits died due to coronary thrombosis, whereas in groups A and B there were no deaths, indicating that antioxidant therapy can provide protection against lipid peroxidation and free radical generation. Aortic lipids and sudanophilia, indicating atherosclerosis, were significantly higher in groups C and D than in groups A and B. Fatty streaks and atheromatous and fibrous plaques were noted in all the rabbits in groups C and D. Intimal fibrosis and medial degeneration were also present in the group C rabbits. While group A (36.4 plus or minus 4.4 microm) and group B (37.1 plus or minus 4.2 microm) rabbits had minimal coronary artery plaque sizes, group C (75.4 plus or minus 10.6 microm) and group D rabbits (69.5 plus or minus 6.2 microm) had significantly greater plaque sizes. Aortic plaque sizes were also greater in groups C and D than in groups A and B. It is possible that combined therapy with antioxidant vitamins C, E, and carotene, and a diet rich in antioxidants, could independently inhibit free radical generation and the development of atherosclerosis.

Serum levels of vitamin E in relation to cardiovascular diseases

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J Clin Pharm Ther 1995 Dec;20(6):335-40

Serum vitamin E levels in healthy people (n = 71) and patients with cardiovascular diseases (n = 62) were determined. The cases of cardiovascular disease comprised patients with acute myocardial infarction (AMI) (n = 31), atherosclerosis (AT) (n = 23) and myocardial ischaemia (MI) (n = 8). The mean (plus or minus SD) serum vitamin E levels of the control group and the group with cardiovascular disease were 1.12 plus or minus 0.27 mg% and 0.98 plus or minus 41 mg%, respectively. Patients with AMI, AT and MI had corresponding levels of 0.97 plus or minus 48 mg%, 1.00 plus or minus 0.39 mg% and 1.01 plus or minus 0.44 mg%, respectively. Overall serum vitamin E levels were lower in the group with cardiovascular disease than in the control group. Patients and the

control group are also discussed with respect to a number of potentially confounding parameters such as age, sex, smoking status, quetelet index (kg/m2), alcohol consumption, dietary intake and serum lipids.

Oxidative susceptibility of low density lipoprotein from rabbits fed atherogenic diets containing coconut, palm, or soybean oils

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Lipids (USA), 1995, 30/12 (1145-1150)

The oxidative susceptibilities of low density lipoproteins (LDL) isolated from rabbits fed high-fat atherogenic diets containing coconut, palm, or soybean oils were investigated. New Zealand white rabbits were fed atherogenic semisynthetic diets containing 0.5% cholesterol and either (i) 13% coconut oil and 2% corn oil (CNO), (ii) 15% refined, bleached, and deodorized palm olein (RBDPO), (iii) 15% crude palm olein (CPO), (iv) 15% soybean oil (SO), or (v) 15% refined, bleached, and deodorized palm olein without cholesterol supplementation (RBDPO(wc)), for a period of twelve weeks. Total fatty acid compositions of the plasma and LDL were found to be modulated (but not too drastically) by the nature of the dietary fats. Cholesterol supplementation significantly increased the plasma level of vitamin E and effectively altered the plasma composition of long-chain fatty acids in favor of increasing oleic acid. Oxidative susceptibilities of LDL samples were determined by Cu2+-catalyzed oxidation which provide the lag times and lag-phase slopes. The plasma LDL from all palm oil diets (RBDPO, CPO, and RBDPO(wc)) were shown to be equally resistant to the oxidation, and the LDL from SO-fed rabbits were most susceptible, followed by the LDL from the CNO-fed rabbits. These results reflect a relationship between the oxidative susceptibility of LDL due to a combination of the levels of polyunsaturated fatty acids and vitamin E.

Coantioxidants make alpha-tocopherol an efficient antioxidant for low-density lipoprotein

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Am J Clin Nutr 1995 Dec;62(6 Suppl):1357S-1364S

The oxidation of low-density lipoproteins (LDLs) is now commonly implicated as an important early event in atherogenesis. The resulting interest in LDL antioxidation has focused on alpha-tocopherol, the biologically and chemically most active form of vitamin E and quantitatively the major lipid-soluble antioxidant in extracts prepared from human LDL. We review advances made in our understanding of the molecular action of alpha-tocopherol in radical-mediated

oxidation of isolated human LDL and how the vitamin's antioxidant activity is enhanced or even dependent on the presence of suitable reducing species, which are referred to as coantioxidants.

Optimal diet for reducing the risk of arteriosclerosis

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Can J Cardiol 1995 Oct;11 Suppl G:118G-122G

The primary objectives of current dietary advice for those at risk from coronary artery disease (CAD) focus on progressive restriction of dietary saturated (and trans) fatty acids and cholesterol intake, combined with exercise-and achievement of ideal body weight. These principles are endorsed by the official bodies of most western nations concerned with reducing CAD mortality and have recently been reaffirmed by the Adult Treatment Panel of the National Cholesterol Education Program. There has been concern, however, in view of the increasing use of drug therapy, that additional strategies should supplement the primary goals to increase the palatability and effectiveness of the diet. These additional strategies include increased intake of foods high in soluble viscous fibres, vegetable proteins, possibly antioxidants such as vitamin E and the isoflavonoids, increased intake of alpha-linolenic acid and, for those with low high density lipoprotein cholesterol levels, increased monounsaturated fat intake. These strategies translate into advice to significantly increase consumption of specific plant foods such as green leafy vegetables, nuts and seeds, and dried legumes, all of which improve the overall nutritional quality of the diet and contain specific active ingredients. These changes represent a regression to a more primitive diet on the evolutionary scale.

Effect of vitamin E, vitamin C and beta-carotene on LDL oxidation and atherosclerosis

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Canadian Journal of Cardiology (Canada), 1995, 11/Suppl. G (97G-103G)

OBJECTIVE: The oxidative modification of low density lipoprotein (LDL) may be early step in atherogenesis. Furthermore, evidence of oxidized LDL has been found in vivo. The most persuasive evidence shows that supplementation of some animal models with antioxidants slows atherosclerosis. The purpose of this review is to examine the roles that vitamin E, vitamin C and beta-carotene may play in reducing LDL oxidation.

DATA SOURCES: English language articles published since 1980, particularly from groups active in this field of research.

STUDY SELECTION: In vitro, animal, and human studies on antioxidants, LDL oxidation, and atherosclerosis were selected.

DATA SYNTHESIS: Vitamin E has shown the most consistent effects with regard to LDL oxidation. Beta-carotene appears to have only a mild or no effect on oxidizability. Ascorbate, although it is not lipophilic, can also reduce LDL oxidative susceptibility.

CONCLUSIONS: LDL oxidizability can be reduced by antioxidant nutrients. However, more research is needed to establish their utility in the prevention of coronary artery disease.

Atherosclerosis: Vitamin E protects coronary arteries

Trapp R., Germany
Deutsche Apotheker Zeitung (Germany), 1995, 135/41 (42+44)

No abstract.

Effects on health of dietary supplementation with 100 mg d-alpha-tocopheryl acetate, daily for 6 years

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J Int Med Res 1995 Sep-Oct;23(5):342-57

To evaluate the clinical antioxidant effects of vitamin E, 161 healthy volunteers aged 39 to 56 years, were given 100 or 3 mg of d-alpha-tocopheryl acetate orally daily for 6 years using a randomized, double-blind design, among the 147 volunteers who qualified for the analysis, seven of the 73 volunteers receiving 3 mg d-alpha-tocopheryl acetate daily and none of the 74 volunteers receiving 100 mg had coronary disorders including myocardial damage ($P < 0.02$). ST or T wave abnormalities on electrocardiograms were considered to indicate coronary disorders (four volunteers). The mean serum total tocopherol (TOC) concentration in the 100-mg group was significantly higher than that in the 3-mg group 6 months after the start of the study, and this raised value was maintained throughout the study; the level in the 3-mg group did not change significantly from the baseline value, The low-density lipoprotein cholesterol/total TOC ratio, a parameter of the inhibition of peroxidation of low-density lipoprotein cholesterol, was the only serum lipid parameter that was significantly different, at baseline, in

the volunteers with coronary disorders compared with the others. These findings indicate that long-term supplementation with 100 mg tocopheryl acetate daily may prevent the early stages of coronary atherosclerosis by decreasing peroxidation of low-density lipoprotein cholesterol.

Mechanisms of the cardioprotective effect of a diet enriched with omega-3 polyunsaturated fatty acids

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Pathophysiology (Netherlands) 1995, 2/3 (131-140)

The review presents current views of metabolic conversions of class omega-3 polyunsaturated fatty acids (omega-3 PUFA) and their effects on the heart function. The role of these compounds in regulation of the membrane lipid composition is discussed. Within the organism, omega-3 PUFA incorporate more effectively into membrane phospholipids of the myocardium in comparison with other organs. In animals kept on a omega-3 PUFA-enriched diet, the intramembrane concentration of omega-6 PUFA, in the first place, of rachidonic acid, decreases. Substitution of omega-3 PUFA for arachidonic acid in the metabolic system of eicosanoid synthesis initiates the synthesis of prostaglandins and thromboxanes possessing lowered biological activity, thus minimizing the risk of clot formation in the cardiovascular system. As omega-3 PUFA are direct substrates for lipid peroxidation, any rise in omega-3 PUFA concentration sharply activates free-radical oxidation in the membranes of internal organs particularly in the liver. Original data are presented that in rats kept on omega-3 PUFA-enriched diets, the kinetic parameters of the Ca2+ transport system do not change. However, the resistance of the system to free radical oxidation increases considerably. This may increase myocardial resistance to free-radical-dependent injuries. A rise in the intramembrane omega-3 PUFA content which brings about structural rearrangements within lipids and changes the activity of membrane-bound enzymes in vitro, has no effect in vivo. This finding points to the existence of a mechanism compensating for changes in the fatty acid composition of foods. Data from literature analysis suggest that one of the most active participants in the compensatory system is alpha-tocopherol, a lipid peroxidation inhibitor and a structural stabilizer of biomembranes. With a rise in omega-3 PUFA concentration, alpha-tocopherol is released from the liver and blood flow and accumulated in the body (predominantly in myocardial membranes). Whereas potent chemical antioxidants display an ability to inhibit physiologically important free-radical reactions occurring in the organism, vitamin E is without side effects even when used at high concentrations. In case of long-term application of omega-3 PUFA-enriched diets, alpha-tocopherol must be added to the diet.

Prevention of atherosclerosis: The potential role of antioxidants

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Postgrad Med 1995 Jul;98(1):175-6, 179-84

Evidence is increasing that oxidation of low-density lipoprotein cholesterol may be instrumental in atherogenesis. As a result a number of studies have been undertaken to evaluate the effects of antioxidant vitamins, beta carotene, selenium, and monounsaturated fat on coronary artery disease. Results in many instances have been promising, particularly in the case of vitamin E supplements. Studies of pro-oxidants, such as iron and copper, are inconclusive at this time, and a trial to assess the value of probucol in hypercholesterolemic patients is currently under way.

Vitamin E: Metabolism and role in atherosclerosis

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Ann Biol Clin (Paris) 1994;52(7-8):515-22

Vitamin E is the term used for eight naturally occurring fat-soluble nutrients. Alpha-tocopherol predominates in many species and has the highest biological activity. Vitamin E is absorbed via the lymphatic pathway and transported in association with CM. Vitamin E is carried in plasma by lipoproteins. It is secreted by the liver in nascent VLDL with a preferential incorporation of alpha-tocopherol. Most of the plasma vitamin E is in LDL and in HDL. Vitamin E is exchanged readily between lipoproteins: tocopherol in HDL readily transfers to apolipoprotein B-containing lipoproteins (VLDL, LDL), with little return of tocopherol from the apolipoprotein B-containing lipoproteins to HDL. The mechanisms of tissue uptake of vitamin E from the lipoproteins is poorly understood. This uptake may occur during catabolism of triacylglycerol-rich lipoproteins by the activity of lipoprotein lipase, via the LDL receptor or by nonreceptor-mediated uptake. Vitamin E may act to prevent the initiation/progression of spontaneous atherosclerosis. This concept is based on in-vitro data: vitamin E influences the responses of cells (vascular endothelial cells, leukocytes, vascular smooth muscle cells) and the modification of lipoproteins (especially LDL) which, at least in principle, could contribute to the initiation/progression of spontaneous atherosclerosis. In vivo studies are clearly required to establish the extent and mode of vitamin E's antiatherosclerotic impact and, hence, its therapeutic potential.

Vitamin C prevents cigarette smoke-induced leukocyte aggregation and adhesion to endothelium in vivo

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Proc. Natl. Acad. Sci. U.S.A. (USA), 1994, 91/16 (7688-7692)

A common feature of cigarette-smoke (CS)-associated diseases such as atherosclerosis and pulmonary emphysema is the activation, aggregation, and adhesion of leukocytes to micro- and macrovascular endothelium. A previous study, using a skinfold chamber model for intravital fluorescence microscopy in awake hamsters, has shown that exposure of hamsters to the smoke generated by one research cigarette elicits the adhesion of fluorescently labeled leukocytes to the endothelium of arterioles and small venules. By the combined use of intravital microscopy and scanning electron microscopy, we now demonstrate in the same animal model that (i) CS-induced leukocyte adhesion is not confined to the microcirculation, but that leukocytes also adhere singly and in clusters to the aortic endothelium; (ii) CS induces the formation in the bloodstream of aggregates between leukocytes and platelets; and (iii) CS-induced leukocyte adhesion to micro- and macrovascular endothelium and leukocyte-platelet aggregate formation are almost entirely prevented by dietary or intravenous pretreatment with the water-soluble antioxidant vitamin C (venules, 21.4 plus or minus 11.0 vs. 149.6 plus or minus 38.7 leukocytes per mm2, $P < 0.01$; arterioles, 8.5 plus or minus 4.2 vs. 54.3 plus or minus 21.6 leukocytes per mm2, $P < 0.01$; aortas, 0.8 plus or minus 0.4 vs. 12.4 plus or minus 5.6 leukocytes per mm2, $P < 0.01$; means plus or minus SD of $n = 7$ animals, 15 min after CS exposure). No inhibitory effect was observed by pretreatment of the animals with the lipid-soluble antioxidants vitamin E or probucol. The protective effects of vitamin C on CS-induced leukocyte adhesion and aggregation were seen at vitamin C plasma levels (55.6 plus or minus 22.2 microM, $n = 7$) that can easily be reached in humans by dietary means or supplementation, suggesting that vitamin C effectively contributes to protection from CS-associated cardiovascular and pulmonary diseases in humans.

Hyperhomocysteinaemia: a role in the accelerated atherogenesis of chronic renal failure?

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Neth J Med (Netherlands) May 1995, 46 (5) p244-51

Moderate hyperhomocysteinaemia has recently been established as an independent risk factor for atherothrombotic disease. It might be caused by heterozygosity for cystathionine beta-synthase deficiency, an enzyme involved in the conversion of methionine to cysteine through the transsulphuration pathway or by inherited thermolability of the enzyme which remethylates homocysteine into

methionine. In chronic renal failure (CRF) homocysteine levels are significantly elevated at a relatively early stage. The normal kidney possibly plays an important role in homocysteine catabolism, which cannot be performed in CRF. Alternatively, decreased extrarenal catabolism can contribute to the hyperhomocysteinaemia in this disease state. Treatment with folic acid, 5 mg daily, significantly lowers homocysteine levels in chronic renal patients. (45 Refs.)

Hyperhomocysteinaemia and endothelial dysfunction in young patients with peripheral arterial occlusive disease.

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Eur J Clin Invest (England) Mar 1995, 25 (3) p176-81

Hyperhomocysteinaemia, defined as an abnormally high plasma homocysteine concentration after an oral methionine load, is common in young (< or = 50 years) patients with peripheral arterial occlusive disease. It is thought to predispose to atherosclerosis by injuring the vascular endothelium. Treatment with pyridoxine and/or folic acid may lower plasma homocysteine levels. In mildly hyperhomocysteinaemic patients with peripheral arterial occlusive disease, we studied the effect of daily treatment with pyridoxine (250 mg) plus folic acid (5 mg) on homocysteine metabolism (i.e. plasma concentrations in the fasting state and after methionine loading, in 48 patients) and on endothelial function (in 18 patients). Endothelial function was estimated as the plasma concentrations of the endothelium-derived proteins, von Willebrand factor (vWF), thrombomodulin ?, and tissue-type plasminogen activator (tPA). At baseline, fasting homocysteine levels were above normal in 24 of the 48 patients (50%); post-load levels, by definition, were above normal in 100% of patients. After 12 weeks of treatment, fasting and post-load levels were normal in 98 and 100% of patients, respectively. Endothelial function was assessed in 18 patients who completed 1 year of treatment. At baseline, median vWF (235%) and TM (57.1 ng mL-1) levels were above normal. At follow-up, vWF levels had decreased to 170% (P = 0.01) and TM levels had decreased to 49 ng mL- 1 (P = 0.04). tPA levels were normal at baseline and did not change. Endothelial dysfunction is present in young patients with peripheral arterial occlusive disease and hyperhomocysteinaemia. Pyridoxine plus folic acid treatment normalizes homocysteine metabolism in virtually all patients, and appears to ameliorate endothelial dysfunction.

Vitamin nutrition status and homocysteine: an atherogenic risk factor.

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Nutr Rev (United States) Nov 1994, 52 (11) p383-7

In an epidemiologic survey, a marginal status of folic acid, vitamin B12, and vitamin B6 was shown to be associated with hyperhomocysteinemia. In a case-control study, a low plasma folate concentration was associated with increased coronary heart disease risk. This phenomenon appears to be mediated by folate's effect on homocysteine metabolism. Both studies offer further perspectives on homocysteine as an atherogenic risk factor.

Homocysteine and coronary artery disease.

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Cleve Clin J Med (United States) Nov-Dec 1994, 61 (6) p438-50

BACKGROUND Homocystinuria is a rare autosomal recessive disease complicated by early and aggressive occlusive arterial disease. This may be related to the grossly increased homocysteine concentrations seen in this disease. More recently, milder hyperhomocysteinemia has been proposed as an independent risk factor for coronary artery disease.

SUMMARY: Many patients with homozygous homocystinuria develop severe premature atherosclerosis and thromboembolism, probably caused by abnormally high concentrations of homocysteine. Homocysteine undergoes metabolism either by remethylation or transsulfuration, and deficiency or dysfunction of any of the substances that regulate these reactions may lead to hyperhomocysteinemia. Homocysteine may have adverse effects on platelets, clotting factors, and endothelial cells. Studies have demonstrated significantly higher plasma homocysteine levels in patients with occlusive arterial disease than in controls. The causes are not clearly understood but may include deficiency of vitamin B6, vitamin B12, and folic acid and heterozygosity for cystathionine synthase deficiency. Vitamin supplementation can lower plasma homocysteine levels.

CONCLUSIONS: Whether measuring plasma homocysteine levels in patients with coronary artery disease should be routine and whether treating hyperhomocysteinemia in these patients may reduce the risk of coronary events remains to be determined. (85 Refs.)

Platelets, carotids, and coronaries. Critique on antithrombotic role of antiplatelet agents, exercise, and certain diets.

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Am J Med (United States) Sep 1984, 77 (3) p513-23

"Antiplatelet" drugs and certain life styles seem to have an "antithrombotic" effect that may help protect against stroke and heart attack. This review of the experience with aspirin, dipyridamole, and sulfinpyrazone offers new interpretations of some of the major clinical trials, suggests guidelines for use of antiplatelet drugs, and integrates novel observations on diet and exercise into the "thromboxane- prostacyclin balance" hypothesis. It is argued that the Canadian stroke study showed that aspirin protects men with transient ischemic attacks from coronary death as well as from stroke, that type II errors may have been made in some clinical trials, that aspirin protects women as well as men, that aspirin benefits patients who have had a heart attack, that the effect of aspirin in angina varies with the type of angina, that the dose of aspirin used may not be critical, that guidelines for use of dipyridamole and sulfinpyrazone are still inconclusive, and that exercise and fish oil supplements may be "antithrombotic." (100 Refs.)

Effects of 11-week increases in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation.

Thorngren M; Gustafson A
Lancet (England) Nov 28 1981, 2 (8257) p1190-3

The effect of a diet rich in eicosapentaenoic acid (EPA) on platelet phospholipid fatty acid composition, platelet aggregation, and bleeding time was studied in 10 healthy men, whose usual diet was partly replaced by fish for 11 weeks. This diet provided 2-3 g EPA per day. Two doses (3.5 and 10 mg/kg body-weight) of acetylsalicylic acid (ASA) were given before and during the diet. The fish diet prolonged bleeding time (by 42%) and decreased platelet aggregability. The changes in platelet phospholipid fatty acid composition consisted of increases in the omega-3 series (C20: 5 and C22:6) and decreases in the omega-6 series (C18:2 and C20:3). The reduction in platelet aggregation induced by collagen and ADP did not parallel the changes in platelet membrane phospholipids and bleeding times. Diminished platelet aggregation induced by collagen lasted only 3 weeks (while subject was still on the diet), whereas the decreased sensitivity to ADP persisted for at least 11 weeks after the volunteers had resumed their normal diet. ASA taken before the diet prolonged bleeding time by as much as did the diet itself. ASA taken during the diet prolonged bleeding time by more than the sum of the increases in bleeding time caused by ASA and by the EPA diet separately, but the synergism was not significantly more than additive. The findings suggest that a diet rich in omega-3 polyunsaturated fatty acids reduces tha interaction between platelets and the vessel wall by mechanisms which are more complex than just a reduction in susceptibility of platelets to the naturally occurring agents collagen and ADP, or an imbalance between proaggregatory and anti- aggregatory prostaglandin derivatives.

N-3 but not N-6 fatty acids reduce the expression of the combined adhesion and scavenger receptor CD36 in human monocytic cells.

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Cell Biochem Funct (England) Sep 1995, 13 (3) p211-6

CD36, a multifunctional adhesion receptor e.g. for thrombospondin and collagen, as well as a scavenger receptor for oxidized low density lipoprotein, is expressed e.g. on platelets and monocytes. By this dual role it might be involved in early steps of atherosclerosis like the recruitment of monocytes and formation of foam cells. We therefore studied the effects of n-3 fatty acids on CD36 expression in human monocytic cells. Incorporation of eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) into cellular phospholipids resulted in a significant reduction of CD36 expression at the mRNA and protein level, whereas arachidonic acid (AA, C20: 4n-6) and linoleic acid (LA, C18:2n-6) tended to increase CD36 expression compared to the control. This specific down-regulation of CD36 by n-3 fatty acids in cells involved in the initiation and progression of atherogenesis and inflammation, represents a further mechanism that may contribute to the beneficial effects of n- 3 polyunsaturated fatty acids (PUFA) in these disorders.

Essential fatty acid metabolism in patients with essential hypertension, diabetes mellitus and coronary heart disease.

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Prostaglandins Leukot Essent Fatty Acids (Scotland) Jun 1995, 52 (6) p387-91

Mortality and morbidity from coronary heart disease (CHD), diabetes mellitus (DM) and essential hypertension (HTN) are higher in people of South Asian descent than in other groups. There is evidence to believe that essential fatty acids (EFAs) and their metabolites may have a role in the pathobiology of CHD, DM and HTN. Fatty acid analysis of the plasma phospholipid fraction revealed that in CHD the levels of gamma- linolenic acid (GLA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are low, in patients with HTN linoleic acid (LA) and AA are low, and in patients with non-insulin dependent diabetes mellitus (NIDDM) and diabetic nephropathy the levels of dihomo-gamma-linolenic acid (DGLA), AA, alpha-linolenic acid (ALA) and DHA are low, all compared to normal controls. These results are interesting since DGLA, AA and EPA form precursors to prostaglandin E1, (PGE1), prostacyclin (PGI2), and PGI3, which are potent platelet anti- aggregators and vasodilators and can prevent thrombosis and atherosclerosis. Further, the levels of lipid peroxides were found to be high in patients with CHD, HTN, NIDDM and diabetic nephropathy. These results suggest that increased formation of lipid peroxides and

an alteration in the metabolism of EFAs are closely associated with CHD, HTN and NIDDM in Indians.

[Changes in fatty acid composition, platelet aggregability and RBC function in elderly subjects with administration of low-dose fish oil concentrate and comparison with younger subjects]

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Ronen Igakkai Zasshi (Japan) Aug 1994, 31 (8) p596-603

Anti-thrombotic and anti-atherogenic effects of eicosapentaenoic acid (EPA) through the modulation of various cell functions related to thrombogenesis have been reported recently. We previously reported that the administration of EPA at low doses could more effectively elevate the plasma EPA concentration in elderly subjects than in younger ones. Magnetic resonance imaging examination of the brain often reveals lacunar lesions in elderly subjects without any signs or symptoms of cerebrovascular diseases. In this study we clarified the effect of administration of low doses of fish oil concentrate on platelet and RBC function in elderly subjects, compared with younger subjects. Thirty six elderly subjects (mean age 78) without any signs or symptoms of cerebrovascular diseases, all receiving the same diet in the same lodging house for the aged, were divided into 3 groups. Different amounts of fish oil concentrate (0.25-0.5 g/day of EPA) were administered to the 3 groups, daily for more than 1 month. Changes of plasma fatty acid composition, platelet aggregability, whole blood viscosity and RBC deformability was examined before and after EPA administration. One month after EPA treatment, the plasma EPA content had increased dose dependently, with suppression of platelet aggregation and improvement of RBC function. In younger subjects receiving the same amount of EPA, the elevation of plasma EPA was less than that observed in the elderly. In summary, low dose EPA administration can improve the function of platelet and RBC to an anti-thrombotic state and would be useful to prevent the occurrence of cerebrovascular diseases in elderly subjects without any side effects.

Do fish oils prevent restenosis after coronary angioplasty?

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Circulation (United States) Nov 1994, 90 (5) p2248-57

BACKGROUND-The omega-3 polyunsaturated fatty acids derived from fish oils have been shown to modulate many factors believed to affect the pathogenesis of atherosclerosis. Because certain features of restenosis following angioplasty

mimic some of the early changes of atherogenesis, some researchers have suggested that fish oil might prevent restenosis following angioplasty. We report the effects of omega-3 fatty acids on the rate of restenosis following percutaneous intraluminal coronary angioplasty (PTCA).

METHODS AND RESULTS-From August 1989 through September 1992, 551 patients were randomized to start receiving a daily dietary supplement of ten 1.0-g capsules containing 80.6% ethyl esters of omega-3 fatty acids providing 4.1 g eicosapentaenoic acid (EPA) and 2.8 g docosahexaenoic acid (DHA) for 6 months or an equal amount of an ethyl ester of corn oil. Four hundred seventy subjects who were well matched for risk factors completed successful angioplasty of one or multiple lesions in native coronary vessels and constituted the study cohort, of whom 447 were evaluable at 6 months after PTCA. The criteria for restenosis were that the quantitative coronary angiography at 6 months show a > 30% increase in narrowing at the stenosis site or loss of at least half of the gain achieved at the time of PTCA and final restenosis with < 50% luminal diameter remaining. In 93% of the patients, the end point was determined by angiography and in all except 1% of these by quantitative coronary angiography. Compliance with the fish oil supplement was good as judged by incorporation of EPA and DHA in plasma and red blood cell phospholipids. The restenosis rate among analyzable patients was 46% for corn oil and 52% for fish oil (P = .37). The addition of 200 mg alpha-tocopherol for all subjects during the study had no effect on restenosis rates.

CONCLUSIONS-This was the largest of such trials to date, and a supplement of 8 g/d of omega-3 fatty acids failed to prevent the usual high rate of restenosis after PTCA. No adverse effects were attributable to this large daily supplement of omega-3 fatty acids.

n-3 fatty acid incorporation into LDL particles renders them more susceptible to oxidation in vitro but not necessarily more atherogenic in vivo.

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Arterioscler Thromb (United States) Jul 1994, 14 (7) p1170-6

The hypothesis that n-3 fatty acid incorporation into low- density lipoprotein (LDL) particles renders them more susceptible to oxidative modification and possibly more atherogenic was tested using two groups of female Yucatan miniature swine (10 animals per group) fed an atherogenic diet for 8 months. As a supplement to the atherogenic diet, the first group received a daily oral dose of the fish oil (FO) concentrate MaxEPA, rich in n-3 fatty acids, while the second group received the same dosage of a control oil (CO) low in n-3 fatty acids but with the same ratio of polyunsaturated to monounsaturated to saturated fatty acids as MaxEPA. At 8 months, the animals were killed and perfusion fixed, and all major vessels were removed for morphological assessment of atherosclerotic lesion area. Before fixation, blood samples were collected from all 20 pigs, and LDL (d =

1.019 to 1.063 g/mL) was separated from the plasma by ultracentrifugation. A series of in vitro oxidative modification reactions were carried out by incubating the LDL with a copper sulfate solution. The susceptibility of each LDL preparation to oxidation was determined by measuring both the formation of conjugated dienes and the relative mobility of each sample in an agarose gel. The incorporation of n-3 fatty acids into LDL particles decreased the lag phase by 30%, resulting in an increased mobility of FO-LDL (compared with CO-LDL) when incubated for 0.5 to 12 hours, but at longer incubation times (18 to 24 hours), the extent of modification between the two groups became equal.

Human atherosclerotic plaque contains both oxidized lipids and relatively large amounts of alpha-tocopherol and ascorbate.

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Arterioscler Thromb Vasc Biol (United States) Oct 1995, 15 (10) p1616-24

We assessed the antioxidant status and contents of unoxidized and oxidized lipids in freshly obtained, homogenized samples of both normal human iliac arteries and carotid and femoral atherosclerotic plaque. Optimal sample preparation involved homogenization of human atherosclerotic plaque for 5 minutes, which resulted in recovery of most of the unoxidized and oxidized lipids without substantial destruction of endogenous vitamins C and E and 87% and 43% recoveries of added standards of alpha- tocotrienol and isoascorbate, respectively. The total protein, lipid, and antioxidant levels obtained from human plaque varied among donors, although the reproducibility of replicates from a single sample was within 3%, except for ubiquinone-10 and ascorbate, which varied by 20% and 25%, respectively. Plaque samples contained significantly more ascorbate and urate than control arteries, with no discernible difference in the vitamin C redox status between plaque and control materials. The concentrations of alpha-tocopherol and ubiquinone-10 were comparable in plaque samples and control arteries. However, approximately 9 mol percent of plaque alpha-tocopherol was present as alpha-tocopherylquinone, whereas this oxidation product of vitamin E was not detectable in control arteries. Coenzyme Q10 in plaque and control arteries was only detected in the oxidized form ubiquinone-10, although coenzyme Q10 oxidation may have occurred during processing. The most abundant of all studied lipids in plaque samples was free cholesterol, followed by cholesteryl oleate and cholesteryl linoleate (Ch18:2). Approximately 30% of plaque Ch18:2 was oxidized, with 17%, 12%, and 1% present as fatty acyl hydroxides, ketones, and hydroperoxides, respectively.

Hyperhomocysteinaemia and end stage renal disease

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Vascular disease is a major cause of morbidity and mortality in end stage renal failure patients and cannot be explained entirely by the prevalence of traditional risk factors for atherosclerosis. A high plasma homocysteine concentration, which is a risk factor for vascular disease is found in patients with end stage renal disease. The exact cause for the hyperhomocysteinaemia seen in these patients is unknown, al metabolism of homocysteine. High homocysteine concentrations may also be attributable to a deficiency of folate, vitamin B6 or vitamin B12 although, because of supplementation, these vitamins may be present in high concentrations in renal patients. The occurrence of hyperhomocysteinaemia despite high plasma vitamin concentration could be due to altered metabolism or inhibition of intracellular vitamin activity. A number of studies have now established hyperhomocystinaemia to be an independent risk factor for atherosclerosis in patients with end-stage renal disease. Plasma homocysteine concentrations can be reduced by administration of folic acid either alone or combined with vitamin B12 or vitamin B6. The effects of such reduction on vascular risk in renal failure patients needs further study.

Dietary pectin influences fibrin network structure in hypercholesterolaemic subjects

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Thrombosis Research (United Kingdom), 1997, 86/3 (183-196)

Fibrinogen is an important risk factor for atherosclerosis, stroke and cardiovascular heart disease (CHD). This risk is increased when associated with a high serum cholesterol. Furthermore, it is also believed that not only fibrinogen concentration, but also the quality of fibrin networks may be an important risk factor for the development of CHD. CHD and stroke as a result of atherosclerosis, plus the related problems of hyperinsulinaemia, hyperlipidaemia and hypertension are strongly related to diet. The 'western' diet, defined by low fibre and high fat, sucrose and animal protein intakes, appears to be a major factor leading to death. It has been established that the water-soluble dietary fibre, pectin, significantly decrease the concentration of serum cholesterol levels. Evidence is also accumulating that a diet rich in fibre may protect against diseases associated with raised clotting factors. This investigation studied the possible effects of pectin on fibrinogen levels and fibrin network architecture. Two groups of 10 male hyperlipidaemic volunteers each, received a pectin supplement (15g/day) or placebo (15g/day) for 3 weeks. Lipid and fibrin network structure variables were measured at baseline and the end of supplementation. Pectin supplementation caused significant decreases in total cholesterol, low-density lind lipoprotein (a). Significant changes in the characteristics of fibrin networks developed in the

plasma of the pectin supplemented group indicated that networks were more permeable and had lower tensile strength. These network structures are believed to be less atherogenic. It is suspected that pectin modified network characteristics by a combination of its effects on metabolism and altered fibrin conversion. This confirms the therapeutic possibilities of dietary intervention. Furthermore, this study also showed that changes in plasma fibrinogen need not be present to induce alterations in fibrin network architecture.

Omega3 fatty acids in the prevention-management of cardiovascular disease

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Epidemiologic studies show that populations who eat fish versus those who do not have a reduced death rate from cardiovascular disease. Experimental studies have shown that omega-3 fatty acids affect the function of cells involved in atherothrombosis in numerous ways, including the modification of eicosanoid products in the cyclooxygenase and lipoxygenase pathways, the reduced synthesis of cytokines and platelet-derived growth factor, and alterations of leukocyte and endothelial cell properties. Intervention studies in patients with restenosis, myocardial infarction, and cardiac arrhythmias with omega-3 fatty acid supplementation have been addressed in several clinical studies. The ingestion of omega-3 fatty acids following one episode of myocardial infarction appears to decrease the rate of cardiac death. These effects of omega-3 fatty acids appear to be due to their antiarrhythmic properties. In fact, fish oil has been shown to reduce ventricular arrhythmias and to be more beneficial than currently used pharmacologic agents. The dose, duration, and mechanisms involved in the prevention and management of cardiovascular disease following omega-3 fatty acid ingestion or supplementation need to be investigated by double blind controlled clinical trials.

Vitamin intake: A possible determinant of plasma homocyst(e)ine among middle-aged adults

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PURPOSE: Many epidemiologic studies have identified elevated plasma homocyst(e)ine as a risk factor for atherosclerosis and thromboembolic diseases. To examine the relationship between vitamin intakes and plasma homocyst(e)ine,

we analyzed dietary intake data from a case-control study of 322 middle-aged individuals with atherosclerosis in the carotid artery and 318 control subjects without evidence of this disease.

METHODS: All of these individuals were selected from a probability sample of 15,800 men and women who participated in the Atherosclerosis Risk in Communities (ARIC) study.

RESULTS: Plasma homocyst(e)ine was inversely associated with intakes of folate, vitamin B6, and vitamin B12 (controls only for this vitamin)-the three key vitamins in homocyst(e)ine metabolism. Among nonusers of vitamin supplement products, on average each fertile increase in intake of these vitamins was associated with 0.4 to 0.7 micromol/L decrease in plasma homocyst(e)ine. An inverse association of plaine was also found with thiamin, riboflavin, calcium, phosphorus, and iron. Methionine and protein intake did not show any significant association with plasma homocyst(e)ine.

CONCLUSIONS: In almost all analyses, cases and controls showed similar associations between dietary variables and plasma homocyst(e)ine. Plasma homocyst(e)ine among users of vitamin supplement products was 1.5 micromol/L lower than that among nonusers. Further studies to examine possible caused relationships among vitamin intake, plasma homocyst(e)ine, and cardiovascular disease are needed.

Dietary soy protein and estrogen replacement therapy improve cardiovascular risk factors and decrease aortic cholesteryl ester content in ovariectomized cynomolgus monkeys

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Metabolism: Clinical and Experimental (USA), 1997, 46/6 (698-705)

Estrogen replacement therapy (ERT) decreases the progression of coronary artery atherosclerosis in monkeys. Dietary soy protein also retards the progression of atherosclerosis relative to animal proteins such as casein. Soy protein contains weakly estrogenic compounds called isoflavones or phytoestrogens that may be responsible for the cardioprotective effects. This study was designed as a 2 x 2 factorial to determine the magnitude of soy protein's effects on cardiovascular risk factors relative to casein and lactalbumin, with or without estradiol treatment. Ovariectomized female monkeys were randomized to four treatment groups based on past dietary cholesterol consumption, their origin, end past reproductive history, end studied for 7 months. The animals were divided into (1) a group fed casein end lactalbumin as the protein source (n = 14), (2) a group fed casein and lactalbumin as the protein source = 13), (3) a group fed soybean protein isolate as the protein source (n = 11), and (4) a group fed soybean protein isolate as the protein source plus E2 (n = 10). Soy protein compared with casein consumption

resulted in a significant improvement in plasma lipid and lipoprotein concentrations, e significant improvement in insulin sensitivity and glucose effectiveness as determined by minimal-model analyses, and a decrease in arterial lipid peroxidation, E2- treated monkeys had a significant reduction in fasting insulin levels and insulin to glucose ratios, total body weight, and amounts of abdominal fat, and had smaller low-density lipoprotein (LDL) particles. In addition. E2 treatment resulted in a significant reduction (P = .001) in aortic cholesteryl ester content. A similar trend (P = .14) was found for soy protein compared with casein. There also was a significant interaction (P = .02) with soy and E2, such that animals consuming soy protein + E2 had the least arterial cholesteryl ester content. These results suggest that both ERT and dietary soybean protein have beneficial effects on cardiovascular risk factors. Interestingly, the two treatments affected different risk factors and together resulted in the greatest reduction in arterial cholesterol content. Further studies are needed to determine the active component of the soy protein and to assess its long-term effects on the cardiovascular system and other organ systems (such as the bones and reproductive system).

Atherogenesis and the homocysteine-folate-cobalamin triad: Do we need standardized analyses?

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Background: Bioscientists, physicians and nutritionists are newly interested in the homocysteine folate cobalamin triad, in part because homocysteine may be important both in atherogenesis and thrombogenesis Homocysteine imbalance may be an early marker for cobalamin disorders because cobalamin is a cofactor in remethylation of homocysteine to methionine.

Methods: In 139 men and 32 women of similar mean age of 65 years, we measured markers which have been cited as risk for atherosclerosis: serum homocysteine, folate, total cobalamin, holotranscobalamin I and II, (TCI and TCII), total serum cholesterol (SCHOL), high density lipoprotein cholesterol (HDLC), triglycerides (STG) as well as red blood cell (RBC) folate, food records and body composition by whole body counting of potassium-forty (40K).

Results: Statistical relationships among the data showed healthy women had lower mean serum homocysteine and their mean RBC folate and TCI and TCII were higher than men. Eighty-three subjects had TCII much lower than 60 pg/ml (subnormal), yet only 11 of these men and two women had total cobalamin <200 pg/ml (abnormal). Fifty-two subjects with serum homocysteine greater than 17.5 nmol/ml had TCII less than 60 pg/ml, suggesting serum homocysteine may be a marker for early cobalamin negative balance. None of the subjects in the study had serum folate below abnormal values, i.e., less than 1.6 mg/ml. All subjects

had RBC folate within normal range. Serum homocysteine showed inverse relationship with RBC folate and serum total cobalamin, TCI and TCII.

CONCLUSIONS:

1) importance of using serum holotranscobalamin TCI and TCII as markers of cobalamin deficiency,

2) necessity to uke if strong comparisons are to be made among quantitative values of serum or plasma homocysteine, folate, cobalamin, and nutrients in food intake.

Fasting total plasma homocysteine and atherosclerotic peripheral vascular disease

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Annals of Vascular Surgery (USA), 1997, 11/3 (217-223)

Fasting total plasma homocysteine levels were measured by rapid ion-exchange chromatography in 100 patients with symptomatic atherosclerotic peripheral vascular disease (PVD) and 100 age and sex-matched control subjects. Demographic data, biochemistry, hematology, and lipid fractions were measured in both groups, and clinical and vascular laboratory disease parameters were recorded for the patient group. Patients with hyperhomocysteinemia (defined as those with fasting homocysteine values exceeding the 90th percentile of the control range) were compared to patients with normal homocysteine with respect to the above parameters. Total fasting homocysteine concentrations were significantly higher in the patient group (28.8 plus or minus 14.9 micromol/l) than in the control subjects (20.3 plus or minus 11.3 micromol/l; $p < 0.001$). Homocysteine levels were also higher in males than in females in both the control and the patient groups. Homocysteine correlates positively only with age in the healthy controls ($r = 0.291$; $p < 0.005$) but not with other standard risk factors. Multivariate analysis of the biochemical risk factors confirmed that total plasma homocysteine concentration is an independent risk factor for PVD ($p < 0.001$). Hyperhomocysteinemia is not associated with vitamin B12 or folate deficiency states. Vitamin B12 concentration was 591 plus or minus 313 ng/l in the control group, and 682 plus or minus 405 ng/l in the patient group (p = NS). Serum relate concentration was lower in the controls (7.2 plus or minus 2.3 microg/l) than in the patients (8.3 plus or minus 2.0 microg/I, $p < 0.001$). Mild hyperhomocysteinemia was detected in 27% of the patients. Patients with hyperhomocysteinemia has a four-fold increase in risk of PVD relative to patients with a normal homocysteine level. There is no significant difference between the two groups with respect to patient demographics, biochemical risk factors, and disease pattern and severity.

Plasma total homocysteine, B vitamins, and risk of coronary atherosclerosis

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Epidemiological research has shown that elevated plasma total homocysteine (tHcy) is a risk factor for atherosclerotic disease. In the present case-control study, we investigated whether fasting or postmethionine-loading they was a stronger predictor of risk of severe coronary atherosclerosis. Furthermore, we studied levels of B vitamins, which are involved in homocysteine metabolism. Subjects were recruited from men and women, aged 25 to 65 years, who underwent coronary angiography between June 1992 and June 1994 in a hospital in Rotterdam, The Netherlands. Cases (n=131) were defined as those with less than or equal to90% occlusion in one and less than or equal to40% occlusion in a second coronary artery, while control subjects (n=88) had less than or equal to50% occlusion in only one coronary vessel. In addition, a population-based control group free from clinical cardiovascular disease (n=101) was studied. Coronary patients were studied at least 2.5 months after angiography or other acute illness, such as myocardial infarction. After adjusting for age and sex differences between the groups, cases had 9% (P=.01) higher geometric mean fasting and 7% (P=.04) higher geometric mean postload they than the combined control groups. Despite higher levels of they for cases, their geometric mean levels of red cell folate and pyridoxal 5'-phosphate were higher than for control subjects, whereas plasma vitamin B12 was only slightly lower in cases. The frequency distribution of they values in cases was slightly shifted toward the right, across the entire range, compared with the distribution in the combined control group. This was somewhat more obvious for fasting than postload they levels. The odds ratio (OR) for severe coronary atherosclerosis (case status) for each 1 SD increase in fasting they (5 micromol/L) was 1.3 (95% confidence interval (CI), 1.0-1.6), similar to the OR for each 1 SD increase (12 micromol/L) in postmethionine-loading they (1.3 (95 CI, 1.0-1.7)), after adjustment for sex, age, and other potential confounders. Furthermore, there was a significant linear trend of increasing fasting they with increasing number of occluded arteries (P=.01), correcting for sex, age, and other potential confounders. Our data show a positive association between plasma they and risk of severe coronary atherosclerosis, of similar strength for fasting and postload they levels. The t that the association exists over a wide range of they levels, without a clear cutoff point below which there is no increased risk.

Correlation between plasma homocyst(e)ine and aortic atherosclerosis

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American Heart Journal (USA), 1997, 133/5 (534-540)

Plasma homocyst(e)ine (H(e)) levels correlate with the prevalence of arterial occlusive diseases. Recently, transesophageal echocardiography (TEE) has been used to evaluate patients with atherosclerotic plaques in the thoracic aorta. The purpose of this study was to determine whether H(e) levels correlate with the degree of atherosclerotic plaque in the thoracic aorta (ATH) as seen on TEE. Maximum plaque areas for three locations in the thoracic aorta (arch, proximal descending, and distal descending) were measured with TEE in 156 patients. Maximum plaque areas for these locations were added to yield an estimate of ATH. ATH and H(e) levels, and levels of folic acid, vitamin B12, and pyridoxal 5'-phosphate were measured in a double-blind manner. Univariate analysis demonstrated a significant correlation of H(e) with ATH ($r=0.3$, $p < 0.001$). On multivariate analysis, H(e) was independently predictive of ATH (r for the model including H(e) was 0.63, $p < 0.0001$). Plasma H(e) levels are therefore significantly and independently correlated with the degree of atherosclerosis in the thoracic aorta.

Cell cycle effects of nitric oxide on vascular smooth muscle cells

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American Journal of Physiology - Heart and Circulatory Physiology (USA), 1997, 272/4 41-4 (H1810-H1818)

We characterized the cell cycle block induced by nitric oxide (NO) on smooth muscle cells (SMC). We hypothesized that the inhibition of SMC proliferation by NO was due to a specific block in cell cycle progression. Treatment of cultured rat aortic SMC with the NO donors S-nitroso-N- acetylpenicillamine or S-nitrosoglutathione (0.1 mM for 48 h) resulted in a 50% decrease ($P < 0.05$) in the fraction of cells in the S and G2+M phases and a corresponding increase in the G1 fraction, suggesting that NO inhibits entry into S phase, causing accumulation of cells in G1 phase. Application of both NO donors to cycling SMC resulted in a short-term, concentration- dependent (0.06-0.3 mM) inhibition of ongoing DNA synthesis as measured by radiothymidine incorporation, demonstrating that NO causes an S-phase arrest. The S-phase arrest by NO was not mimicked by exogenous guanosine 3',5'- cyclic monophosphate (cGMP, 10 mM) and was associated with, but not due to, a 20% inhibition of RNA synthesis. The S-phase block was completely reversed within 2 h of removal of the NO donors, similar to inhibition by the ribonucleotide reductase inhibitor hydroxyurea. Prolonged treatment of SMC with either NO donor (0.1 mM) did not synchronize cells at the G1-S boundary as expected after a prolonged S-phase arrest, but instead induced a quiescent G0-like state characterized by a 12- to 18-h lag before DNA synthesis returned to normal levels after NO removal. These findings demonstrate that NO

inhibition of SMC proliferation is associated with two distinct and reversible cell cycle arrests, an immediate cGMP-independent S-phase block followed by a shift back in the cell cycle from the G1-S boundary to a quiescent G0-like state.

Effects of dehydroepiandrosterone on proliferation of human aortic smooth muscle cells

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Life Sciences (USA), 1997, 60/11 (833-838)

Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) have ession of coronary atherosclerosis in clinical and in vivo studies. However, the mechanisms responsible for the association have not been determined. In the present study, we found that DHEA influences the in vitro growth of vascular smooth muscle cells obtained from the human aorta (hASMC). The concentrations of DHEA ranging from 10-8 M to 10-6 M significantly stimulated the mitogenesis of hASMC in serum-free culture. On the other hand, 4 hrs of pretreatment with DHEA attenuated the fetal calf serum induced proliferative effect in a dose-dependent manner. However, the in vitro effects of DHEA on the mitogenesis observed in hASMC were not seen in rat-derived aortic smooth muscle cell lines (A10 cells). With respect to DHEAS, the hormone, at concentrations up to 10-5 M did not affect the growth of either hASMC orA10 cells in vitro. The growth response of hASMC to DHEA in vitro was markedly affected by the culture conditions. The differential proliferative effects of DHEA on smooth muscle cells between rat and human are of interest. We conclude that the effects of DHEA on mitogenesis of hASMC may, at least in part, explain the association between DHEA and atherosclerosis.

Dietary fish oil: Influence on lesion regression in the porcine model of atherosclerosis

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We examined the influence of dietary fish oil on lesion regression in a porcine model of atherogenesis. Thirty-two female Yucatan miniature pigs were fed an atherogenic diet for 8 months. A no-regression group (n=8) was killed to determine the extent of atherosclerosis at 8 months. Three regression groups were switched to normal minipig chow supplemented with either MaxEPA fish oil (FO group, n=8), a control oil with the ratio of polyunsaturated to monounsaturated to saturated fatty acid matched to that of the fish oil (CO group, n=8), or no oil supplement (NO group, n=8) for a further 4 months. Plasma cholesterol levels reached between 15 and 20 mmol/L during the atherogenic phase and returned to

normal (2 mmol/L) within 2 months of the beginning of the regression diet. Compared with the NO group, fish oil supplementation during the regression phase caused a decrease in VLDL and HDL cholesterol and an increase in LDL cholesterol. Similarly, the control oil also caused a decrease in VLDL cholesterol; however, in contrast to the FO group, HDL cholesterol increased and LDL cholesterol was unchanged. FO LDL, which had decreased levels of 20:4 (n-6 fatty acid) and increased levels of 18:3, 20:5, and 22:6 (n-3 fatty acids), was shown to be twice as susceptible to copper-mediated oxidation as CO LDL particles. Morphological examination of the major blood vessels revealed a significant reduction in lesion area in the ascending and thoracic aorta as well as the carotid artery after the regression diet; however, there was no significant difference between the fish oil and control oil groups in any of the vessels measured. Therefore, despite increased LDL, decreased HDL and an increased susceptibility to in vitro oxidation of LDL, fish oil supplementation of a regression diet did not influence lesion regression.

Additive hypocholesterolemic effect of psyllium and cholestyramine in the hamster: Influence on fecal sterol and bile acid profiles

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Journal of Lipid Research (USA), 1997, 38/3 (491-502)

Recent findings suggest that the effects of cholestyramine and psyllium in combination could be additive for cholesterol-lowering. We therefore examined the effect of both agents, alone and in combination, on lipoprotein cholesterol and neutral and acidic steroid excretion in the hamster. Animals (n = 8/group) were fed for 21 days, either a basal chow diet supplemented with 10% palm oil and 0.2% cholestertreatments consisting of the basal diet plus: 5.5% cellulose; 5% psyllium with 0.5% cellulose; 0.5% cholestyramine with 5% cellulose; or 5% psyllium with 0.5% cholestyramine. Psyllium and cholestyramine both had significant hypocholesterolemic effects, but in combination produced additive reductions in lipoprotein and hepatic cholesterol. Psyllium, cholestyramine, and the combination increased total bile acid excretion by 26%, 57%, and 79%, respectively. Psyllium affected only unconjugated bile acid excretion while cholestyramine also increased the excretion of conjugated and primary bile acids. Neither agent, nor the combination, affected fetal neutral sterol excretion. We conclude that, while both agents lower cholesterol by a mechanism of increased bile acid excretion, these studies indicate that psyllium does not bind bile acids in vivo and lend further support for the concomitant use of these agents for cholesterol-lowering.

Vitamin E inhibits low-density lipoprotein-induced adhesion of monocytes to human aortic endothelial cells in vitro

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USA
Arteriosclerosis, Thrombosis, and Vascular Biology (USA), 1997, 17/3 (429-436)

Monocyte adhesion to human aortic endothelial cells (ECs) is one of the early events in the development of atherogenesis. ECs were used to investigate the role of vitamin E in human monocyte adhesion to ECs in vitro. ECs incubated with 40 to 193 mg/dL of low-density lipoprotein cholesterol (LDL) for 22 hours exhibited increasing dose-dependent adherence for untreated, isolated human monocytes (P<.05). ECs exposed to the highest dose of LDL (193 mg/dL) but pretreated with 19 micromol/L alpha-ocopherol for 24 hours showed a trend to lower adherence for monocytes compared with nontreated ECs (4.4 plus or minus 1.2% versus 7.6 plus or minus 1.9%; P = .09). This effect of vitamin E became more significant (P<.05) when ECs were exposed to a lower level of LDL (40 mg/dL) or were pretreated with a higher level of alpha- tocopherol (42 micromol/L) and then exposed to 80 mg/dL LDL. Presupplementation of Ecs with 15, 19, and 37 micromol/L alpha-tocopherol significantly (P<.05) reduced monocyte adhesion by 6plus or minus1%, 37plus or minus6%, and 69plus or minus17%, respectively. Levels of soluble intercellular adhesion molecule-1 (sICAMn molecules for monocytes, increased after incubation of ECs with LDL 80 mg/dL (4.7plus or minus0.7 versus 6.4plus or minus1.2 ng/mL, respectively; P<.05). Treatment of Ecs with alpha-tocopherol (42 micromol/L) significantly reduced induction of sICAM-1 by LDL to 2.2plus or minus2.3 ng/mL. After exposure to LDL, prostaglandin I2 production by ECs was diminished, whereas presupplementation of ECs with alpha- tocopherol partially reversed the LDL effect. Production of interleukin-1beta was not detectable when ECs were treated with alpha-tocopherol, LDL, or alpha- tocopherol followed by LDL. Our findings indicate that vitamin E has an inhibitory effect on LDL-induced production of adhesion molecules and adhesion of monocytes to ECs via its antioxidant function and/or its direct regulatory effect on sICAM-1 expression.

Nitric oxide synthase: Role in the genesis of vascular disease

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Annual Review of Medicine (USA), 1997, 48/- (489-509)

The product of nitric oxide (NO) synthase is the most potent endogenous vasodilator known. NO not only is a potent vasodilator, it also inhibits platelet adherence and aggregation, reduces adherence of leukocytes to the endothelium, and suppresses proliferation of vascular smooth muscle cells. A number of disorders are associated with reduced synthesis and/or increased degradation of vascular NO. These include hypercholesterolemia, diabetes mellitus, hypertension, and tobacco use. The endothelial dysfunction caused by these disorders contributes to the alterations in vascular function and structure observed in these conditions. A reduction in the activity of vascular NO likely plays a significant role in the development of atherosclerosis. Insights into the

mechanisms by which NO production or activity is altered in these states will lead to new therapeutic strategies in the treatment of a number of vascular disorders, including hypertension, atherosclerosis, restenosis, and thrombosis.

Hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans

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Circulation (USA), 1997, 95/5 (1119-1121)

Background: Hyperhomocyst(e)inemia is a risk factor for atherosclerosis and is prevalent in the elderly. The objective of this study was to determine whether hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans.

Methods and Results: High- resolution vascular ultrasonography was used to study endothelium-dependent and -independent vasodilation in a nonatherosclerotic peripheral conduit artery of 26 elderly hyperhomocyst(e)inemic subjects and 15 age- and sex- matched subjects with normal homocysteine levels. Flow-mediated, endothelium-dependent (nitric oxide-mediated) vasodilation was assessed by measuring the percent change in brachial artery diameter during reactive hyperemia. Endothelium-independent vasodilation was assessed after the administration of 0.4 mg sublingual nitroglycerin. Endothelium-dependent asodilalion was significantly impaired in the hyperhomocyst(e)inemic subjects compared with control subjects (3.7plus or minus0.6% versus 8.1plus or minus1.2%; P=.004), whereas endothelium-independent vasodilation was not different between the two groups (10.1plus or minus1.6% versus 9.3plus or minus1.5%; P= NS). In a linear regression analysis with serum homocysteine concentration, folic acid, age, sex, cholesterol (serum total, LDL, or HDL cholesterol), mean arterial blood pressure, use of antihypertensive medication, and baseline brachial artery diameter included as covariates, serum homocysteine concentration emerged as the only significant predictor of flow-mediated vasodilation.

Conclusions: These data indicate that hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans and suggest that the bioavailability of nitric oxide is decreased in hyperhomocyst(e)inemic humans.

The role of folic acid in deficiency states and prevention of disease

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Journal of Family Practice (USA), 1997, 44/2 (138-144)

Folic acid, a water-soluble vitamin, has been used since the 1940s to treat some cases of macrocytic anemia without neurologic disease. Folate deficiency is best diagnosed with red blood cell folate levels along with macrocytosis and/or megaloblastic anemia. In addition to reversing overt deficiency, the vitamin may reduce the incidence of neural tube defects by 45% in women who receive 400 microg per400 microg of folate per day. Elevations in homocysteine levels, a metabolite intimately associated with folate, are also being found with increasing regularity in those with cardiovascular diseases. Homocysteine levels are reduced by folic acid administration. Therefore, there is some biologic plausibility, but not currently direct proof, for the assumption that folate supplements may prevent heart disease, stroke, and peripheral arterial disease. Controlled trials should take place before widespread food supplementation with folate is carried out on a large scale because of the possibility of outbreaks of permanent B12-related neurologic damage in those with undiagnosed pernicious anemia. However, if a patient has a premature cardiovascular event and has minimal risk factors, ordering a test to determine homocysteine level may be advisable, and if elevated, treating with folic acid supplement as long as B12 deficiency does not coexist.

Effects of vitamin D on aortic smooth muscle cells in culture

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Toxicology in Vitro (United Kingdom), 1996, 10/6 (701-711)

Earlier investigations on vitamin-induced experimental atherosclerosis in rats suggested that smooth muscle cells (SMCs) play a pivotal role in development of these vascular abnormalities. This study demonstrates the effects of vitamin D (ergocalciferol) on SMCs of rat aorta in tissue culture. SMCs were obtained from aortas of newborn rats by enzymatic digestion and maintained for 6 wk in primary culture with vitamin D (1.2 nM) in the culture medium. The effects of vitamin D on SMCs, as compared with control SMCs cultures, were evaluated by light and electron microscopy. Growth of SMCs was characterized by cell counting, measurement of DNA and protein content, and by analysis of the nucleolar organizing regions. Vitamin D had no effect on proliferation of SMCs but stimulated synthesis and intercellular deposition of elastic fibres and had a stabilizing effect on the musculo-elastic multilayer formed by the cultured cells. In addition, it prevented degeneration of SMCs, with long-term preservation of the typical phenotype in primary culture.

Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques

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Fertility and Sterility (USA), 1997, 67/1 (148-154)

Objective: To examine the effects of soy phytoestrogens on coronary vascular reactivity in atherosclerotic male and female rhesus monkeys.

Design: A prospective, randomized, blinded, controlled study.

Setting: Comparative Medicine Clinical Research Center of an academic medical center.

Patient(s): Twenty-two young adult rhesus monkeys with pre-existing diet-induced atherosclerosis. Intervention(s): Monkeys were fed soy-based diets for 6 months identical in composition, except that the isoflavones were extracted from one (low-isoflavone) and intact in the other (high- isoflavone). Quantitative coronary angiography was performed at the end of the study period. Females in the low-isoflavone group underwent a second angiography after an acute IV dose of genistein.

Main Outcome Measure(s): Percent change in diameter of the proximal left circumflex coronary artery in response to intracoronary acetylcholine and nitroglycerin, compared with control diameter.

Result(s): Arteries from males constricted in response to acetylcholine. Arteries from females in the low-isoflavone group constricted (-6.2% + 2.8%, mean plus or minus SEM), whereas arteries from females in the high- isoflavone group dilated (6.4% plus or minus 1.2%, mean plus or minus SEM). Intravenous administration of genistein caused dilation in the previously constricting low-isoflavone females (3.39% plus or minus 2.8%).

Conclusion(s): Like mammalian estrogens, dietary soy isoflavones enhance the dilator response to acetylcholine of atherosclerotic arteries in female monkeys.

Common mutation in methylenetetrahydrofolate reductase: Correlation with homocysteine metabolism and late-onset vascular disease

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Circulation (USA), 1996, 94/12 (3074-3078)

Background: Increased homocysteine levels are a risk factor for atherosclerosis and its sequelae. A common genetic mutation in methylenetetrahydrofolate reductase (MTHFR), an enzyme required for efficient homocysteine metabolism, creates a thermolabile enzyme with reduced activity. We determined the

prevalence of this mutation in many subjects with and without vascular disease and related it to homocysteine and folate levels.

Methods and Results: DNA from 247 older subjects with vascular disease and 594 healthy subjects without vascular disease (in three different control groups) was screened for the MTHFR 677 C-to-T mutation. Within each group, 9% to 17% of the subjects were homozygous for this mutation, and the mutant allele frequency was 31% to 39%. The genotype distributions, homozygote frequencies, and allele frequencies did not differ significantly between the study groups. In the vascular disease subjects, despite significantly lower folate levels in MTHFR homozygotes, there was no significant difference in homocysteine levels among the MTHFR genotype groups. The negative slope of the regression line relating homocysteine and folate was significantly steeper for those with a homozygous MTHFR mutation compared with those without this mutation.

Conclusions: Although the thermolabile MTHFR mutation is very common, it does not appear to be a significant genetic risk factor for typical late-onset vascular disease. Because MTHFR homozygotes have increased homocysteine with low folate levels, this mutation may contribute to early-onset or familial vascular disease. The genotype dependence of the folate-homocysteine correlation further suggests that homozygotes for this mutation may have both an exaggerated hyperhomocysteinemic response to folic acid depletiacid therapy.

Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations

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Circulation (USA), 1996, 94/11 (2743-2748)

Background: A high level of total plasma homocysteine is a risk factor for atherosclerosis, which is an important cause of death in renal failure. We evaluated the role of this as a risk factor for a vascular complications of end-stage renal disease.

Methods and Results: Total fasting plasma homocysteine and other risk factors were documented in 176 dialysis patients (97 men, 79 women; mean age 56.3plus or minus14.8 years). Folate, vitamin B12, and pyridoxal phosphate concentrations were also determined. The prevalence of high total homocysteine values was determined by comparison with a normal reference population, and the risk of associated vascular complications was estimated by multiple logistic regression. Total homocysteine concentration was higher in patients than in the normal population (26.6plus or minus1.5 versus 10.1plus or minus1.7 micromol/L; P<.01). Abnormally high concentrations (>95th percentile for control subjects,

16.3 micromol/L) were seen in 149 patients (85%) with end- stage renal disease (P<.001). Patients with a homocysteine concentration in the upper two quintiles (>27.8 micromol/L) had an independent odds ratio of 2.9 (CI, 1.4 to 5.8; P=.007) of vascular complications. B vitamin levels were lower in patients with vascular complications than in those without. Vitamin B6 deficiency was more frequent in patients than in the normal reference populatio versus 2%; P<.01).

Conclusions: A high total plasma homocysteine concentration is an independent risk factor for atherosclerotic complications of end-stage renal disease. Such patients may benefit from higher doses of B vitamins than those currently recommended.

Dietary fats and coronary heart disease

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The prevention and treatment of coronary heart disease (CHD) necessitates vigorous dietary intervention so as to lower the serum cholesterol level by at least 6%. Greater decreases in serum cholesterol can bring about reversal of atherosclerosis. The critical dietary change is the reduction in intake of saturated fat and cholesterol. Some of this fat may be replaced by unsaturated fats, especially monounsaturated fat (olive or canola oil). Fish and the omega-3 fats they contain may also be useful for the prevention of CHD. The benefits of omega-3 fats occur within a few months and probably involve an anti-thrombotic effect. There is evidence that the intake of trans-fatty acids formed by the hydrogenation of oils should be reduced as they are associated with CBD. Hypolipidaemic drugs may be useful for persons at very high risk of CHD but should generally be avoided for primary prevention.

Homocystinuria: What about mild hyperhomocysteinaemia?

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Postgraduate Medical Journal (United Kingdom), 1996, 72/851 (513-518)

Hyperhomocysteinaemia is associate risk of atherosclerotic vascular disease and thromboembolism, in both men and women. A variety of conditions can lead to elevated homocysteine levels, but the relation between high levels and vascular disease is present regardless of the underlying cause. Pooled data from a large number of studies demonstrate that mild hyperhomocysteinaemia after a standard methionine load is present in 21% of young patients with coronary artery disease, in 24% of patients with cerebrovascular disease, and in 32% of patients with

peripheral vascular disease. From such data an odds ratio of 13.0 (95% confidence interval 5.9 to 28.1), as an estimate of the relative risk of vascular disease at a young age, can be calculated in subjects with an abnormal response to methionine loading. Furthermore, mild hyperhomo-cysteinaemia can lead to a two- or three-fold increase in the risk of recurrent venous thrombosis. Elevated homocysteine levels can be reduced to normal in virtually all cases by simple and safe treatment with vitamin B6, folic acid, and betaine, each of which is involved in methionine metabolism. A clinically beneficial effect of such an intervention, currently under investigation, would make large-scale screening for this risk factor mandatory.

Effect of low dose omega-3 fatty acid supplementations on plasmalipids and lipoproteins in patients with coronary sclerosis and dyslipoproteinaemia

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In a prospective study, 20 patients (aged 48-67 years) with primary hyperlipoproteinaemia of phenotypes IIa, IIb, IV and with proven coronary sclerosis received four different doses of long-chain polyunsaturated omega-3 fatty acids. 0.18 to 1.1 g per day were administered in the form of fish oil capsules over four 2-week periods. The aim was to study the effect of different low dose supplementations of n-3 fatty acids on the plasmalipid- and lipoprotein composition and to determine a threshold of effectiveness. Significant reduction of the triglyceride level was registered in all subjects with the greatest decrease in those patients who presented with the highest base levels. The cholesterol and LDL-cholesterol values on average remained almost unchanged, apart from a significant increase of LDL-cholesterol in patients with type IV hyperlipoproteinaemia. The HDL-cholesterol fraction also showed a significant increase in type Iib patients which was related to alterations of the HDL-3 subfraction. The minimal effective dose of a daily administration of omega-3 fatty acids can be expected between 0.18 g and 0.35 g. The observed changes of plasmalipids and lipoproteins reflect the beneficial effect of aturated omega-3 fatty acids in respect to plasma-triglyceride reduction and HDL-cholesterol increase as seen in other studies, despite the use of supplementations far below 1 g per day.

Antioxidant of the coronary diet and disease

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High levels of cholesterol and Low Density Lipoproteins (LDL) in plasma are related to high risk to develop Coronary Heart Disease (CHD). LDL-chosterol is a primary ingredient of the atherosclerotic plaque; its accumulation in the subendothelial space is due to peroxidative reactions. Natural antioxidants such as carotenes, polyphenolic flavonoids, vitamin E and C show defensive properties against lipid peroxidation, hence it is possible to apply these molecules in clinical therapy in the prevention of the CHD. On the other hand, alcohol, and special red wine, as well as the intake of selenium can afford a cardioprotective effect. Blood cholesterol reduction, dietary and/or due to pharmacological interventions, could modulate lipid peroxidation through a decreased production of O2.-, pivotal step in the peroxidative chain of reactions. The importance of other dietary components (fresh fruits, nuts, garlic and other vegetables as well as olive oil) have been analyzed to assess its influence and protective action in the prevention of CHD.

Enhanced capacity of n-3 fatty acid-enriched macrophages to oxidize low density lipoprotein mechanisms and effects of antioxidant vitamins

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Atherosclerosis (Ireland), 1996, 124/2 (157-169)

We have investigated possible mechanisms by which n-3 fatty acid-enriched macrophages enhance the oxidation of low density lipoprotein (LDL), and the ability of antioxidant vitamins to prevent this. Macrophages were enriched with n-3 fatty acids (eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid) following incubation with fish oil. These macrophages produced large amount of TEARS in medium containing metals, and showed enhanced capacity to oxidize LDL (3-4 fold increase compared to control cells) and to accumulate the modified LDL. 5,8,11,14-eicosatetraynoic acid (ETYA, 15-lipoxygenase inhibitor) and superoxide dismutase (SOD) did not inhibit the enhanced capacity of n-3 fatty acid-enriched cells to oxidize LDL. However antioxidants, (vitamin E-enriched macrophages or vitamin C in the medium), inhibited this enhanced capacity. Medium conditioned by n-3 fatty acid-enriched cells had pro-oxidant effects on metal-initiated LDL oxidation. We conclude that n-3 fatty acid-enriched macrophages display increased oxidant capacity which is not inhibited by ETYA or SOD, and that antioxidant vitamins inhibit the enhanced capacity to oxidize LDL.

Prevention of preatheromatous lesions in sand rats by treatment with a nutritional supplement

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Arzneimittel-Forschung/Drug Research (Germany), 1996, 46/6 (610-614)

Sand rats fed a hypercholesterolaemic diet containing 0.01% of the anti-thyroid agent 2-mercapto-1-imidazole develop preatheromatous lesions similar to those found in humans, in addition to obesity and insulin resistance. The effects of a nutritional supplement rich in essential fatty acids and garlic extract (Arterodiet (R)) on the appearance and evolution of the lesions were studied. Treatment with this nutritional supplement significantly decreased circulating triglycerides and low-density lipoprotein (LDL)-cholesterol levels but did not alter plasma insulin or glucose levels. Intra-arterial cholesterol levels were also decreased by the treatment which resulted in a normalisation of the atherosclerotic lesions in these animals.

Dietary methionine imbalance, endothelial cell dysfunction and atherosclerosis

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Nutrition Research (USA), 1996, 16/7 (1251-1266)

Dietary factors can play a crucial role in the development of atherosclerosis. High fat, high calorie diets are well known risk factors for this disease. In addition, there is strong evidence that dietary animal proteins also can contribute to the development of atherosclerosis. Atherogenic effects of animal proteins are related, at least in part, to high levels of methionine in these proteins. An excess of dietary methionine may induce atherosclerosis by increasing plasma lipid levels and/or by contributing to endothelial cell injury or dysfunction. In addition, methionine imbalance elevates plasma/tissue homocysteine which may induce oxidative stress and injury to endothelial cells. Methionine and homocysteine metabolism is regulated by the cellular content of vitamins B6, B12, riboflavin and folic acid. Therefore, deficiencies of these vitamins may significantly influence methionine and homocysteine levels and their effects on the development of atherosclerosis.

Fish oil supplementation in patients with heterozygous familial hypercholesterolemia

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Recenti Progressi in Medicina (Italy), 1996, 87/3 (102-105)

Familial hypercholesterolemia is associated with premature coronary heart disease. In patients with familial hypercholesterolemia, monotherapy with hydroxymethylglutaryl coenzyme A reductase inhibitors rarely achieves the goal of desirable low-density lipoprotein levels. Epidemiological studies suggest that populations with a high dietary intake of marine n3 fatty acids are protected against coronary heart disease. Hepatic synthesis and secretion of very low density lipoproteins are reduced during fish oil supplementation while other effects on lipid and lipoprotein metabolism are controversial. Fourteen patients affected by familial heterozygous hypercholesterolemia on chronic treatment with simvastatin were enrolled in a double blind, placebo controlled, randomized cross-over trial that evaluated the effect of fish oil ethyl ester (Esapent, 5.1 g/day) on lipid and lipoprotein serum concentrations. Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, apoprotein B, apoprotein AI, lipoprotein (a) did not show any significant variation during the four week treatment period with fish oil ethyl ester. The present data suggest that the possible favourable influence of fish oil on the progression of atherosclerosis in these high-risk patients might involve mechanisms which are different from lipid metabolism.

Increased serum level of total homocysteine in CAPD patients: Despite fish oil therapy

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Peritoneal Dialysis International (Canada), 1996, 16/Suppl. 1(S246-S249)

It has been shown that serum total homocysteine (HC) is a risk factor for vascular disease which characterizes endothelial damage. The incidence of vascular disease is increased in continuous ambulatory peritoneal dialysis (CAPD) patients. Our aim was to investigate:

(1) whether concentration of HC correlates with atherosclerotic and inflammatory events, and
(2) if fish oil therapy can retard the disturbance In lipid metabolism which promotes atherosclerosis.

Fourteen patients with various degrees of impaired peritoneal clearance and lipid metabolism were observed. In all patients the serum HC was elevated. Seven patients were treated with fish oil for three months. The results indicate an average increase of HC (+18%), total cholesterol (+6.6%), aggregation of erythrocytes (+9%), and an average decrease of dialysate-to-plasma creatinine (D/P) ratio (-7%), deformability of erythrocytes (-8%), and normalization of elevated soluble interleukin-2 receptor (sIL-2R) values. Regression analysis of all data demonstrated a significant correlation between HC and parameters of lipid metabolism and hemorheology. There were no significant correlations between HC and peritoneal function and serum cytokine levels. We conclude that the treatment in CAPD patients with fish oil did not improve the lipid metabolism

disturbances in atherosclerosis and peritoneal function. Elevated HC confirms the progression of the disease.

Metabolism of linoleic and alpha-linolenic acids in cultured cardiomyocytes: Effect of different n-6 and n-3 fatty acid supplementation

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The metabolites of linoleic (LA) and a-linolenic (ALA) acids are involved in coronary heart disease. Both n-6 and n-3 essential fatty acids (EFAs) are likely to be important in prevention of atherosclerosis since the common risk factors are associated with their reduced 6-desaturation. We previously demonstrated the ability of heart tissue to desaturate LA. In this study we examined the ability of cultured cardiomyocytes to metabolize both LA and ALA in vivo, in the absence and in the presence of gamma linolenic acid (GLA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) alone or combined together. In control conditions, about 25% of LA and about 90% of ALA were converted in PUFAs. GLA supplementation had no influence on LA conversion to more unsaturated fatty acids, while the addition of n-3 fatty acids, alone or combined together, significantly decreased the formation of interconversion products from LA. Using the combination of n-6 and n-3 PUFAs, GLA seemed to counterbalance partially the inhibitory effect of EPA and DHA on LA. desaturation/elongation. The conversion of ALA to more unsaturated metabolites was greatly affected by GLA supplementation. Each supplemented fatty acid was incorporated to a significant extent into cardiomyocyte lipids, as revealed by gas chromatographic analysis. The n-6/n-3 fatty acid ratio was greatly influenced by the different supplementations; the ratio in GLA+EPA+DHA supplemented cardiomyocytes was the most similar to that recorded in control cardiomyocytes. Since important risk factors for coronary disease may be associated with reduced 6-desaturation of the parent EFAs, administration of n-6 or n-3 EFA metabolites alone could cause undesirable effects. Since they appear to have different and synergistic roles, only combined treatment with both n-6 and n-3 metabolites is likely to achieve optimum results.

Homocysteine, folate, and vascular disease

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Journal of Myocardial Ischemia (USA), 1996, 8/2 (60-63)

Current evidence indicates that the genesis of atherosclerotic disease is multifactorial. One of the newly recognized factors that contributes to this process

is raised homocysteine blood levels. A variety of atherosclerotic procd by elevated homocysteine levels, including stimulation of smooth muscle cell growth, impairment of endothelial regeneration, oxidation of LDL particles, and thrombogenesis. A generic defect may account for some instances of hyperhomocysteinemia, but the majority of persons with high levels do not have known genetic defects to account for their elevations. Low levels of folic acid, vitamin B12, and pyridoxine appear to underlie most cases of elevated homocysteine levels. Adding folic acid to the diet may reduce homocysteine levels, but a link between increasing folic acid and lower risk of atherosclerotic disease has yet to be demonstrated in clinical trials. However, increasing daily folic acid intake is not unjustified in some patients. Since this may mask B12 deficiency, a supplement of cobalamin, 1 mg/d, has been proposed. In the final analysis, a clinical trial is needed to determine the true significance of hyperhomocysteinemia. Meanwhile, physicians and patients can consider increasing the daily folate intake by eating more oranges, leafy vegetables, wheat products, and cereals.

Nutritional interest of flavonoids

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Polyphenols represent a complex group of compounds including several categories such as 4-oxo-flavonoids, anthocyanins and tannins. Some of these molecules are present in substantial amounts in various beverages and in plant foods (fruits, vegetables...), and several investigations have established that they were liable to cross the intestinal barrier in mammals. Significant concentrations of flavonoid or polyphenol metabolites are likely to circulate in blood plasma in humans, and it appears thus important to assess their potential biological effects. Some interesting properties have already been reported, especially as to 4-oxo-flavonoids: they have antioxidizing and metal-complexing properties, and they are liable to modulate the activity of enzymes governing important cell functions. By protecting L.D.L. from oxidative alterations and by affecting platelet functions and plasma cholesterol, flavonoids might play a protective role against atherosclerosis. Some 4-oxo-flavonoids (quercetin, genistein...) show antiproliferative properties in vitro and inhibit the development of chimio-induced cancers in animal models. Thus, together with other micronutriments, their occurence in fruits and legumes could explain the preventive effects towards cancer risk of plant foods. Isoflavones which present a phytoestrogenic activity could be more specifically involved in the prevention of breast cancer risk. Further investigations are required to determine the actual bioavailability of the different classes of flavonoids, and to fully understand the underlying mechanisms of their biological effects.

The effect of reduced glomerular filtration rate on plasma total homocysteine concentration

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Scandinavian Journal of Clinical and Laboratory Investigation (Norway), 1996, 56/1 (41-46)

The concentration of homocysteine in plasma has been shown to be increased in renal failure, possibly contributing to the accelerated atherosclerosis observed in uraemic patients. The aim of the present study was to document the relationship between plasma total homocysteine (tHcy) concentrations and glomerular filtration rates (GFR) in highly selected patients, with renal function ranging from normal to dialysis dependency. GFR was defined as the plasma clearance of iohexol; a more accurate method than the creatinine-based estimations applied in previous studies. Plasma tHcy concentrations were highly correlated to GFR ($r=0.70$, $p<0.0001$) and were significantly increased already in moderate renal failure. According to a multiple regression analysis, GFR and red cell folate concentrations independently predicted plasma tHcy concentrations, whereas those of serum creatinine, plasma pyridoxal-5-phosphate, urine albumin and urine alpha-l-microglobulin (a marker of tubular damage) did not. Thus, GFR seems to be a better determinant of plasma tHcy concentration than serum creatinine concentration. Plasma total cysteine and total cysteinylglycine concentrations followed the same pattern as those of tHcy.

Effects of diet and exercise on qualitative and quantitative measures of LDL and its susceptibility to oxidation

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Arteriosclerosis, Thrombosis, and Vascular Biology (USA), 1996, 16/2 (201-207)

The purpose of this study was to investigate the effects of all intensive diet and exercise program on the quantity and quality of LDL as well as its susceptibility to in vitro oxidation. The diet was low in fat (<10% kcal) and cholesterol (<100 mg/d), while high in complex, unrefined carbohydrates (>70% kcal) and fiber (35 g/1000 kcal). The study was composed of 80 participants in a 3-week residential program where food was provided ad libitum and there was daily aerobic exercise, primarily walking. In each subject, preparticipation and postparticipation fasting blood samples were drawn and LDL was isolated via density gradient ultracentrifugation. LDL particle diameter was determined by gradient gel electrophoresis of serum (n = 23). Isolated LDL was either separated into 6 subfractions by saline gradient equilibrium ultracentrifugation (n=26) or subjected to in vitro copper oxidation (n=32). Significant reductions (P<.01) in serum levels

of cholesterol (20%), LDL-cholesterol (20%), HDL-cholesterol (17%), triglycerides (26%), and glucose (16%) as well as in body weight (4%) were noted for the tibial population. The mean particle diameter of the LDL increased (242 plus or minus 0.2 to 25.1 plus or minus 0.14 nm, P < .01) and was correlated with the reduction in serum triglycerides (r=58, P<.01). Six of 22 subjects changed in LDL phenotype from B (less than or equal to25.5 nm) to A (>25.5 nm). The percentage of LDL-cholesterol carried in the more dense subfractions fell significantly, while that carried by the less dense fractions increased. Initial oxidation levels fell (21%), while the lag time before copper-induced oxidation increased (13%). Reductions were observed in both the rate of oxidation (16%) and peak oxidation (20%). All of these changes should result in a dramatic reduction in the risk for atherosclerosis and its clinical sequelae.

Homocysteine: Relation with ischemic vascular diseases

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Revue de Medecine Interne (France), 1996, 17/1 (34-45)

Homocysteine, a sulfur-containing amino acid, is an intermediate metabolite of methionine. Patients with homocystinuria and severe hyperhomocysteinemia develop premature arteriosclerosis and arterial thrombotic events, and venous thromboembolism. Studies suggest that moderate hyperhomocysteinemia can be considered as an independent risk factor in the development of premature cardiovascular disease. In vitro, homocysteine has toxic effects on endothelial cells. Homocysteine can promote lipid peroxidation and damage vascular endothelial cells. Moreover, homocysteine interferes with the natural anticoagulant system and the fibrinolytic system. Homocysteinemia should be known in patients with premature vascular diseases, especially in subjets with no risk factors. Folic acid, vitamin B6 can lower homocysteine levels.

Evaluation of hydroxyl radical-scavenging property of garlic

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Garlic has been reported to provide protection against hypercholesterolemic atherosclerosis and ischemia-reperfusion-induced arrhythmias and infarction. Oxygen free radicals (OFRs) have been implicated as causative factors in these diseases and antioxidants have been shown to be effective against these conditions. The effectiveness of garlic in these disease states could be due to its ability to scavenge OFRs. However, the OFR-scavenging activity of garlic is not

known. Also it is not known if its activity is affected by cooking. We therefore investigated, using high pressure liquid chromatography, the ability of garlic extract (heated or unheated) to scavenge exogenously generated hydroxyl radical (.OH). .OH was generated by photolysis of H2O2 (1.2-10 micromoles/ml) with ultraviolet (UV) light and was trapped with salicylic acid (500 nmoles/ml). H2O2 produced .OH in a concentration-dependent manner as estimated by .OH adduct products 2,3-dihydroxybenzoic acid (DHBA) and 2,5-DHBA. Garlic extract (5 - 100 microl/ml) produced an inhibition (30 -100%) of 2,3-DHBA and 2,5-DHBA generated by photolysis of H2O2 (5.00 pmoles/ml) in concentration-dependent manner. Its activity is reduced by 10% approximately when heated to 100degreeC for 20, 40 or 60 min. The extent of reduction in activity was similar for the three heating periods. Garlic extract prevented the .OH-induced formation of malondialdehyde in the rabbit liver homogenate in a concentration-dependent manner. It alone did not affect the MDA levels in the absence of .OH. These results indicate that garlic extract is a powerful scavenger of .OH and that heating reduces its activity slightly.

Effects of interaction of RRR-alpha-tocopheryl acetate and fish oil on low-density-lipoprotein oxidation in postmenopausal women with and without hormone-replacement therapy

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We evaluated the effects of RRR-alpha-tocopheryl acetate (alpha-tocopheryl acetate) and hormone-replacement therapy (HRT) on the oxidative susceptibility of low-density lipoprotein (LDL) in postmenopausal women consuming a fish oil supplement. The independent effect of fish oil was also assessed. Forty-eight women, equally divideed in a double-blind cross over trial. Each of the four periods lasted 5 wk and was followed by a 4-wk washout interval. During each period all subjects were given a 15-g supplement of fish oil and either 0 (placebo), 100, 200, or 400 mg alpha-tocopheryl acetate daily. LDL resistance to oxidative modification was assessed by calculating lag time, propagation rate, and maximum production of conjugated dienes. Supplementation with fish oil and placebo shortened lag time and slowed propagation rate in women both using and not using HRT. After subjects consumed fish oil, supplementation with alpha-tocopheryl acetate in creased plasma and LDL alpha-tocopherol contents significantly and lengthened lag time (at even the lowest concentration) but had no significant effect on propagation rate or maximum production compared with values measured after consumption of fish oil alone. Women not using HRT had faster propagation rates and higher maximum production than women using HRT; after supplementation with fish oil and alpha-tocopheryl acetate these differences prevailed. Supplements as low as 100 mg alpha-tocopheryl acetate/d increase the resistance of LDL to oxidation when fish oil supplements are used. HRT and fish oil supplements may independently affect LDL oxidative susceptibility.

Therapeutic actions of garlic constituents

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Most studies on garlic during the past 15 years have been primarily in the fields of cardiovascular and ctherosclerosis, where effects were examined on serum cholesterol, LDL, HDL, and triglycerides. Although the studies were not consistent in relation to the dosage, standardization of garlic preparations, and period of treatment, most findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. Lowering of serum lipids by garlic ingestion may decrease the atherosclerosis process. The other major beneficial effect of garlic is due to its antithrombotic actions. This field of garlic research has been extensively studied. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents of garlic because of their in vitro effects. Since both allicin and adenosine are rapidly metabolized in human blood and other tissues, it is doubtful that these compounds contribute to any antithrombotic actions in the body. In addition, ajoene also seems not to be an active antiplatelet principle, because it is not naturally present in garlic, garlic powders, or other commercial garlic preparations. Only a small amount of ajoene can be found in garlic oil-macerates; however, ajoene is being developed as a drug for treatment of thromboembolic disorders. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts are interesting, and may have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory, and anticancer actions. Epidemiological studies have suggested that garlic plays a significant role in the reduction of deaths caused by malignant diseases. This had led many investigators to examine garlic and garlic constituents for their antitumor and cytotoxic actions both in vitro and in laboratory animals. The data from these investigations suggest that garlic contains several potentially important agents that possess antitumor and anticarcinogenic properties. In summary, the epidemiological, clinical, and laboratory data have proved that garlic contains many biologically and pharmacologically important compounds, which are beneficial to human health from cardiovascular, neoplastic, and several other diseases. Numerous studies are in progress all over the world to develop effective and odorless garlic preparations, as well as to isolate the active principles that may be therapeutically useful.

Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys

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Although the beneficial effects of dietary soybean protein compared with animal proteins on plasma lipids, lipoproteins and atherosclerosis have been known for about 50 years, it has been uncertain whether these effects are due to its amino acid concentrations or other components in soybeans. To assess the effect of soybean protein's alcohol-extractable components (including the isoflavonic phytoestrogens genistein and daidzein) on plasma lipid and lipoprotein concentrations and to este fed 27 peripubertal male and female rhesus monkeys moderately atherogenic diets in which the source of dietary protein was a soy isolate (20% by weight), either containing phytoestrogens (also termed isoflavones) or with the phytoestrogens removed by alcohol extraction. The study was a crossover design with each period lasting for 6 mo. The phytoestrogen-intact soy protein (compared with the alcohol-extracted soy protein) had favorable effects on plasma lipid and lipoprotein concentrations, specifically by significantly reducing LDL + VLDL cholesterol concentrations in both males and females (similar30-40% lower), significantly increasing high density lipoprotein cholesterol (HDLC) concentrations for females (similar15% higher) and significantly lowering total plasma cholesterol (TPC):HDLC ratios (similar20% lower for males and 50% lower for females). The phytoestrogens had no adverse effects on the reproductive systems of either the males or females, as evaluated by reproductive hormone concentrations and organ weights at necropsy. Thus, the isoflavones in soy protein improve cardiovascular disease risk factors without apparent deleterious effects on the reproductive system of peripubertal rhesus monkeys.

High dose B-vitamin treatment of hyperhomocysteinemia in dialysis patients

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Kidney International (USA), 1996, 49/1 (147-152)

Hyperhomocysteinemia, an arteriosclerotic risk factor, persists in 75% of dialysis patients despite routine low dose supplementation with the B-vitamin co-factors/substrates for homocysteine (Hcy) metabolism, and normal or supernormal plasma status of these vitamins (Atherosclerosis 114:93, 1995). We conducted a placebo-controlled eight-week trial of the effect on plasma homocysteine of adding supraphysiologic dose folic acid (15 mg/day), B-6 (100 mg/day), and B-12 (1 mg/day) to the usual daily dosing of 1 mg folic acid, 10 mg B-6, and 12 microg B-12, in 27 hyperhomocysteinemic dialysis patients. Total plasma homocysteine was measured at baseline, and after four and eight weeks. Blinded analyses revealed no evidence of toxicity in the group randomized to

supraphysiologic dose B-vitamin supplementation. Plasma homocysteine was significantly reduced after both four weeks (-29.8% vs. -2.0%; P = 0.0024)and eight weeks (-25.8% vs. +0.6%; P = 0.0009) of active versus placebo treatment. Also, 5 of 15 treated versus 0 of 12 placebo group patients had their plasma Hey reduced to within the normative range (< 15 micromol/liter). Supraphysiologic doses of B-vitamins may be required to correct hyperhomocysudy.

Long-term folic acid (but not pyridoxine) supplementation lowers elevated plasma homocysteine level in chronic renal failure

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Moderate hyperhomocysteinemia, a risk factor for premature atherosclerosis, is present in chronic uremic patients. We prospectively evaluated the effects of sequential supplementation with pyridoxine (70 mg/day) and folic acid (10 mg/day) for two 3-month periods in 37 nondialyzed patients (29 males) with creatinine clearance (C(Cr)) ranging from 10 to 80 ml/min, whose plasma vitamin B12 and folate level was in the normal range. Mean (plus or minus SD) baseline plasma total homocysteine (Hcy) was 14.9 plus or minus 5.2, 16.5 plus or minus 5.1 and 26.1 plus or minus 12.1 micromol/l (upper limit in 45 healthy controls 14.1 micromol/l) in patients with C(Cr) 40-80, 20-40 and < 20 ml/min, respectively. Following pyridoxine Hcy did not significantly decrease whereas following folic acid Hcy decreased significantly to 9.9 plus or minus 2.9 (-33% vs. baseline), 10.3 plus or minus 3.4 (-37%) and 15.4 plus or minus 5.5 (-40%), respectively (Student's paired t test, $p < 0.001$) in the 3 groups. We conclude that folate (but not pyridoxine) pharmacologic supplementation is effective in lowering elevated plasma Hcy in chronic renal failure patients, thus suggesting that enhancing the Hcy remethylation pathway may overcome hyperhomocysteinemia in such patients. In view of the potential atherogenic effects of hyperhomocysteinemia, long-term folate supplementation should be considered in uremic patients.

Ascorbate and urate are the strongest determinants of plasma antioxidative capacity and serum lipid resistance to oxidation in Finnish men

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Atherosclerosis (Ireland), 1997, 130/1 (223-233)

Copper-induced plasma lipoprotein oxidation resistance has usually been determined innsity lipoprotein (LDL) fractions, that do not contain water-soluble

antioxidants present in blood plasma. The aim of this study was to find the main determinants of the measurements of copper-induced lipid oxidation istance (lag time) in whole serum and plasma total peroxyl radical trapping capacity (TRAP) in a population sample of smoking (n = 25) or non-smoking (n = 26) middle aged men at high risk of cardiovascular diseases. Smokers had significantly lower plasma ascorbic acid values, but only slightly lower alpha-tocopherol, beta-carotene and serum urate values than non-smokers. Plasma ascorbic acid concentration explained 23.5% of the lag time variation (standardized regression coefficient beta = 0.48; P = 0.004) in smokers and 5.6% in non-smokers. Serum urate concentration was the strongest determinant of lag time in non-smokers (beta = 0.64, P < 0.001). In addition, serum albumin, lipid standardized alpha-tocopherol and serum high density lipoprotein (HDL) cholesterol entered the multivariate regression model for lag time. For plasma TRAP, only urate and ascorbic acid entered the multivariate regression model. Lag times in serum and in isolated very low density lipoprotein (VLDL) and LDL fraction did not correlate, but the maximal rate of these reactions correlated significantly. These results confirm that lipid peroxidation resistance in serum or plasma are associated with ascorbic acid, urate, alpha-tocopherol, albumin and HDL concentrations. The measurement of lipid oxidation resistance in whole serum might be more physiological than in isolated lipoprotein fraction, as the effects of water-soluble antioxidants are not artificially removed.

Antioxidants in the prevention of atherosclerosis

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Current Opinion in Lipidology (United Kingdom), 1996, 7/6 (374-380)

Four antioxidant treatry heart disease are scrutinized: probucol , beta-carotene, alpha-tocopherol and anti-iron treatment. A pattern seems to have emerged in which some treatments look promising, but others are disappointing. Most published studies of antioxidation in atherosclerosis have been ad-hoc in that the primary endpoint of the study has not been a diagnosis related to atherosclerosis; this may be misleading. The most promising antioxidant seems to be alpha-tocopherol, supported by the results of the Cambridge Heart Antioxidant Study. Probucol has the drawback of decreasing high density lipoprotein concentration and is therefore unlikely to influence atheroma in people. beta-Carotene has been repeatedly shown to be ineffective against coronary heart disease. Anti-iron treatment has not yet been tested in animal models or in man. More has to be learned of the role of antioxidation in atherosclerosis before the effectiveness of this treatment modality can be established

The carotenoids beta-carotene, canthaxanthin and zeaxanthin inhibit macrophage-mediated LDL oxidation

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Human monocyte-macrophages were incubated for 24 h in Ham's F-10 medium with human low-density lipoprotein (LDL) in the presence or absence of beta-carotene, canthaxanthin or zeaxanthin, at final concentrations of 2.5, 12.5 and 25 mg/l. LDL oxidation, measured by agarose gel electrophoresis, the thcarotenoids in a concentration-dependent manner. Canthaxanthin was more effective when incorporated into LDL before addition to the cultures whereas beta-carotene and zeaxanthin were more effective when added simultaneously with LDL. The results suggest that dietary carotenoids might help slow atherosclerosis progression.

Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men

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Atherosclerosis and thrombosis may lead to cognitive impairment through cerebral infarcts or white matter hyperintensities. Oxidative stress is now seen as a major contributor to the process of atherogenesis. High intake of polyunsaturated fatty acids, e.g., linoleic acid, or low intake of antioxidants can increase oxidative stress. High intake of n-3 polyunsaturated fatty acids and its main source, fish, may reduce the risk of thrombosis. Little is known, however, about the relation between these dietary factors and cognitive function. The authors investigated this relation with data derived from a cohort of men, aged 69-89 years, who were participants in the Zutphen Elderly Study. The 30-point Mini-Mental State Examination was used to assess cognitive impairment in 1990 (score less than or equal to25 in 153/476 men, 32%) and cognitive decline from 1990 to 1993 (drop >2 points in 51/342 men, 15%). Food intake was estimated in 1985 and 1990 by the cross- check dietary history method. High linoleic acid intake was associated with cognitive impairment after adjustment for age, education, cigarette smoking, alcohol consumption, and energy intake (odds ratio (OR) for highest vs. lowest tertile = 1.76, 95% confidence interval (CI) 1.04-3.01). Intake of n- 3 polyunsaturated fatty acids was not associated with cognitive impairment, whereas high fish consumption tended to be inversely associated with cognitive impairment (OR = 0.63, 95% CI 0.33-1.21) and cognitive decline (OR = 0.45, 95% CI 0.17-1.16). Intakes of beta-carotene, vitamins C and E, and flavonoids were not inversely associated with cognitive impairment or decline. This study raises the possibility that high linoleic acid intake is positively associated with cognitive impairment and high fish consumption inversely associated with cognitive impairment.

Animal studies on antioxidants

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The wealth of existing epidemiologic evidence suggests that antioxidant intake limits the clinical expression of coronary artery disease. Because the oxidative modification of low-density lipoprotein is an important event in atherogenesis, it has been attractive to speculate that antioxidants act by limiting low-density lipoprotein orientation and, as a consequence, atherosclerotic lesion development. Early studies on animals also suggested that a number of structurally distinct antioxidant compounds could limit the extent of lesion development in animal models of atherosclerosis. More recently, however, secure evidence linking the antioxidant protection of low-density lipoprotein with a reduction in atherosclerosis has been elusive. This discrepancy may be explained by emerging evidence demonstrating that antioxidants may prove beneficial through tissue-specific effects that are not strictly related to the antioxidant protection of low-density lipoprotein.

Alpha-Tocopherol and beta-carotene serum levels in post-menopausal women treated with transdermal estradiol and oral medroxyprogesterone acetate

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Hormone and Metabolic Research (Germany), 1996, 28/10 (558-561)

Estrogens exert a protective effect against atherosclerosis. It is well known that hormone replacement therapy (HRT) can effectively decrease LDL-cholesterol and increase HDL-cholesterol and Apo-Al serum levels. Some recent studies have suggested that estrogens alone or in association with progestins may exert an antioxidant effect on lipids. Besides sex steroids, also vitamins exert an antioxidant effect on LDL and may preserve the endogenous antioxidants of LDL. The aim of our study was to evaluate whether HRT can improve alpha-tocopherol and beta-carotene serum levels in post-menopausal women. Fifteen postmenopausal women with climacteric symptoms were treated with 50 microg/24 h estradiol transdermally applied twice a week for 21 days. A daily dose of 10 mg oral medroxyprogesterone acetate was added for 12 days in each treatment cycle. This therapy lasted 6 months. A significant reduction was found in total cholesterol and LDL-cholesterol after treatment. Besides, our study has shown that alpha-toc/LDL and beta-car/LDL ratios significatively increased after treatment, while alpha-tocopherol and beta-carotene serum levels did not change

significantly after therapy. These preliminary findings suggest that HRT can preserve the content of alpha-tocopherol and beta-carotene in LDLte.

Antioxidant status of hypercholesterolemic patients treated with LDL apheresis

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Oxidation of low density lipoprotein is involved in the pathogenesis of atherosclerosis. Epidemiological studies suggest a negative correlation between the occurrence of cardiovascular diseases and blood concentrations of lipophilic antioxidants such as vitamins A and E and beta-carotene. Trace elements, such zymes glutathione peroxidase and superoxide dismutase. The aim of this study was to determine the antioxidant and trace element status of patients with severe hypercholesterolemia who had been treated with dextran-sulphate low-density lipoprotein apheresis in comparison with two control populations, normocholesterolemic subjects and untreated hypercholesterolemic patients. Our results showed that, patients treated with LDL apheresis, compared with normocholesteromic subjects, were not deficient in vitamin E, beta-carotene, and copper, but had low plasma levels of selenium, zinc, and vitamin A. The low selenium and vitamin A levels were due to the LDL apheresis treatment, and the hypercholesterolemia might have provoked the low plasma levels of zinc.This study pointed out the potential benefits of supplemental selenium, zinc, and vitamin A in patients being treated with LDL apheresis.

Abnormal antioxidant vitamin and carotenoid status in chronic renal failure

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Oxidative modification of plasma lipoproteins increases their atherogenicity. Nutritive antioxidants, including carotenoids, can prevent such lipoperoxidation and may protect against atherosclerosis. Plasma retinol, ascorbate, alpha-tocopherol and four carotenoids (lutein, lycopene, alpha-carotene and beta-carotene) were measured using HPLC in 45 patients with chronic renal failure (CRF) and in 21 controls. Plasma retinol was significantly increased in patients with CRF (conservative therapy mean of 3.7micromol/l vs. 1.9micromol/l; p <

0.001). Plasma lycopene was significantly lower in patients with CRF (healthy mean 0.44 micromol/l vs. conservative therapy mean 0.27 micromol/l and haemodialysis mean of 0.17 micromol/l; $p < 0.001$), a finding that persisted even after adjusting for plasma cholesterol. Low circulating antioxidant lycopene levels may contribute to an already impaired antioxidant defence system in patients with CRF. The process of haemodialysis further compromises antioxidant defences, principally by removing water-soluble ascorbate and urate, but does not appear to affect circulating carotenoid concentrations.

Antioxidants in cardiovascular disease: Randomized trials

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Nutrition (USA), 1996, 12/9 (583-588)

The hypothesis that antioxidant vitamins might reduce cardiovascular disease risk is based on a large body of both basic and human epidemiologic research. One of the most consistent findings in dietary research is that those who consume higher amounts of fruits and vegetables have lower rates of heart disease and stroke as well as cancer. Recent attention has focused on the antioxidant content of fruits and vegetables as a possible explanation for the apparent protective effects. Basic research provides a plausible mechanism by which antioxidants might reduce the risk of atherosclerosis. A large number of descriptive, case-control and cohort studies provide data suggesting that consumption of antioxidant vitamins is associated with reduced risks of cardiovascular disease. These data raise the question of a possible role of antioxidants, such as vitamins C and E, and beta carotene, in the primary prevention of cardiovascular disease but do not provide a definitive answer. Results from several large-scale randomized trials of antioxidant supplements are now available; however, results are not entirely consistent. The results of the major trials do not prove or disprove the value of antioxidant vitamins, nor do they incriminate them as harmful. They do, however, raise the possibility that some of the benefits from observational epidemiology may have been overestimated and that there may be some adverse effects. At this point randomized trial data are not yet sufficient to fully assess the risk-to-benefit ratios for antioxidant supplements. More reliable data should be forthcoming in the near future which will better define the role of antioxidants in the primary and secondary prevention of atherosclerotic disease as well as cancer.

Dietary antioxidants and cognitive function in a population-based sample of older persons: The Rotterdam study

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Antioxidants have been implicated in processes related to atherosclerosis, aging, and selective neuronal damage, all of which may ultimately affect cognitive function. In a sample of older persons, the authors examined the cross-sectional relation between cognitive function and dietary intake of beta-carotene and vitamins C and E. The data were derived from 5,182 community participants aged 55-95 years in the population-based Rotterdam Study in the period 1990 to 1993. Dietary intake was estimated from a semi-quantitative food frequency questionnaire and categorized into five levels of intake. Cognitive function was measured with the 30-point Mini- Mental State Examination (MMSE) and characterized as unimpaired (>25 points) or impaired (less than or equal to25 points). Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for cognitive impairment. After adjustment for age, education, sex, smoking, total caloric intake, and intake of other antioxidants, a lower intake of beta-carotene was associated with impaired cognitive function (<0.9 mg vs. less than or equal to2.1 mg intake, OR = 1.9, 95% CI 1.2-3.1; p for trend < 0.04). There was no association between cognitive function and intake of vitamins C and E. These cross-sectional observations are compatible with the view that beta-carotene-rich foods may protect against cognitive impairment in older people. The finding could also reflect unmeasured confounding, measurement error, or a change in food habits that resulted from rather than preceded the onset of cognitive impairment.

Lack of correlation between the alpha-tocopherol content of plasma and LDL, but high correlations for gamma-tocopherol and carotenoids

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Journal of Lipid Research (USA), 1996, 37/9 (1936-1946)

In 59 healthy human subjects (37 male and 22 female) the concentrations of the lipid-soluble antioxidants alpha and gamma-tocopherol, alpha- and beta-carotene, lycopene, cryptoxanthin, canthaxanthin, and lutein + zeaxanthin were determined in plasma (micromol/L) and in isolated low density lipoproteins (LDL) (micromol/mmol cholesterol). Plasma alpha-tocopherol concentrations were significantly correlated with plasma total cholesterol concentrations (r2 = 0.51, P < 0.0001) yet not with the LDL alpha-tocopherol content (r2 = 0.05, ns). Plasma gamma-tocopherol concentrations were weakly correlated with plasma total cholesterol (r2 = 0.12, P < 0.003) and both absolute and cholesterol standardized plasma gamma-tocopherol concentrations correlated strongly with the LDL gamma-tocopherol content (r2 = (0.58 and r2 = 0.72, respectively). In contrast, carotenoid concentrations did not correlate with cholesterol concentrations, but their LDL content correlated significantly with the respective plasma concentrations (r2 = 0.67 to 0.92, all P < 0.0001). In a subgroup of study subjects

(n = 13) the distribution of vitamin E and carotenoids among LDL was calculated. The proportion of plasma alpha- and gamma- tocopherol found in LDL was 48 plus or minus 7 (range, 36-61%) and 41 plus or minus 7%, respectively, suggesting that LDL was in most of these subjects not the main carrier for these antioxidants. The lipophilic carotenoids, however, were predominantly carried by LDL (e.g., beta-carotene: 87 plus or minus 10%), whereas the proportion of the more polar ones carried by LDL was much smaller (e.g., lutein + zeaxanthin: 36 plus or minus 6%). The results of this study show that plasma alpha-tocopherol concentrations are not predictive for the alpha-tocopherol content of LDL in nonsupplemented individuals. This finding could have implications in interpreting the cause of the inverse relationship between plasma alpha- tocopherol and risk of atherosclerosis.

Oxidized low density lipoproteins in atherogenesis: Role of dietary modification

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Annual Review of Nutrition (USA), 1996, 16/- (51-71)

The development of atherosclerosis is a complex and multistep process. There are many determinants in the pathogenesis of this condition, with different factors presumably playing key roles at different times in the evolution of the atherosclerotic plaque. It has been suggested that oxidation of low density lipoproteins (LDL) by cells in the artery wall leads to a proatherogenic particle that may help initiate early lesion formation. For this reason, understanding the determinants of LDL susceptibility to oxidation is essential for developing therapeutic strategies to inhibit this process. Oxidation of LDL begins with the abstraction of hydrogen from polyunsaturated fatty acids; thus, LDL fatty acid composition undoubtedly contributes to the process of LDL oxidation. Since dietary fatty acids influence the fatty acid composition of LDL and cell membranes, the amount and type of fat in the diet may effect susceptibility of LDL and cells to oxidative damage. Additionally, since cell membrane fatty acid composition also influences cellular formation of reactive oxygen species, dietary fatty acids may help determine the prooxidant activity of artery wall cells. Both cells and lipoproteins contain a variety of antioxidants that provide protection against oxidative stress. A major source of these antioxidants is the diet. Enrichment of the diet with foods high in such antioxidants as vitamin E, beta-carotene, or vitamin C, or supplementation of the diet with antioxidant vitamins, may inhibit oxidation and the process of atherosclerosis.

Effect of dietary supplementation of beta-carotene on human monocyte - macrophage-mediated oxidation of low density lipoprotein

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Israel Journal of Medical Sciences (Israel), 1996, 32/6 (473-478)

Oxidative modification of low density lipoprotein (LDL), a key step in early atherosclerosis, is protected by the lipoprotein-associated antioxidants. The present study analyzes the effect of beta-carotene in plasma, in LDL and in monocyte-macrophages, on macrophage-mediated oxidation of LDL. We investigated the effect of dietary supplementation of beta-carotene on plasma lipid peroxidation (induced by AAPH (2,2-Azobis-2-amidinopropane hydrochloride)l and on cell-free and cell-mediated oxidation of LDL by human monocyte-derived macrophages (HMDM) in the presence of CuSO4. Significant enrichment with beta-carotene was noted in plasma (twofold), in LDL (2.6-fold) and in HMDM (1.6-fold) 2 weeks after dietary supplementation with 180 mg/day of beta-carotene. Plasma lipid peroxidation analyzed by conjugated dienes generation decreased by 22% ($P < 0.01$) and LDL susceptibility to oxidation analyzed by malondialdehyde generation decreased by 40% ($P < 0.01$). After beta-carotene supplementation, beta-carotene-enrichment of HMDM did not affect HMDM capacity to oxidize native LDL, whereas beta-carotene enrichment of LDL significantly reduced LDL oxidation. In conclusion, then, our results suggest that beta-carotene content of LDL, but not that of the macrophages, is responsible for the inhibition of oxidation of LDL.

Increased oxidation resistance of atherogenic plasma lipoproteins at high vitamin E levels in non-vitamin E supplemented men

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Atherosclerosis (Ireland), 1996, 124/1 (83-94)

The oxidative modification of human low density lipoprotein (LDL) has been widely investigated. However, there are no tein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein fraction, although all of them are atherogenic and contain antioxidants such as alpha-tocopherol. We investigated the oxidation susceptibility and oxidation resistance of VLDL + LDL (including IDL) fraction by induction with CuCl2 and its relation to plasma alpha-tocopherol concentration and lipid standardised alpha-tocopherol concentration in 406 non-vitamin E-supplemented men from eastern Finland. Even though we did not give oral vitamin E or any other antioxidant supplementation to our study participants, we observed a significant, consistent relationship between measurements of oxidation resistance and plasma content of vitamin E. In the multivariate regression model, a high plasma content of vitamin E or lipid standardised vitamin E concentration were the most important determinants of lag time to maximal oxidation rate (standardised regression coefficient = 0.244, $P < 0.0001$ for vitamin E and 0.211, $P < 0.0001$ for lipid standardised vitamin E). After statistical adjustment for age, use of cigarettes, hypolipidemic medication (yes vs.

no), month of the measurements, plasma concentrations of total ascorbic acid (ascorbic acid +dehydroascorbic acid), beta-carotene and phospholipids, serum concentrations of LDL cholesterol and triglycerides and dietary intake of linoleic acid, the lag time to maximal oxidation rate was 10% (95% C.I. 6.0-13.5%) longer in men in the highest fifth than in the lowest fifth of plasma vitamin E content ($P < 0.0001$ for trend). When the fifths of lipid standardised vitamin E were compared, the lag time to maximal oxidation rate was 6% (95% C.I. 1.8-10.1%) longer in men in the highest than in the lowest fifth ($P < 0.0001$ for trend). Our data suggest that alpha-tocopherol is an important antioxidant preventing the in vitro oxidation of VLDL + LDL fraction even in non-supplemented subjects.

Increased levels of autoantibodies to cardiolipin and oxidised low density lipoprotein are inversely associated with plasma vitamin C status in cigarette smokers

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Atherosclerosis (Ireland), 1996, 124/1 (75-81)

In this study we have measured circulating levels of autoantibodies to cardiolipin and oxidised low-density lipoprotein (ox-LDL) and correlated these with plasma concentrations of the anti-oxidant nutrients vitamin C, vitamin E and beta-carotene, in a group (79) of asymptomatic, male cigarette smokers and in non-smoking control subjects. Cigarette smoking, a well-known risk factor for development of atherosclerosis, was found to be associated with moderately elevated levels of autoantibodies to both cardiolipin and ox-LDL. Increased levels of these autoantibodies were most evident in the older smokers (> 30 years) and were significantly and inversely corrrelated with plasma vitamin C, but not with vitamin E or beta-carotene. Absorption studies designed to investigate the specificity of these autoantibodies demonstrated a high degree of cross-reactivity of cardiolipin antibodies with ox-LDL, while antibodies to the oxidatively modified lipoprotein tended to be specific for this antigen. These findings suggest that cigarette smoking promotes formation of autoantibodies to both cardiolipin and ox-LDL and that these may be involved in the initiation and/or perpetuation of atherosclerosis. Dietary intake of vitamin C may be a determinant of susceptibility to development of this cardiovascular disorder.

Antioxidant vitamins and risk of cardiovascular diseases

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Sang, thrombose, vaisseaux: STV, Vol. 8, No. 4, p. 210

In recent years, an increasing number of basic and clinical research reports have pointed out the role of reactive metabolites of oxygen, the free radicals, in the processes of atherogenesis and also the protective and/or preventive effects of antioxidant molecules such as beta-carotene, vitamin C, vitamin E, selenium and zinc. Epidemiological data obtained by cross-sectional, case-control and prospective studies also provide strong supportive arguments in favour of the relationship between intake of antioxidant vitamins (or biological status in antioxidant vitamins) and cardiovascular risk. However, the epidemiological nature of the studies does not enable confirmation of a causal role. Cause-effect relationships would require controlled intervention trials of antioxidant vitamins versus placebo to assess potential effects on cardiovascular morbidity and mortality.

Nutritional supplement program halts progression of early coronary atherosclerosis documented by ultrafast computed tomography

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USA
Journal of Applied Nutrition (USA), 1996, 48/3 (68-78)

The aim of this study was to determine the effect of a defined nutritional supplement program on the natural progression of coronary artery disease. This nutritional supplement program was composed of vitamins, amino acids, minerals, and trace elements, including a combination of essential nutrients patented for use in the prevention and reversal of cardiovascular disease. The study was designed as a prospective intervention before-after trial over a 12 month period and included 55 patients (age 44-67) with various stages of coronary heart disease. Changes in the progression of coronary artery calcification before and during the nutritional supplement intervention were determined by Ultrafast Computed Tomography (Ultrafast CT). The natural progression rate of coronary artery calcification before the intervention averaged 44% per year. The progression of coronary artery calcification decreased on average 15% over the course of one year of nutritional supplementation. In a sub-group of patients with early stages of coronary artery disease, a statistically significant decrease occurred, and no further progression of coronary calcification was observed. In individual cases, reversal and complete disappearance of previously existing coronary calcifications were documented. This is the first clinical study documenting the effectiveness of a defined nutritional supplement program in halting early forms of coronary artery disease within one year. The nutritional supplement program tested here should be considered an effective and safe approach to prevention and adjunct therapy of cardiovascular disease.

Metal excretion and magnesium retention in patients with intermittent claudication treated with intravenous disodium EDTA

Guldager B, Jorgensen PJ, Grandjean P
Department of Surgery, Hillerod Hospital, Denmark.
Clin Chem 1996 Dec;42(12):1938-42

Sixty patients with intermittent claudication participated in a double-blind placebo-controlled trial of 20 courses of intravenous chelation therapy with 3 g of disodium EDTA vs placebo during 5-9 weeks. After the first infusion, the 24-h urinary excretion of lead and zinc was similar 25-fold higher in the EDTA-treated group; relative differences for copper and calcium were smaller. Urinary magnesium excretion in the EDTA-treated group was one-third less than in the control group. After the treatment period, the blood lead concentration had decreased by similar73% and the serum zinc concentration by similar34%; other changes in blood concentrations were negligible. The loss of essential minerals and the possible redistribution of lead in the body may constitute a disadvantage that should be taken into account in repeated intravenous EDTA treatment.

8. Attention Deficit Hyperactivity Disorder

Preventative and curative options include:

Vitamins B and C, zinc, magnesium, choline, DMAE, glutamine, GABA, DHEA, phosphatidylserine, fish oil, ginkgo, ginseng, theanine.

Alternative treatments for adults with attention-deficit hyperactivity disorder.

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Ann N Y Acad Sci 2001 Jun;931:310-41

A previous review of alternative treatments (Tx) of ADHD--those other than psychoactive medication and behavioral/psychosocial Tx--was supplemented with an ADDitional literature search focused on adults with ADHD. Twenty-four alternative Tx were identified, ranging in scientific documentation from discrediting controlled studies through mere hypotheses to positive controlled double-blind clinical trials. Many of them are applicable only to a specific subgroup. Although oligoantigenic (few-foods) diets have convincing double-blind evidence of efficacy for a properly selected subgroup of children, they do not appear promising for adults. Enzyme-potentiated desensitization, relaxation/EMG biofeedback, and deleading also have controlled evidence of efficacy. Iron supplementation, magnesium supplementation, Chinese herbals, EEG biofeedback, massage, meditation, mirror feedback, channel-specific perceptual training, and vestibular stimulation all have promising prospective pilot data, many of these tests reasonably controlled. Single-vitamin megadosage has some intriguing pilot trial data. Zinc supplementation is hypothetically supported by systematic case-control data, but no systematic clinical trial. Laser acupuncture has promising unpublished pilot data and may be more applicable to adults than children. Essential fatty acid supplementation has promising systematic case-control data, but clinical trials are equivocal. RDA vitamin supplementation, non-Chinese herbals, homeopathic remedies, and antifungal therapy have no systematic data in ADHD. Megadose multivitamin combinations are probably ineffective for most patients and are possibly dangerous. Simple sugar restriction seems ineffective. Amino acid supplementation is mildly effective in the short term, but not beyond 2-3 months. Thyroid treatment is effective in the presence of documented thyroid abnormality. Some alternative Tx of ADHD are effective or probably effective, but mainly for certain patients. In some cases, they are the Tx of choice, and initial evaluation should consider the relevant etiologies. A few have failed to prove effective in controlled trials. Most need research to determine whether they are effective and/or to define the applicable subgroup. Some of them, although not safer than standard Tx, may be preferable for an etiologic subgroup.

Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder?

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J Child Adolesc Psychopharmacol 2000 SUMMMER;10(2):111-7

Zinc is an important co-factor for metabolism relevant to neurotransmitters, fatty acids, prostaglandins, and melatonin, and indirectly affects dopamine metabolism, believed intimately involved in attention-deficit/hyperactivity disorder (ADHD). To explore the relationship of zinc nutrition to essential fatty acid supplement and stimulant effects in treatment of ADHD, we re-analyzed data from an 18-subject double-blind, placebo-controlled crossover treatment comparison of d-amphetamine and Efamol (evening primrose oil, rich in gamma-linolenic acid). Subjects were categorized as zinc-adequate (n = 5), borderline zinc (n = 5), and zinc-deficient (n = 8) by hair, red cell, and urine zinc levels; for each category, placebo-active difference means were calculated on teachers' ratings. Placebo-controlled d-amphetamine response appeared linear with zinc nutrition, but the relationship of Efamol response to zinc appeared U-shaped; Efamol benefit was evident only with borderline zinc. Placebo-controlled effect size (Cohen's d) for both treatments ranged up to 1.5 for borderline zinc and dropped to 0.3-0.7 with mild zinc deficiency. If upheld by prospective research, this post-hoc exploration suggests that zinc nutrition may be important for treatment of ADHD even by pharmacotherapy, and if Efamol benefits ADHD, it likely does so by improving or compensating for borderline zinc nutrition.

Relationships between serum-free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note.

Bekaroglu M, Aslan Y, Gedik Y, Deger O, Mocan H, Erduran E, Karahan C. Department of Psychiatry, Technical University, Faculty of Medicine, Trabzon, Turkey.

J Child Psychol Psychiatry 1996 Feb;37(2):225-7

The purpose of this study is to evaluate the relationships between serum free fatty acids (FFA) and zinc, and attention deficit hyperactivity disorder (ADHD). Forty eight children with ADHD (33 boys, 15 girls) were included in the patient group and 45 healthy volunteer children (30 boys, 15 girls) constituted the control group. The mean serum FFA level in the patient group was 0.176 +/- 0.102 mEq/L and in control group, 0.562 +/- 0.225 mEq/L (< .001). The mean serum zinc level of patient group was 60.6 +/- 9.9 micrograms/dl and that of the control group, 105.8 +/- 13.2 micrograms/dl (< .001). A statistically significant correlation was found between zinc and FFA levels in the ADHD group. These findings indicate that zinc deficiency may play a role in aetiopathogenesis of ADHD. Although we observed decreased FFA levels in ADHD cases, it is necessary to determine whether this condition is a principal cause of ADHD or is secondary to zinc deficiency.

Attention deficit and infantile hyperactivity.

Berdonces JL. Universitat de Barcelona.

Rev Enferm 2001 Jan;24(1):11-4

Hyperactivity is a very common disorder in children (specially males) that today is considered as a clinical syndrome by scientific medicine. American Psychiatric Association establishes 10 symptoms to diagnose it, but they can be resumed in three characteristics: Impulsivity, Distraction, and Hyperactivity. There are different ways to treat it, but psychiatric medication has major risks in children. From complementary medicine we can find several aids in changing diet patterns and supplementing with vitamins or minerals. Chocolate, sugar, sweeteners, additives, preservatives, dyes, can enhance the incidence of this syndrome; instead the supplementation with lipids rich in PUFA's can prevent it. B complex vitamins, magnesium, copper, manganese or calcium can be interesting and in herbal medicine, sedative plants like passion flower, valerian or lemon balm are useful aids. Also liquorice, fennel and berries can be used for different physiological actions.

The effect of pyridoxine hydrochloride on blood serotonin and pyridoxal phosphate contents in hyperactive children.

Bhagavan HN, Coleman M, Coursin DB

Pediatrics 1975 Mar;55(3):437-41

The contents of serotonin (hydroxytryptamine) and pyridoxal phosphate (PLP) in the blood of 11 hyperactive children and 11 controls were determined on an outpatient basis. A significant decrease in serotonin content was found in blood samples from hyperactive patients as compared with controls. There were no differences in PLP content of blood between the two groups. Four children were selected for a study of the effects of pyridoxine hydrochloride (vitamin B6) on low serotonin levels. Oral doses of pyridoxine resulted in an appreciable increase in the serotonin content and a very large increase in the PLP content of blood in these hyperactive patients.

Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder.

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Am J Clin Nutr 2000 Jan;71(1 Suppl):327S-30S

Attention-deficit hyperactivity disorder (ADHD) is the diagnosis used to describe children who are inattentive, impulsive, and hyperactive. ADHD is a widespread condition that is of public health concern. In most children with ADHD the cause

is unknown, but is thought to be biological and multifactorial. Several previous studies indicated that some physical symptoms reported in ADHD are similar to symptoms observed in essential fatty acid (EFA) deficiency in animals and humans deprived of EFAs. We reported previously that a subgroup of ADHD subjects reporting many symptoms indicative of EFA acid than did ADHD subjects with few such symptoms or control subjects. In another study using deficiency (L-ADHD) had significantly lower proportions of plasma arachidonic acid and docosahexaenoic contrast analysis of the plasma polar lipid data, subjects with lower compositions of total n-3 fatty acids had significantly more behavioral problems, temper tantrums, and learning, health, and sleep problems than did those with high proportions of n-3 fatty acids. The reasons for the lower proportions of long-chain polyunsaturated fatty acids (LCPUFAs) in these children are not clear; however, factors involving fatty acid intake, conversion of EFAs to LCPUFA products, and enhanced metabolism are discussed. The relation between LCPUFA status and the behavior problems that the children exhibited is also unclear. We are currently testing this relation in a double-blind, placebo-controlled intervention in a population of children with clinically diagnosed ADHD who exhibit symptoms of EFA deficiency.

On the role of cortical glutamate in obsessive-compulsive disorder and attention-deficit hyperactivity disorder, two phenomenologically antithetical conditions.

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Acta Psychiatr Scand. 2000 Dec;102(6):401-13.

OBJECTIVE: The objective of the present study was to compare the phenomenology and pathophysiology of obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder/deficits in attention, motor control and perception (ADHD/DAMP).

METHOD: Through detailed studies of the literature on OCD and ADHD/DAMP the phenomenology of these two conditions is compared, and possible underlying pathophysiological mechanisms involving interactions between glutamate, dopamine, serotonin and acetylcholine are discussed, with emphasis on OCD. The present paper also discusses possible mechanisms of action for current pharmacological treatments of OCD and ADHD, as well as possible future treatment strategies for these disorders.

RESULTS: OCD and ADHD/DAMP are common neuropsychiatric conditions which in many regards appear to be each other's antipodes with respect to clinical manifestations, associated personality traits and brain biochemistry, notably prefrontal cortical glutamate activity. Future pharmacological treatments of these disorders may involve manipulations with glutamate, dopamine D1, serotonin 2A and nicotine receptors.

CONCLUSION: It appears that OCD is a hyperglutamatergic and ADHD a hypoglutamatergic condition, with prefrontal brain regions being especially affected.

The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment.

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Nutr Neurosci 2001;4(2):121-34

Phosphatidylserine (PS) is a phospholipid widely sold as a nutritional supplement. PS has been claimed to enhance neuronal membrane function and hence cognitive function, especially in the elderly. We report the results of a clinical trial of soybean-derived PS (S-PS) in aging subjects with memory complaints. Subjects were 120 elderly (< 57 years) of both sexes who fulfilled the more stringent criteria for age-associated memory impairment (AAMI); some also fulfilled the criteria for age-associated cognitive decline. Subjects were allocated at random to one of the three treatment groups: placebo, 300mg S-PS daily, or 600mg S-PS daily. Assessments were carried out at baseline, after 6 and 12 weeks of treatment, and after a wash-out period of 3 weeks. Tests of learning and memory, choice reaction time, planning and attentional functions were administered at each assessment. Delayed recall and recognition of a previously learned word list comprised the primary outcome measures. No significant differences were found in any of the outcome variables between the treatment groups. There were also no significant interactions between treatment and 'severity of memory complaints'. In conclusion, a daily supplement of S-PS does not affect memory or other cognitive functions in older individuals with memory complaints.

Attention deficit/hyperactivity disorder (ADHD) in children: rationale for its integrative management.

Kidd PM.

Altern Med Rev 2000 Oct;5(5):402-28

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common behavioral disorder in children. ADHD is characterized by attention deficit, impulsivity, and sometimes overactivity ("hyperactivity"). The diagnosis is empirical, with no objective confirmation available to date from laboratory measures. ADHD begins in childhood and often persists into adulthood. The exact etiology is unknown; genetics plays a role, but major etiologic contributors also include adverse responses to food additives, intolerances to foods, sensitivities to environmental chemicals, molds, and fungi, and exposures to neurodevelopmental toxins such as heavy metals and organohalide pollutants. Thyroid hypofunction may be a common denominator linking toxic insults with ADHD symptomatologies.

Abnormalities in the frontostriatal brain circuitry and possible hypofunctioning of dopaminergic pathways are apparent in ADHD, and are consistent with the benefits obtained in some instances by the use of methylphenidate (Ritalin) and other potent psychostimulants. Mounting controversy over the widespread use of methylphenidate and possible life-threatening effects from its long-term use make it imperative that alternative modalities be implemented for ADHD management. Nutrient deficiencies are common in ADHD; supplementation with minerals, the B vitamins (added in singly), omega-3 and omega-6 essential fatty acids, flavonoids, and the essential phospholipid phosphatidylserine (PS) can ameliorate ADHD symptoms. When individually managed with supplementation, dietary modification, detoxification, correction of intestinal dysbiosis, and other features of a wholistic/integrative program of management, the ADHD subject can lead a normal and productive life.

Herbs of activating blood circulation to remove blood stasis.

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Clin Hemorheol Microcirc 2000;23(2-4):127-31

Drugs with the efficacy of modifying rheological properties of blood, blood vessels and their interactions are denoted by "hemorheologicals". Drugs of anti-hyperviscosemia, anti-coagulants, anti-platelet drugs, anti-thrombotics, vasodilators, endothelial cell protectors and anti-arthrosclerosis should be considered as hemorheologicals due to the actions in keeping blood fluidity and in maintaining normal vascular functions. The studies in hemorheology indicate that a tendency of hyperviscosity, hypercoagulation and being prone to thrombosis is prevalent in the elderly. Hemorheologicals are importance for and aging and life-threatening diseases. Blood stasis syndrome is a common pathological syndrome in the elderly. In traditional Chinese medicine, the treatment for the syndrome is by herbs which activates blood circulation to remove blood stasis. The herbs have the efficacy of improving hemorheological events. Therefore, the herbs are the source for developing hemorheologicals. Ligustrazine isolated from Chuangxiong is an example. It showed significant inhibition on shear induced platelet aggregation and on platelet intracellular calcium demonstrated by laser confocal microscope.

Effect of the herbal extract combination Panax quinquefolium and Ginkgo biloba on attention-deficit hyperactivity disorder: a pilot study.

Lyon MR, Cline JC, Totosy de Zepetnek J, Shan JJ, Pang P, Benishin C. Oceanside Functional Medicine Research Institute, Nanaimo, BC.

J Psychiatry Neurosci 2001 May;26(3):221-8

OBJECTIVE: A combination herbal product containing American ginseng extract, Panax quinquefolium, (200 mg) and Ginkgo biloba extract (50 mg) (AD-

FX; CV Technologies, Edmonton, Alta.) was tested for its ability to improve the symptoms of attention-deficit hyperactivity disorder (ADHD).

DESIGN: Open study.

PATIENTS: 36 children ranging in age from 3 to 17 years who fit the diagnostic criteria for ADHD.

INTERVENTIONS: AD-FX capsules were taken twice a day on an empty stomach for 4 weeks. Patients were instructed not to change any other medications during the study.

OUTCOME MEASURES: At the beginning of the study, after 2 weeks, and then at the end of the 4-week trial, parents completed the Conners' Parent Rating Scale--revised, long version, a questionnaire that assesses a broad range of problem behaviours (and was used as an indication of ADHD symptom severity).

RESULTS: After 2 weeks of treatment, the proportion of the subjects exhibiting improvement (i.e., decrease in T-score of at least 5 points) ranged from 31% for the anxious-shy attribute to 67% for the psychosomatic attribute. After 4 weeks of treatment, the proportion of subjects exhibiting improvement ranged from 44% for the social problems attribute to 74% for the Conners' ADHD index and the DSM-IV hyperactive-impulsive attribute. Five (14%) of 36 subjects reported adverse events, only 2 of which were considered related to the study medication.

CONCLUSIONS: These preliminary results suggest AD-FX treatment may improve symptoms of ADHD and should encourage further research on the use of ginseng and Ginkgo biloba extracts to treat ADHD symptoms.

The potential role of fatty acids in attention-deficit/hyperactivity disorder.

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Prostaglandins Leukot Essent Fatty Acids 2000 Jul-Aug;63(1-2):79-87

As currently defined, attention-deficit/hyperactivity disorder (ADHD) encompasses a broad constellation of behavioural and learning problems and its definition and diagnosis remain controversial. The aetiology of ADHD is acknowledged to be both complex and multifactorial. The proposal considered here is that at least some features of ADHD may reflect an underlying abnormality of fatty acid metabolism. Clinical and biochemical evidence is discussed which suggests that a functional deficiency of certain long-chain polyunsaturated fatty acids could contribute to many of the features associated with this condition. The implications in terms of fatty acid treatment proposals are also discussed; such a form of treatment is relatively safe compared to existing pharmacological interventions, although further studies are still needed in order to evaluate its potential efficacy in the management of ADHD symptoms.

A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties.

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Prog Neuropsychopharmacol Biol Psychiatry 2002 Feb;26(2):233-9

(1) The authors tested the prediction that relative deficiencies in highly unsaturated fatty acids (HUFAs) may underlie some of the behavioral and learning problems associated with attention-deficit/hyperactivity disorder (ADHD) by studying the effects of HUFA supplementation on ADHD-related symptoms in children with specific learning difficulties (mainly dyslexia) who also showed ADHD features. (2) Forty-one children aged 8-12 years with both specific learning difficulties and above-average ADHD ratings were randomly allocated to HUFA supplementation or placebo for 12 weeks. (3) At both baseline and follow-up, a range of behavioral and learning problems associated with ADHD was assessed using standardized parent rating scales. (4) At baseline, the groups did not differ, but after 12 weeks mean scores for cognitive problems and general behavior problems were significantly lower for the group treated with HUFA than for the placebo group; there were significant improvements from baseline on 7 out of 14 scales for active treatment, compared with none for placebo. Group differences in change scores all favored HUFA, reaching conventional significance levels for 3 out of 14 scales. (5) HUFA supplementation appears to reduce ADHD-related symptoms in children with specific learning difficulties. Given the safety and tolerability of this simple treatment, results from this pilot study strongly support the case for further investigations.

The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial.

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J Altern Complement Med 2000 Feb;6(1):7-17

CONTEXT: Numerous studies conducted in juvenile correctional institutions have reported that violence and serious antisocial behavior have been cut almost in half after implementing nutrient-dense diets that are consistent with the World Health Organization's guidelines for fats, sugar, starches, and protein ratios. Two controlled trials tested whether the cause of the behavioral improvements was psychological or biological in nature by comparing the behavior of offenders who either received placebos or vitamin-mineral supplements designed to provide the micronutrient equivalent of a well-balanced diet. These randomized trials reported that institutionalized offenders, aged 13 to 17 years or 18 to 26 years, when given active tablets produced about 40% less violent and other antisocial behavior than

the placebo controls. However, generalization could not be made to typical schoolchildren without a controlled trial examining violence and antisocial behavior in public schools.

OBJECTIVES: To determine if schoolchildren, aged 6 to 12 years, who are given low dose vitamin-mineral tablets will produce significantly less violence and antisocial behavior in school than classmates who are given placebos.

DESIGN: A stratified randomized, double-blind, placebo-controlled trial with pretest and post-test measures of antisocial behavior on school property.

SETTINGS AND SUBJECTS: Two "working class," primarily Hispanic elementary schools in Phoenix, Arizona. Approximately half of the potential schoolchildren participated, i.e., 468 students aged 6 to 12 years.

INTERVENTION: Daily vitamin-mineral supplementation at 50% of the U.S. recommended daily allowance (RDA) for 4 months versus placebo. The supplement was designed to raise vitamin-mineral intake up to the levels currently recommended by the National Academy of Sciences for children aged 6 to 11 years.

OUTCOME MEASURE: Violent and nonviolent delinquency as measured by official school disciplinary records.

RESULTS: Of the 468 students randomly assigned to active or placebo tablets, the 80 who were disciplined at least once between September 1st and May 1st served as the research sample. During intervention, the 40 children who received active tablets were disciplined, on average, 1 time each, a 47% lower mean rate of antisocial behavior than the 1.875 times each for the 40 children who received placebos (95% confidence interval, 29% to 65%, < 5 .020). The children who took active tablets produced lower rates of antisocial behavior in 8 types of recorded infractions: threats/fighting, vandalism, being disrespectful, disorderly conduct, defiance, obscenities, refusal to work or serve, endangering others, and nonspecified offenses.

CONCLUSION: Poor nutritional habits in children that lead to low concentrations of water-soluble vitamins in blood, impair brain function and subsequently cause violence and other serious antisocial behavior. Correction of nutrient intake, either through a well-balanced diet or low-dose vitamin-mineral supplementation, corrects the low concentrations of vitamins in blood, improves brain function and subsequently lowers institutional violence and antisocial behavior by almost half. This paper adds to the literature by enabling previous research to be generalized from older incarcerated subjects with a history of antisocial behavior to a normal population of younger children in an educational setting.

The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test.

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Magnes Res 1997 Jun;10(2):149-56

Children with ADHD are 'a group at risk' as far as their further emotional and social development and educational possibilities are concerned, and the consequences of the lack of an appropriate therapy appears to be serious. Some of these children do not respond to prevailing therapy methods. It is reported that dietetic factors can play a significant role in the etiology of ADHD syndrome, and magnesium deficiency can help in revealing hyperactivity in children. The aim of our work was to assess the influence of magnesium supplementation on hyperactivity in patients with ADHD. The examination comprised 50 hyperactive children, aged 7-12 years, who fulfilled DSM IV criteria for ADHD syndrome, with recognized deficiency of magnesium in the blood (blood serum and red blood cells) and in hair using atomic absorption spectroscopy. In the period of 6 months those examined regularly took magnesium preparations in a dose of about 200 mg/day. 30 of those examined with ADHD showed coexisting disorders specific to developmental age, and 20 of them showed disruptive behaviour. The control group consisted of 25 children with ADHD and magnesium deficiency, who were treated in a standard way, without magnesium preparations. 15 members of this group showed coexisting disorders specific for developmental age, and 10 members showed disruptive behaviour. Hyperactivity was assessed with the aid of psychometric scales: the Conners Rating Scale for Parents and Teachers, Wender's Scale of Behavior and the Quotient of Development to Freedom from Distractibility. In the group of children given 6 months of magnesium supplementation, independently of other mental disorders coexisting with hyperactivity, an increase in magnesium contents in hair and a significant decrease of hyperactivity of those examined has been achieved, compared to their clinical state before supplementation and compared to the control group which had not been treated with magnesium.

Is attention-deficit/hyperactivity disorder an energy deficiency syndrome?

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Biol Psychiatry 2001 Aug 1;50(3):151-8

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable yet clinically heterogeneous syndrome associated with hypocatecholamine function in subcortical and prefrontal cortical regions and clinical response to medications that enhance catecholamine function. The goal of this article is to present a hypothesis about the etiology of ADHD by synthesizing these findings with recent experiments indicating that activity-dependent neuronal energy consumption is regulated by cortical astrocytes. The scientific literature was searched from 1966 to the present using MEDLINE and relevant key words. Inattention and impulsivity may be related to hypofunctionality of catecholamine projection pathways to prefrontal cortical areas, resulting in decreased neuronal

energy availability. This may be mediated by astrocyte catecholamine receptors that normally regulate energy availability during neuronal activation. At least some forms of ADHD may be viewed as cortical, energy-deficit syndromes secondary to catecholamine-mediated hypofunctionality of astrocyte glucose and glycogen metabolism, which provides activity-dependent energy to cortical neurons. Several tests of this hypothesis are proposed.

Spirulina maxima prevents induction of fatty liver by carbon tetrachloride in the rat.

Torres-Duran PV, Miranda-Zamora R, Paredes-Carbajal MC, Mascher D, Diaz-Zagoya JC, Juarez-Oropeza MA. Departamento de Bioquimica, UNAM, Mexico, D.F., Mexico.

Biochem Mol Biol Int. 1998 Apr;44(4):787-93

The aim of the present work was to assess the capacity of Spirulina maxima to prevent fatty liver development induced in rats by an intraperitoneal single dose (1 ml/kg) of carbon tetrachloride. Liver and serum lipids were quantified two or four days after treatment with this agent. Liver lipid concentration did not differ in rats fed on a purified diet with or without Spirulina. However, after carbon tetrachloride treatment, liver triacylglycerols were significantly lower in rats fed on a diet with Spirulina 5% than in rats without Spirulina in their diet (< 0.05). Furthermore, the increased liver cholesterol values, induced by carbon tetrachloride treatment, were not observed in rats that received Spirulina. These results support the potential hepatoprotective role of Spirulina.

A randomized, double-blind, placebo-controlled trial of docosahexanoic acid supplementation in children with attention-deficit/hyperactivity disorder.

Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. Division of Developmental and Behavioral Pediatrics, Mayo Clinic, Rochester, Minnesota 55905, USA.

J Pediatr. 2001 Aug;139(2):189-96.

OBJECTIVE: To determine whether docosahexaenoic acid (DHA) supplementation for 4 months decreases the symptoms of attention-deficit/hyperactivity disorder (ADHD).

STUDY DESIGN: Sixty-three 6- to-12-year-old children with ADHD, all receiving effective maintenance therapy with stimulant medication, were assigned randomly, in a double-blind fashion, to receive DHA supplementation (345 mg/d) or placebo for 4 months. Outcome variables included plasma phospholipid fatty acid patterns, scores on laboratory measures of inattention and impulsivity (Test of Variables of Attention, Children's Color Trails test) while not taking stimulant medication, and scores on parental behavioral rating scales (Child Behavior Checklist, Conners' Rating Scale). Differences between groups after 4 months of DHA supplementation or placebo administration were determined by analysis of

variance, controlling for age, baseline value of each outcome variable, ethnicity, and ADHD subtype.

RESULTS: Plasma phospholipid DHA content of the DHA-supplemented group was 2.6-fold higher at the end of the study than that of the placebo group (4.85 +/- 1.35 vs 1.86 +/- 0.87 mol % of total fatty acids; < 001). Despite this, there was no statistically significant improvement in any objective or subjective measure of ADHD symptoms.

CONCLUSION: A 4-month period of DHA supplementation (345 mg/d) does not decrease symptoms of ADHD.

9. Bacterial Infections

Preventative and curative options include:

Vitamin and trace-elements, herbs, lactoferrin, oregano oil, grapefruit seed extract, sarsaparilla root, shark liver oil, bromelain, arginine, cranberry juice, honey, bee propolis, zinc, probiotics, garlic, ionic silver, aloe vera.

Influence of lactoferrin feeding and injection against systemic staphylococcal infections in mice.

Bhimani RS, Vendrov Y, Furmanski P. Department of Biology, New York University, NY, USA.

J Appl Microbiol 1999 Jan;86(1):135-44

Human and bovine lactoferrins (Lfs) and bovine lactoferrin hydrolysate (LH) were assessed in vitro and in vivo for their antibacterial effects on Staphylococcus aureus. Lactoferrins showed weak in vitro antibacterial activity while Fe-saturated Lfs and LH showed no activity. Lactoferrin-treated mice (1 mg, i.v.) when injected i.v. with 10(6) staphylococci, showed 30-50% reduction in kidney infections, and viable bacterial counts in the kidneys decreased 5-12-fold. The inhibitory effect was dose-dependent up to 1 mg Lf. Lactoferrins were effective when given 1 day prior to the bacterial challenge, after which there was no significant effect even at doses up to 5 mg. Apo- and Fe-saturated forms of human and bovine Lfs were all equally effective, while LH was not protective. Human and bovine Lfs with different degrees of iron saturation (9-97%) were found to be equipotent. Feeding mice with 2% bLf in drinking water also reduced the kidney infections by 40-60%, and viable bacterial counts, 5-12-fold. The results suggest a potential for the use of Lfs as natural antibacterial proteins for preventing bacterial infections.

Bromelain protects piglets from diarrhoea caused by oral challenge with K88 positive enterotoxigenic Escherichia coli.

Chandler DS, Mynott TL. Victorian Institute of Animal Science, Attwood, Australia.

Gut. 1998 Aug;43(2):196-202.

BACKGROUND: K88 positive enterotoxigenic Escherichia coli (K88+ ETEC) is an important cause of diarrhoea in young piglets. K88+ ETEC pathogenesis relies on attachment to specific glycoprotein receptors located on the intestinal mucosa. Proteolytic treatment of these receptors in vitro and in vivo prevents attachment of K88+ ETEC to piglet small intestines and may be of clinical use to prevent K88+ ETEC pathogenesis. AIMS: To determine whether bromelain, a proteolytic extract obtained from pineapple stems, would protect piglets against K88+ ETEC

diarrhoea and to confirm and extend earlier findings on the effects of bromelain on K88+ ETEC receptors in vivo.

METHODS: Bromelain (0, 12.5, or 125 mg) was orally administered to just weaned piglets for 10 days. One day following commencement of bromelain treatment, piglets were challenged with K88+ ETEC (5 x 10(10) K88ac:0149) for seven days. Intestinal contents from unchallenged piglets were obtained via an intestinal fistula, and tested for their ability to bind K88+ ETEC before and after bromelain treatment.

RESULTS: Both doses of bromelain were successful in reducing the incidence of K88+ ETEC diarrhoea and protected piglets from life threatening disease. Bromelain treated pigs also had significantly increased weight gain compared with untreated pigs. Bromelain only temporarily inhibited K88+ ETEC receptor activity, with receptor activity being regenerated 30 hours following treatment, consistent with the regeneration of new enterocytes.

CONCLUSION: Results show that bromelain can temporarily inactivate ETEC receptors in vivo and protect against ETEC induced diarrhoea. Bromelain may therefore be an effective prophylaxis against ETEC infection.

Antibiotic properties of bovine lactoferrin on Helicobacter pylori.

Dial EJ, Hall LR, Serna H, Romero JJ, Fox JG, Lichtenberger LM. Department of Integrative Biology, The University of Texas-Houston Medical School, 77225, USA.

Dig Dis Sci 1998 Dec;43(12):2750-6

To investigate a potential new treatment for gastric Helicobacter pylori infection, we have examined the use of the natural antibiotic lactoferrin, found in bovine milk, for activity against Helicobacter species both in vitro and in vivo. Lactoferrin was bacteriostatic to H. pylori when cultured at concentrations < or =0.5 mg/ml. Growth of H. pylori was not inhibited by another milk constituent, lysozyme, or by a metabolite of lactoferrin, lactoferricin B, but growth was inhibited by the iron chelator deferoxamine mesylate. Lactoferrin inhibition of growth could be reversed by addition of excess iron to the medium. Lactoferrin in retail dairy milk was found to be more stable intragastrically than unbuffered, purified lactoferrin. Treatment of H. felis-infected mice with lactoferrin partially reversed mucosal disease manifestations. It is concluded that bovine lactoferrin has significant antimicrobial activity against Helicobacter species in vitro and in vivo. Bovine lactoferrin should be further investigated for possible use in H. pylori infections in man.

New support for a folk remedy: cranberry juice reduces bacteriuria and pyuria in elderly women.

Fleet JC. Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111.

Nutr Rev 1994 May;52(5):168-70

Cranberry juice has developed a following as a simple, nonpharmacologic means to reduce or treat urinary tract infections, yet the scientific basis for such a claim has been lacking. A new study suggests that bacterial infections (bacteriuria) and associated influx of white blood cells into the urine (pyuria) can be reduced by nearly 50% in elderly women who drink 300 mL ofcranberry juice cocktail each day over the course of a 6-month study. The results of this study suggest that consumption of cranberry juice is more effective in treating than preventing bacteriuria and pyuria. Along with earlier reports on the ability of cranberry juice to inhibit bacterial adherence to urinary epithelial cells in cell culture, this new work suggests that drinking cranberry juice each day may be clinically useful. Additional work must be conducted, however, to more completely define the efficacy of cranberry juice.

Human lactoferrin and peptides derived from a surface-exposed helical region reduce experimental Escherichia coli urinary tract infection in mice.

Haversen LA, Engberg I, Baltzer L, Dolphin G, Hanson LA, Mattsby-Baltzer I. Departments of Clinical Immunology, Goteborg, Sweden.

Infect Immun 2000 Oct;68(10):5816-23

Lactoferrin (LF) is a multifunctional immunoregulatory protein that has been associated with host defense at mucosal surfaces through its antibacterial properties. The antibacterial and anti-inflammatory properties of LF were further explored with an animal model of experimental urinary tract infection. Bovine LF (bLF), human LF (hLF), and synthetic peptide sequences based on the antibacterial region of hLF (amino acid residues 16 to 40 [HLD1] and 18 to 40 [HLD2]) were given orally to female mice 30 min after the instillation of 10(8) Escherichia coli bacteria into the urinary bladder. The control groups received phosphate-buffered saline or water. C3H/Tif mice were treated with hLF or bLF, and C3H/HeN mice were treated with bLF only. The numbers of bacteria in the kidneys and bladder of C3H/Tif and C3H/HeN mice were significantly reduced 24 h later by the LF treatments compared to the findings for the control group. The hLF-treated group showed the strongest reduction compared with the vehicle-treated-group (P values were 0.009 and 0.0001 for the kidneys and bladder, respectively). The urinary leukocyte response was diminished in the hLF-treated group. The hLF treatment also significantly reduced the urinary interleukin-6 (IL-6) levels at 2 h and the systemic IL-6 levels at 24 h after infection (P values were 0.04 < 0.002, respectively). In the bLF-treated animals, no such strong anti-inflammatory effects were obtained. In another series of experiments, C3H/Tif mice perorally treated with HLD1 or HLD2 also showed reduced numbers of bacteria in the kidneys compared with the vehicle-treated mice, although the results were significantly different only for HLD2 (< 0.01). Analysis of urine from hLF-fed C3H/Tif mice showed that hLF was excreted into the urinary tract at 2 h after feeding. Testing of the in vitro bactericidal activity of LF (1 mg/ml) or the peptides (0.1 mg/ml) in mouse urine against the E. coli bacteria revealed moderate killing only by HLD2. In conclusion, these results demonstrate for the

first time that oral administration of hLF or peptides thereof is effective in reducing infection and inflammation at a remote site, the urinary tract, possibly through transfer of hLF or its peptides to the site of infection via renal secretion. The antibacterial mechanism is suggested to involve bactericidal capacities of LF, fragments thereof, or its peptides.

Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women.

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BMJ 2001 Jun 30;322(7302):1571

OBJECTIVE: To determine whether recurrences of urinary tract infection can be prevented with cranberry-lingonberry juice or with Lactobacillus GG drink. Design: Open, randomised controlled 12 month follow up trial.

SETTING: Health centres for university students and staff of university hospital.

PARTICIPANTS: 150 women with urinary tract infection caused by Escherichia coli randomly allocated into three groups. Interventions: 50 ml of cranberry-lingonberry juice concentrate daily for six months or 100 ml of lactobacillus drink five days a week for one year, or no intervention. Main outcome measure: First recurrence of symptomatic urinary tract infection, defined as bacterial growth < =10(5)colony forming units/ml in a clean voided midstream urine specimen.

RESULTS: The cumulative rate of first recurrence of urinary tract infection during the 12 month follow up differed significantly between the groups (P=0.048). At six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had had at least one recurrence. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, P=0.023, number needed to treat=5, 95% confidence interval 3 to 34).

CONCLUSION: Regular drinking of cranberry juice but not lactobacillus seems to reduce the recurrence of urinary tract infection.

The gut. A key metabolic organ protected by lactoferrin during experimental systemic inflammation in mice.

Kruzel ML, Harari Y, Chen CY, Castro GA. Department of Integrative Biology, Pharmacology and Physiology, University of Texas Medical School, Houston, USA.

Adv Exp Med Biol 1998;443:167-73

The gastrointestinal tract may be viewed as an ecologic system in which a balance between the host and bacterial flora exists. Two major host components appear to be involved in maintaining this balance. The first is a non-specific structural barrier provided by the epithelial layer of the gastrointestinal mucosae. The second component involves functional immunological elements found in the mucosal and submucosal compartments, e.g., gut associated lymphoid tissue. When gut integrity is disrupted by invasive pathogens or by trauma, a myriad of pro-inflammatory mediators are released from cells in the gut wall that exert actions in the tissue or gut lumen. One of these mediators is lactoferrin, and iron binding protein found in high concentration in most human exocrine secretions. Despite controversies on its physiological role, evidence is emerging that lactoferrin plays an important role in host defense against toxic metabolites and antigenic components of potential pathogens2-4. This manuscript is intended to provide an overview of work related to lactoferrin's modulatory roles in inflammation, and to present observations from experimental studies on the preservation of intestinal structure and function by lactoferrin during intestinal inflammation. The possibility that lactoferrin limits the autodestructive inflammatory responses presents a new alternative for the future management of systemic inflammation.

Sensitivity of food pathogens to garlic (Allium sativum).

Kumar M, Berwal JS. Department of Animal Products Technology, CCS Haryana Agricultural University, Hisar, India.

J Appl Microbiol 1998 Feb;84(2):213-5

The inhibitory activity of garlic (Allium sativum) against Staphylococcus aureus, Salmonella typhi, Escherichia coli and Listeria monocytogenes was measured by the 'turbidity' method. Minimum inhibitory concentration (MIC) of garlic at 80% inhibition level was calculated for these bacteria. All bacterial pathogenic strains tested were inhibited by garlic; E. coli was most sensitive and Listeria monocytogenes was least sensitive. Therefore, garlic has potential for the preservation of processed foods.

Direct evidence of the generation in human stomach of an antimicrobial peptide domain (lactoferricin) from ingested lactoferrin.

Kuwata H, Yip TT, Tomita M, Hutchens TW. Department of Food Science and Technology, University of California, Davis 95616, USA. hidi@msn.com

Biochim Biophys Acta 1998 Dec 8;1429(1):129-41

The ability to define specific alterations in the structure and function of proteins as they are introduced and processed in vivo remains an important goal. We have evaluated the generation, in vivo, of an antimicrobial peptide (lactoferricin) derived from ingested bovine lactoferrin by surface-enhanced laser desorption/ionization (SELDI). SELDI was used in the affinity mass spectrometry operational mode to detect and quantify lactoferricin directly from unfractionated

gastric contents using a chemically defined ligand with a terminal n-butyl group as the lactoferricin affinity capture device. By this method, we were able to detect and quantify lactoferricin directly upon examination of unfractionated gastric contents recovered from an adult subject 10 min after ingestion of bovine lactoferrin (200 ml of 10 mg/ml (1.2 x 10(-4) mol/l) solution). Lactoferricin produced in vivo was directly captured by a surface-enhanced affinity capture (SEAC) device composed of molecules with a terminal n-butyl group and analyzed by laser desorption/ionization time-of-flight mass spectrometry. The recovery of standard lactoferricin or lactoferrin added to an aliquot of the gastric contents was determined to be nearly 100%, confirming the efficiency of this method. The amount of lactoferricin detected in the gastric contents was 16.9+/-2.7 microg/ml (5.4+/-0.8 x 10(-6) mol/l). However, a large proportion of ingested lactoferrin was found to be incompletely hydrolyzed. Lactoferrin fragments containing the lactoferricin region were analyzed by in situ pepsin hydrolysis after being captured on the SEAC device. Partially degraded lactoferrin fragments containing the lactoferricin region, including fragments corresponding to positions 17-43, 17-44, 12-44, 9-58 and 16-79 of the bovine lactoferrin sequence, were found to be present at concentrations as high as 5.7+/-0.7 x 10(-5) mol/l. These results suggest that significant amounts of bovine lactoferricin would be produced in the human stomach following ingestion of food, such as infant formula, supplemented with bovine lactoferrin. We propose that physiologically functional quantities of human lactoferricin could be generated in the stomach of breast-fed infants, and possibly, in the case of adults, from lactoferrin secreted into saliva.

The protective effects of lactoferrin feeding against endotoxin lethal shock in germfree piglets.

Lee WJ, Farmer JL, Hilty M, Kim YB. Finch University of Health Sciences/The Chicago Medical School, Illinois 60064, USA.

Infect Immun 1998 Apr;66(4):1421-6

The unique germfree, colostrum-deprived, immunologically "virgin" piglet model was used to evaluate the ability of lactoferrin (LF) to protect against lethal shock induced by intravenously administered endotoxin. Piglets were fed LF or bovine serum albumin (BSA) prior to challenge with intravenous Escherichia coli lipopolysaccharide (LPS), and temperature, clinical symptoms, and mortality were tracked for 48 h following LPS administration. Prefeeding with LF resulted in a significant decrease in piglet mortality compared to feeding with BSA (16.7 versus 73.7% mortality, < 0.001). Protection against the LPS challenge by LF was also correlated with both resistance to induction of hypothermia by endotoxin and an overall increase in wellness, as quantified by a toxicity score developed for these studies. In vitro studies using a flow cytometric assay system demonstrated that LPS binding to porcine monocytes was inhibited by LF in a dose-dependent fashion, suggesting that the mechanism of LF action in vivo may be inhibition of LPS binding to monocytes/macrophages and, in turn, prevention of induction of monocyte/macrophage-derived inflammatory-toxic cytokines.

Impedance measurements to study the antimicrobial activity of essential oils from Lamiaceae and Compositae.

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Int J Food Microbiol 2001 Aug 5;67(3):187-95

A wide range of essential oils from sage, mint, hyssop, camomile and oregano were tested for their inhibitory effects against nine strains of gram-negative bacteria and six strains of gram-positive bacteria. Three principles were used in describing the antimicrobial effects of the essential oils: the overall antimicrobial activity determined by use of an impedometric method, the bactericidal effect determined as colony forming units after exposure to the essential oils, and the number of apparent dead cells determined after further enrichment. The data obtained indicate that while the essential oils of sage, mint, hyssop and camomile had generally a bacteriostatic activity, the essential oil from oregano appeared to be bactericidal at concentrations above 400 ppm, probably because of high contents in phenolic compounds. For the other essential oils, the chemical analysis was unable to explain the antimicrobial effect. The bacteriostatic activity was more marked against gram-positive bacteria; in contrast, the bactericidal activity was greatest against gram-negative bacteria. The most sensitive strain was Escherichia coli O157:H7 and, of the gram-positive species even at the lowest oil concentrations, Listeria innocua was the most sensitive. The data obtained from the study of the bactericidal effect of oregano essential oil indicated that the major part of the species was irreversibly inactivated, i.e. they could not be revived by enrichment.

Immunochemical and physico-chemical characteristics of lactoferrin in human body fluids. [Article in Russian]

Nikolaev AA, Anshakova NI.

Vopr Med Khim 1985 May-Jun;31(3):128-32

It is proved that lactoferrins of different human body fluids (sperm, saliva, milk, tears, urine, bile, sweat, liquor, lymph, blood serum) are immunochemically identical. The lactoferrin is purified from milk, saliva and sperm and the identity of physical and chemical properties of lactoferrins of various origins is proved. The quantitative estimation of the contents of this protein in normal body fluids is given. It is detected the dependence of this protein' electrophoretic mobility and isoelectric point of degree of iron saturation. It is found that lactoferrin is capable to form complexes with esterase.

Antibacterial activity of Hydrastis canadensis extract and its major isolated alkaloids.

Scazzocchio F, Cometa MF, Tomassini L, Palmery M. Istituto di Microbiologia, Universita "La Sapienza", Roma, Italia.

Planta Med 2001 Aug;67(6):561-4

The antibacterial activity of extract and isolated major alkaloids (berberine, beta-hydrastine, canadine and canadaline) of Hydrastis canadensis L. (Ranunculaceae) was evaluated against 6 strains of microorganism: Staphylococcus aureus (ATCC 25 993 and ATCC 6538P), Streptococcus sanguis (ATCC 10 556), Escherichia coli (ATCC 25 922), Pseudomonas aeruginosa (ATCC 27 853). Bactericidal activity was evaluated by contact test by measuring the "killing time" on a low density bacterial inoculum, and bacteriostatic activity in liquid medium by M.I.C. values. The results provide a rational basis for the traditional antibacterial use of Hydrastis canadensis.

Electron microscopic and microcalorimetric investigations of the possible mechanism of the antibacterial action of a defined propolis provenance.

Takaisi-Kikuni NB, Schilcher H Department de Microbiologie, Faculte de Pharmacie, Universite de Kinshasa, Zaire.

Planta Med. 1994 Jun;60(3):222-7

Microcalorimetric and electron microscopic studies on the mode of the antibacterial action of propolis were performed on Streptococcus agalactiae. It was shown that propolis inhibits bacterial growth by preventing cell division, thus resulting in the formation of pseudo-multicellular streptococci. In addition, propolis disorganized the cytoplasm, the cytoplasmic membrane, and the cell wall, caused a partial bacteriolysis, and inhibited protein synthesis. It was evident that the mechanism of action of propolis on bacterial cells is complex and a simple analogy cannot be made to the mode of action of any classic antibiotics.

Antimicrobial peptides of lactoferrin.

Tomita M, Takase M, Wakabayashi H, Bellamy W. Nutritional Science Laboratory, Morinaga Milk Industry Co. Ltd., Kanagawa, Japan.

Adv Exp Med Biol 1994;357:209-18

Lactoferrin was found to contain an antimicrobial sequence near its N-terminus which appears to function by a mechanism distinct from iron chelation. Antimicrobial peptides representing this domain were isolated following pepsin cleavage of human lactoferrin and bovine lactoferrin. The antimicrobial sequence was found to consist mainly of a loop of 18 amino acid residues formed by a disulfide bond between cysteine residues 20 and 37 of human lactoferrin, or 19 and 36 of bovine lactoferrin. The identified domain contains a high proportion of basic residues, like various other antimicrobial peptides known to target microbial membranes and it appears to be located on the surface of the folded protein allowing its interaction with surface components of microbial cells. The isolated domain, "lactoferrin", was shown to have potent broad spectrum antimicrobial properties and its effect was lethal causing a rapid loss of colony-forming capability. Such evidence points to the conclusion that this domain is the

structural region responsible for the microbicidal properties of lactoferrin. The evidence also suggests the possibility that active peptides produced by enzymatic digestion of lactoferrin may contribute to the host defense against microbial disease.

Antimicrobial activity of some commercial extracts of propolis prepared with different solvents.

Tosi B.; Donini A.; Romagnoli C.; Bruni A. Institute of Botany, University of Ferrara, Corso Porta Mare 2,I-44100 Ferrara Italy

Phytotherapy Research (United Kingdom) 1996, 10/4 (335-336)

Some commercial extracts of propolis obtained with different solvents were tested to evaluate their antibacterial and antifungal activity. All propolis preparations exhibited antimicrobial activity, particularly against Gram- positive bacteria, yeasts and dermatophytes with zones of inhibition ranging from 3 to 30 min. Against yeasts and dermatophytes, oil, ethanol and propylene glycol solutions showed an inhibition for more 2 weeks, while the glycerine solution maintained inhibition only for some days. The results indicate that the solvent employed for the extraction may enhance the potency of the antimicrobial activity of propolis. Consistency in the properties and characteristics of propolis were related to the formulation of extraction procedures.

Lactoferricin of bovine origin is more active than lactoferricins of human, murine and caprine origin.

Vorland LH, Ulvatne H, Andersen J, Haukland H, Rekdal O, Svendsen JS, Gutteberg TJ. Department of Medical Microbiology, University Hospital, Tromso, Norway.

Scand J Infect Dis 1998;30(5):513-7

The antimicrobial peptide lactoferricin is generated by gastric pepsin cleavage of lactoferrin. We have examined the antimicrobial activity of lactoferricins derived from lactoferrin of human, murine, caprine and bovine origin with minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) against E. coli ATCC 25922 and S. aureus ATCC 25923. We found that lactoferricin of bovine origin (Lf-cin B) was the most efficacious of the lactoferricins tested. By comparing the linear and cyclic Lf-cin B we found the cyclic peptide to be the most active. Lactoferricin B was moderately active against E. coli ATCC 25922 and S. aureus ATCC 25923, but had no activity against P. mirabilis or Y. enterocolitica. Lf-cin B showed good activity against C. albicans, C. tropicalis and C. neoformans.

Effects of nitric oxide synthase inhibitors on systemic hypotension, cytokines and inducible nitric oxide synthase expression and lung injury following endotoxin administration in rats.

Wang D, Wei J, Hsu K, Jau J, Lieu MW, Chao TJ, Chen HI. Department of Medical Research, Cheng Hsin General Hospital, Taipei, Republic of China.

J Biomed Sci 1999 Jan;6(1):28-35

Endotoxin shock is characterized by systemic hypotension, hyporeactiveness to vasoconstrictors and acute lung edema. A nitric oxide synthase (NOS) inhibitor, NG-monomethyl-L-arginine (L-NMMA) has been shown to be effective in reversing acute lung injury. In the present study, we evaluated the effects of NOS blockade by different mechanisms on the endotoxin-induced changes. In anesthetized rats, lipopolysaccharide (LPS, Klebsiella pneumoniae) was administered intravenously in a dose of 10 mg/kg. LPS caused sustained systemic hypotension accompanied by an eightfold increase of exhaled NO during an observation period of 4 h. After the experiment, the lung weight was obtained and lung tissues were taken for the determination of mRNA expressions of inducible NOS (iNOS), interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha-(TNF-alpha). Histological examination of the lungs was also performed. In the control group injected with saline solution, mRNA expressions of iNOS, IL-1beta and TNF-alpha were absent. Four hours after LPS, the mRNA expressions of iNOS and IL-1beta were still significantly enhanced, but TNF-alpha was not discernibly expressed. LPS also caused a twofold increase in lung weight. Pathological examination revealed endothelial damage and interstitial edema. Various NOS inhibitors were given 1 h after LPS administration. These agents included Nomega-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg), a constitutive NOS and iNOS inhibitor; S, S'-1,4-phenylene-bis-(1,2-ethanedinyl) bis-isothiourea dihydrobromide (1,4-PBIT, 10 mg/kg), a relatively specific iNOS inhibitor, and dexamethasone (3 mg/kg), an inhibitor of iNOS expression. These NOS inhibitors all effectively reversed the systemic hypotension, reduced the exhaled NO concentration and prevented acute lung injury. The LPS-induced mRNA expressions of iNOS and IL-1beta were also significantly depressed by these NOS inhibitors. Our results suggest that NO production through the iNOS pathway is responsible for endotoxin-induced lung injury. Certain cytokines such as IL-1beta are possibly involved. These changes are minimized by NOS inhibitors through different mechanisms.

Interspecies coaggregation of plaque bacteria with a cranberry juice constituent.

Weiss EI, Lev-Dor R, Kashamn Y, Goldhar J, Sharon N, Ofek I. Department of Oral Biology, Maurice and Gabriela Goldschlager School of Dental Medicine, Tel Aviv University, Israel.

J Am Dent Assoc 1998 Dec;129(12):1719-23

Dental plaque stability depends on bacterial adhesion to acquired pellicle, and on interspecies adhesion (or coaggregation). A high-molecular-weight cranberry constituent at 0.6 to 2.5 milligrams per milliliter reversed the coaggregation of 49 (58 percent) of 84 coaggregating bacterial pairs tested. It acted preferentially on pairs in which one or both members are gram-negative anaerobes frequently

involved in periodontal diseases. Thus, the anticoaggregating cranberry constituent has the potential for altering the subgingival microbiota, resulting in conservative control of gingival and periodontal diseases. However, the high dextrose and fructose content of the commercially available cranberry juice makes it unsuitable for oral hygiene use, and the beneficial effect of the high-molecular-weight constituent requires animal and clinical studies.

Lactoferrin binding by leukemia cell lines.

Yamada Y, Amagasaki T, Jacobsen DW, Green R.

Blood 1987 Jul;70(1):264-70

Monocytes and macrophages have receptors for the iron-binding protein lactoferrin. Lactoferrin acts as a potent inhibitor of granulocyte-macrophage colony stimulating factor production when it binds to these cells. Using a rosette assay and immunofluorescence, we have shown that cultured leukemia cells, including the human erythroid leukemia cell line K562, also have lactoferrin binding sites. The number of binding sites on K562 cells was estimated using soluble 59Fe-lactoferrin. Inhibition studies demonstrate that lactoferrin binding sites are distinct and unrelated to receptors for transferrin or the Fc portion of IgG, which are present on K562 cells. However, electrostatic forces may be important for lactoferrin binding, since other polycationic proteins (eg, protamine) inhibit lactoferrin binding. Prior treatment of K562 cells with trypsin nearly abolishes lactoferrin binding. However, these cells recover their ability to bind lactoferrin when trypsin is removed. Unlike transferrin receptors, the expression of lactoferrin binding sites is not regulated by cellular iron status. Cytosine arabinoside arrests the proliferation of K562 cells and simultaneously leads to a reduction in lactoferrin surface binding, suggesting that lactoferrin binding may be dependent on cell proliferation.

Effects of copper and zinc ions on the germicidal properties of two popular pharmaceutical antiseptic agents, cetylpyridinium chloride and povidone-iodine.

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Analyst (United Kingdom), 1998, 123/3 (503-507)

The effects of copper and zinc ions on the rate of killing of Gram-negative bacterium Pseudomonas aeruginosa, Gram-positive bacterium Staphylococcus aureus and fungal yeast Candida albicans by antiseptic agents cetylpyridinium chloride and povidone-iodine (Betadine) were investigated. In the 48 test cases copper and zinc ions clearly potentiated the antiseptic agents in 28 (58.3%) cases and exhibited an improved (not clear potentiation) activity in 15 (31.3%) cases. In five (10.4%) cases there was no change in the antiseptics' antimicrobial activity. In general zinc potentiated the antiseptic agents more than copper. If an 'improved

activity' was the only criterion for this study, then a more rapid antimicrobial effect was observed in 43 out of the 48 test cases, i.e., 90%.

Bromelain prevents secretion caused by Vibrio cholerae and Escherichia coli enterotoxins in rabbit ileum in vitro

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Gastroenterology (United States) 1997, 113/1 (175-184)

Background and Aims: Diarrhea is a major cause of illness and death in children and young animals. The aim of this study was to investigate the possible therapeutic effect of bromelain, a proteolytic extract obtained from pineapple stems on bacterial toxin and second-messenger agonist-induced intestinal secretion.

Methods: The effect of bromelain pretreatment on short- circuit responses to Escherichia coli heat-labile enterotoxin, heat-stable enterotoxin, and Vibrio cholerae cholera toxin was evaluated in rabbit ileum mounted in Ussing chambers.

Results: Bromelain was 62% effective in preventing heat-stable enterotoxin-induced secretion, 51% effective against cholera toxin, and 35% effective against heat-labile enterotoxin. Bromelain also prevented secretory changes caused by prostaglandin Einf 2, theophylline, calcium-ionophore A23187, 8-bromoadenosine 3':5'-cyclic monophosphate, and 8- bromoguanosine 3':5'-cyclic monophosphate, well-known intracellular mediators of ion secretion. The efficacy of bromelain was not caused by reduced tissue viability resulting from its proteolytic effects on enterocytes, indicated by experiments measuring uptakes of nutrients into intestinal cells and experiments measuring short-circuit responses to glucose.

Conclusions: Bromelain prevents intestinal fluid secretion mediated by secretagogues that act via adenosine 3':5'-cyclic monophosphate, guanosine 3':5'-cyclic monophosphate, and calcium-dependent signaling cascades. It may be clinically useful as an antidiarrheal drug.

New support for a folk remedy: Cranberry juice reduces bacteriuria and pyuria in elderly women

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Nutrition Reviews (United States) 1994, 52/5 (168-170)

Cranberry juice has developed a following as a simple, nonpharmacologic means to reduce or treat urinary tract infections, yet the scientific basis for such a claim

has been lacking. A new study suggests that bacterial infections (bacteriuria) and associated influx of white blood cells into the urine (pyuria) can be reduced by nearly 50% in elderly women who drink 300 mL of cranberry juice cocktail each day over the course of a 6-month study. The results of this study suggest that consumption of cranberry juice is more effective in treating than preventing bacteriuria and pyuria. Along with earlier reports on the ability of cranberry juice to inhibit bacterial adherence to urinary epithelial cells in cell culture, this new work suggests that drinking cranberry juice each day may be clinically useful. Additional work must be conducted, however, to more completely define the efficacy of cranberry juice.

Relationship between residual metal ions in a solution and the inhibitory capability of the metal ions for pathogenic bacterial growth

Zhao Z.-H.; Sakagami Y.; Osaka T. Z.-H. Zhao, Satosen Co., Ltd., 2-20-65 Tamadenishi, Nishinari-ku, Osaka 557 Japan

Bulletin of the Chemical Society of Japan (Japan), 1998, 71/4 (939-945)

The inhibitory capability of various low concentrations of six kinds of metal ions [silver(I), copper(II), cobalt(II), nickel(II), zinc(II), and dichromate] for pathogenic bacterial (gram-positive bacteria Staphylococcus aureus and MRSA, gram-negative bacteria Escherichia coli and Pseudomonas aeruginosa) growth was quantitatively determined exactly. Residual metal-ion concentrations in a phosphate buffer solution after being incubated with pathogenic bacteria were then measured by an atomic-absorption spectrophotometer. We found that the inhibitory capability of metal ions correlated with the residual metal concentrations. Based on the biochemical and chemical situation, the mechanisms of the inhibitory capability of the metal ions are discussed. In addition, the determined minimum inhibitory concentration (MIC) values of metal ions on tested bacteria are considered.

Effects of zinc oxide on the attachment of Staphylococcus aureus strains

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Journal of Dermatological Science (Ireland), 1998, 17/1 (67-74)

We examined the attachment of Staphylococcus aureus to plastic tissue- culture coverslips after incubation for 24 h. The attachment to coverslips was weaker in rabbit plasma with 5% zinc oxide (ZnO) than in the control rabbit plasma without ZnO (< 0.01). Plasma coagulation by S. aureus strains was not detected in plasma with 5% ZnO after incubation for 24 h. The membranous structure (an immature biofilm) was formed on the coverslips by S. aureus cells in plasma after incubation for 24 h. The colony counts of S. aureus cells on the membranous structures were lower in plasma with 5% ZnO, plasma with 0.2% hinokitiol, plasma with 5% ZnO + 0.2% hinokitiol, plasma with cefdinir at 4 minimum

inhibitory concentration (MIC) and plasma with levofloxacin at 4 MIC, than in the control plasma after incubation for 24 h (< 0.01). The colonies on the membranous structures completely disappeared in the case of plasma with 5% ZnO and 0.2% hinokitiol. The colony counts on membranous structures were lower in plasma with cefdinir at 4 MIC or levofloxacin at 4 MIC containing 5% ZnO than in plasma with cefdinir at 4 MIC or levofloxacin at 4 MIC only, (< 0.05). The MICs of hinokitiol against S. aureus strains peaked at an MIC distribution of 16-32 microg/ml. The peak shifted to below 1 microg/ml by adding 5% ZnO in agar plate method. The results suggest that the attachment of S. aureus cells to the coverslips is suppressed in the presence of 5% ZnO and that antistaphylococcal activities of cefdinir, levofloxacin and hinokitiol increase in the presence of 5% ZnO.

Toxicity of hydrogen peroxide produced by electroplated coatings to pathogenic bacteria

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Canadian Journal of Microbiology (Canada), 1998, 44/5 (441-447)

The ability of various electroplated coatings (cobalt, zinc, copper, and cobalt-containing alloys of nickel, zinc, chromium, etc.) to inhibit the growth of pathogenic bacteria (Gram-positive bacteria Enterococcus faecalis and methicillin-resistant Staphylococcus aureus and Gram-negative bacteria Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae) was determined by a drop-method antibacterial experiment. The amounts of H2O2, produced and metal ions dissolved from the surfaces of various electroplated coatings were measured and it was found that the inhibitory ability of coatings corresponded to the amounts of H2O2 produced. The more significant the inhibition of the coating to bacterial growth, the greater the amount of H2O2 production. In addition, the bacterial survival rates on the surfaces of coatings were almost zero when H2O2 was produced in amounts greater than 10-6 mmol/cm2. However, the dominant concentrations of metal ions dissolved from coatings were outside of the bacterial lethal range.

Small bowel bacterial overgrowth syndrome

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Scand. J. Gastroenterol. Suppl. (Norway), 1983, 18/85 (83-93)

Different aspects of the small bowel bacterial overgrowth syndrome are reviewed. Special emphasis is put on the newly recognized structural and functional abnormalities of the small intestinal mucosa, abnormalities that may not be fully reversed by effective antimicrobic therapy. The pathogenetic mechanisms involved in the malabsorption of different substances are discussed and the available diagnostic tests are briefly presented. The current therapy, surgical, medical and supportive, are outlined. It is pointed out that abnormal overgrowth

flora of the small intestine can occur unassociated with malabsorption. Thus, the clinician must assess the potential benefit to be derived from treatment, once the presence of absorptive abnormalities is documented.

Screening of oriental herbal medicines for antibacterial activities

O Sung Bae; Jae Ock Hwang; Duk Kyun Ahn; Woo E.-R.; Seon Hee Seo; Hyoung Ja Kim; Park H. E.-R. Woo, Division of Applied Medicine, Korea Inst. of Sci. and Technology, P.O. Box 131, Cheongryang, Seoul 130-650 South Korea

Natural Product Sciences (South Korea), 1998, 4/1 (32-37)

The water extracts of oriental herbal medicines which have been clinically used to treat bacterial infections in Korea were screened for in vitro antibacterial activity by the paper disc assay method Two Gram positive bacteria, Staphylococcus aureus SG511, Bacillus subtilis ATCC 6633 and two Gram negative bacteria, Escherichia coli 055, Pseudomonas aeruginosa 9027 were used as test organisms. Among 83 of the extracts tested, 25 were active against Staphylococcus aureus SG 511, 9 were active against Bacillus subtilis ATCC 6633, while none showed inhibitory activity against Eschelichia coli 055 and Pseudomonas aeruginosa 9027. Among them, Hwangyonhaedoktang plus hwangyon, Chongwisan, and Ssangbaksan showed remarkably potent antibacterial activity.

Antimicrobial activity of honey on selected microorganisms: A preliminary study

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Biomedical Research (India), 1998, 9/1 (51-54)

This prospective study was undertaken to investigate the in-vitro antimicrobial activity of honey. Two hundred and forty-six bacterial strains of which 233 were multiple-drug resistant clinical isolates and 13 Difco antibiotic susceptibility control strains obtained from the American Type Culture Collection (ATCC) and Center for Disease Control (CDC) cultures were tested against crude unprocessed honey. This type of honey exhibited a fairly good antimicrobial activity against both Gram-negative and Gram-positive bacteria. A remarkable activity was observed with Klebsiella pneumoniae, Pseudomonas aeruginosa and Staphylococcus aureus.

Malnutrition and bacterial infections in hepatic cirrhosis

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GED - Gastrenterologia Endoscopia Digestiva (Brazil), 1997, 16/6 226-230)

Malnutrition is an important factor in the pathogenesis of hepatic diseases and, due to its relation to immunologic alterations, it may lead to the onset of infections. The aim of this study was to prospectively evaluate the nutritional status of 170 hospitalized patients who presented with alcoholic cirrhosis, whether or not associated to bacterial infections. All patients were submitted to biochemical and hepatic blood tests, bacteriological and bacterioscopic analyses, blood and ascitic fluid cultures, Child-Pugh classification, and nutritional evaluation through subjective and objective analyses using biochemical and anthropometric assessment. Results showed that in any of the parameters evaluated, malnutrition was more severe among the patients with bacterial infections. Malnutrition was also more frequent among C cirrhotic patients (according to Child-Pugh classification). Moreover, there was a higher rate of death: 30% in the infected group versus 5.55% in the group presenting no bacterial infections (< 0.0001). The authors concluded that malnutrition is an important factor which may lead to the onset of bacterial infections, causing high death rate. Dietetic measures that may restore the nutritional status should be implemented early.

Momordica charantia and Allium sativum: Broad spectrum antibacterial activity

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Korean Journal of Pharmacognosy (South Korea), 1998, 29/3 (155-158)

In the Asian sub-continent Momordica charantia and Allium sativum are extensively used as food and are popular in herbal medicine. The two were screened against 15 pathogens and both exhibited broad spectrum antimicrobial activity. As compared to the standard antibiotics. M. charantia demonstrated broader and higher level of activity against most of the organisms. On the other hand A. savitum showed comparable activity to the standard antibiotics. Both M. charantia and A. sativum are proposed as non toxic, safe, broad spectrum antibacterial agents.

Partial purification and some properties of an antibacterial compound from Aloe vera

Levin H.; Hazenfratz R.; Friedman J.; Palevitch D.; Perl M. Agricultural Research Organization, The Volcani Center, Bet Dagan 50 250 Israel

Phytotherapy Research (United Kingdom) 1988, 2/2 (67-69)

Aqueous or ethanolic extracts of Aloe leaves were examined for antibacterial properties. The crude extrudes strongly stimulated bacterial growth. Separation of various fractions by thin layer chromatography (TLC) resulted in a fraction which inhibited the growth of Bacillus subtilis. A concomitant examination of protein and nucleic acisynthesis in B. subtilis in the presence of the inhibitory compound indicated that the plant extract inhibits primarily nucleic acid synthesis, after

which protein synthesis is also inhibited. The inhibitor seemed to be present in all examined Aloe species but at different concentrations. On a dry weight basis, the inhibitory effect was equally distributed between the skin and the gel fraction.

Activation of serum complement leads to inhibition of ascorbic acid transport

Padh H, Aleo JJ

Proc Soc Exp Biol Med 1987 Jun;185(2):153-7

Ascorbic acid is transported into 3T6 fibroblasts by a carrier-mediated, energy-dependent saturable active process with a K(m) of 112 muM and V(max) of 158 pmole/min/mg protein. The transport is dependent on extracellular Nasup + concentration which reduces the K(m). It was recently observed in this laboratory that bovine serum contained a heat-labile factor which, after interaction with bacterial endotoxin (lipopolysaccharides), inhibited ascorbic acid transport (J.J. Alleo and H. Padh, Proc Soc Exp Biol Med 179:128-131, 1985). We report here that the inhibition of ascorbic acid transport by endotoxin is mediated by the activation of serum complement. This was done by examining the activation of complement by other activators like zymosan and immunocomplexes (e.g., albumin and antibodies to albumin). Ascorbate transport was inhibited by the mixture of unheated serum and the activators. No inhibition was observed with serum devoid of C3 (component 3 of the complement). When C3-deficient serum was reconstituted by the addition of purified C3, the endotoxin-induced inhibition of ascorbate transport was restored. The implication of these findings is that in spite of a normal intake and blood level of the vitamin, tissues may not be getting adequate vitamin C during disease states when the complement in serum is activated. In other words, what may be considered an adequate intake of vitamin C under health conditions may not be adequate under disease conditions.

Effects of vitamins A, C, and E on aflatoxin Bsub 1-induced mutagenesis in Salmonella typhimurium TA-98 and TA-100

Raina V.; Gurtoo H.L.

Teratog Carcinog Mutagen 1985;5(1):29-40

The effects of retinoids (vitamin A analogs) and vitamins C and E on the aflatoxin Bsub 1-(AFBsub 1)-induced mutagenesis in Salmonella typhimurium TA-98 and TA-100 were investigated. The bioassay was performed under conditions that permitted the effects of vitamins on carcinogen metabolism to be assessed separately from effects on the expression of the mutated bacterial cell. Both retinoic acid and retinol inhibited (up to 50%) AFBsub 1-induced mutagenesis in S. typhimurium TA-98, but only retinol inhibited (up to 75%) mutagenesis in TA-100. Retinoic acid inhibition of mutagenesis in S. typhimurium TA-98 was pronounced over a wide concentration range (i.e., 2 x 10sup -sup 1sup 0 to 2 x 10sup -sup 8 M); however, at the higher concentrations (i.e., 2 x 10sup -sup 8 to 2 x 10sup -sup 6 M range) the predominant effect was the inhibition of the

metabolism of AFBsub 1 to its mutagenic metabolites. Vitamin E was more potent in inhibiting the expression of AFBsub 1-induced mutagenesis than vitamin C. However, the major inhibitory effects of vitamin E were related to the metabolism of AFBsub 1, whereas vitamin C was inhibitory at both metabolic and the post-metabolic levels of the AFBsub 1 mutagenesis assay. The results of these investigations suggest that vitamins A, C, or E inhibit both AFBsub 1 metabolism to its mutagenic metabolites as well as the expression of AFBsub 1-induced mutated bacterial cells.

Effect of vitamin A supplementation on lectin-induced diarrhoea and bacterial translocation in rats

Shoda R; Mahalanabis D(a); Islam K N; Wahed M A; Albert M J

Nutrition Research (USA), 1996, 16/3 (459-465)

In a rat model of lectin-induced diarrhoea with translocation of enteric bacteria into mesenteric lymph nodes we evaluated the role of prior vitamin A supplementation in correcting diarrhoea and bacterial translocation. Although intraperitoneal vitamin A palmitate injection (900 microg retinol equivalents twice a week for 5 weeks) substantially increased liver retinol concentration (154.83 plus or minus 23.57 vs 56.65 plus or minus 39.92 microg/< .01), it had no significant effect on faecal wet weight (2.64 plus or minus 1.21 vs 2.86 plus or minus 1.06 g/d), body weight loss (-36.7 plus or minus 16.7 vs -36.5 plus or minus 8.6 g/per 10 days) or rate of translocation (83% vs 100% positive) in supplemented rats compared to unsupplemented rats. However, the mean bacterial count in mesenteric lymph nodes was significantly reduced in vitamin A supplemented group (log colony forming units/g:3.53 plus or minus 0.77 vs 4.03 plus or minus 0.86, < .05). These findings suggest that vitamin A supplementation did not prevent diarrhoea and weight loss but reduced the severity of intestinal bacterial translocation to mesenteric lymph nodes in red kidney bean-induced diarrhoea and malabsorption. These results are compatible with the demonstrated effect of vitamin A supplementation in reducing childhood mortality in developing countries but with no effect on overall diarrhoea morbidity.

Increased translocation of Escherichia coli and development of arthritis in vitamin A-deficient rats

Wiedermann U, Hanson LA, Bremell T, Kahu H, Dahlgren UI Department of Clinical Immunology, University of Goteborg, Sweden.

Infection and Immunity (USA), 1995, 63/8 (3062-3068)

We studied the immune response and the colonization pattern in vitamin A-deficient rats that were colonized with the Escherichia coli O6 K13 pomp 21 strain, which is genetically manipulated to produce ovalbumin and to be resistant to ampicillin. In the vitamin A-deficient rats, the number of bacteria per gram of feces was about five times higher than in the paired fed control rats 4 weeks after colonization. In the control rats, the colon and the lower part of the ileum were

colonized, while in the vitamin A-deficient rats all parts of the small intestine, as well as the colon, were heavily inhabited by bacteria. Furthermore, in 75% of the vitamin A-deficient rats, the E. coli bacteria were found in the mesenteric lymph nodes, and in 50% of the rats E. coli were found in the kidneys. These animals also developed severe arthritis. The levels of serum immunoglobulin G (IgG), IgM, IgE, and biliary IgA antibodies against the bacterial antigens were significantly higher in the vitamin A-deficient rats than in the control rats. The number of IgA-producing cells in the lamina propria of the small intestine was significantly lower in the vitamin A-deficient rats than in the control rats; however, there was an increase in the number of CD8+ cells and transforming growth factor beta-producing cells in the lamina propria of the vitamin A-deficient rats. Disturbances in T-cell function were demonstrated, since spleen cells from the vitamin A-deficient rats produced more gamma interferon and interleukin-2 in vitro than control spleen cells. In summary, vitamin A deficiency led to a decrease in the ability to control the localization of intestinal bacteria and an increase in translocation, which was followed by development of arthritis regardless of substantial levels of antibacterial antibodies. The bacterial invasion made the animals hyperresponsive to the bacterial antigens, despite the fact that vitamin A deficiency is normally associated with suppressed antibody production, as previously shown by us and others.

Vitamin A supplementation improves macrophage function and bacterial clearance during experimental salmonella infection

Hatchigian EA, Santos JI, Broitman SA, Vitale JJ Department of Pathology, Boston University School of Medicine, Massachusetts 02118.

Proc. Soc. Exp. Biol. Med. (USA), 1989, 191/1 (47-54)

The effects of additional but nontoxic amounts of vitamin A on susceptibility to salmonella infection was studied by comparing rates of bacterial clearance and phagocytosis. Forty-eight male Lewis rats were divided into a treatment group receiving a total of 6000 units of vitamin A palmitate weekly for 5 weeks and a control group was given an equal volume of saline. After completion of the treatment regimen, one-half from each group were infected intraperitoneally with 105 Salmonella typhimurium; the other half received intraperitoneal injection of saline. At this time no differences in weight gain were noted and all animals were sacrificed within 2 weeks. At 72 hr after bacterial challenge, all saline-treated control animals displayed bacteremia. Cultures of liver and splenic homogenates were positive in 89 and 100% of infected control animals vs 0 and 44% for treated animals during the first week of infection. Kupffer cell, peritoneal, and splenic macrophages of the vitamin A-treated group had greater phagocytic activity than controls as assessed by the percentage of cells ingesting yeast particles and by the number of particles ingested (phagocytic index). These results suggest that vitamin A in moderate amounts may benefit the host's response to infection by enhancing phagocytic cell function.

Inhibition by retinoic acid of multiplication of virulent tubercle bacilli in cultured human macrophages

Crowle AJ, Ross EJ Webb-Waring Lung Institute, University of Colorado, Health Sciences Center, Denver 80262.

Infect. Immun. (USA), 1989, 57/3 (840-844)

The immunologically active vitamin retinoic acid (RA) was tested for the ability to increase the resistance of cultured human macrophages (MP) to experimental infection with virulent Mycobacterium tuberculosis Erdman (tubercle bacilli (TB)). It was added to MP in various concentrations and addition regimens. Protection against TB was measured by counting live TB (CFU) in lysates of samples of MP taken at 0, 4, and 7 days after MP infection. RA was protective when added after infection at the pharmacologic concentration of 10-5 M and when added before infection at the physiologic concentration of 10-7 M. The protection lengthened intracellular generation times for TB, occasionally caused bacteriostasis, and regularly kept CFU counts at 7 days (end of the period of infection) 1 to 2 log10 CFU below control values. Significant protection was seen in a series of 16 experiments with MP from seven different donors, but the degree of protection varied considerably. The protection depended partly on and was inversely proportional to concentrations of a serum substitute or autologous serum used as a supplement in the RPMI 1640 MP culture medium. It was strongest at concentrations of serum below 1%. RA at concentrations used in the MP cultures did not inhibit TB in the absence of MP. These results suggest that RA (vitamin A), like vitamin D, may have some immunoprotective role against human tuberculosis, as historically intimated by the regular use of vitamin A- and D-rich cod liver oil for the treatment of tuberculosis before the introduction of modern chemotherapy.

Antibacterial, antifungal, antiamoebic, antiinflammatory and antipyretic studies on propolis bee products

Dobrowolski JW, Vohora SB, Sharma K, Shah SA, Naqvi SA, Dandiya PC Institute of Management and Protection of Environment, Krakow, Poland.J Ethnopharmacol. 1991 Oct;35(1):77-82

Propolis bee preparations revealed good antibacterial (particularly against Gram-positive bacteria), antifungal (against those responsible for superficial and dermatomycoses) and antiinflammatory (against acute and chronic models of inflammation) effects but no antiamoebic or antipyretic capacity.

Antibacterial properties of propolis (bee glue)

Grange JM, Davey RW Department of Microbiology, National Heart & Lung Institute, London.

J R Soc Med. 1990 Mar;83(3):159-60. Review.

Propolis (bee glue) was found to have antibacterial activity against a range of commonly encountered cocci and Gram-positive rods, including the human tubercle bacillus, but only limited activity against Gram-negative bacilli. These

findings confirm previous reports of antimicrobial properties of this material, possibly attributable to its high flavonoid content.

Biological properties and clinical application of propolis. III. Investigation of the sensitivity of staphylococci isolated from pathological cases to ethanol extract of propolis (EEP)

Scheller S, Tustanowski J, Kurylo B, Paradowski Z, Obuszko Z

Arzneimittelforschung. 1977 Jul;27(7):1395.

Staphylococci isolated from pathological material exhibited a reduced sensitivity to ethanol extract of propolis (EEP) in 90% of cases. No cross-resistance of the staphylococci to EEP and to any commonly used antibiotics was found. The induction of resistance to EEP in laboratory strain of Staphylococcus aureus (Oxford 209 P) can be achieved already after serial passages on nutrient media containing EEP. Culturing Staphylococcus resistant to EEP in an environment devoid of this compound caused a remission to sensitivity of the strain investigated.

Biological properties and clinical application of propolis. I. Some physico chemical properties of propolis

Scheller S, Szaflarski J, Tustanowski J, Nolewajka E, Stojko A

Arzneimittelforschung. 1977;27(4):889-90

The presence of 19 elements has been shown in the ethanol extracts of propolis (EEP). Three fractions have been obtained by filtration through a structural gel that did not show an initial antibacterial activity when investigated separately. Fractions 2 and 3 joined together have regained this activity. EEP solutions maintain their antibacterial activity in acidic or neutral pH. Insensitivity of EEP solutions on temperature of 75degr.C for 30 min has been found.

Oral administration of bovine lactoferrin for treatment of tinea pedis. A placebo-controlled, double-blind study.

Yamauchi K, Hiruma M, Yamazaki N, Wakabayashi H, Kuwata H, Teraguchi S, Hayasawa H, Suegara N, Yamaguchi H. Nutritional Science Laboratory, Morinaga Milk Industry Co., Ltd, Kanagawa, Japan.

Mycoses 2000;43(5):197-202

A clinical study was conducted to evaluate the effectiveness of lactoferrin, which is a protein component of cow's milk, in the treatment of tinea pedis. Doses of either 600 mg or 2000 mg of lactoferrin, or a placebo was orally administered daily for 8 weeks to 37 adults who were judged to have mild or moderate tinea pedis. Dermatological improvement and antifungal efficacy were assessed. In the analysis of all subjects, dermatological symptoms scores in all groups decreased

but the differences were not statistically significant comparing the three groups. However, in the analysis limited to subjects with moderate vesicular or interdigital tinea pedis, dermatological symptoms scores in the lactoferrin-treated groups decreased significantly in comparison with the placebo group (< 0.05). The organisms isolated were Trichophyton rubrum and Trichophyton mentagrophytes. A mycological cure was not seen in any of the subjects. In the 37 subjects there were no adverse events and no subject withdrew from the study because of an adverse event. These results suggest that orally administered lactoferrin can improve the dermatological symptoms in some subjects. The potential usefulness of lactoferrin as a functional food material for treating tinea pedis was seen for the first time in this study.

Lactoferrin protects gut mucosal integrity during endotoxemia induced by lipopolysaccharide in mice.

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Inflammation 2000 Feb;24(1):33-44

The hypothesis that lactoferrin protects mice against lethal effects of bacterial lipopolysaccharide (LPS) is the subject of experimental investigations described in this article. Lipopolysaccharide is a powerful toxin produced by gram negative bacteria that when injected into humans or experimental animals reproduce many of the pathophysiologic and immune responses caused by live bacteria. Lactoferrin administered intraperitoneally 1 hr prior to injection of LPS significantly enhanced the survival of mice, reducing LPS-induced mortality from 83.3% to 16.7%. Changes in locomotor and other behavioral activities resulting from LPS injection were not present in mice treated with lactoferrin. Also, histological examination of intestine revealed remarkable resistance to injury produced by LPS if mice were pretreated with lactoferrin. Severe villus atrophy, edema and epithelial vacuolation were observed in LPS-treated animals but not in lactoferrin-treated counterparts. Electrophysiological parameters were used to assess secretory and absorptive functions in the small intestine. In mice treated with LPS, transmural electrical resistance was reduced and absorption of glucose was increased. Lactoferrin treatment had no significant influence on basal electrophysiological correlates of net ion secretion or glucose absorption nor on changes induced by LPS. Collectively, these results suggest that lactoferrin attenuates the lethal effect of LPS and modulates behavioral and histopathological sequela of endotoxemia.

10. Breast Cancer

Preventative and curative options include:

Indole-3-carbinol, curcumin, green tea extract, CLA or CLA with Guarana, sulphoraphane, se-methylselenocysteine, CoQ10, fish oil, vitamin D3, vitamin A, vitamin E succinate, gamma E Tocopherol/Tocotrienol, vitamin C, linolenic acid, whey protein concentrate-isolate, calcium, magnesium, vitamin K, silicon, multinutrients, melatonin, selenium.

Curcumin is an in vivo inhibitor of angiogenesis.

Arbiser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, Fisher C, Flynn E, Byers HR. Department of Dermatology, Harvard Medical School, Boston, Massachusetts, USA. jlarbiser@bics.bwh.harvard.edu

Mol Med 1998 Jun;4(6):376-83

BACKGROUND: Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In animal models, curcumin and its derivatives have been shown to inhibit the progression of chemically induced colon and skin cancers. The genetic changes in carcinogenesis in these organs involve different genes, but curcumin is effective in preventing carcinogenesis in both organs. A possible explanation for this finding is that curcumin may inhibit angiogenesis.

MATERIALS AND METHODS: Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin and its derivatives were subsequently tested for their ability to inhibit bFGF-induced corneal neovascularization in the mouse cornea. Finally, curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production.

RESULTS: Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin and its derivatives demonstrated significant inhibition of bFGF-mediated corneal neovascularization in the mouse. Curcumin had no effect on phorbol ester-stimulated VEGF production.

CONCLUSIONS: These results indicate that curcumin has direct antiangiogenic activity in vitro and in vivo. The activity of curcumin in inhibiting carcinogenesis in diverse organs such as the skin and colon may be mediated in part through angiogenesis inhibition.

The dietary pigment curcumin reduces endothelial tissue factor gene expression by inhibiting binding of AP-1 to the DNA and activation of NF-kappa B.

Bierhaus A, Zhang Y, Quehenberger P, Luther T, Haase M, Muller M, Mackman N, Ziegler R, Nawroth PP. Department of Internal Medicine I, University of Heidelberg, Germany.

Thromb Haemost 1997 Apr;77(4):772-82

The natural occurring pigment curcumin, a major component of the spice tumeric, has been described to have antioxidative, anti-tumorpromoting, anti-thrombotic and anti-inflammatory properties. It appears, that the pleiotropic effects of curcumin are at least partly due to inhibition of the transcription factors NF-kappa B and AP-1. This study investigates the effect of curcumin on the TNF alpha induced expression of endothelial Tissue Factor (TF), the central mediator of coagulation known to be controlled by AP-1 and NF-kappa B. When bovine aortic endothelial cells (BAEC) were preincubated in the presence of curcumin, TNF alpha induced TF gene transcription and expression were reduced. Transient transfection studies with TF-promoter plasmids revealed that both, NF-kappa B and AP-1 dependent TF expression, were reduced by curcumin action. The observed inhibitions were due to distinct mechanisms. Curcumin inhibited TNF alpha induced I kappa B alpha degradation and the nuclear import of NF-kappa B. In contrast, inhibition of AP-1 was due to a direct interaction of curcumin with AP-1-binding to its DNA binding motif. Thus, curcumin inhibits NF-kappa B and AP-1 by two different mechanisms and reduces expression of endothelial genes controlled by both transcription factors in vitro.

Coenzymes Q: stimulants of the phagocytic activity in rats and immune response in mice.

Bliznakov, E., Casey, A., Premuzic, E.

Experientia 1970: 26(9): 953-4.

No Abstract

Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence.

Block G, Patterson B, Subar A. Dept. of Social and Administrative Health Sciences, School of Public Health, University of California, Berkeley 94720.

Nutr Cancer 1992;18(1):1-29

Approximately 200 studies that examined the relationship between fruit and vegetable intake and cancers of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary are reviewed. A statistically significant protective effect of fruit and vegetable consumption was found in 128

of 156 dietary studies in which results were expressed in terms of relative risk. For most cancer sites, persons with low fruit and vegetable intake (at least the lower one-fourth of the population) experience about twice the risk of cancer compared with those with high intake, even after control for potentially confounding factors. For lung cancer, significant protection was found in 24 of 25 studies after control for smoking in most instances. Fruits, in particular, were significantly protective in cancers of the esophagus, oral cavity, and larynx, for which 28 of 29 studies were significant. Strong evidence of a protective effect of fruit and vegetable consumption was seen in cancers of the pancreas and stomach (26 of 30 studies), as well as in colorectal and bladder cancers (23 of 38 studies). For cancers of the cervix, ovary, and endometrium, a significant protective effect was shown in 11 of 13 studies, and for breast cancer a protective effect was found to be strong and consistent in a meta analysis. It would appear that major public health benefits could be achieved by substantially increasing consumption of these foods.

Effects of dietary indole-3-carbinol on estradiol metabolism and spontaneous mammary tumors in mice.

Bradlow HL, Michnovicz J, Telang NT, Osborne MP. Institute for Hormone Research, New York, NY 10016.

Carcinogenesis 1991 Sep;12(9):1571-4

Indole-3-carbinol (I3C) is a potent inducer of cytochrome P450 enzymes in many species, including humans. We therefore studied alterations in the cytochrome P450-dependent metabolism of estradiol in different strains of mice consuming I3C in semisynthetic powdered diets at doses ranging from 250 to 5000 p.p.m. (34-700 mg/kg/day) for different periods of time. In short-term metabolic studies (3 weeks), wet liver weight increased in SW and C3H/OuJ mice in a dose-responsive manner. Dietary I3C increased the cytochrome P450 content measured in hepatic microsomes, as well as the extent of estradiol 2-hydroxylation, up to 5-fold. In a long-term feeding experiment (8 months), female C3H/OuJ mice consumed synthetic diets containing I3C at 0, 500 or 2000 p.p.m. Mammary tumor incidence and multiplicity were significantly lower at both doses of I3C, and tumor latency was prolonged in the high-dose group. We conclude that I3C is an inducer of hepatic P450-dependent estrogen metabolism in mice, and that it is chemopreventive in the C3H/OuJ mouse mammary tumor model. This protective effect may be mediated in part by the increased 2-hydroxylation and consequent inactivation of endogenous estrogens.

Indole-3-carbinol and diindolylmethane as aryl hydrocarbon (Ah) eceptor agonists and antagonists in T47D human breast cancer cells.

Chen I, Safe S, Bjeldanes L. Veterinary Physiology and Pharmacology, Texas A&M University, College Station 77843-4466, USA.

Biochem Pharmacol 1996 Apr 26;51(8):1069-76

Indole-3-carbinol (I3C) is a major component of Brassica vegetables, and diindolylmethane (DIM) is the major acid-catalyzed condensation product derived from I3C. Both compounds competitively bind to the aryl hydrocarbon (Ah) receptor with relatively low affinity. In Ah-responsive T47D human breast cancer cells, I3C and DIM did not induce significantly CYP1A1-dependent ethoxyresorufin O-deethylase (EROD) activity or CYP1A1 mRNA levels at concentrations as high as 125 or 31 microM, respectively. A 1 nM concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induced EROD activity in these cells, and cotreatment with TCDD plus different concentrations of I3C (1-125 microM) or DIM (1-31 microM) resulted in a < 90% decrease in the induced response at the highest concentration of I3C or DIM. I3C or DIM also partially inhibited (< 50%) induction of CYP1A1 mRNA levels by TCDD and reporter gene activity, using an Ah-responsive plasmid construct in transient transfection assays. In T47D cells cotreated with 5 nM [3H]TCDD alone or in combination with 250 microM I3C or 31 microM DIM, there was a 37 and 73% decrease, respectively, in formation of the nuclear Ah receptor. The more effective inhibition of induced EROD activity by I3C and DIM was due to in vitro inhibition of enzyme activity. Thus, both I3C and DIM are partial Ah receptor antagonists in the T47D human breast cancer cell line.

Prevention by coenzyme Q10 of the electrocardiographic changes induced by adriamycin in rats.

Choe JY, Combs AB, Folkers K.

Res Commun Chem Pathol Pharmacol 1979 Jan;23(1):199-202

The administration of adriamycin (ADM) to rats has consistently caused a widening of the QRS complex of the electrocardiogram. When coenzyme Q10 was also administered, beginning two days before ADM, this widening of the QRS complex and the elongation of the Q-T interval were reduced or totally prevented, depending upon conditions. ADM alone or with coenzyme Q10 did not alter the P-R interval. Some control by coenzyme Q10 of the cardiotoxicity of adriamycin in cancer patients is promising.

Reduction by coenzyme Q10 of the acute toxicity of adriamycin in mice.

Combs AB, Choe JY, Truong DH, Folkers K.

Res Commun Chem Pathol Pharmacol 1977 Nov;18(3):565-8

Pretreatment for four days with coenzyme Q10 (COQ10) reduced the acute toxicity in mice treated with adriamycin. In two sequential protocols, adriamycin allowed only 36 and 42% survival, respectively. Pretreatment with COQ10 allowed 80 and 86% survival, respectively. The differences are significant, p less than 0.05. The mechanism for this reduction in the acute toxicity may be based upon the prevention by the supplementary COQ10 of the inhibition caused by adriamycin to COQ10-dependent enzymes in cardiac and and other tissues. The

prospect of diminishing the toxicity of adriamycin in cancer patients remains promising and important.

Indole-3-carbinol inhibits the expression of cyclin-dependent kinase-6 and induces a G1 cell cycle arrest of human breast cancer cells independent of estrogen receptor signaling.

Cover CM, Hsieh SJ, Tran SH, Hallden G, Kim GS, Bjeldanes LF, Firestone GL. Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, California 94720, USA.

J Biol Chem 1998 Feb 13;273(7):3838-47

Indole-3-carbinol (I3C), a naturally occurring component of Brassica vegetables such as cabbage, broccoli, and Brussels sprouts, has been shown to reduce the incidence of spontaneous and carcinogen-induced mammary tumors. Treatment of cultured human MCF7 breast cancer cells with I3C reversibly suppresses the incorporation of [3H]thymidine without affecting cell viability or estrogen receptor (ER) responsiveness. Flow cytometry of propidium iodide-stained cells revealed that I3C induces a G1 cell cycle arrest. Concurrent with the I3C-induced growth inhibition, Northern blot and Western blot analyses demonstrated that I3C selectively abolished the expression of cyclin-dependent kinase 6 (CDK6) in a dose- and time-dependent manner. Furthermore, I3C inhibited the endogenous retinoblastoma protein phosphorylation and CDK6 phosphorylation of retinoblastoma in vitro to the same extent. After the MCF7 cells reached their maximal growth arrest, the levels of the p21 and p27 CDK inhibitors increased by 50%. The antiestrogen tamoxifen also suppressed MCF7 cell DNA synthesis but had no effect on CDK6 expression, while a combination of I3C and tamoxifen inhibited MCF7 cell growth more stringently than either agent alone. The I3C-mediated cell cycle arrest and repression of CDK6 production were also observed in estrogen receptor-deficient MDA-MB-231 human breast cancer cells, which demonstrates that this indole can suppress the growth of mammary tumor cells independent of estrogen receptor signaling. Thus, our observations have uncovered a previously undefined antiproliferative pathway for I3C that implicates CDK6 as a target for cell cycle control in human breast cancer cells. Moreover, our results establish for the first time that CDK6 gene expression can be inhibited in response to an extracellular antiproliferative signal.

Indole-3-carbinol and tamoxifen cooperate to arrest the cell cycle of MCF-7 human breast cancer cells.

Cover CM, Hsieh SJ, Cram EJ, Hong C, Riby JE, Bjeldanes LF, Firestone GL. Department of Molecular and Cell Biology and The Cancer Research Laboratory, The University of California at Berkeley, 94720-3200, USA.

Cancer Res 1999 Mar 15;59(6):1244-51

The current options for treating breast cancer are limited to excision surgery, general chemotherapy, radiation therapy, and, in a minority of breast cancers that

rely on estrogen for their growth, antiestrogen therapy. The naturally occurring chemical indole-3-carbinol (I3C), found in vegetables of the Brassica genus, is a promising anticancer agent that we have shown previously to induce a G1 cell cycle arrest of human breast cancer cell lines, independent of estrogen receptor signaling. Combinations of I3C and the antiestrogen tamoxifen cooperate to inhibit the growth of the estrogen-dependent human MCF-7 breast cancer cell line more effectively than either agent alone. This more stringent growth arrest was demonstrated by a decrease in adherent and anchorage-independent growth, reduced DNA synthesis, and a shift into the G1 phase of the cell cycle. A combination of I3C and tamoxifen also caused a more pronounced decrease in cyclin-dependent kinase (CDK) 2-specific enzymatic activity than either compound alone but had no effect on CDK2 protein expression. Importantly, treatment with I3C and tamoxifen ablated expression of the phosphorylated retinoblastoma protein (Rb), an endogenous substrate for the G1 CDKs, whereas either agent alone only partially inhibited endogenous Rb phosphorylation. Several lines of evidence suggest that I3C works through a mechanism distinct from tamoxifen. I3C failed to compete with estrogen for estrogen receptor binding, and it specifically down-regulated the expression of CDK6. These results demonstrate that I3C and tamoxifen work through different signal transduction pathways to suppress the growth of human breast cancer cells and may, therefore, represent a potential combinatorial therapy for estrogen-responsive breast cancer.

Characterization of the biological activity of gamma-glutamyl-Se-methylselenocysteine: a novel, naturally occurringanticancer agent from garlic.

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Cancer Res 2001 Apr 1;61(7):2923-8

Gamma-glutamyl-Se-methylselenocysteine (GGMSC) has recently been identified as the major Se compound in natural garlic and selenized garlic. Our working hypothesis is that GGMSC serves primarily as a carrier of Se-methylselenocysteine (MSC), which has been demonstrated in past research to be a potent cancer chemopreventive agent in animal carcinogenesis bioassays. The present study was designed to examine the in vivo responses to GGMSC or MSC using a variety of biochemical and biological end points, including (a) urinary Se excretion as a function of bolus dose; (b) tissue Se accumulation profile; (c) anticancer efficacy; and (d) gene expression changes as determined by cDNA array analysis. Our results showed that like MSC, GGMSC was well absorbed p.o., with urinary excretion as the major route for eliminating excess Se. When fed chronically, the profile of Se accumulation in various tissues was very comparable after treatment with either GGMSC or MSC. In rats that had been challenged with a carcinogen, supplementation with either GGMSC or MSC resulted in a lower prevalence of premalignant lesions in the mammary gland, and fewer mammary carcinomas when these early lesions were allowed to progress. More importantly, we found that a short term GGMSC/MSC treatment schedule of 4 weeks immediately after carcinogen dosing was sufficient to provide

significant cancer protection, even in the absence of a sustained exposure past the initial 4-week period. With the use of the Clontech Atlas Rat cDNA Array, we further discovered that the gene expression changes induced in mammary epithelial cells of rats that were given either GGMSC or MSC showed a high degree of concordance. On the basis of the collective biology, biochemistry, and molecular biology data, we conclude that GGMSC is an effective anticancer agent with a mechanism of action very similar to that of MSC.

The chemoprevention of cancer by mevalonate-derived constituents of fruits and vegetables.

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J Nutr 1994 May;124(5):607-14

Anutritive isoprenoid constituents of fruits, vegetables, cereal grains and essential oils exhibit a spectrum of anticarcinogenic activities. The induction of hepatic Phase II detoxifying activities by dietary isoprenoids appears to underlie their blocking action. The second anticarcinogenic action of the dietary isoprenoids, suppression of the growth of chemically initiated andtransplanted tumors is, we suggest, secondary to the inhibition of mevalonate pathway activities. Mevinolin, a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, depletes cells of the intermediate products of the pathway that are required for the posttranslational modification of proteins, a process giving the proteins lipophilic anchors that bind to membranes. As a consequence, nuclear lamins and ras oncoproteins remain in nascent states, and cells do not proliferate. gamma-Tocotrienol, perillyl alcohol, geraniol and d-limonene suppress hepatic HMG-CoA reductase activity, a rate-limiting step in cholesterol synthesis, and modestly lower serum-cholesterol levels of animals. These isoprenoids also suppress tumor growth. The HMG-CoA reductase of neoplastic tissues differs from that of sterologenic tissues in being markedly resistant to sterol feedback inhibition. Our review suggests that the mevalonate pathway of tumor tissues is uniquely sensitive to the inhibitory actions of the dietary isoprenoids.

Relevance of the biosynthesis of coenzyme Q10 and of the four bases of DNA as a rationale for the molecular causes of cancer and a therapy.

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Biochem Biophys Res Commun 1996 Jul 16;224(2):358-61

In the human, coenzyme Q10 (vitamin Q10) is biosynthesized from tyrosine through a cascade of eight aromatic precursors. These precursors indispensably require eight vitamins, which are tetrahydrobiopterin, vitamins B6, C, B2, B12, folic acid, niacin, and pantothenic acid as their coenzymes. Three of these eight vitamins (the coenzyme B6, and the coenzymes niacin and folic acid) are indispensable in the biosynthesis of the four bases (thymidine, guanine, adenine,

and cytosine) of DNA. One or more of the three vitamins required for DNA are known to cause abnormal pairing of the four bases, which can then result in mutations and the diversity of cancer. The coenzyme B6, required for the conversion of tyrosine to p-hydroxybenzoic acid, is the first coenzyme required in the cascade of precursors. A deficiency of the coenzyme B6 can cause dysfunctions, prior to the formation of vitamin Q10, to DNA. Former data on blood levels of Q10 and new data herein on blood levels of B6, measured as EDTA, in cancer patients established deficiencies of Q10 and B6 in cancer. This complete biochemistry relating to biosyntheses of Q10 and the DNA bases is a rationale for the therapy of cancer with Q10 and other entities in this biochemistry.

Chemoprevention of chemically-induced mammary carcinogenesis by indole-3-carbinol.

Grubbs CJ, Steele VE, Casebolt T, Juliana MM, Eto I, Whitaker LM, Dragnev KH, Kelloff GJ, Lubet RL. Department of Nutrition Sciences, University of Alabama at Birmingham 35924, USA.

Anticancer Res 1995 May-Jun;15(3):709-16

Indole-3-carbinol, a component of cruciferous vegetables, was evaluated for it efficacy in the prevention of chemically-induced mammary tumors using three different protocols. Because this compound was unstable, it was administered by gavage rather than in the diet. A preliminary dose range study revealed that dose levels of 100 and 50 mg/day, 5x/week, were not toxic to female Sprague-Dawley rats. Initial studies in the DMBA model showed that administering indole-3-carbinol during the initiation and promotion phases were highly effective chemopreventive methods (91-96% reduction in cancer multiplicity). Subsequent studies showed that the administration of indole-3-carbinol only during the initiation phase (7 days prior to until 7 days post DMBA) was also highly effective as a chemopreventive agent. Determination of enzyme levels in the livers of animals treated long-term with indole-3-carbinol showed high levels of induction of various phase I and phase II drug metabolizing enzymes. Finally, indole-3-carbinol when administered both prior to and after MNU (a direct acting carcinogen) caused a significant decrease (65%) in mammary tumor multiplicity. These results support previous studies that indole-3-carbinol can prevent mammary carcinogenesis by direct and indirect acting carcinogens. Therefore, indole-3-carbinol might be a good candidate for chemoprevention of breast cancer in women.

Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination.

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J Nutr 1997 Mar;127(3):544S-548S

Tocotrienols are a form of vitamin E, having an unsaturated isoprenoid side-chain rather than the saturated side-chain of tocopherols. The tocotrienol-rich fraction (TRF) from palm oil contains alpha-tocopherol and a mixture of alpha-, gamma- and delta-tocotrienols. Earlier studies have shown that tocotrienols display anticancer activity. We previously reported that TRF, alpha-, gamma- and delta-tocotrienols inhibited proliferation of estrogen receptor-negative MDA-MB-435 human breast cancer cells with 50% inhibitory concentrations (IC50) of 180, 90, 30 and 90 microg/mL, respectively, whereas alpha-tocopherol had no effect at concentrations up to 500 microg/mL. Further experiments with estrogen receptor-positive MCF-7 cells showed that tocotrienols also inhibited their proliferation, as measured by [3H] thymidine incorporation. The IC50s for TRF, alpha-tocopherol, alpha-, gamma- and delta-tocotrienols were 4, 125, 6, 2 and 2 microg/mL, respectively. Tamoxifen, a widely used synthetic antiestrogen inhibits the growth of MCF-7 cells with an IC50 of 0.04 microg/mL. We tested 1:1 combinations of TRF, alpha-tocopherol and the individual tocotrienols with tamoxifen in both cell lines. In the MDA-MB-435 cells, all of the combinations were found to be synergistic. In the MCF-7 cells, only 1:1 combinations of gamma- or delta-tocotrienol with tamoxifen showed a synergistic inhibitory effect on the proliferative rate and growth of the cells. The inhibition by tocotrienols was not overcome by addition of excess estradiol to the medium. These results suggest that tocotrienols are effective inhibitors of both estrogen receptor-negative and -positive cells and that combinations with tamoxifen should be considered as a possible improvement in breast cancer therapy.

Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells.

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Proc Natl Acad Sci U S A 1991 Jun 15;88(12):5292-6

Curcumin, a dietary pigment responsible for the yellow color of curry, is a potent inhibitor of tumor promotion by phorbol esters. Functional activation of transcriptional factor c-Jun/AP-1 is believed to play an important role in signal transduction of phorbol 12-myristate 13-acetate-induced tumor promotion. Suppression of the c-Jun/AP-1 activation by curcumin is observed in mouse fibroblast cells. In vitro experiments indicate that inhibition of c-Jun/AP-1 binding to its cognate motif by curcumin may be responsible for the inhibition of c-Jun/AP-1-mediated gene expression. These findings show that the effect of curcumin on phorbol 12-myristate 13-acetate-induced inflammation/tumor promotion could be studied at the molecular level.

Comparison of selenium and sulfur analogs in cancer prevention.

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Carcinogenesis 1992 Jul;13(7):1167-70

Several organoselenium compounds have been shown to have powerful anticarcinogenic activity. In view of certain similarities between selenium and sulfur biochemistry, we have evaluated the chemopreventive efficacy of three pairs of analogs using the 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumor model in rats. The compounds tested were selenocystamine/cysteamine, Semethylselenocysteine/S-methylcysteine, selenobetaine/sulfobetaine. In the first study, each agent was added to the basal AIN-76A diet and was given before and continued after DMBA treatment until the end. All three selenium compounds were active; a 50% inhibition was achieved at approximately 25 x 10(-6) mol/kg with Se-methylselenocysteine and selenobetaine and at approximately 40 x 10(-6) mol/kg with selenocystamine. In the sulfur series, only cysteamine and S-methylcysteine produced anticancer activity, and the levels required for comparable responses were 500- to 750-fold higher compared to the corresponding selenium analogs. Sulfobetaine was inactive even when present at near maximally tolerated levels. In the second study, Se-methylselenocysteine and S-methylcysteine were chosen for further examination during the initiation and post-initiation phases of mammary carcinogenesis. Se-Methylselenocysteine was effective when it was given either before or after DMBA administration. In contrast, S-methylcysteine was effective only after DMBA treatment. Thus, compared to the sulfur structural analogs, selenium compounds are much more active in cancer protection and may have a multi-modal mechanism in preventing cellular transformation as well as in delaying or inhibiting the expression of malignancy after carcinogen exposure.

Conjugated linoleic acid-enriched butter fat alters mammary gland morphogenesis and reduces cancer risk in rats.

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J Nutr 1999 Dec;129(12):2135-42

Conjugated linoleic acid (CLA) is a potent cancer preventive agent in animal models. To date, all of the in vivo work with CLA has been done with a commercial free fatty acid preparation containing a mixture of c9,t11-, t10,c12- and c11,t13-isomers, although CLA in food is predominantly (80-90%) the c9,t11-isomer present in triacylglycerols. The objective of this study was to determine whether a high CLA butter fat has biological activities similar to those of the mixture of free fatty acid CLA isomers. The following four different endpoints were evaluated in rat mammary gland: 1) digitized image analysis of epithelial mass in mammary whole mount; 2) terminal end bud (TEB) density; 3) proliferative activity of TEB cells as determined by proliferating cell nuclear antigen immunohistochemistry; and 4) mammary cancer prevention bioassay in the methylnitrosourea model. It should be noted that TEB cells are the target cells for mammary chemical carcinogenesis. Feeding butter fat CLA to rats during the time of pubescent mammary gland development reduced mammary epithelial mass by 22%, decreased the size of the TEB population by 30%, suppressed the proliferation of TEB cells by 30% and inhibited mammary tumor yield by 53% (P

< 0.05). Furthermore, all of the above variables responded with the same magnitude of change to both butter fat CLA and the mixture of CLA isomers at the level of CLA (0.8%) present in the diet. Interestingly, there appeared to be some selectivity in the uptake or incorporation of c9,t11-CLA over t10,c12-CLA in the tissues of rats given the mixture of CLA isomers. Rats consuming the CLA-enriched butter fat also consistently accumulated more total CLA in the mammary gland and other tissues (four- to sixfold increases) compared with those consuming free fatty acid CLA (threefold increases) at the same dietary level of intake. We hypothesize that the availability of vaccenic acid (t11-18:1) in butter fat may serve as the precursor for the endogenous synthesis of CLA via the Delta9-desaturase reaction. Further studies will be conducted to investigate other attributes of this novel dairy product.

Methylselenocysteine modulates proliferation and apoptosis biomarkers in premalignant lesions of the rat mammary gland.

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Anticancer Res 2001 Mar-Apr;21(2A):863-7

In the rat mammary carcinogenesis model, premalignant lesions known as intraductal proliferations (IDPs) are detectable within a few weeks after carcinogen treatment. These early transformed colonies are the precursors for the eventual formation of carcinomas. Our past research indicated that methylselenocysteine added to the diet of rats reduced the development of IDPs of all sizes (the size of each IDP was estimated operationally by the number of 5-micron serial sections showing the same pathology). The appearance of an IDP lesion represents a balance between cell proliferation and cell death. The modulation of these two cellular events by methylselenocysteine was investigated. The abdominal-inguinal mammary gland was excised 6 weeks after MNU administration. Proliferation and apoptosis were evaluated by BrdU labeling and the TUNEL assay, respectively. The expression levels of several cell cycle and apoptosis regulatory proteins, including cyclin D1, cyclin A, p27, p16, bcl-2, box and bak, were also assessed. All of the above endpoints were quantified by immunohistochemistry in paraffin-embedded sections. The results showed that the magnitude of the response to methylselenocysteine intervention seemed to depend on the size of the IDP lesion. For the purpose of this study, the small and large lesions were classified as those containing < or = 30 or > 30 serial sections, respectively. With the small lesions, methylselenocysteine significantly inhibited BrdU labeling and the expression of cyclin D1 and cyclin A, but increased the expression of p27. Interesting, only p27 was upregulated in the larger IDP lesions, while BrdU labeling and the cyclins were not affected. It is possible that the transformed phenotype becomes less sensitive to selenium-mediated arrest of proliferation once it progresses to a more advanced pathological stage. In contrast, methylselenocysteine stimulated apoptosis (TUNEL assay) by 3 to 4 fold, and this increase was evident in both the small and large IDP lesions. Consistent with the induction of apoptosis, a reduced

expression of bcl-2 was also observed in the methylselenocysteine group. In summary, our data suggest that exposure to methylselenocysteine blocks clonal expansion of premalignant lesions at an early stage. This is achieved by simultaneously modulating certain molecular pathways that are responsible for inhibiting cell proliferation and enhancing apoptosis.

Chemoprevention of mammary cancer with Se-allylselenocysteine and other selenoamino acids in the rat.

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Anticancer Res 1999 Jul-Aug;19(4B):2875-80

The present study examined the mammary cancer chemopreventive activity of Se-methylselenocysteine, Se-propylselenocysteine and Se-allylselenocysteine in the rat methylnitrosourea (MNU) model. Each compound was supplemented in the diet at a level of 2 ppm Se for the entire duration of the experiment after MNU dosing. Se-Allylselenocysteine was the most active and caused a reduction in total tumor yield by 86%. Se-Methylselenocyteine and Se-propylselenocysteine were similar but less effective, and both produced a decrease of about 50% in tumorigenesis. All three compounds were very well absorbed through the gastrointestinal tract. However, more selenium was excreted in urine after gavaging with Se-propylselenocysteine or Se-allylselenocysteine compared with Se-methylselenocysteine. Analysis of selenium in the mammary gland and other organs showed that tissue selenium levels did not appear to be correlated with differences in chemopreventive activity. A lyase activity capable of catalyzing scission of the Se-alkyl group from the remainder of the amino acid was demonstrated. This activity was found to be high in liver and kidney, but relatively low in mammary gland and intestine. Minimal variations in enzyme activity towards each of the substrates were observed. Our results support the concept that Se-alkylselenoamino acids could be used as precursors for delivering the Se-alkyl moiety and that intrinsic chemical differences in the Se-alkyl substituent of the test compounds are likely to be important determinants of their biological effects.

Conjugated linoleic acid inhibits proliferation and induces apoptosis of normal rat mammary epithelial cells in primary culture.

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Exp Cell Res 1999 Jul 10;250(1):22-34

The trace fatty acid conjugated linoleic acid (CLA) inhibits rat mammary carcinogenesis when fed prior to carcinogen during pubertal mammary gland development or during the promotion phase of carcinogenesis. The following

studies were done to investigate possible mechanisms of these effects. Using a physiological model for growth and differentiation of normal rat mammary epithelial cell organoids (MEO) in primary culture, we found that CLA, but not linoleic acid (LA), inhibited growth of MEO and that this growth inhibition was mediated both by a reduction in DNA synthesis and a stimulation of apoptosis. The effects of CLA did not appear to be mediated by changes in epithelial protein kinase C (PKC) since neither total activity nor expression nor localization of PKC isoenzymes alpha, betaII, delta, varepsilon, eta, or zeta were altered in the epithelium of CLA-fed rats. In contrast, PKCs delta, varepsilon, and eta were specifically upregulated and associated with a lipid-like, but acetone-insoluble, fibrillar material found exclusively in adipocytes from CLA-fed rats. Taken together, these observations demonstrate that CLA can act directly to inhibit growth and induce apoptosis of normal MEO and may thus prevent breast cancer by its ability to reduce mammary epithelial density and to inhibit the outgrowth of initiated MEO. Moreover, the changes in mammary adipocyte PKC expression and lipid composition suggest that the adipose stroma may play an important in vivo role in mediating the ability of CLA to inhibit mammary carcinogenesis.

Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells.

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J Invest Dermatol 1998 Oct;111(4):656-61

Curcumin, a potent antioxidant and chemopreventive agent, has recently been found to be capable of inducing apoptosis in human hepatoma and leukemia cells by way of an elusive mechanism. Here, we demonstrate that curcumin also induces apoptosis in human basal cell carcinoma cells in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic change. In our study, consistent with the occurrence of DNA fragmentation, nuclear p53 protein initially increased at 12 h and peaked at 48 h after curcumin treatment. Prior treatment of cells with cycloheximide or actinomycin D abolished the p53 increase and apoptosis induced by curcumin, suggesting that either de novo p53 protein synthesis or some proteins synthesis for stabilization of p53 is required for apoptosis. In electrophoretic mobility gel-shift assays, nuclear extracts of cells treated with curcumin displayed distinct patterns of binding between p53 and its consensus binding site. Supportive of these findings, p53 downstream targets, including p21(CIP1/WAF1) and Gadd45, could be induced to localize on the nucleus by curcumin with similar p53 kinetics. Moreover, we immunoprecipitated extracts from basal cell carcinoma cells with different anti-p53 antibodies, which are known to be specific for wild-type or mutant p53 protein. The results reveal that basal cell carcinoma cells contain exclusively wild-type p53; however, curcumin treatment did not interfere with cell cycling. Similarly, the apoptosis suppressor Bcl-2 and promoter Bax were not changed with the curcumin treatment. Finally, treatment of cells with p53 antisense oligonucleotide could effectively prevent curcumin-induced intracellular

p53 protein increase and apoptosis, but sense p53 oligonucleotide could not. Thus, our data suggest that the p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. This evidence also suggests that curcumin may be a potent agent for skin cancer prevention or therapy.

Se-methylselenocysteine induces apoptosis mediated by reactive oxygen species in HL-60 cells.

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Free Radic Biol Med 2001a Aug 15;31(4):479-89

Recent studies have implicated apoptosis as one of the most plausible mechanisms of the chemopreventive effects of selenium compounds, and reactive oxygen species (ROS) as important mediators in apoptosis induced by various stimuli. In the present study, we demonstrate that Se-methylselenocysteine (MSC), one of the most effective selenium compounds at chemoprevention, induced apoptosis in HL-60 cells and that ROS plays a crucial role in MSC-induced apoptosis. The uptake of MSC by HL-60 cells occurred quite early, reaching the maximum within 1 h. The dose-dependent decrease in cell viability was observed by MSC treatment and was coincident with increased DNA fragmentation and sub-G(1) population. 50 microM of MSC was able to induce apoptosis in 48% of cell population at a 24 h time point. Moreover, the release of cytochrome c from mitochondria and the activation of caspase-3 and caspase-9 were also observed. The measurement of ROS by dichlorofluorescein fluorescence revealed that dose- and time-dependent increase in ROS was induced by MSC. N-acetylcysteine, glutathione, and deferoxamine blocked cell death, DNA fragmentation, and ROS generation induced by MSC. Moreover, N-acetylcysteine effectively blocked caspase-3 activation and the increase of the sub-G(1) population induced by MSC. These results imply that ROS is a critical mediator of the MSC-induced apoptosis in HL-60 cells.

EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells.

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Br J Cancer 2001b Mar 23;84(6):844-50

Catechins are key components of teas that have antiproliferative properties. We investigated the effects of green tea catechins on intracellular signalling and VEGF induction in vitro in serum-deprived HT29 human colon cancer cells and in vivo on the growth of HT29 cells in nude mice. In the in vitro studies, (-)-epigallocatechin gallate (EGCG), the most abundant catechin in green tea extract, inhibited Erk-1 and Erk-2 activation in a dose-dependent manner. However, other

tea catechins such as (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) did not affect Erk-1 or 2 activation at a concentration of 30 microM. EGCG also inhibited the increase of VEGF expression and promoter activity induced by serum starvation. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day(-1)mouse(-1)starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth (58%), microvessel density (30%), and tumour cell proliferation (27%) and increased tumour cell apoptosis (1.9-fold) and endothelial cell apoptosis (3-fold) relative to the control condition (P< 0.05 for all comparisons). EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF. Copyright 2001 Cancer Research Campaign.

Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases.

Lockwood K, Moesgaard S, Yamamoto T, Folkers K. Pharma Nord, Vejle, Denmark.

Biochem Biophys Res Commun 1995 Jul 6;212(1):172-7

Over 35 years, data and knowledge have internationally evolved from biochemical, biomedical and clinical research on vitamin Q10 (coenzyme Q10; CoQ10) and cancer, which led in 1993 to overt complete regression of the tumors in two cases of breast cancer. Continuing this research, three additional breast cancer patients also underwent a conventional protocol of therapy which included a daily oral dosage of 390 mg of vitamin Q10 (Bio-Quinone of Pharma Nord) during the complete trials over 3-5 years. The numerous metastases in the liver of a 44-year-old patient "disappeared," and no signs of metastases were found elsewhere. A 49-year-old patient, on a dosage of 390 mg of vitamin Q10, revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma in one breast, after lumpectomy and 390 mg of CoQ10, showed no cancer in the tumor bed or metastases. Control blood levels of CoQ10 of 0.83-0.97 and of 0.62 micrograms/ml increased to 3.34-3.64 and to 3.77 micrograms/ml, respectively, on therapy with CoQ10 for patients A-MRH and EEL.

Protection against anthramycin-induced toxicity in mice by coenzyme Q10.

Lubawy WC, Dallam RA, Hurley LH.

J Natl Cancer Inst 1980 Jan;64(1):105-9

Pretreatment of Swiss Webster mice with coenzyme Q10 (CoQ) markedly reduced the lethality of the antitumor antibiotic anthramycin as well as its ability to decrease ventricular weights. In tumor-bearing mice CoQ pretreatment did not produce any consistent alteration of radioactivity levels in blood, heart, tumor, lungs, kidneys, liver, muscles, brain, or spleen after [15-3H]anthramycin

administration. Gross alterations in anthramycin distribution is probably not the mechanism by which CoQ alters the cardiotoxicity and lethality of anthramycin.

Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias?

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J Clin Epidemiol 1999 May;52(5):429-39

It has been suggested that recall bias may explain the discrepant results between case-control and cohort studies on diet and the risk of breast cancer. Two control groups were used for this case-control study of 25 to 75-year-old breast cancer cases (n = 310). The first group consisted of population controls drawn from the Finnish National Population Register (n = 454). The second group consisted of women who were referred to the same examinations as were the cases because of clinical suspicion of breast disease but who were later diagnosed as healthy (referral controls; n = 506). Because the diagnosis was unknown at the time of interview, it was possible to assess by comparing the two control groups whether the self-reporting of diet changed under the threat of disease. Dietary habits were examined using a validated, self-administered food-frequency questionnaire. Premenopausal women misreported their consumption of liquid milk products, tea, and sugar. Reporting bias was also associated with the intake of fat and vitamins. Postmenopausal women misreported consumption of milk products. When recall bias was taken into consideration, milk was associated with increased risk of premenopausal breast cancer, whereas high consumption of poultry or high intake of monounsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, and vitamin E were related to lower risk. The study suggested that oil, milk, cheese, coffee and beta-carotene may act as protective factors in postmenopausal women, whereas butter and cream may be risk factors for breast cancer. In summary, it is possible that some food items may be overreported or underreported under the threat of disease in health-conscious population. However, most of the results in this study were not modified by recall bias.

Activation of PPARgamma may mediate a portion of the anticancer activity of conjugated linoleic acid.

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Med Hypotheses 2000 Sep;55(3):187-8

A number of human cancer cell lines express the PPARgamma transcription factor, and agonists for PPARgamma are reported to promote apoptosis in these cell lines and impede their clonal expansion both in vitro and in vivo. Conjugated linoleic acid (CLA) can activate PPARgamma in rat adipocytes, possibly explaining CLA's antidiabetic effects in Zucker fatty rats. It is thus reasonable to suspect that a portion of CLA's broad spectrum anticarcinogenic activity is mediated by PPARgamma activation in susceptible tumors.

Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells.

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Proc Soc Exp Biol Med 2000 Sep;224(4):292-301

Studies were conducted to determine the comparative effects of tocopherols and tocotrienols on preneoplastic (CL-S1), neoplastic (-SA), and highly malignant (+SA) mouse mammary epithelial cell growth and viability in vitro. Over a 5-day culture period, treatment with 0-120 microM alpha- and gamma-tocopherol had no effect on cell proliferation, whereas growth was inhibited 50% (IC50) as compared with controls by treatment with the following: 13, 7, and 6 microM tocotrienol-rich-fraction of palm oil (TRF); 55, 47, and 23 microM delta-tocopherol; 12, 7, and 5 microM alpha-tocotrienol; 8, 5, and 4 microM gamma-tocotrienol; or 7, 4, and 3 microM delta-tocotrienol in CL-S1, -SA and +SA cells, respectively. Acute 24-hr exposure to 0-250 microM alpha- or gamma-tocopherol (CL-S1, -SA, and +SA) or 0-250 microM delta-tocopherol (CL-S1) had no effect on cell viability, whereas cell viability was reduced 50% (LD50) as compared with controls by treatment with 166 or 125 microM delta-tocopherol in -SA and +SA cells, respectively. Additional LD50 doses were determined as the following: 50, 43, and 38 microM TRF; 27, 28, and 23 microM alpha-tocotrienol; 19, 17, and 14 microM gamma-tocotrienol; or 16, 15, or 12 microM delta-tocotrienol in CL-S1, -SA, and +SA cells, respectively. Treatment-induced cell death resulted from activation of apoptosis, as indicated by DNA fragmentation. Results also showed that CL-S1, -SA, and +SA cells preferentially accumulate tocotrienols as compared with tocopherols, and this may partially explain why tocotrienols display greater biopotency than tocopherols. These data also showed that highly malignant +SA cells were the most sensitive, whereas the preneoplastic CL-S1 cells were the least sensitive to the antiproliferative and apoptotic effects of tocotrienols, and suggest that tocotrienols may have potential health benefits in preventing and/or reducing the risk of breast cancer in women.

Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans.

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J Natl Cancer Inst 1997 May 21;89(10):718-23

BACKGROUND: The oxidative metabolism of estrogens in humans is mediated primarily by cytochrome P450, many isoenzymes of which are inducible by dietary and pharmacologic agents. One major pathway, 2-hydroxylation, is induced by dietary indole-3-carbinol (I3C), which is present in cruciferous vegetables (e.g., cabbage and broccoli).

PURPOSE: Because the pool of available estrogen substrates for all pathways is limited, we hypothesized that increased 2-hydroxylation of estrogens would lead to decreased activity in competing metabolic pathways.

METHODS: Urine samples were collected from subjects before and after oral ingestion of I3C (6-7 mg/kg per day). In the first study, seven men received I3C for 1 week; in the second study, 10 women received I3C for 2 months. A profile of 13 estrogens was measured in each sample by gas chromatography-mass spectrometry.

RESULTS: In both men and women, I3C significantly increased the urinary excretion of C-2 estrogens. The urinary concentrations of nearly all other estrogen metabolites, including levels of estradiol, estrone, estriol, and 16alpha-hydroxyestrone, were lower after I3C treatment.

CONCLUSIONS: These findings support the hypothesis that I3C-induced estrogen 2-hydroxylation results in decreased concentrations of several metabolites known to activate the estrogen receptor. This effect may lower estrogenic stimulation in women.

IMPLICATIONS: I3C may have chemopreventive activity against breast cancer in humans, although the long-term effects of higher catechol estrogen levels in women require further investigation.

Altered estrogen metabolism and excretion in humans following consumption of indole-3-carbinol.

Michnovicz JJ, Bradlow HL. Institute for Hormone Research, New York, NY 10016.

Nutr Cancer 1991;16(1):59-66

Research studies have demonstrated a strong association between estrogen metabolism and the incidence of breast cancer, and we have therefore sought pharmacological means of favorably altering both metabolism and subsequent risk. Indole-3-carbinol (I3C), obtained from cruciferous vegetables (e.g., cabbage, broccoli, etc.), is a known inducer of oxidative P-450 metabolism in animals. We investigated the effects in humans of short-term oral exposure to this compound (6-7 mg/kg/day over 7 days). We used an in vivo radiometric test, which provided a highly specific and reproducible measure of estradiol 2-hydroxylation before and after exposure to I3C. In a group of 12 healthy volunteers, the average extent of reaction increased by approximately 50% during this short exposure (p less than 0.01), affecting men and women equally. We also measured the urinary excretion of two key estrogen metabolites, 2-hydroxyestrone (2OHE1) and estriol (E3). We found that the excretion of 2OHE1 relative to that of E3 was significantly increased by I3C, further confirming the ongoing induction of 2-hydroxylation. These results indicate that I3C predictably alters endogenous estrogen metabolism toward increased catechol estrogen production and may thereby provide a novel "dietary" means for reducing cancer risk.

Tocotrienols inhibit growth of ZR-75-1 breast cancer cells.

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Int J Food Sci Nutr 2000;51 Suppl:S95-103

The vitamin E component of palm oil provides a rich source of tocotrienols which have been shown previously to be growth inhibitory to two human breast cancer cell lines: responsive MCF7 cells and unresponsive MDA-MB-231 cells. Data presented here shows that the tocotrienol-rich fraction (TRF) of palm oil and individual fractions (alpha, gamma and delta) can also inhibit the growth of another responsive human breast cancer cell line, ZR-75-1. At low concentrations in the absence of oestrogen tocotrienols stimulated growth of the ZR-75-1 cells, but at higher concentrations in the presence as well as in the absence of oestradiol, tocotrienols inhibited cell growth strongly. As for MCF7 cells, alpha-tocopherol had no effect on growth of the ZR-75-1 cells in either the absence or presence of oestradiol. In studying the effects of tocotrienols in combination with antioestrogens, it was found that TRF could further inhibit growth of ZR-75-1 cells in the presence of tamoxifen (10(-7) M and 10(-8) M). Individual tocotrienol fractions (alpha, gamma, delta) could inhibit growth of ZR-75-1 cells in the presence of 10(-8) M oestradiol and 10(-8) M pure antioestrogen ICI 164,384. The immature mouse uterine weight bioassay confirmed that TRF could not exert oestrogen antagonist action in vivo. These results provide evidence of wider growth-inhibitory effects of tocotrienols beyond MCF7 and MDA-MB-231 cells, and with an oestrogen-independent mechanism of action, suggest a possible clinical advantage in combining administration of tocotrienols with antioestrogen therapy.

Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status.

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Lipids 1998 May;33(5):461-9

Potential antiproliferative effects of tocotrienols, the major vitamin E component in palm oil, were investigated on the growth of both estrogen-responsive (ER+) MCF7 human breast cancer cells and estrogen-unresponsive (ER-) MDA-MB-231 human breast cancer cells, and effects were compared with those of alpha-tocopherol (alphaT). The tocotrienol-rich fraction (TRF) of palm oil inhibited growth of MCF7 cells in both the presence and absence of estradiol with a nonlinear dose-response but such that complete suppression of growth was achieved at 8 microg/mL. MDA-MB-231 cells were also inhibited by TRF but with a linear dose-response such that 20 microg/mL TRF was needed for complete growth suppression. Separation of the TRF into individual tocotrienols revealed that all fractions could inhibit growth of both ER+ and ER- cells and of

ER+ cells in both the presence and absence of estradiol. However, the gamma- and delta-fractions were the most inhibitory. Complete inhibition of MCF7 cell growth was achieved at 6 microg/mL of gamma-tocotrienol/delta-tocotrienol (gammaT3/deltaT3) in the absence of estradiol and 10 microg/mL of deltaT3 in the presence of estradiol, whereas complete suppression of MDA-MB-231 cell growth was not achieved even at concentrations of 10 microg/mL of deltaT3. By contrast to these inhibitory effects of tocotrienols, alphaT had no inhibitory effect on MCF7 cell growth in either the presence or the absence of estradiol, nor on MDA-MB-231 cell growth. These results confirm studies using other sublines of human breast cancer cells and demonstrate that tocotrienols can exert direct inhibitory effects on the growth of breast cancer cells. In searching for the mechanism of inhibition, studies of the effects of TRF on estrogen-regulated pS2 gene expression in MCF7 cells showed that tocotrienols do not act via an estrogen receptor-mediated pathway and must therefore act differently from estrogen antagonists. Furthermore, tocotrienols did not increase levels of growth-inhibitory insulin-like growth factor binding proteins (IGFBP) in MCF7 cells, implying also a different mechanism from that proposed for retinoic acid inhibition of estrogen-responsive breast cancer cell growth. Inhibition of the growth of breast cancer cells by tocotrienols could have important clinical implications not only because tocotrienols are able to inhibit the growth of both ER+ and ER- phenotypes but also because ER+ cells could be growth-inhibited in the presence as well as in the absence of estradiol. Future clinical applications of TRF could come from potential growth suppression of ER+ breast cancer cells otherwise resistant to growth inhibition by antiestrogens and retinoic acid.

Melatonin and steroid-dependent carcinomas.

Oosthuizen JM, Bornman MS, Barnard HC, Schulenburg GW, Boomker D, Reif S. Department of Physiology, University of the Orange Free State, Bloemfontein, South Africa.

Andrologia 1989 Sep-Oct;21(5):429-31

In this study the concentrations of plasma melatonin in patients with either prostatic or breast carcinoma were compared to the levels of controls. The mean melatonin was statistically lower in patients with breast cancer as compared to controls (p less than 0.005). In prostatic carcinoma patients, the mean melatonin was statistically higher than in the control group (p less than 0.005). From the results it would seem that low melatonin levels could possibly play a role in breast carcinoma, but the same did not necessarily applied to prostatic cancer.

Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex.

Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, Farrow S, Howells L. MRC Toxicology Unit, University of Leicester, Leicester, LE1 9HN, UK.

Oncogene 1999 Oct 28;18(44):6013-20

Colorectal cancer is a major cause of cancer deaths in Western countries, but epidemiological data suggest that dietary modification might reduce these by as much as 90%. Cyclo-oxygenase 2 (COX2), an inducible isoform of prostaglandin H synthase, which mediates prostaglandin synthesis during inflammation, and which is selectively overexpressed in colon tumours, is thought to play an important role in colon carcinogenesis. Curcumin, a constituent of turmeric, possesses potent anti-inflammatory activity and prevents colon cancer in animal models. However, its mechanism of action is not fully understood. We found that in human colon epithelial cells, curcumin inhibits COX2 induction by the colon tumour promoters, tumour necrosis factor alpha or fecapentaene-12. Induction of COX2 by inflammatory cytokines or hypoxia-induced oxidative stress can be mediated by nuclear factor kappa B (NF-kappaB). Since curcumin inhibits NF-kappaB activation, we examined whether its chemopreventive activity is related to modulation of the signalling pathway which regulates the stability of the NF-kappaB-sequestering protein, IkappaB. Recently components of this pathway, NF-kappaB-inducing kinase and IkappaB kinases, IKKalpha and beta, which phosphorylate IkappaB to release NF-kappaB, have been characterised. Curcumin prevents phosphorylation of IkappaB by inhibiting the activity of the IKKs. This property, together with a long history of consumption without adverse health effects, makes curcumin an important candidate for consideration in colon cancer prevention.

Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients.

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Clin Biochem 2000 Jun;33(4):279-84

OBJECTIVES: An increasing amount of experimental and epidemiological evidence implicates the involvement of oxygen derived radicals in the pathogenesis of cancer development. Oxygen derived radicals are able to cause damage to membranes, mitochondria, and macromolecules including proteins, lipids and DNA. Accumulation of DNA damages has been suggested to contribute to carcinogenesis. It would, therefore, be advantageous to pinpoint the effects of oxygen derived radicals in cancer development.

DESIGN AND METHODS: In the present study, we investigated the relationship between oxidative stress and breast cancer development in tissue level. Breast cancer is the most common malignant disease in Western women. Twenty-one breast cancer patients, who underwent radical mastectomy and diagnosed with infiltrative ductal carcinoma, were used in the study. We determined coenzyme Q10 (Q) concentrations, antioxidant enzyme activities (mitochondrial and total superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase), and malondialdehyde (MDA) levels in tumor and surrounding tumor-free tissues.

RESULTS: Q concentrations in tumor tissues significantly decreased as compared to the surrounding normal tissues (p < 0.001). Higher MDA levels were observed in tumor tissues than noncancerous tissues (p < 0.001). The activities of MnSOD, total SOD, GSH-Px and catalase in tumor tissues significantly increased (p < 0.001) compared to the controls.

CONCLUSIONS: These findings may support that reactive oxygen species increased in malignant cells, and may cause overexpression of antioxidant enzymes and the consumption of coenzyme Q10. Increased antioxidant enzyme activities may be related with the susceptibility of cells to carcinogenic agents and the response of tumor cells to the chemotherapeutic agents. Administration of coenzyme Q10 by nutrition may induce the protective effect of coenzyme Q10 on breast tissue.

Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase.

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FEBS Lett 1994 Mar 14;341(1):19-22

Recently, we reported that curcumin (diferuloylmethane) inhibits the growth of several different kinds of tumor cells. In order to investigate the mechanism of this inhibition, we examined the effects of curcumin on different protein kinases: highly purified protein kinase A (PkA), protein kinase C (PkC), protamine kinase (cPK), phosphorylase kinase (PhK), autophosphorylation-activated protein kinase (AK) and pp60c-src tyrosine kinase. While all kinases tested were inhibited by curcumin, only PhK was completely inhibited at relatively lower concentrations. At around 0.1 mM curcumin, PhK, pp60c-src, PkC, PkA, AK, and cPK were inhibited by 98%, 40%, 15%, 10%, 1%, and 0.5%, respectively. Lineweaver-Burk plot analysis indicated that curcumin is a non-competitive inhibitor of PhK with a Ki of 0.075 mM. Overall, our results indicate that curcumin is a potent and selective inhibitor of phosphorylase kinase, a key regulatory enzyme involved in the metabolism of glycogen. This has important implications for the anti-proliferative effects of curcumin.

Natural products and their derivatives as cancer chemopreventive agents.

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Prog Drug Res 1997;48:147-71

This review summarizes currently available data on the chemopreventive efficacies, proposed mechanisms of action and relationships between activities and structures of natural products like vitamin D, calcium, dehydroepidandrosterone, coenzyme Q10, celery seed oil, parsley leaf oil,

sulforaphane, isoflavonoids, lignans, protease inhibitors, tea polyphenols, curcumin, and polysaccharides from Acanthopanax genus.

Serum fatty acid imbalance in bone loss: example with periodontal disease.

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Clin Nutr 2000 Aug;19(4):271-6

Among the numerous factors of bone remodelling, the local action of arachidonic acid metabolites together with cytokines, is particularly important, especially that of prostaglandin PGE2. It has been suggested that the alveolar bone destruction in periodontal disease and osteoporosis can be treated by reducing the ratio of arachidonic acid in phospholipids, which would diminish prostaglandin production. The aim of this study was to evaluate the main serum polyunsaturated fatty acids and a possible alteration in the level of arachidonic acid in patients suffering from periodontal bone loss. Of the 105 patients who participated the study, 78 were suffering from periodontal bone loss and 27 served as a control group. The fatty acids were measured in serum by gas-chromatography. The results showed that the level of fatty acids of the n-6 pathway was higher in our patients with bone loss than in the control group, whereas the reverse was observed with fatty acids of the n-3 pathway. In conclusion, our patients' bone losses are linked with an imbalance between n-6 and n-3 fatty acids, which seems to justify a diet increase in 20- and 22-carbon fatty acids. Copyright 2000 Harcourt Publishers Ltd.

Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol.

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Free Radic Biol Med 1991;10(5):263-75

d-Alpha-tocopherol (2R,4'R,8'R-Alpha-tocopherol) and d-alpha-tocotrienol are two vitamin E constituents having the same aromatic chromanol "head" but differing in their hydrocarbon "tail": tocopherol with a saturated and toctrienol with an unsaturated isoprenoid chain. d-Alpha-tocopherol has the highest vitamin E activity, while d-alpha-tocotrienol manifests only about 30% of this activity. Since vitamin E is considered to be physiologically the most important lipid-soluble chain-breaking antioxidant of membranes, we studied alpha-tocotrienol as compared to alpha-tocopherol under conditions which are important for their antioxidant function. d-Alpha-tocotrienol possesses 40-60 times higher antioxidant activity against (Fe2+ + ascorbate)- and (Fe2+ + NADPH)-induced lipid peroxidation in rat liver microsomal membranes and 6.5 times better protection of cytochrome P-450 against oxidative damage than d-alpha-tocopherol. To clarify the mechanisms responsible for the much higher antioxidant potency of d-alpha-tocotrienol compared to d-alpha-tocopherol, ESR

studies were performed of recycling efficiency of the chromanols from their chromanoxyl radicals. 1H-NMR measurements of lipid molecular mobility in liposomes containing chromanols, and fluorescence measurements which reveal the uniformity of distribution (clusterizations) of chromanols in the lipid bilayer. From the results, we concluded that this higher antioxidant potency of d-alpha-tocotrienol is due to the combined effects of three properties exhibited by d-alpha-tocotrienol as compared to d-alpha-tocopherol: (i) its higher recycling efficiency from chromanoxyl radicals, (ii) its more uniform distribution in membrane bilayer, and (iii) its stronger disordering of membrane lipids which makes interaction of chromanols with lipid radicals more efficient. The data presented show that there is a considerable discrepancy between the relative in vitro antioxidant activity of d-alpha-tocopherol and d-alpha-tocotrienol with the conventional bioassays of their vitamin activity.

Intervention in free radical mediated hepatotoxicity and lipid peroxidation by indole-3-carbinol.

Shertzer HG, Berger ML, Tabor MW. Department of Environmental Health, University of Cincinnati Medical Center, OH 45267-0056.

Biochem Pharmacol 1988 Jan 15;37(2):333-8

The cytoprotective effect of the natural dietary constituent indole-3-carbinol (I-3-C) on carbon tetrachloride (CCl4) mediated hepatotoxicity in mice was examined. I-3-C pretreatment by gavage 1 hr prior to intraperitoneal injection of CCl4 produced a 63% decrease in CCl4-mediated centrolobular necrosis and a related 60% decrease in plasma alanine aminotransferase activity (a marker of liver necrosis). Since the toxicological effects of CCl4 are mediated by radical species generated during reductive metabolism by cytochrome P-450, we examined the potential ability of I-3-C to scavenge reactive radicals. Three systems were used to evaluate the ability of I-3-C to intervene in free radical mediated lipid peroxidation. These systems consisted of the following: (1) phospholipid dissolved in chlorobenzene, with peroxidation initiated by the thermal and photo decomposition of azobisisobutyronitrile (AIBN); (2) sonicated phospholipid vesicles in phosphate buffer (pH 7.4), with peroxidation initiated by ferrous/ascorbate; and (3) mouse liver microsomes containing an NADPH-regenerating system, with peroxidation initiated with CCl4. Lipid peroxidation was measured in these three systems as thiobarbiturate-reacting material. In the AIBN and ferrous/ascorbate systems, I-3-C inhibited lipid peroxidation, with greater inhibition under conditions of low rates of free radical generation. I-3-C was not as effective an antioxidant as butylated hydroxytoluene (BHT) or tocopherol, but it inhibited peroxidation in a dose-response manner. I-3-C was most effective as a radical scavenger in the microsomal CCl4-initiated system by inhibiting lipid peroxidation in a dose-dependent fashion, with 50% inhibition at 35-40 microM I-3-C. This concentration is about one-third of the concentration of I-3-C achieved in liver after treatment of mice by gavage with 50 mg I-3-C/kg body weight. These data suggest that I-3-C may be a natural antioxidant in the human diet and, as such, may intervene in toxicological or carcinogenic processes that are mediated by radical mechanisms.

Enhancement of wound healing by curcumin in animals.

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Wound Repair Regen 1998 Mar-Apr;6(2):167-77

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and remodeling of the tissue. In this study, we evaluated the in vivo effects of curcumin (difeurloylmethane), a natural product obtained from the rhizomes of Curcuma longa on wound healing in rats and guinea pigs. We observed faster wound closure of punch wounds in curcumin-treated animals in comparison with untreated controls. Biopsies of the wound showed reepithelialization of the epidermis and increased migration of various cells including myofibroblasts, fibroblasts, and macrophages in the wound bed. Multiple areas within the dermis showed extensive neovascularization, and Masson's Trichrome staining showed greater collagen deposition in curcumin-treated wounds. Immunohistochemical localization of transforming growth factor-beta1 showed an increase in curcumin-treated wounds as compared with untreated wounds. In situ hybridization and polymerase chain reaction analysis also showed an increase in the mRNA transcripts of transforming growth factor-beta1 and fibronectin in curcumin-treated wounds. Because transforming growth factor-beta1 is known to enhance wound healing, it may be possible that transforming growth factor-beta1 plays an important role in the enhancement of wound healing by curcumin.

Effects of methylselenocysteine on PKC activity, cdk2 phosphorylation and gadd gene expression in synchronized mouse mammary epithelial tumor cells.

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Cancer Lett 1999 Nov 15;146(2):135-45

Methylselenocysteine (MSC), an organic selenium compound is an effective chemopreventive agent against mammary cell growth both in vivo and in vitro but its mechanism of action is still not understood. We have previously demonstrated that MSC is able to inhibit growth in a synchronized TM6 mouse mammary epithelial tumor cell line at 16 h time point followed by apoptosis at 48 h. The decrease in cdk2 kinase activity was coincident with prolonged arrest of cells in S-phase. The present set of experiments showed that cdk2 phosphorylation was reduced by 72% in the MSC-treated cells at 16 h time point. Expression for gadd34, 45 and 153 was elevated 2.5 to 7 fold following MSC treatment only after 16 h time point. In order to investigate a possible upstream target for MSC, we analyzed protein kinase C (PKC) in this model. Total PKC activity was

reduced in TM6 cells by MSC (50 microM) within 30 min of treatment, both in cytosolic (55.4 and 77.6%) and membrane (35.2 and 34.1%) fractions for calcium-dependent and independent PKCs, respectively. PMA significantly elevated the PKC activity in membrane fraction (P < 0.01) and MSC inhibited this activation by more than 57%. The effect of MSC was selenium specific as selenomethionine and sulfurmethyl-L-cysteine (SMC) did not alter PKC activity either in cytosolic or membrane fraction. Immunoblot analysis showed that PKC-alpha was translocated to the membrane by PMA and MSC did not alter this translocation. PKC-delta was faintly detectable in membrane fractions of control and MSC-treated cells. MSC treatment slightly reduced levels of PKC-e (in cytosolic and membrane fractions) and PKC-zeta (cytosolic fractions). The data presented herein suggest that PKC is a potential upstream target for MSC that may trigger one or all of the downstream effects; i.e. the decrease of cdk2 kinase activity, decreased DNA synthesis, elevation of gadd gene expression and finally apoptosis.

Inhibition of cdk2 kinase activity by methylselenocysteine in synchronized mouse mammary epithelial tumor cells.

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Carcinogenesis 1997 Aug;18(8):1541-7

Methylselenocysteine (MSC), an organic selenium compound has significant anticarcinogenic activity against mammary tumorigenesis. Previous experiments have demonstrated that MSC and inorganic selenite inhibit mammary cell (TM6 cell line) growth through different pathways. The present investigation demonstrated that MSC arrested cells in S phase during the TM6 cell cycle, which was followed by cells entering apoptosis at 48 h. Methylselenocysteine specifically affected the cdk2 kinase activity of the TM6 cells (54% reduction) at 16 h after release from growth arrest. The cdk4 kinase activity did not change during the cell cycle, confirming that cells had passed the G1 checkpoint and had entered S phase. The amount of cyclin E associated with cdk2 was increased by MSC by the 12 h time point, thereby facilitating entry of cells into S phase. Afterwards, cyclin E and cyclin A associated with cdk2 did not change for the remainder of the cell cycle. The data demonstrate that inhibition of mammary cell growth by MSC is mediated by alterations in progression of cells through S phase. The decrease in cdk2 kinase activity is coincident with prolonged arrest in S phase. One consequence of prolonged arrest may be apoptosis.

Effect of dietary palm oils on mammary carcinogenesis in female rats induced by 7,12-dimethylbenz(a)anthracene.

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Cancer Res 1989 Mar 15;49(6):1447-51

Female Sprague-Dawley rats, 50 days of age, were treated with a single dose of 5 mg of 7,12-dimethylbenz(a)anthracene intragastrically. 3 days after carcinogen treatment, the rats were put on semisynthetic diets containing 20% by weight of corn oil (CO), soybean oil (SBO), crude palm oil (CPO), refined, bleached, deodorized palm oil (RBD PO) and metabisulfite-treated palm oil (MCPO) for 5 months. During the course of experiments, rats fed on different dietary fats had similar rate of growth. Rats fed 20% CO or SBO diet have higher tumor incidence than rats fed on palm oil (PO) diets; however differences of mean tumor latency periods among the groups were not statistically significant. At autopsy, rats fed on high CO or SBO diets had significantly more tumors than rats fed on the three PO diets. Our results showed that high PO diets did not promote chemically induced mammary tumorigenesis in female rats when compared to high CO or SBO diets. CO and SBO differ greatly from the palm oils in their contents of tocopherols, tocotrienols, and carotenes. But further experiments would be required to determine whether the observed differences in tumor incidence and tumor numbers were due to the differences in these minor components or due to the unique triglyceride structure of the palm oils. Analysis of the fatty acid profiles of plasma total lipids of tumor-bearing rats and of the tumor total lipids showed that, with the exception of arachidonic acid, the fatty acid profiles reflect the nature of the dietary fats. At autopsy, there were no differences in the plasma total cholesterol contents among rats fed on different dietary fats, but rats fed on palm oil diets had a significantly higher plasma triglyceride level than that of rats fed CO or SBO diets. As for the tumor lipids, there were no significant differences in the triglyceride, diglyceride, and phospholipid levels when the CO or SBO groups were compared to the palm oil groups.

Inhibition of proliferation and modulation of estradiol metabolism: novel mechanisms for breast cancer prevention by the phytochemical indole-3-carbinol.

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Proc Soc Exp Biol Med 1997 Nov;216(2):246-52

Aberrant proliferation is an early-occurring intermediate event in carcinogenesis whose inhibition may represent preventive intervention. Indole-3-carbinol (I3C), a glucosinolate metabolite from cruciferous vegetables, inhibits organ site carcinogenesis in rodent models. Clinically relevant biochemical and cellular mechanisms for the anticarcinogenic effects of I3C, however, remain unclear. Experiments were conducted on reduction mammoplasty derived 184-B5 cells initiated with chemical carcinogen (184-B5/BP) or with oncogene (184-B5/HER), and on mammary-carcinoma-derived MDA-MD-231 cells to examine whether (i) I3C inhibits aberrant proliferation in initiated and transformed cells, and (ii) inhibition of aberrant proliferation is associated with altered cell-cycle progression, estradiol (E2) metabolism, and apoptosis. Aberrant proliferation in 184-B5/BP, 184-B5/HER, and MDA-MB-231 cells was evident by a 55%-67% decrease in the ratio of quiescent (Q = G0) to proliferative (P = S + M) phase of

the cell cycle, a 72%-90% decrease in apoptosis, and a 76%-106% increase in anchorage-dependent growth. These cells also exhibited a 88%-90% decrease in the ratio of C2 to C16alpha-hydroxylation products of E2. Treatment of 184-B5/BP, 184-B5/HER, and MDA-MB-231 cells to cytostatic dose of 50 microM I3C resulted in an 137%-210% increase in Q/P I3C ratio, a 4- to 18-fold increase in E2 metabolite ratio, a 2-fold increase in cellular apoptosis, and a 54%-61% inhibition of growth. The preventive efficacy of I3C on human mammary carcinogenesis may be due in part to its ability to regulate cell-cycle progression, increase the formation of antiproliferative E2 metabolite, and induce cellular apoptosis.

Tocotrienol: a review of its therapeutic potential.

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Clin Biochem 1999 Jul;32(5):309-19

OBJECTIVES: To summarize new knowledge surrounding the physiological activity of tocotrienol, a natural analogue of tocopherol.

RESULTS: The biological activity of vitamin E has generally been associated with its well-defined antioxidant property, specifically against lipid peroxidation in biological membranes. In the vitamin E group, alpha-tocopherol is considered to be the most active form. However, recent research has suggested tocotrienol to be a better antioxidant. Moreover, tocotrienol has been shown to possess novel hypocholesterolemic effects together with an ability to reduce the atherogenic apolipoprotein B and lipoprotein(a) plasma levels. In addition, tocotrienol has been suggested to have an anti-thrombotic and anti-tumor effect indicating that tocotrienol may serve as an effective agent in the prevention and/or treatment of cardiovascular disease and cancer.

CONCLUSION: The physiological activities of tocotrienol suggest it to be superiorr than alpha-tocopherol in many situations. Hence, the role of tocotrienol in the prevention of cardiovascular disease and cancer may have significant clinical implications. Additional studies on its mechanism of action, as well as, long-term intervention studies, are needed to clarify its function. From the pharmacological point-of-view, the current formulation of vitamin E supplements, which is comprised mainly of alpha-tocopherol, may be questionable

Possible prevention from the progression of cardiotoxicity in adriamycin-treated rabbits by coenzyme Q10.

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Toxicol Lett 1982 Jun;12(1):75-82

The cumulative dose-dependent cardiotoxicity induced by doxorubicin (adriamycin, ADR) and its possible prevention by coenzyme Q10 (CoQ10) were studied in rabbits. In the group that received ADR alone, ADR dose-dependent electrocardiography (ECG) abnormalities and severe myocardial damage on electron microscopic examination were observed. In the group that received ADR + CoQ10, these alterations occurred in lesser degree, and ECG changes seemed to be improved. The results indicated that CoQ10 might prevent the progression of cardiotoxicity in ADR treated rabbits.

Induction of apoptosis in human breast cancer cells by tocopherols and tocotrienols.

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Nutr Cancer 1999;33(1):26-32

The apoptosis-inducing properties of RRR-alpha-, beta-, gamma-, and delta-tocopherols, alpha-, gamma-, and delta-tocotrienols, RRR-alpha-tocopheryl acetate (vitamin E acetate), and RRR-alpha-tocopheryl succinate (vitamin E succinate) were investigated in estrogen-responsive MCF7 and estrogen-nonresponsive MDA-MB-435 human breast cancer cell lines in culture. Apoptosis was characterized by two criteria: 1) morphology of 4,6-diamidino-2-phenylindole-stained cells and oligonucleosomal DNA laddering. Vitamin E succinate, a known inducer of apoptosis in several cell lines, including human breast cancer cells, served as a positive control. The estrogen-responsive MCF7 cells were more susceptible than the estrogen-nonresponsive MDA-MB-435 cells, with concentrations for half-maximal response for tocotrienols (alpha, gamma, and delta) and RRR-delta-tocopherol of 14, 15, 7, and 97 micrograms/ml, respectively. The tocotrienols (alpha, gamma, and delta) and RRR-delta-tocopherol induced MDA-MB-435 cells to undergo apoptosis, with concentrations for half-maximal response of 176, 28, 13, and 145 micrograms/ml, respectively. With the exception of RRR-delta-tocopherol, the tocopherols (alpha, beta, and gamma) and the acetate derivative of RRR-alpha-tocopherol (RRR-alpha-tocopheryl acetate) were ineffective in induction of apoptosis in both cell lines when tested within the range of their solubility, i.e., 10-200 micrograms/ml. In summary, these studies demonstrate that naturally occurring tocotrienols and RRR-delta-tocopherol are effective apoptotic inducers for human breast cancer cells.

Curcumin inhibits cyclooxygenase-2 transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial cells.

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Carcinogenesis 1999 Mar;20(3):445-51

We investigated whether curcumin, a chemopreventive agent, inhibited chenodeoxycholate (CD)- or phorbol ester (PMA)-mediated induction of cyclooxygenase-2 (COX-2) in several gastrointestinal cell lines (SK-GT-4, SCC450, IEC-18 and HCA-7). Treatment with curcumin suppressed CD- and PMA-mediated induction of COX-2 protein and synthesis of prostaglandin E2. Curcumin also suppressed the induction of COX-2 mRNA by CD and PMA. Nuclear run-offs revealed increased rates of COX-2 transcription after treatment with CD or PMA and these effects were inhibited by curcumin. Treatment with CD or PMA increased binding of AP-1 to DNA. This effect was also blocked by curcumin. In addition to the above effects on gene expression, we found that curcumin directly inhibited the activity of COX-2. These data provide new insights into the anticancer properties of curcumin.

Vitamin E concentration in breast adipose tissue of breast cancer patients (Kuopio, Finland).

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Cancer Causes Control 1996 Nov;7(6):591-5

Previous data on animals and humans suggest that vitamin E may be a protective factor against cancer. A low dietary vitamin E intake has been suggested to increase the risk of breast cancer. We examined the dietary intake and the concentration of vitamin E in breast adipose tissue of women in Kuopio, Finland, diagnosed between 1990 and 1992 with benign breast disease (n = 34) and with breast cancer (n = 32). In postmenopausal women, lower dietary intake (P = 0.006) and a smaller concentration of vitamin E in breast adipose tissue (P = 0.024) were observed in breast cancer patients than in subjects with benign breast disease. Partial correlation showed that the vitamin E concentration in the breast adipose tissue correlated positively with the dietary intake of vitamin E (r = 0.25, P = 0.023), indicating that the vitamin E concentration in breast adipose tissue reflects the dietary intake of vitamin E.

11. Cholesterol reduction

Preventative and curative options include:

Garlic, curcumin, gugulipid, artichoke extract, chitosan, psyllium, guar gum, pectin, green tea, niacin, fish oil, soy protein extract, vitamin E, vitamin C, selenium, policosanol, Co-Enzyme Q10, ginseng, ginkgo biloba, zinc.

Dietary isoflavones reduce plasma cholesterol and atherosclerosis in C57BL/6 mice but not LDL receptor-deficient mice.

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J Nutr (United States) Jun 1998, 128 (6) p954-9

Susceptibility to atherosclerosis is determined by a combination of genetic and environmental factors, including diet. Consumption of diets rich in soy protein has been claimed to protect against the development of atherosclerosis. Potential mechanisms include cholesterol lowering, inhibition of lipoprotein oxidation and inhibition of cell proliferation by soy proteins or isoflavones, such as genistein , that are present in soy . This study was designed to determine whether soy isoflavones confer protection against atherosclerosis in mice and whether they reduce serum cholesterol levels and lipoprotein oxidation. C57BL/6 and LDL receptor-deficient (LDLr-null) mice were fed soy protein-based, high fat diets with isoflavones present (IF+, 20.85 g/100 g protein, 0.027 g/100 g genistein , 0.009 g/100 g daidzein) or diets from which isoflavones , and possibly other components, had been extracted (IF-, 20.0 g/100 g protein, 0.002 g/100 g genistein , 0.001 g/100 g daidzein). Because LDLr-null mice develop extensive atherosclerosis and hypercholesterolemia after minimal time on a high fat diet, they were fed the diets for 6 wk, whereas C57BL/6 mice were fed the diets for 10 wk. Plasma cholesterol levels did not differ between LDLr-null mice fed IF- and those fed IF+, but were 30% lower in C57BL/6 mice fed the IF+ diet than in those fed the IF- diet. Susceptibility of LDL to oxidative modification, measured as the lag phase of conjugated diene formation in LDLr-null mice, was not altered by isoflavone consumption. All LDLr-null mice developed atherosclerosis, and the presence or deficiency of dietary isoflavones did not influence atherosclerotic lesion area. In contrast, atherosclerotic lesion area was significantly reduced in C57BL/6 mice fed IF+ compared with those fed IF-. Thus, this study demonstrates that although the isoflavone-containing diet resulted in a reduction in cholesterol levels in C57BL/6 mice, it had no effect on cholesterol levels or on susceptibility of LDL to oxidative modification in LDLr-null mice. Further, dietary isoflavones did not protect against the development of atherosclerosis in LDLr-null mice but did decrease atherosclerosis in C57BL/6 mice. These findings suggest that soy isoflavones might lower cholesterol levels by increasing LDL receptor activity, and the reduction in cholesterol may offer some protection against atherosclerosis.

Evolution of the health benefits of soy isoflavones

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Proceedings of the Society for Experimental Biology and Medicine (United States), 1998, 217/3 (386-392)

Soy is a unique dietary source of the isoflavones , genistein and daidzein. It has been part of the Southeast Asian diet for nearly five millenia, whereas consumption of soy in the United States and Western Europe has been limited to the 20th century. Heavy consumption of soy in Southeast Asian populations is associated with reduction in the rates of certain cancers end cardiovascular disease. Recent experimental evidence suggests that phytochemicals in soy are responsible for its beneficial effects, which may also include prevention of osteoporosis, a hereditary chronic nose bleed syndrome, and autoimmune diseases. Exposure of soy formula-fed infants to the potential estrogenizing effects of the isoflavones is limited by the first pass effect of the liver following the uptake of isoflavones from the gut. Several mechanisms of action of isoflavones have been proposed-both through estrogen-dependent and estrogen-independent pathways.

Polyphenols produced during red wine ageing.

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Biofactors (Netherlands) 1997, 6 (4) p403-10

Over the past few years, it has been accepted that a moderate red wine consumption is a factor beneficial to human health. Indeed, people of France and Italy, the two major wine-producing European countries, eat a lot of fatty foods but suffer less from fatal heart strokes than people in North-America or in the northern regions of Europe, where wine is not consumed on a regular basis. For a time, ethanol was thought to be the "good" chemical species hiding behind what is known as the "French paradox". Researchers now have turned their investigations towards a family of natural substances called "polyphenols", which are only found in plants and are abundant in grapes . It is well known that these molecules behave as radical scavengers and antioxidants, and it has been demonstrated that they can protect cholesterol in the LDL species from oxidation, a process thought to be at the origin of many fatal heart attacks. However, taken one by one, it remains difficult to demonstrate which are the best polyphenols as far as their antioxidant activities are concerned. The main obstacle in that kind of research is not the design of the chemical and biological tests themselves, but surprisingly enough, the limited access to chemically pure and structurally elucidated

polyphenolic compounds. In this article, particular attention will be paid to polyphenols of red wine made from Vitis vinifera cultivars. With respect to the "French paradox", we address the following question: are wine polyphenolic compounds identical to those found in grapes (skin, pulp and seed), or are there biochemical modifications specifically taking place on the native flavonoids when a wine ages? Indeed, structural changes occur during wine conservation, and one of the most studied of those changes concerns red wine colour evolution, called "wine ageing". As a wine ages, it has been demonstrated that the initially present grape pigments slowly turn into new more stable red pigments. That phenomenon goes on for weeks, months and years. Since grape and wine polyphenols are chemically distinct, their antioxidant activities cannot be the same. So, eating grapes might well lead to beneficial effects on human health, due to the variety and sometimes large amounts of their polyphenolic content. However, epidemiological surveys have focused on wines,not on grapes .... (35 Refs.)

Fats in indian diets and their nutritional and health implications

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Lipids (USA), 1996, 31/3 Suppl. (S287-S291)

To arrive at fat requirements for Indians, the contribution of invisible fat should be determined. Total lipids were extracted from common Indian foods, and their fatty acid compositions were determined. This data and information on intake of various foods were used to estimate the contents of 'invisible' fat and fatty acids in Indian diets. Taking into account World Health Organization (WHO) guidelines and the invisible fat intake of Indians, recommendations were made for lower and upper limits of visible fats. In the rural poor, the 'visible'-fat intakes are much lower than estimated minimum requirements. Therefore, to meet the energy needs of low income groups, particularly young children, visible-fat intakes must be increased to recommended levels. The urban high-income group, however, should reduce dietary fat. Data on intake of various fatty acids in total diet shows that even the recommended lower limit of oil can meet linoleic acid requirements. Intake of alpha-linolenic acid is low, however. Increase in dietary n-3 polyunsaturated fatty acid (PUFA) produces hypolipidemic, anti-inflammatory, and antithrombotic effects. Effects of n-3 PUFA on blood lipids, platelet fatty acid composition, and platelet aggregation were therefore investigated in Indian subjects consuming cereal based diets. Supplementation of fish oils (long-chain n-3 PUFA) as well as the use of rapeseed oil (alpha-linolenic acid) produced beneficial effects. Since the requirements of alpha-linolenic acid and/or long-chain n-3 PUFA are related to linoleic acid intake, use of more than one oil (correct choice) is recommended for providing a balanced intake of various fatty acids. Analysis of Indian food showed that some foods are good sources of alpha-linolenic acid. Regular consumption of these foods can also improve the quality of fat in Indian diets. Nonvegetarians, however, have the choice of eating fish to accomplish this.

The effects of natural dietary fiber from fruit and vegetables with oxalate from spinach on plasma minerals, lipids and other metabolites in men

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Nutr. Res. (USA), 1990, 10/4 (367-378)

Diets high in fiber and oxalate may result in decreased mineral bioavailability. However, increased fiber intake can reduce risk factors for some diseases. Twelve men were fed diets containing 25 g or 5 g of neutral detergent fiber with 450 mg/day of oxalic acid for six weeks each in a crossover design to determine whether plasma minerals and other metabolites would be affected. High dietary oxalate levels were fed throughout the study. The fiber sources were fruit and vegetables or their juices and spinach was the source of oxalate. Five minerals and cholesterol , triglycerides, uric acid, glucose and urea nitrogen (BUN) were measured in fasting plasma and correlated with fecal oxalate, mineral intake and apparent mineral balance. Fiber level had no effect on the plasma constituents. Plasma inorganic phosphorus (P(i)) decreased ($p = 0.002$), while BUN, calcium and copper increased ($p < 0.010$), ($p = 0.004$), ($p = 0.011$) with time. BUN and P(i) changes which occurred may have been related to ingestion of high levels of oxalate for eighty-four days.

Medical nutrition therapy lowers serum cholesterol and saves medication costs in men with hypercholesterolemia.

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J Am Diet Assoc (United States) Aug 1998, 98 (8) p889-94; quiz 895-6

This study was designed to evaluate whether medical nutrition therapy administered by registered dietitians could lead to a beneficial clinical and cost outcome in men with hypercholesterolemia. Ninety-five subjects participating in a cholesterol -lowering drug study took part in an 8-week nutrition intervention program before initiating treatment with a cholesterol -lowering medication, Patient records were reviewed via a retrospective chart review to determine plasma lipid levels at the beginning and end of the program and the number and length of sessions with a dietitian. Complete information was available for 74 subjects aged 60.8 n+/- 9.8 years (mean +/- SD). Medical nutrition therapy lowered total serum cholesterol levels 13% ($P < .001$), low-density lipoprotein cholesterol (LDL-C) 15% ($P < .0001$), triglyceride 11% ($P < .05$), and high-density lipoprotein- cholesterol (HDL-C) 4% ($P < .05$). Total dietitian intervention time was 144 +/- 21 minutes (range = 120 to 180 minutes) in 2.8 +/-

0.7 sessions (range = 2 to 4) during 6.81 +/- 0.7 weeks of medical nutrition therapy (range = 6 to 8 weeks). Analysis of covariance was conducted to examine whether mean change in LDL-C differed by number of dietitian visits. Results showed a marginal difference between the number of dietitian visits and change in LDL-C (f = 2.6, P < .084). However, the magnitude of LDL-C reduction was significantly higher with 4 dietitian visits (180 minutes) than with 2 visits (120 minutes) (21.9% vs 12.1%; P = .027). Lipid drug eligibility was obviated in 34 of 67 (51%) subjects per the National Cholesterol Treatment Program guidelines algorithm. The estimated annualized cost savings from the avoidance of lipid medications was $60,561.68. Therefore, we conclude that 3 or 4 individualized dietitian visits of 50 minutes each over 7 weeks are associated with a significant serum cholesterol reduction and a savings of health care dollars.

Effects of crystalline nicotinic acid-induced hepatic dysfunction on serum low-density lipoprotein cholesterol and lecithin cholesteryl acyl transferase.

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Am J Cardiol (United States) Mar 15 1998, 81 (6) p805-7

Marked lowering of plasma total and low-density lipoprotein cholesterol levels that occur during treatment of dyslipidemia with pharmacologic doses of nicotinic acid result from hepatotoxicity. Therefore, a marked reduction in low-density lipoprotein may suggest generalized liver toxicity and drug treatment should be discontinued.

A randomized trial of the effects of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia. Collaborative Atorvastatin Study Group.

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Am J Med (United States) Feb 1998, 104 (2) p137-43

BACKGROUND: To assess the lipid-lowering effects and safety of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia.

METHODS: We performed a randomized, open-label, parallel-design, active-controlled, study in eight centers in the United States. We enrolled 108 patients with total cholesterol (TC) of > or =200 mg/dL, serum triglycerides (TG) > or =200 and < or =800 mg/dL, and apolipoprotein B (apo B) > or =110 mg/dL. Patients were randomly assigned to receive atorvastatin 10 mg once daily (n=55)

or immediate-release niacin 1 g three times daily for 12 weeks (n=53). Patients were stratified based on low-density lipoprotein cholesterol (LDL-C): Patients with LDL-C > or =135 mg/dL were considered to have combined hyperlipidemia and patients with LDL-C <135 mg/dL were considered to have isolated hypertriglyceridemia. The primary outcome measure was percent change from baseline in LDL-C. Other lipid levels were evaluated as secondary parameters.

RESULTS: Atorvastatin reduced LDL-C 30% and TC 26% from baseline, and increased high-density lipoprotein cholesterol (HDL-C) 4%. Total TG were reduced 17%. Niacin reduced LDL-C 2%, TC 7%, increased HDL-C 25%, and reduced total TG 29% from baseline. There was a significant difference in LDL-C reduction , the primary efficacy parameter, between the two treatment groups (P <0.05, favoring atorvastatin), as well as a significant difference in the improvement in HDL-C (P <0.05, favoring niacin). The effect of atorvastatin was relatively consistent between patients with combined hyperlipidemia and isolated hypertriglyceridemia, whereas there was more variability between these strata in the niacin treatment group. Atorvastatin was better tolerated than niacin .

CONCLUSION: Atorvastatin may allow patients with combined hyperlipidemia to be treated with monotherapy and offers an efficacious and well-tolerated alternative to niacin for the treatment of patients with isolated hypertriglyceridemia.

Use of niacin , statins, and resins in patients with combined hyperlipidemia.

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Am J Cardiol (United States) Feb 26 1998, 81 (4A) p52B-59B

Patients in the original Familial Atherosclerosis Treatment Study (FATS) cohort were subgrouped into those with triglyceride levels < or = 120 mg/dL (n = 26) and those with triglyceride levels > or = 190 mg/dL (n = 40). Their therapeutic responses to niacin plus colestipol, lovastatin plus colestipol, colestipol alone, or placebo were determined. Therapeutic response was also determined in the same 2 triglyceride subgroups (n = 12 and n = 27, respectively) of patients selected for low levels of high-density lipoprotein (HDL) cholesterol and coronary artery disease. These triglyceride criteria were chosen to identify patient subgroups with high likelihood of "pattern A" (normal-size low-density lipoprotein [LDL] particles and triglyceride < or = 120 mg/dL) or "pattern B" (small dense LDL and triglyceride > or = 190 mg/dL). Our findings in these small patient subgroups are consistent with the emerging understanding that coronary artery disease patients presenting with high triglyceride levels have lower HDL-C, smaller less buoyant LDL-C, and greater very low-density lipoprotein (VLDL) cholesterol and VLDL apolipoprotein B, and are more responsive to therapy as assessed by an increase in HDL-C and reduction in triglycerides, VLDL-C, and VLDL apolipoprotein B. In

the FATS high-triglyceride subgroup with these characteristics, a tendency toward greater therapeutic improvement in coronary stenosis severity was observed among those treated with either of the 2 forms of intensive cholesterol -lowering therapy. This improvement is associated with therapeutic reduction of LDL-C and elevation of HDL-C, but also appears to be associated with drug-induced improvement in LDL buoyancy. (20 Refs.)

Hypocoagulant and lipid-lowering effects of dietary n-3 polyunsaturated fatty acids with unchanged platelet activation in rats.

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Arterioscler Thromb Vasc Biol (United States) Sep 1998, 18 (9) p1480-9

We investigated the effects of dietary polyunsaturated fatty acids (PUFAs) on blood lipids and processes that determine hemostatic potential: platelet activation, coagulation, and fibrinolysis. For 8 to 10 weeks, Wistar rats were fed a high-fat diet containing various amounts (2% to 16%) of n-3 PUFAs derived from fish oil (FO) or a diet enriched in n-6 PUFAs from sunflower seed oil (SO). Only the FO diets caused a reduction in mean platelet volume, platelet arachidonate level, and formation of thromboxane B2 by activated platelets, but neither of the diets had a measurable effect on platelet activation. The FO-rich diets decreased the plasma concentrations of triglycerides and cholesterol , whereas the SO diet reduced triglycerides only. Parameters of fibrinolysis and standard coagulation times, ie, activated partial thromboplastin time and prothrombin time, were only marginally influenced by these diets. In contrast, dietary FO, but not SO, led to decreased levels of the vitamin K-dependent coagulation factors prothrombin and factor VII, while the level of antithrombin III was unchanged. The endogenous thrombin potential (ETP) was measured with an assay developed to detect the hypocoagulable state of plasma. After activation with tissue factor and phospholipids, the ETP was reduced by 23% or more in plasma from animals fed a diet with >4% FO. No significant effect of the SO diet on ETP was observed. Control experiments with plasma from warfarin-treated rats indicated that the ETP was more sensitive to changes in prothrombin concentration than in factor VII concentration. Taken together, these results indicate that in rats, prolonged administration of n-3 but not n-6 PUFAs can lead to a hypocoagulable state of plasma through a reduced capacity of vitamin K-dependent thrombin generation, with unchanged thrombin inactivation by antithrombin III.

Effects of dietary fish oil on serum lipids and VLDL kinetics in hyperlipidemic apolipoprotein E*3-Leiden transgenic mice.

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J Lipid Res (United States) Jun 1998, 39 (6) p1181-8

Studying the effects of dietary fish oil on VLDL metabolism in humans is subject to both large intra- and interindividual variability. In the present study we therefore used hyperlipidemic apolipoprotein (APO) E*3-Leiden mice, which have impaired chylomicron and very low density lipoprotein (VLDL) remnant metabolism, to study the effects of dietary fish oil on serum lipids and VLDL kinetics under highly standardized conditions. For this, female APOE*3-Leiden mice were fed a fat- and cholesterol -containing diet supplemented with either 0, 3 or 6% w/w (i.e. 0, 6, or 12% of total energy) of fish oil . Fish oil -fed mice showed a significant dose-dependent decrease in serum cholesterol (up to -43%) and triglyceride levels (up to -60%), mainly due to a reduction of VLDL (-80%). LDL and HDL cholesterol levels were not affected by fish oil feeding. VLDL-apoB kinetic studies showed that fish oil feeding resulted in a significant 2-fold increase in VLDL-apoB fractional catabolic rate (FCR). Hepatic VLDL-apoB production was, however, not affected by fish oil feeding. VLDL-triglyceride turnover studies revealed that fish oil significantly decreased hepatic VLDL-triglyceride production rate (-60%). A significant increase in VLDL-triglyceride FCR was observed (+70%), which was not related to increased lipolytic activity. We conclude that APOE*3-Leiden mice are highly responsive to dietary fish oil . The observed strong reduction in serum very low density lipoprotein (VLDL) is primarily due to an effect of fish oil to decrease hepatic VLDL triglyceride production rate and to increase VLDL-apoB fractional catabolic rate.

Effect of fish - oil -enriched margarine on plasma lipids, low-density-lipoprotein particle composition, size, and susceptibility to oxidation.

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Am J Clin Nutr (United States) Aug 1998, 68 (2) p235-41

We investigated the effect of incorporating n-3 polyunsaturated fatty acids (PUFAs) into the diet on the lipid-class composition of LDLs, their size, and their susceptibility to oxidation. Forty-seven healthy volunteers incorporated 30 g sunflower-oil (SO) margarine/d into their habitual diet during a 3-wk run-in period and then used either SO or a fish -oil -enriched sunflower oil (FO) margarine for the following 4 wk. Plasma concentrations of total cholesterol , triacylglycerols, HDL cholesterol , LDL cholesterol , and apolipoproteins A-I and B did not differ significantly between the groups during intervention. The FO margarine increased the concentration of n-3 very-long-chain PUFAs in the LDL particles, showing 93% (P < or = 0.0001), 8% (P = 0.05), and 35% (P = < 0.0001) increases in eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, respectively, in the FO group compared with 3%, 7%, and 7%, respectively,

in the SO group during the intervention. The cholesterol content of the LDL particles increased in the FO group [total cholesterol : 6% (P = 0.008); cholesterol ester: 12% (P = 0.014)], although it was not significantly different from that in the control group, whereas the other lipid classes and the size of the LDL particles remained unchanged in both groups. A reduction in the alpha-tocopherol content in LDL (6%, P = 0.005) was observed in the FO group. Ex vivo oxidation of LDL induced with Cu2+ showed a significantly reduced lag time (from 91 to 86 min, P = 0.003) and lower maximum rate of oxidation (from 10.5 to 10.2 nmol x mg(-1) x min(-1), P = 0.003) after intake of the FO margarine. The results indicate that consumption of the FO compared with the SO margarine had no effect on LDL size and lipid composition and led to minor changes in LDL a-tocopherol content and oxidation resistance.

Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampal cortex from Alzheimer's disease patients and its relationship to acetyl CoA content.

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Int J Biochem Cell Biol (England) Feb 1998, 30 (2) p197-207

The long-chain fatty acid composition of cholesterol esters, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI) from parahippocampal cortex of Alzheimer's disease (AD) patients and control subjects was examined. In general the PC fraction contained less polyunsaturated long-chain fatty acids than did PE, PS or PI. Of the n-6 polyunsaturated long-chain fatty acids, PI contained the greatest incorporation of these acids followed by PE. There were significant differences between controls and AD patients in total n-6 EFAs. Arachidonic acid (C20:4n-6) was the predominant fatty acid of this family found to be present. In AD, PE and PS showed a deficit of adrenic acid (C22:4n-6) content and PE also contained less arachidonic acid. In AD subjects, the cholesterol esters contained significantly less n-3 polyunsaturated fatty acids with, specifically, a reduction in alpha-linolenic acid. Acetyl CoA content of hippocampal cortex was greater in AD patients than in control subjects indicating either an increased extent of oxidative metabolism or a failure to utilise acetyl CoA for anabolic processes. Abnormal magnitude of oxidative processes could give rise to the biosynthesis of PE and PS species containing less n-6 polyunsaturated fatty acids than occurs in control subjects.

Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate

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Arch Intern Med (United States) Jun 8 1998, 158 (11) p1181-7

BACKGROUND: The Mediterranean dietary pattern is thought to reduce the risk of cancer in addition to being cardioprotective. However, no trial has been conducted so far to prove this belief.

METHODS: We compared overall survival and newly diagnosed cancer rate among 605 patients with coronary heart disease randomized in the Lyon Diet Heart Study and following either a cardioprotective Mediterranean-type diet or a control diet close to the step 1 American Heart Association prudent diet.

RESULTS: During a follow-up of 4 years, there were a total of 38 deaths (24 in controls vs 14 in the experimental group), including 25 cardiac deaths (19 vs 6) and 7 cancer deaths (4 vs 3), and 24 cancers (17 vs 7). Exclusion of early cancer diagnoses (within the first 24 months after entry into the trial) left a total of 14 cancers (12 vs 2). After adjustment for age, sex, smoking, leukocyte count, cholesterol level, and aspirin use, the reduction of risk in experimental subjects compared with control subjects was 56% (P=.03) for total deaths, 61% (P=.05) for cancers, and 56% (P=.01) for the combination of deaths and cancers. The intakes of fruits, vegetables, and cereals were significantly higher in experimental subjects, providing larger amounts of fiber and vitamin C (P<.05). The intakes of cholesterol and saturated and polyunsaturated fats were lower and those of oleic acid and omega - 3 fatty acids were higher (P<.001) in experimental subjects. Plasma levels of vitamins C and E (P<.05) and omega -3 fatty acids (P<.001), measured 2 months after randomization, were higher and those of omega-6 fatty acids were lower (P<.001) in experimental subjects.

CONCLUSIONS: This randomized trial suggests that patients following a cardioprotective Mediterranean diet have a prolonged survival and may also be protected against cancer. Further studies are warranted to confirm the data and to explore the role of the different lipids and fatty acids in this protection.

Dietary (n-3) and (n-6) polyunsaturated fatty acids rapidly modify fatty acid composition and insulin effects in rat adipocytes.

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J Nutr (United States) Mar 1998, 128 (3) p512-9

The influence of dietary (n-3) compared with (n-6) polyunsatured fatty acids (PUFA) on the lipid composition and metabolism of adipocytes was evaluated in rats over a period of 1 week. Isocaloric diets comprised 16.3 g/100 g protein, 53.8 g/100 g carbohydrate and 21.4 g/100 g lipids, the latter containing either (n-3) PUFA (32.4 mol/100 mol) or (n-6) PUFA (37.8 mol/100 mol) but having identical contents of saturated, monounsaturated and total unsaturated fatty acids and

identical polyunsaturated to saturated fatty acid ratios and double bond indexes. Despite comparable food intake, significantly smaller body weight increments and adipocyte size were observed in rats of the (n-3) diet group after feeding for 1 wk. Rats fed the (n-3) diet also had significantly lower concentrations of serum triglycerides, cholesterol and insulin compared with those fed the (n-6) diet, although levels of serum glucose and free fatty acids did not differ in the two dietary groups. In the (n-6) diet group, the (n-6) and (n-3) PUFA contents of plasma triglycerides, free fatty acids and phospholipids were 30-60% higher and 60-80% lower, respectively, than in the (n-3) diet group, whereas adipocyte plasma membrane phospholipids showed a significantly higher unsaturated to saturated fatty acid ratio and greater fluidity. Glycerol release in response to noradrenaline was significantly higher in the adipocytes of rats fed the (n-3) diet, whereas the antilipolytic effect of insulin generally did not differ in the two groups. Finally, insulin stimulated the transport of glucose and its incorporation into fatty acids to a lesser extent in adipocytes of (n-3) diet fed rats compared with (n-6) diet fed rats. This reduction in the metabolic effects of insulin in rats fed a (n-3) diet for 1 wk could be related to smaller numbers and a lower binding capacity of the insulin receptors on adipocytes and/or to a lesser degree of phosphorylation of the 95 kDa beta subunit of the receptor. In conclusion, dietary intake for 1 wk of (n-3) rather than (n-6) PUFA is sufficient to induce significant differences in the lipid composition and metabolic responses to insulin of rat adipocytes.

Effects of omega- 3 fatty acids and/or antioxidants on endothelial cell markers

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European Journal of Clinical Investigation (United Kingdom), 1998, 28/8 (629-635)

Background. Increased expression of cell adhesion molecules and increased procoagulant activity of the vascular endothelium have been postulated to characterize dysfunctional endothelium. The cellular effects of n-3 fatty acids (n-3 FAs) and antioxidants are still not clarified.

Methods. In a randomized, factorial two-by-two design study, we have investigated 41 male smokers with hyperlipidaemia before and after 6 weeks of supplementation with either n-3 FAs (4.8 g daily) or placebo with the addition of antioxidants (1.50 mg of vitamin C, 75 mg of vitamin E and 15 mg of p-carotene daily) or placebo with regard to the effects on some endothelial cell markers: thrombomodulin (sTM), von Willebrand factor (vWF), tissue plasminogen activator antigen (tPAag) and soluble forms of the cell adhesion molecules E-selectin, P-selectin and vascular cell adhesion molecule 1 (VCAM-1).

Results. In the n-3 FA group, significant reductions in the plasma levels of vWF (P = 0.034) and sTM (P<0.001) were demonstrated compared with placebo, whereas increased levels were found for E-selectin (P = 0.001) and VCAM-1 (P = 0.010). In the antioxidant group, no differences in changes were noted for any of the variables.

Conclusion. The reduction in the levels of sTM and VWF with n-3 FA supplementation could indicate an improvement with regard to the haemostatic markers of endothelial dysfunction, whereas the simultaneous increase in the soluble forms of E-selectin and VCAM-1 may suggest an adverse effect on the inflammatory system. The antioxidants seem to be neutral in their effect on these endothelial cell markers in our study population of smokers. The interpretation of the soluble forms of these molecules are, however, still debatable.

Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients

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Clinical Drug Investigation (New Zealand), 1998, 15/6 (473-482)

This study investigated whether an ethyl ester preparation of fish oil (omega-3) could normalise raised plasma concentrations of triglycerides, apolipoprotein CIII on apolipoprotein B-containing particles (LP CIII:B) found in patients with recent acute myocardial infarction. We also studied the effect of fish oil on antithrombin III levels. Out of 75 patients with a plasma triglyceride value less than or equal to 2.0 mmol/L, 22 normalised their triglycerides during diet and were therefore not randomised. The remaining patients were randomly assigned to 12 weeks' treatment with a daily dose of 4g omega-3 or placebo. Mean plasma triglyceride concentrations were reduced by 24% from 3.10 plus or minus 1.15 (SD) to 2.53 plus or minus 0.94 mmol/L ($p < 0.001$) on omega-3 ($p < 0.001$ vs placebo). The reduction was due to decreases in very low density lipoprotein concentrations. Total apolipoprotein CIII decreased significantly. This was due to reductions in LP CIII:non B concentrations, but the ratio LP CIII:non B/LP CIII:B was unaffected because of a slight insignificant decrease in LP CIII:B. The plasma triglyceride decreasing effect of omega-3 could therefore not be due to redistribution of CIII between lipoproteins. Low density lipoprotein (LDL) cholesterol increased significantly with omega-3 by 7%, and antithrombin III increased significantly with fish oil . In conclusion, omega-3 had a moderate plasma triglyceride lowering effect and increased LDL cholesterol slightly, while antithrombin III increased in patients with hypertriglyceridaemia who had recently experienced a myocardial infarction. Myocardial infarction starts via a thrombotic process at an atherosclerotic lesion in a coronary artery. Most patients developing this disease have an abnormal plasma lipoprotein pattern consisting of slightly raised triglycerides (TGs), moderately elevated total cholesterol , and low high density lipoprotein (HDL) cholesterol values predisposing to atherosclerosis.

Hypertriglyceridaemia may be associated with a greater risk for thrombosis in postmyocardial infarction patients because of a reduced fibrinolytic capacity. The dyslipidaemia may also indicate an unfavourable distribution of plasma lipoprotein particles in patients with myocardial infarction. Dietary changes normalise the dyslipidaemia in some patients but are inadequate in others. In these latter patients pharmacological lipid-lowering treatment is necessary. The myocardial infarction patient with an athero-thrombogenic syndrome could theoretically therefore benefit from a pharmacological agent acting on both the thrombotic and lipidaemic pathophysiological pathways. The pharmacological potency of the omega -3 -fatty acids allows for this possibility. It has been known since the mid 1970s that omega -3 -fatty acids are effective in lowering plasma triglyceride concentrations. They also increase the concentration of HDL cholesterol slightly. Their effects on cholesterol have varied, with some studies showing increases and others decreases. These fatty acids also inhibit platelet aggregation. It was therefore of interest to expand the experience of this type of treatment to effects on plasma lipoprotein particle distribution. We also studied parameters of fibrinolysis since the literature shows diverging results of omega - 3 - fatty acids on these parameters. In the present study we tested a new compound, omega-3, an oil consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with the aim of normalising dyslipidaemia, and reducing the thrombotic tendency in a potentially important target population for such treatment, postmyocardial infarction patients. The high EPA and DHA concentration in omega-3 made a convenient intake of only four capsules daily possible. The design of the study followed the current guidelines for secondary prevention of ischaemic heart disease.

One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations

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Atherosclerosis (Ireland), 1998, 137/2 (419-427)

n-3 Fatty acids in the form of ethyl esters (EE) allow lower daily doses and improved compliance. Administration of n-3 fatty acids to patients with glucose intolerance has led to controversial findings, some studies indicating worsening of the disorder, others no effect, or an improvement. A total of 935 patients with hypertriglyceridemia, associated with additional cardiovascular risk factors, i.e. glucose intolerance, NIDDM and/or arterial hypertension were entered a double blind (DB) protocol lasting 6 months with n-3 BE versus placebo, followed by a further 6 months of open study (n = 868) on 2 g a day of n-3 EE. At the end of the DB period, triglyceridemia in the total group was reduced significantly more by n-3 EE, without alterations in glycemic parameters. In the 6 months open follow up, patients on n-3 EE with type IIB hyperlipoproteinemia showed a significant reduction of total cholesterol , both in cases with (- 4.15% vs. the 6 month levels)

and without NIDDM (- 3.8%). HDL-cholesterol had an overall mean rise of 7.4%, maximal in type IV patients with (+9.1%) and without (+ 10.1%) NIDDM. No alterations in glycemic parameters were detected in treated patients. Administration of n-3 EE to patients with hypertriglyceridemia associated with NIDDM or impaired glucose tolerance appears safe and effective.

The effects of an omega-3 ethyl ester concentrate on blood lipid concentrations in patients with hyperlipidaemia

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The objective of this study was to investigate the effects and tolerability of an omega-3 ethyl ester concentrate (Omacor (R)) on serum lipid concentrations in patients with hyperlipidaemia. A multicentre, double-blind, randomised, placebo-controlled trial was performed in the hospital and general practice setting. 84 patients with hyperlipidaemia were given a therapeutic lipid-lowering diet for 10 weeks. Of these, 55 patients were randomised to a 12-week treatment period. 47 patients completed the study and two patients withdrew because of adverse events. Randomised patients received omega-3 ethyl ester concentrate or corn oil (placebo), both administered at a dose of 2 g twice daily in soft gelatin capsules. Main outcome measures included changes in eicosapentaenoic acid (EPA)/ docosahexaenoic acid (DHA) content of serum phospholipids, total serum triglycerides, total serum cholesterol , and high density lipoprotein (HDL) cholesterol between baseline (week 10) and the end of treatment (week 22). After 12 weeks of treatment, patients receiving the omega-3 ethyl ester concentrate showed a significant increase in the EPA/DHA content of serum phospholipids ($p < 0.0001$). No significant changes in serum phospholipids were observed in the patients given placebo. A mean [standard deviation (SD)] reduction in serum triglyceride of 28.3 (19.1)% ($p = 0.0001$) occurred in patients given the omega-3 ethyl ester concentrate. Patients receiving corn oil showed a nonsignificant mean (SD) increase in serum triglyceride of 9.1 (24.8)%. Therefore, a difference between the groups of 37.4% in favour of active treatment was found ($p < 0.0001$). Total serum cholesterol did not change significantly in either treatment group. Mean (SD) HDL cholesterol concentrations showed an increase of 0.9 (21.6)% in patients receiving omega-3 ethyl ester concentrate and 3.6 (24.3)% in the corn-oil group; however, neither increase was significant. In conclusion, omega-3 ethyl ester concentrate, 4 g/day, produced a significant reduction in mean serum triglyceride concentration in patients with hyperlipidaemia and was well tolerated.

On the effect of 2-deuterium- and 2-methyl-eicosapentaenoic acid derivatives on triglycerides, peroxisomal beta-oxidation and platelet aggregation in rats

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Biochimica et Biophysica Acta - Biomembranes (Netherlands), 1998, 1369/2 (193-203)

A series of 2-substituted eicosapentaenoic acid (EPA) derivatives (as ethyl esters) have been synthesized and evaluated as hypolipidemic and antithrombotic agents in feeding experiments in rats. Repeated administration of purified 2-methyleicosapentaenoic acid and its deuterium analogues (all as ethyl esters) to rats resulted in a decrease in plasma triglycerides and high density lipoprotein cholesterol . The 2-methyl-EPA analogues were, apparently, four times more potent than EPA in inducing the triglyceride lowering effect. The 2-deuterium-2-methyl-EPA decreased plasma cholesterol level to similar 40%. A moderate enlargement of the liver was observed in 2-methyl-EPA treated rats. This was accompanied with an acute reduction in the liver content of triglycerides and a stimulation of peroxisomal beta-oxidation and fatty acyl-CoA oxidase activity. The results suggest that the triglyceride-lowering, effect of 2-methyl-EPA may be due to a reduced supply of fatty acids for hepatic triglyceride biosynthesis because of increased fatty acid oxidation. Platelet aggregation with ADP and A23187 was performed ex vivo in platelet-rich plasma, after administration of different doses of the EPA-derivatives for five days. EPA and 2,2-dideuterium EPA had no effect on ADP-induced aggregation, while 2-deuterium-, 2-methyl- and 2-deuterium-2-methyl EPA produced a biphasic effect, i.e. potentiation and inhibition at low (250 mg/day kg body weight) and higher doses (600-1300 mg/day kg body weight), respectively. A23187-induced platelet aggregation was affected in a similar way by feeding the 2-substituted EPA derivatives, except that 2-deuterium-2-methyl EPA had no effect relative to EPA itself and that the inhibition was far greater than that for ADP-induced aggregation (similar 100% inhibition with 600 mg 2-methyl-EPA/day kg body weight). The ranking order of the EPA-derivatives to affect platelet aggregation and to cause hypolipidemia was different, suggesting different mechanisms. Our observations suggest that the effects of the EPA derivatives on platelet aggregation could be related to the degree of bulkiness around C2 and that an asymmetric substitution at C2 caused inhibition of platelet aggregation while a symmetric substitution did not. It is suggested that the bulky, asymmetric derivatives inhibit platelet aggregation by altering platelet membrane phospholipid packing.

Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease.

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Prostaglandins Leukot Essent Fatty Acids (Scotland) Apr 1998, 58 (4) p257-63

Thirty patients with coronary artery disease (CAD) were administered garlic (study group) while another 30 patients received the placebo (control group).

Various risk parameters were determined at 1.5 and 3 months of garlic administration. Garlic , administered in a daily dose of 2 x 2 capsules (each capsule containing ethyl acetate extract from 1 g peeled and crushed raw garlic), reduced significantly total serum cholesterol and triglycerides, and increased significantly HDL- cholesterol and fibrinolytic activity. There was no effect on the fibrinogen and glucose levels. In vitro effects of the garlic oil on platelet aggregation (PAg) and eicosanoid metabolism were examined; it inhibited PAg induced by several platelet agonists, and also platelet thromboxane formation. Two important paraffinic polysulphides - diallyl disulphide (DADS) and diallyl trisulphide (DATS) - derived from garlic and are usual constituents of garlic oil, showed antiplatelet activity, and also inhibited platelet thromboxane formation. In this respect DATS was more potent than DADS. The nature of inhibition of PAg by DATS was found to be reversible.

Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial.

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Arch Intern Med (United States) Jun 8 1998, 158 (11) p1189-94

BACKGROUND: Garlic powder tablets have been reported to lower serum cholesterol levels. There is widespread belief among the general public that garlic powder tablets aid in controlling cholesterol levels. However, much of the prior data demonstrating the cholesterol -lowering effect of garlic tablets involved studies that were inadequately controlled.

OBJECTIVE: To determine the lipid-lowering effect of garlic powder tablets in patients with hypercholesterolemia.

METHODS: This was a randomized, double-blind, placebo-controlled, 12-week, parallel treatment study carried out in 2 outpatient lipid clinics. Entry into the study after 8 weeks of diet stabilization required a mean low-density lipoprotein cholesterol level on 2 visits of 4.1 mmol/L (160 mg/dL) or lower and a triglyceride level of 4.0 mmol/L (350 mg/dL) or lower. The active treatment arm received tablets containing 300 mg of garlic powder (Kwai) 3 times per day, given with meals (total, 900 mg/d). This is equivalent to approximately 2.7 g or approximately 1 clove of fresh garlic per day. The placebo arm received an identical-looking tablet, also given 3 times per day with meals. The main outcome measures included levels of total cholesterol , triglycerides, low-density lipoprotein cholesterol , and high-density lipoprotein cholesterol after 12 weeks of treatment.

RESULTS: Twenty-eight patients (43% male; mean +/- SD age, 58 +/- 14 years) received garlic powder treatment and 22 (68% male; mean +/- SD age, 57 +/- 13 years) received placebo treatment. There were no significant lipid or lipoprotein

changes in either the placebo- or garlic -treated groups and no significant difference between changes in the placebo-treated group compared with changes in the garlic -treated patients.

CONCLUSION: Garlic powder (900 mg/d) treatment for 12 weeks was ineffective in lowering cholesterol levels in patients with hypercholesterolemia.

Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial.

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JAMA (United States) Jun 17 1998, 279 (23) p1900-2

CONTEXT: Garlic -containing drugs have been used in the treatment of hypercholesterolemia even though their efficacy is not generally established. Little is known about the mechanisms of action of the possible effects on cholesterol in humans.

OBJECTIVE: To estimate the hypocholesterolemic effect of garlic oil and to investigate the possible mechanism of action.

DESIGN: Double-blind, randomized, placebo-controlled trial.

SETTING: Outpatient lipid clinic.

PATIENTS: We investigated 25 patients (mean age, 58 years) with moderate hypercholesterolemia.

INTERVENTION: Steam-distilled garlic oil preparation (5 mg twice a day) vs placebo each for 12 weeks with wash-out periods of 4 weeks.

MAIN OUTCOME MEASURES: Serum lipoprotein concentrations, cholesterol absorption, and cholesterol synthesis.

RESULTS: Baseline lipoprotein profiles were (mean [SD]): total cholesterol , 7.53 (0.75) mmol/L (291 [29] mg/dL); low-density lipoprotein cholesterol (LDL-C), 5.35 (0.78) mmol/L (207 [30] mg/dL); high-density lipoprotein cholesterol (HDL-C), 1.50 (0.41) mmol/L (58 [16] mg/dL); and triglycerides, 1.45 (0.73) mmol/L (127 [64] mg/ dL). Lipoprotein levels were virtually unchanged at the end of both treatment periods (mean difference [95% confidence interval]): total cholesterol , 0.085 (-0.201 to 0.372) mmol/L (3.3 [-7.8 to 14.4] mg/dL), P=.54; LDL-C, 0.001 (-0.242 to 0.245) mmol/L (0.04 [-9.4 to 9.5] mg/dL), P=.99; HDL-C, 0.050 (-0.028 to 0.128) mmol/L (1.9 [-1.1 to 4.9] mg/dL), P=.20; triglycerides, 0.047 (-0.229 to 0.135) mmol/L (4.2 [-20.3 to 12.0]) mg/dL, P=.60. Cholesterol absorption (37.5% [10.5%] vs 38.3% [10.7%0], P=.58), cholesterol synthesis

(12.7 [6.5] vs 13.4 [6.6] mg/kg of body weight per day, P=.64), mevalonic acid excretion (192 [66] vs 187 [66] microg/d, P=.78), and changes in the ratio of lathosterol to cholesterol in serum (4.4% [24.3%] vs 10.6% [21.1%], P=.62) were not different in garlic and placebo treatment.

CONCLUSIONS: The commercial garlic oil preparation investigated had no influence on serum lipoproteins, cholesterol absorption, or cholesterol synthesis. Garlic therapy for treatment of hypercholesterolemia cannot be recommended on the basis of this study.

[Influence of lifestyle on the use of supplements in the Brandenburg nutrition and cancer study]

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Z Ernahrungswiss (Germany) Mar 1998, 37 (1) p38-46

Differences in dietary habits and lifestyle factors associated with a high dietary intake of fruit and vegetables are discussed and used to explain the disparity between results of observational epidemiologic studies consistently showing antioxidative vitamins to exert a protective effect on chronic diseases, and intervention studies so far not confirming this association. Within the scope of the "Brandenburger Ernahrungs- und Krebsstudie", the East German contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined whether study participants using supplements on a regular basis--minerals, vitamins, protein formulation, bran/linseed, fiber, yeast or garlic pills--differed from those who did not report use of supplements according to selected lifestyle factors and dietary intake of vitamins, minerals, fiber, cholesterol , and fat from food. The study sample consisted of 10,522 participants (4,500 men and 6,022 women) aged 35-65 years enrolled in the cohort from January 1995 to July 1996. Regular intake of one or more supplements during the past year was reported by 32.6% of women and 25.5% of men. Vitamin supplements were used by 18.8% of the women and 15.8% of the men. Figures for minerals were 14.2% for women and 8.6% for men, respectively. Garlic pills were taken regularly by 9.7% of men and 9.3% of women. Prevalence of supplement use was generally higher in women and was more pronounced in elderly participants. The most frequently used combinations were vitamin and mineral supplements, followed by a combination of garlic and either vitamin or mineral supplements. Increased use of supplements was significantly associated with higher level of education attained, regular engagement in sporting activities, health complaints, and dietary change during the previous year. No association between use of supplements and smoking status nor elevated alcohol consumption was observed. Body mass index above 30 was significantly related to increased intake of garlic pills, and in women to significantly increased use of vitamin and mineral supplements. For both men and women, age-adjusted consumption of fruit and vegetables and intake of vitamins, minerals, and fiber from food was higher for participants using mineral but also vitamin supplements compared to those who did not use these

supplements. For the cohort of the "Brandenburger Ernahrungs- und Krebsstudie" we observed on the one hand that age, gender, and health-conscious lifestyle factors were related to supplement use. On the other hand presence of subjective health complaints was related to supplement use, especially for use of vitamins and minerals. Participants, who regularly consumed minerals and vitamins were also shown to have a higher intake of foods and nutrients considered to exert an antioxidative effect.

In vitro effect of garlic powder extract on lipid content in normal and atherosclerotic human aortic cells.

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Lipids (United States) Oct 1997, 32 (10) p1055-60

In the present study, the mechanism of the in vitro effect of garlic powder extract (GPE) on lipid content of cultured human aortic cells was investigated. The addition of GPE abolished atherogenic blood serum-induced accumulation of free cholesterol , triglycerides, and cholesteryl esters in smooth muscle cells derived from uninvolved (normal) intima. In cells isolated from atherosclerotic plaque, GPE lowered these lipids. GPE inhibited lipid synthesis both in normal and atherosclerotic cells. It inhibited acyl-CoA:cholesterol acyltransferase activity that participates in the cholesteryl ester formation and stimulated cholesteryl ester hydrolase that degrades cholesteryl esters. This may explain the lipid reduction caused by GPE in atherosclerotic cells. GPE inhibited the uptake of modified low density lipoprotein and degradation of lipoprotein-derived cholesteryl esters, thus considerably reducing the intracellular accumulation of cholesteryl esters. This suggests the mechanism responsible for the prevention of lipid accumulation in aortic cells caused by atherogenic blood serum.

Modulation of lipid profile by fish oil and garlic combination.

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J Natl Med Assoc (United States) Oct 1997, 89 (10) p673-8

Fish consumption has been shown to influence epidemiology of heart disease, and garlic has been shown to influence triglyceride levels. This study was undertaken to evaluate the effect of fish oil and garlic combinations as a dietary supplement on the lipid subfractions. Forty consecutive subjects with lipid profile abnormalities were enrolled in a single-blind, placebo-controlled crossover study. Each subject received placebo for 1 month and fish oil (1800 mg of eicosapentanoic acid [EPA] + 1200 mg of docosahexanoic acid) with garlic powder (1200 mg) capsules daily for 1 month. Lipid fractionation was performed

prior to study initiation, after the placebo period, and after the intervention period. Subjects all had cholesterol levels > 200. Subjects were instructed to maintain their usual diets. Supplementation for 1 month resulted in an 11% decrease in cholesterol , a 34% decrease in triglyceride, and a 10% decrease in low-density lipoprotein (LDL) levels, as well as a 19% decrease in cholesterol /high-density lipoprotein (HDL) risk. Although not significant, there was a trend toward increase in HDL. There was no significant placebo effect. These results suggest that in addition to the known anticoagulant and antioxidant properties of both fish oil and garlic , the combination causes favorable shifts in the lipid subfractions within 1 month. Triglycerides are affected to the largest extent. The cholesterol lowering and improvement in lipid/HDL risk ratios suggests that these combinations may have antiatherosclerotic properties and may protect against the development of coronary artery disease.

Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men

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Am J Clin Nutr (United States) Feb 1997, 65 (2) p445-50

This study examined the effects of garlic and fish-oil supplementation (alone and in combination) on fasting serum lipids and lipoproteins in hypercholesterolemic subjects. After an initial run-in phase, 50 male subjects with moderate hypercholesterolemia were randomly assigned for 12 wk to one of four groups: 1) 900 mg garlic placebo/d + 12 g oil placebo/d; 2) 900 mg garlic /d + 12 g oil placebo/d; 3) 900 mg garlic placebo/d + 12 g fish oil/d, providing 3.6 g n-3 fatty acids/d; and 4) 900 mg garlic /d + 12 g fish oil/d. In the placebo group, mean serum total cholesterol , low-density-lipoprotein cholesterol (LDL-C), and triacylglycerols were not significantly changed in relation to baseline. Mean group total cholesterol concentrations were significantly lower with garlic +fish oil (-12.2%) and with garlic (-11.5%) after 12 wk but not with fish oil alone. Mean LDL-C concentrations were reduced with garlic +fish oil (-9.5%) and with garlic (-14.2%) but were raised with fish oil (+8.5%). Mean triacylglycerol concentrations were reduced with garlic +fish oil (-34.3%) and fish oil alone (-37.3%). The garlic groups (with and without fish oil) had significantly lower ratios of total cholesterol to high-density-lipoprotein cholesterol (HDL-C) and LDL-C to HDL-C. In summary, garlic supplementation significantly decreased both total cholesterol and LDL-C whereas fish-oil supplementation significantly decreased triacylglycerol concentrations and increased LDL-C concentrations in hypercholesterolemic men. The combination of garlic and fish oil reversed the moderate fish-oil-induced rise in LDL-C. Coadministration of garlic with fish oil was well-tolerated and had a beneficial effect on serum lipid and lipoprotein concentrations by providing a combined lowering of total cholesterol , LDL-C, and triacylglycerol concentrations as well as the ratios of total cholesterol to HDL-C and LDL-C to HDL-C.

Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis.

Neil HA; Silagy CA; Lancaster T; Hodgeman J; Vos K; Moore JW; Jones L; Cahill J; Fowler GH
Department of Public Health and Primary Care, University of Oxford.
J R Coll Physicians Lond (England) Jul-Aug 1996, 30 (4) p329-34

OBJECTIVE: To determine the effect of 900 mg/day of dried garlic powder (standardised to 1.3% allicin) in reducing total cholesterol .

DESIGN: Double-blind, randomised six-month parallel trial.

SUBJECTS: 115 individuals with a repeat total cholesterol concentration of 6.0-8.5 mmol/l and low-density lipoprotein (LDL) cholesterol of 3.5 mmol/l or above after six weeks of dietary advice.

INTERVENTION: The active treatment group received dried garlic tablets (standardised to 1.3% allicin) at a dosage of 300 mg three times daily. The control group received a matching placebo.

OUTCOME MEASURES: Primary end-point: total cholesterol concentration; secondary end-points: concentrations of LDL and high-density lipoprotein cholesterol , apolipoproteins (apo) A1 and B, and triglycerides.

RESULTS: There were no significant differences between the groups receiving garlic and placebo in the mean concentrations of serum lipids, lipoproteins or apo A1 or B, by analysis either on intention-to-treat or treatment received. In a meta-analysis which included the results from this trial, garlic was associated with a mean reduction in total cholesterol of -0.65 mmol/l (95% confidence intervals: -0.53 to -0.76).

CONCLUSIONS: In this trial, garlic was less effective in reducing total cholesterol than suggested by previous meta-analyses. Possible explanations are publication bias, overestimation of treatment effects in trials with inadequate concealment of treatment allocation, or a type 2 error. We conclude that meta-analyses should be interpreted critically and with particular caution if the constituent trials are small.

Isolation of cholesteryl ester transfer protein inhibitors from Panax ginseng roots.

Kwon BM; Nam JY; Lee SH; Jeong TS; Kim YK; Bok SH
Korea Research Institute of Bioscience & Biotechnology, Taejon.
Chem Pharm Bull (Tokyo) (Japan) Feb 1996, 44 (2) p444-5

We have isolated cholesteryl ester transfer protein (CETP) inhibitors from the extract of Korean Panax ginseng C. A. Meyer roots and identified them as polyacetylene analogs. These compounds inhibit human CETP with IC50 values of around 20-35 mg/ml.

A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids.

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Am J Clin Nutr (United States) Dec 1996, 64 (6) p866-70

A double-blind crossover study comparing the effect of aged garlic extract with a placebo on blood lipids was performed in a group of 41 moderately hypercholesterolemic men [cholesterol concentrations 5.7-7.5 mmol/L (220-290 mg/dL)]. After a 4-wk baseline period, during which the subjects were advised to adhere to a National Cholesterol Education Program Step I diet, they were started on 7.2 g aged garlic extract per day or an equivalent amount of placebo as a dietary supplement for a period of 6 mo, then switched to the other supplement for an additional 4 mo. Blood lipids, blood counts, thyroid and liver function measures, body weight, and blood pressure were followed over the entire study period. The major findings were a maximal reduction in total serum cholesterol of 6.1% or 7.0% in comparison with the average concentration during the placebo administration or baseline evaluation period, respectively. Low-density-lipoprotein cholesterol was also decreased by aged garlic extract, 4% when compared with average baseline values and 4.6% in comparison with placebo period concentrations. In addition, there was a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure in response to aged garlic extract. We conclude that dietary supplementation with aged garlic extract has beneficial effects on the lipid profile and blood pressure of moderately hypercholesterolemic subjects.

Perspectives on soy protein as a nonpharmacological approach for lowering cholesterol.

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J Nutr (United States) Mar 1995, 125 (3 Suppl) p675S-678S

Dietary therapy is the first step in the treatment of hyperlipidemia. However, some patients are unable to lower their cholesterol concentrations to a desirable range with diet alone. For primary prevention of coronary artery disease,

physicians and patients often wish to avoid pharmacologic therapy of elevated cholesterol concentrations. The use of adjuncts to diet such as soluble fibers, garlic and soy protein may allow target lipid concentrations to be reached without the use of drugs. Soy protein incorporated into a low-fat diet can reduce cholesterol and LDL- cholesterol concentrations. The main obstacles to greater use of soy protein in the therapy of hyperlipidemia include lack of knowledge by physicians and patients of its effects and lack of availability of easily used products. Although soy products such as tofu and soymilk are available in many stores, consumers may be unaware of their presence and uses. Without the publication of articles in mainstream medical journals on the cholesterol - lowering effects of soy protein, few physicians are likely to know of possible uses. Readily available packaged products, recipes and cookbooks also will be necessary to make incorporation of soy protein into the American diet a reality. (30 Refs.)

Consumption of a garlic clove a day could be beneficial in preventing thrombosis.

Ali M; Thomson M
Department of Biochemistry, Faculty of Science, Kuwait University, Safat, Kuwait.
Prostaglandins Leukot Essent Fatty Acids (Scotland) Sep 1995, 53 (3) p211-2

The effect of the consumption of a fresh clove of garlic on platelet thromboxane production was examined. A group of male volunteers in the age range 40-50 years participated in the study. Each volunteer consumed one clove (approximately 3 g) of fresh garlic daily for a period of 16 weeks. Each participant served as his own control. Thromboxane B2 (TXB2, a stable metabolite of thromboxane A2), cholesterol and glucose were determined in serum obtained after blood clotting. After 26 weeks of garlic consumption, there was an approximately 20% reduction of serum cholesterol and about 80% reduction in serum thromboxane. No change in the level of serum glucose was observed. Thus, it appears that small amounts of fresh garlic consumed over a long period of time may be beneficial in the prevention of thrombosis.

On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia.

Simons LA; Balasubramaniam S; von Konigsmark M; Parfitt A; Simons J; Peters W
University of New South Wales Lipid Research Department, St Vincent's Hospital, Darlinghurst, Australia.
Atherosclerosis (Ireland) Mar 1995, 113 (2) p219-25

The ingestion of garlic has been reported to have many cardiovascular effects, including a reduction in plasma cholesterol concentration and the susceptibility of LDL to oxidation. A double-blind, placebo-controlled, randomised crossover study was conducted in subjects with mild to moderate hypercholesterolaemia who were subject to strict dietary supervision and assessment. After a baseline dietary period of 28 days, subjects took Kwai garlic powder tablets 300 mg three times daily or matching placebo for 12 weeks, followed by 28 days washout, followed by a 12 weeks crossover on the alternative preparation. In the analysis hypercholesterolaemia was defined as those subjects in the range 5.5-8.05 mmol/l. Three subjects were withdrawn, one allocated to garlic and complaining of garlic body odour, one using placebo having intercurrent health problems, and one with a baseline cholesterol below 5.5 mmol/l, yielding analysable results in 28 subjects. Comparing the period on garlic with that on placebo, there were no significant differences in plasma cholesterol , LDL cholesterol , HDL cholesterol , plasma triglycerides, lipoprotein(a) concentrations, or blood pressure. Mean LDL cholesterol concentration was 4.64 +/- 0.52 mmol/l on garlic and 4.60 +/- 0.59 mmol/l on placebo. There was no demonstrable effect of garlic on oxidisability of LDL, on the ratio of plasma lathosterol/ cholesterol (a measure of cholesterol synthesis), nor on LDL receptor expression in lymphocytes. This study found no demonstrable effect of garlic ingestion on lipids and lipoproteins.

Direct anti-atherosclerosis-related effects of garlic.

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Institute of Experimental Cardiology, Russian Academy of Medical Sciences, Moscow.
Ann Med (England) Feb 1995, 27 (1) p63-5

Direct anti-atherosclerosis-related effects of garlic were studied using cell culture. An aqueous extract from garlic powder (GPE) was added to smooth muscle cells cultured from atherosclerotic plaques of human aorta. During a 24-hour incubation, GPE significantly reduced the level of cholesteryl esters and free cholesterol in these cultured cells and inhibited their proliferative activity. In addition, GPE significantly reduced cholesterol accumulation and inhibited cell proliferation stimulated by blood serum taken from patients with angiographically assessed coronary atherosclerosis, i.e. GPE reduced atherogenic manifestations of patients' serum. Garlic effect on blood atherogenicity of patients with coronary atherosclerosis has also been studied ex vivo. Following a 24-hour incubation with cultured cells, patients' blood serum caused an increase of total cell cholesterol . Blood serum taken 2 hours after an oral administration of 300 mg garlic powder tablet caused substantially less cholesterol accumulation in cultured cells. This suggests that garlic powder manifests direct anti-atherogenic-related action not only in vitro but also in vivo.

Cardiovascular disease.

Gore JM; Dalen JE
University of Massachusetts Medical School, Worcester.
JAMA (United States) Jun 1 1994, 271 (21) p1660-1

The GUSTO angiographic trial helps to confirm the open artery theory. Cholesterol levels in US adults continue to decrease. The consumption of one-half to one clove of garlic per day reduces cholesterol levels by approximately 9%.

Garlic as a lipid lowering agent--a meta-analysis.

Silagy C; Neil A
Department of Public Health and Primary Care, University of Oxford.
J R Coll Physicians Lond (England) Jan-Feb 1994, 28 (1) p39-45

Garlic supplements may have an important role to play in the treatment of hypercholesterolaemia. To determine the effect of garlic on serum lipids and lipoproteins relative to placebo and other lipid lowering agents, a systematic review, including meta-analysis, was undertaken of published and unpublished randomised controlled trials of garlic preparations of at least four weeks' duration. Studies were identified by a search of MEDLINE and the ALTERNATIVE MEDICINE electronic databases, from references listed in primary and review articles, and through direct contact with garlic manufacturers. Sixteen trials, with data from 952 subjects, were included in the analyses. Many of the trials had methodological shortcomings. The pooled mean difference in the absolute change (from baseline to final measurement in mmol/l) of total serum cholesterol, triglycerides, and high-density lipoprotein (HDL)- cholesterol was compared between subjects treated with garlic therapy against those treated with placebo or other agents. The mean difference in reduction of total cholesterol between garlic -treated subjects and those receiving placebo (or avoiding garlic in their diet) was -0.77 mmol/l (95% CI: -0.65, -0.89 mmol/l). These changes represent a 12% reduction with garlic therapy beyond the final levels achieved with placebo alone. The reduction was evident after one month of therapy and persisted for at least six months. In the dried garlic powders, in which the allicin content is standardised, there was no significant difference in the size of the reduction across the dose range of 600-900 mg daily. Dried garlic powder preparations also significantly lowered serum triglyceride by 0.31 mmol/l compared to placebo (95% CI: -0.14, -0.49).(ABSTRACT TRUNCATED AT 250 WORDS)

Limitation of the deterioration of lipid parameters by a standardized garlic - ginkgo combination product. A multicenter placebo-controlled double-blind study.

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Arzneimittelforschung (Germany) Sep 1993, 43 (9) p978-81

The efficacy of a garlic -ginkgo combination product (Allium plus) was analyzed in a randomized placebo-controlled double-blind study under extreme dietary conditions. The Christmas/New Year's season was chosen for this 2 months lasting investigation analyzing whether the known cholesterol lowering effect of garlic was even effective during the period of the year with the most cholesterol - rich meals. 43 patients with elevated total cholesterol levels ranging between 230-390 mg/dl completed the study. There were no significant changes of the total cholesterol values in both treatment groups. Nevertheless the analysis of improvement or deterioration of total cholesterol values revealed a clear difference between verum and placebo. 20% of the patients in the placebo group showed an improvement of their total cholesterol level, while there was a significant greater improvement rate of 35% in the verum group ($p < 0.05$). The responders of the verum group showed a reduction in the total cholesterol values from 298.5 +/- 53.8 to 293.0 +/- 56.4 mg/dl after 1 month and a total reduction of 10.4% after 2 months to 267.6 +/- 44.4 mg/dl. The difference after 2 months of treatment was significantly different from the starting value ($p < 0.05$). After the 2 months treatment phase there was a 2 weeks wash-out period. During this period the total cholesterol value returned to 293.5 +/- 90.1 mg/dl showing the effectiveness of garlic treatment, but indicating the need for a continuous long-term therapy.

Effect of garlic on total serum cholesterol. A meta-analysis

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Ann Intern Med (United States) Oct 1 1993, 119 (7 Pt 1) p599-605

OBJECTIVE: To assess the size and consistency of garlic 's effect on total serum cholesterol in persons with cholesterol levels greater than 5.17 mmol/L (200 mg/dL).

DATA SOURCES: Clinical trials were identified by a computerized literature search of MEDLINE and by an assessment of the bibliographies of published studies and reviews.

STUDY SELECTION: Trials were selected if they were randomized and placebo-controlled and if at least 75% of their patients had cholesterol levels greater than 5.17 mmol/L (200 mg/dL). Studies were excluded if they did not provide enough data to compute effect size. Five of 28 studies were selected for review.

DATA EXTRACTION: Details of study design, patient characteristics, interventions, duration of therapy, and cholesterol measurements were extracted by one author and were verified by another.

DATA SYNTHESIS: Study quality was evaluated by multiple reviewers using a closed-ended questionnaire. Patients treated with garlic consistently showed a greater decrease in total cholesterol levels compared with those receiving placebo.

Meta-analysis of homogeneous trials estimated a net cholesterol decrease attributable to garlic of 0.59 mmol/L (95% CI, 0.44 to 0.74) (23 mg/dL [CI, 17 to 29]) ($P < 0.001$).

CONCLUSIONS: Meta-analysis of the controlled trials of garlic to reduce hypercholesterolemia showed a significant reduction in total cholesterol levels. The best available evidence suggests that garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 9% in the groups of patients studied.

Effects of garlic coated tablets in peripheral arterial occlusive disease.

Kiesewetter H; Jung F; Jung EM; Blume J; Mrowietz C; Birk A; Koscielny J; Wenzel E
Abteilung fur Klinische Hamostaseologie und Transfusionsmedizin, Universitat des Saarlandes, Homburg/Saar.
Clin Investig (Germany) May 1993, 71 (5) p383-6

For the first time, a weak clinical efficacy of a 12-week therapy with garlic powder (daily dose, 800 mg) is demonstrated in patients with peripheral arterial occlusive disease stage II. The increase in walking distance in the verum group by 46 m (from 161.0 +/- 65.1 to 207.1 +/- 85.0 m) was significantly higher ($P < 0.05$) than in the placebo group (by 31 m, from 172.0 +/- 60.9 to 203.1 +/- 72.8). Both groups received physical therapy twice a week. The diastolic blood pressure, spontaneous thrombocyte aggregation, plasma viscosity, and cholesterol concentration also decreased significantly. Body weight was maintained. It is quite interesting that the garlic -specific increase in walking distance did not appear to occur until the 5th week of treatment, connected with a simultaneous decrease in spontaneous thrombocyte aggregation. Therefore, garlic may be an appropriate agent especially for the long-term treatment of an incipient intermittent claudication.

Can garlic reduce levels of serum lipids? A controlled clinical study.

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Clinical Research Center, New Orleans, Louisiana 70112.
Am J Med (United States) Jun 1993, 94 (6) p632-5

PURPOSE: To assess the effects of standardized garlic powder tablets on serum lipids and lipoproteins, glucose, and blood pressure.

SUBJECTS AND METHODS: Forty-two healthy adults (19 men, 23 women), mean age of 52 +/- 12 years, with a serum total cholesterol (TC) level of greater than or equal to 220 mg/dL received, in a randomized, double-blind fashion, either 300 mg three times a day of standardized garlic powder in tablet form or

placebo. Diets and physical activity were unchanged. This study was conducted in an outpatient, clinical research unit.

RESULTS: The baseline serum TC level of 262 +/- 34 mg/dL was reduced to 247 +/- 40 mg/dL ($p < 0.01$) after 12 weeks of standard garlic treatment. Corresponding values for placebo were 276 +/- 34 mg/dL before and 274 +/- 29 mg/dL after placebo treatment. Low-density lipoprotein cholesterol (LDL-C) was reduced by 11% by garlic treatment and 3% by placebo ($p < 0.05$). There were no significant changes in high-density lipoprotein cholesterol, triglycerides, serum glucose, blood pressure, and other monitored parameters.

CONCLUSIONS: Treatment with standardized garlic 900 mg/d produced a significantly greater reduction in serum TC and LDL-C than placebo. The garlic formulation was well tolerated without any odor problems.

Hypertension and hyperlipidaemia: garlic helps in mild cases.

Auer W; Eiber A; Hertkorn E; Hoehfeld E; Koehrle U; Lorenz A; Mader F; Merx W; Otto G; Schmid-Otto B; et al
Incorporated Society, Nittendorf, West Germany.
Br J Clin Pract Suppl (England) Aug 1990, 69 p3-6

Forty-seven non-hospitalised patients with mild hypertension took part in a randomised, placebo-controlled, double-blind trial conducted by 11 general practitioners. The patients who were admitted had diastolic blood pressures between 95 and 104 mmHg after a two-week acclimatization phase. The patients then took either a preparation of garlic powder (Kwai) or a placebo of identical appearance for 12 weeks. Blood pressure and plasma lipids were monitored during treatment after four, eight and 12 weeks. Significant differences between the placebo and the drug group were found during the course of therapy. For example, the supine diastolic blood pressure in the group having garlic treatment fell from 102 to 91 mmHg after eight weeks (p less than 0.05) and to 89 mmHg after 12 weeks (p less than 0.01). The serum cholesterol and triglycerides were also significantly reduced after eight and 12 weeks of treatment. In the placebo group, on the other hand, no significant changes occurred.

Therapy with garlic: results of a placebo-controlled, double-blind study.

Vorberg G; Schneider B
University of Hannover, West Germany.
Br J Clin Pract Suppl (England) Aug 1990, 69 p7-11

A double-blind study of 40 hypercholesterolaemic out-patients was carried out over a period of four months to examine the effects of a garlic powder preparation*. The drug group received 900 mg garlic powder per day, equivalent

to 2,700 mg of fresh garlic . During the therapy, the drug group showed significantly lower total cholesterol, triglycerides and blood pressure than those of the placebo group. In addition, results of a self-evaluation questionnaire indicated that patients in the drug group had a greater feeling of 'well-being'.

The effect of a garlic preparation on the composition of plasma lipoproteins and erythrocyte membranes in geriatric subjects.

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Chair of Internal Medicine-Gerontology, University of Erlangen-Nuremberg, West Germany.
Br J Clin Pract Suppl (England) Aug 1990, 69 p12-9

This study evaluated the effect of a dried garlic powder preparation, standardised to 1.3% alliin, on the composition of plasma lipoproteins and erythrocyte membranes. Forty volunteers, aged 70 years and over, took 600 mg of garlic powder per day for three months. In participants with initially normal plasma cholesterol levels (CH less than 200 mg/dl; n = 11) after three months of garlic tablet administration, little or no change in CH values was registered, as for most of the other parameters. In contrast, in volunteers with initially elevated CH levels (CH greater than 200 mg/dl, n = 29), the CH levels were reduced by -7.7% (p less than 0.001). This reduction took place primarily in the esterified cholesterol fraction (-12%, p less than 0.001), whereas free cholesterol concentrations were not altered significantly. Triglycerides (-15.9%, p less than 0.05) and plasma choline phospholipids (-4.6%, p less than 0.01) were also reduced. No change of the plasma LDL-CH to HDL-CH ratio was observed in this group. Based on the weight of lyophilised, haemoglobin-free erythrocytes, the mean membrane concentration of phospholipids and cholesterol in the total cohort (n = 40) increased by 5.7% (p less than 0.001) and 6.1% (p less than 0.01), respectively. These increases were more pronounced the lower the body mass indices (kg/m2) were, and the longer the duration of garlic administration was. The molar ratio of membrane phospholipids to cholesterol remained unchanged. The results are discussed with regard to a possible role of the garlic -induced membrane effects in the plasma lipid-lowering potency of garlic and preparations made from it.

Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate.

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Arzneimittelforschung (Germany) Dec 1992, 42 (12) p1473-7

The efficacy and tolerance of a garlic preparation (Sapec, Kwai) was investigated in a randomized double-blind study vs. bezafibrate. This multi-centre study was

conducted in 5 general medical practices and involved 98 patients with primary hyperlipoproteinaemia. The daily doses of the active substances were 900 mg of garlic powder (standardized as to 1.3% alliin) and 600 mg of bezafibrate, respectively. The pre-phase with placebo lasted 6 weeks, the treatment period covered 12 weeks. All patients were advised to observe a low-fat "step-1 diet" for the duration of the study. The 98 case report forms allowed the statistical evaluation of total cholesterol, HDL cholesterol and triglyceride levels for 94 patients, and of LDL cholesterol values for 92 patients. In the course of the treatment both study medications caused a statistically highly significant reduction in total cholesterol, in LDL cholesterol and triglycerides, and an increase in HDL cholesterol . However, there was no significant difference in the efficacies of both medication groups. Side effects were mentioned by 5 patients each in both treatment groups, none of which led to the withdrawal of the patients. Concerning the garlic preparation, there was no correlation between the perception of garlic odour and the influence on the cholesterol level.

[Postprandial lipemia under treatment with Allium sativum. Controlled double-blind study of subjects with reduced HDL2- cholesterol]

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Institut fur Klinische Chemie und Laboratoriumsdiagnostik, Universitat Leipzig.
Arzneimittelforschung (Germany) Oct 1992, 42 (10) p1223-7

Postprandial Lipaemia under Treatment with Allium sativum/Controlled double-blind study in healthy volunteers with reduced HDL2-cholesterol levels. The effectiveness of a standardized garlic powder preparation (Sapec, Kwai) on alimentary hypertriglyceridaemia after intake of a standardized fatty test meal containing 100 g butter was analyzed in a randomized placebo-controlled double-blind study. 24 volunteers with HDL2- cholesterol concentrations in plasma of less than 10 mg/dl (men) respectively 15 mg/dl (women) participated in the study. The volunteers received 3 times 1 tablet daily over a period of 6 weeks equivalent to a daily dosage of 900 mg garlic powder in the active treated group. Control measurements were made on the 1st, 22nd and 43rd day of treatment and 0, 3 and 5 h after intake of the meal. The postprandial increase of triglycerides was clearly reduced under garlic medication as compared to placebo treatment. The determined AUC-values for the triglycerides were up to 35% lower in the garlic group compared to the placebo group. The regular intake of the garlic preparation over the period of 6 weeks showed a significant lowering of the fasting values of triglycerides in comparison to placebo. Under garlic medication HDL2-cholesterol increased more than under placebo in tendency.

Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects.

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J Postgrad Med (India) Jul 1991, 37 (3) p128-31

The effect of raw garlic on serum cholesterol, fibrinolytic activity and clotting time was studied in 50 medical students of the age group of 17 to 22 years before and after feeding raw garlic . All pre-experimental values ranged within normal limits. The volunteers were then divided into experimental and control groups. The subjects of the experimental group were given 10 gm of raw garlic daily after breakfast for two months. Fasting blood samples of all the subjects were investigated after two months. In the control group, there was no significant change in any of the above parameters. In the experimental group, there was a significant decrease in serum cholesterol and an increase in clotting time and fibrinolytic activity. Hence, garlic may be an useful agent in prevention of thromboembolic phenomenon.

Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors.

Kiesewetter H; Jung F; Pindur G; Jung EM; Mrowietz C; Wenzel E
Department of Clinical Hemostasiology and Transfusion Medicine, University of the Saarland, Homburg.
Int J Clin Pharmacol Ther Toxicol (Germany) Apr 1991, 29 (4) p151-5

Significant positive effects could be achieved in a placebo-controlled double-blind study through the administration of 800 mg of garlic powder over a period of four weeks. Spontaneous thrombocyte aggregation disappeared, the microcirculation of the skin increased by 47.6% (from 0.63 +/- 0.13 to 0.93 +/- 0.22 mm/s), plasma viscosity decreased by 3.2% (from 1.25 +/- 0.34 to 1.21 +/- 0.43 mPas), diastolic blood pressure by 9.5% (from 74 +/- 9 to 67 +/- 5 mmHg), and blood glucose concentration by 11.6% (from 89.4 +/- 8.8 to 79.0 +/- 11.9 mg/dl). The vascular protection of garlic as atherosclerosis prevention by influencing the mentioned risk parameters for cardiovascular diseases must be pointed out. Especially interesting is the thrombocyte aggregation inhibiting effect. Thus, the application of garlic may be useful in case of acetylsalicyclic acid intolerance.

[Garlic as phytogenic antilipemic agent. Recent studies with a standardized dry garlic powder substance]

Brosche T; Platt D
Lehrstuhl fur Innere Medizin-Gerontologie, Universitat Erlangen-Nurnberg.
Fortschr Med (Germany) Dec 20 1990, 108 (36) p703-6

Garlic (Allium sativum L.) is a commonplace drug. It is now available in the form of dragees made of garlic powder, standardized to 1.3% alliin. The lipid-lowering potential of such preparations has not been reviewed yet. In 7 out of 8 studies, including over 500 patients, a daily dose of 0.6 g to 0.9 g garlic powder reduced plasma cholesterol and triglyceride levels by 5 to 20 percent. The metabolic mechanisms of these reductions are not known. (0 Refs.)

Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study.

Mader FH
Study Group on Phytotherapy of the German Association of General Practitioners, Nittendorf.
Arzneimittelforschung (Germany) Oct 1990, 40 (10) p1111-6

In a multicentric placebo-controlled randomised study the effect of standardized garlic -powder tablets (Kwai, Sapec) in the treatment of hyperlipidaemia was investigated. A total of 261 patients of 30 general practitioners in West Germany with total cholesterol and/or triglyceride values more than 200 mg/dl (mostly hyperlipoproteinaemia type II a/II b) took part in the study. Patients were randomly allocated to take tablets containing a total of 800 mg garlic powder (standardized to 1.3% of alliin content) daily or the same number of placebo tablets for 16 weeks (monthly controlled). 221 patients were used for statistical analysis of total cholesterol and 219 patients for the analysis of triglyceride values. Mean serum cholesterol levels dropped in the verum group from 266 to 235 mg/dl (i.e. 12%) during the 4 month treatment period, mean triglyceride values fell in the verum group from 226 to 188 mg/dl (i.e. 17%). The best cholesterol lowering effects were seen in the patients with initial total cholesterol values between 250-300 mg/dl. The difference between the verum and placebo group was highly significant (p less than 0.001). A mild garlic smell was observed in up to 21% of the verum group and up to 9% in the placebo group. Only one of the patients left the study for this reason. Standardized garlic tablets have been shown to be effective in the treatment of hyperlipidaemia by lowering total cholesterol values by an average of 12% and triglyceride values by an average of 17%.

Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations

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Br J Clin Pharmacol (England) Nov 1989, 28 (5) p535-44

1. Claims for beneficial effects on cholesterol levels, fibrinolytic activity, and platelet aggregation are attributed both to fresh garlic and onions (or their extracts) and to commercially available preparations.

2. Regarding fresh garlic, the claims have been confirmed, but so far only at very high dosages.

3. For onions and commercially available supplements contradictory results have been reported.

4. All published trials showed severe methodological shortcomings. Some trials were not randomized and/or not blinded whilst this was possible, and in only one of every three studies more than 25 patients participated in each treatment group. In no trial was prognostic comparability of the treatment and the control groups ascertained. At the moment there is inadequate scientific justification for garlic supplementation. (39 Refs.)

Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia.

Harenberg J; Giese C; Zimmermann R
First Medical Department, Klinikum Mannheim, University of Heidelberg, F.R.G.
Atherosclerosis (Netherlands) Dec 1988, 74 (3) p247-9

The effects of intake of dried garlic on blood coagulation, fibrinolysis, platelet aggregation, serum cholesterol levels, and blood pressure were studied in 20 patients with hyperlipoproteinemia over a period of four weeks. Fibrinogen and fibrinopeptide A significantly decreased by 10%. Streptokinase activated plasminogen and fibrinopeptide B beta 15-42 significantly increased by about 10%. Serum cholesterol levels significantly decreased by 10%. Systolic and diastolic blood pressure decreased. ADP and collagen induced platelet aggregation were not influenced.

Lack of efficacy of dried garlic in patients with hyperlipoproteinemia.

Luley C; Lehmann-Leo W; Moller B; Martin T; Schwartzkopff W
Arzneimittelforschung (Germany, West) Apr 1986, 36 (4) p766-8

The effects of dried garlic on blood lipids, apolipoproteins and blood coagulation parameters in hyperlipemic patients were studies in two controlled, randomized, double-blind studies. Both studies comprised placebo and therapy periods of 6 weeks each. The doses administered were 3 X 198 mg in Study I (34 patients) and 3 X 450 mg in Study II (51 patients). In both studies, the following serum parameters were measured every 3 weeks: total cholesterol, HDL (high density lipoprotein)- and LDL (low density lipoprotein)- cholesterol, triglycerides and

several safety parameters. In addition, apolipoproteins A and B, euglobulin lysis time, fibrin split products, prothrombin time, whole blood coagulation time and fibrinogen levels were determined in the second study only. The results indicated that neither dosage of dried garlic showed any significant effect on any of the parameters measured. It is therefore concluded that, if there is any effect of garlic on the parameters measured, it is not apparent when using a dried preparation in the dosage studied.

Bulgarian traditional medicine: a source of ideas for phytopharmacological investigations.

Petkov V
J Ethnopharmacol (Switzerland) Feb 1986, 15 (2) p121-32

Some data about the use of medicinal plants in Bulgarian traditional medicine in the Middle Ages and in modern times are presented and the results of 40-year-long experimental-pharmacological investigations on many medicinal plants used in Bulgarian traditional medicine are reviewed. In-depth discussion is presented on the investigations of garlic (Allium sativum L.), a plant widely used by Bulgarian people for treating different diseases. Data from studies on a large number of plants used for treatment of hypertension, infectious diseases and as diuretic and spasmolytic remedies are summarized. (51 Refs.)

Influence of garlic on serum cholesterol, serum triglycerides, serum total lipids and serum glucose in human subjects.

Bakhsh R; Chughtai MI
Nahrung (Germany, East) 1984, 28 (2) p159-63

Human subjects were used for a garlic experiment. The subjects were given a fat-rich diet for 7 days and on the 8th day the fasting blood was analyzed for serum cholesterol, serum triglycerides, serum total lipids and serum glucose. The human subjects were then given a fat-rich diet with 40 g of garlic for 7 days and on the 15th day the fasting blood was analyzed for the above investigations. On a fat-rich diet the serum cholesterol, serum triglycerides and serum total lipids were significantly increased as compared to normally fed diet. When 40 g of garlic was substituted in fat-rich diet for 7 days, the garlic significantly reduced the serum cholesterol and serum triglycerides.

[Garlic therapy? Theories of a folk remedy (author's transl)]

Ernst E
MMW Munch Med Wochenschr (Germany, West) Oct 9 1981, 123 (41) p1537-8

Garlic has had a firm place in folk medicine since ancient times. More recent results are summarized here which show that extracts of the plant have an antimicrobial action, they are capable of lowering blood cholesterol and of reducing secondary vascular changes. They raise fibrinolytic activity and inhibit thrombocyte aggregation. Therefore the plant contains highly active therapeutic principles which appear to be particularly suitable for prophylaxis of arteriosclerosis.

The structure-hemolysis relationship of oleanolic acid derivatives and inhibition of the saponin-induced hemolysis with sapogenins.

Hase J; Kobashi K; Mitsui K; Namba T; Yoshizaki M; Tomimori T
J Pharmacobiodyn (Japan) Nov 1981, 4 (11) p833-7

Chikusetsusaponin IV and V, whose genin is oleanolic acid, exhibited weak hemolytic activities. Removal of glucose residue at position 29 of chikusetsusaponin V by partial hydrolysis increased the activity more than 30-fold. Methylation of the carboxyl group at position 28 increased the activity furthermore by about 10-fold, showing HD50 value of 3.77 microM. On the other hand, removal of the sugar chain at position 3 of chickusetsusaponin V by partial hydrolysis completely lost the activity. These facts suggest that the sugar chain at position 3 of oleanolic acid is essential but that at position 29 is pernicious for the activity. The cytolytic agents, whose target has been regarded as membrane cholesterol, were inactivated not only by cholesterol but also by sapogenins such as oleanolic acid, gitogenin and hederagenin. Among saponins tested, akebia saponin B and C were inactivated by cholesterol, but not by the genins, probably because their affinities for the genins are too low to form complexes.

The long-term use of garlic in ischemic heart disease--an appraisal.

Arora RC; Arora S; Gupta RK
Atherosclerosis (Netherlands) Oct 1981, 40 (2) p175-9

The hypocholesterolemic and fibrinolysis-enhancing properties of garlic were assessed in patients with ischemic heart disease (IHD) and in healthy control subjects. The peak of blood fibrinolytic activity (BFA) achieved at the 4th week of garlic therapy was not sustained despite its continuous use and returned to about the pre-garlic values at the 12th week. Garlic withdrawal did not cause any further change in BFA. Under the same conditions serum total cholesterol (STC) values did not show any significant change. Both of the foregoing features were observed in the IHD as well as in the control group. Garlic therapy for 12 weeks did not cause any appreciable changes in serum triglyceride, beta-lipoprotein, plasma fibrinogen levels or coagulation time in either IHD or control subjects. The evidence cited above does not appear to substantiate the prevalent popular

belief in the efficacy of garlic in the management of IHD either as a hypocholesterolemic or as a fibrinolytic agent.

Comparative effect of clofibrate, garlic and onion on alimentary hyperlipemia.

Arora RC; Arora S
Atherosclerosis (Netherlands) Jul 1981, 39 (4) p447-52

The effect of clofibrate on the same subjects in similar test conditions were used as a control to verify the alleged beneficial effects from garlic and onion on alimentary hyperlipemia in normals and in cases with ischemic heart disease. The results showed that clofibrate checked the fat-induced (a) rises of serum triglyceride and plasma fibrinogen, and (b) falls of coagulation time (CT) and blood fibrinolytic activity (BFA). Only garlic had a clofibrate-like effect on CT but both garlic and onion checked the postprandial fall of BFA. Clofibrate, however, increased BFA even above the fasting level. Serum cholesterol and beta-lipoprotein were not appreciably affected by fat with or without any drug. Thus, surprisingly, the so-called beneficial effects of garlic and onion were not seen in subjects who had shown significant changes after clofibrate.

Effect of garlic on normal blood cholesterol level.

Bhushan S; Sharma SP; Singh SP; Agrawal S; Indrayan A; Seth P
Indian J Physiol Pharmacol (India) Jul-Sep 1979, 23 (3) p211-4

The effect of raw garlic on normal blood cholesterol level in males of the age group of 18-35 years was studied. The subjects, who never ingested garlic before, were given 10 g of garlic daily with their diet for two months. Fasting blood samples were investigated in respect of cholesterol before and after two months of garlic intake. Initially the blood cholesterol level ranged between 160-250 mg% which decreased significantly in all the subjects of experimental group after two months of ingestion of garlic . The slight decrease or increase in the blood cholesterol level of control group was not significant. The raw garlic can be advocated for daily ingestion in order to lower one's blood cholesterol level even if it is within normal limits.

Effect of the essential oils of garlic and onion on alimentary hyperlipemia.

Bordia A; Bansal HC; Arora SK; Singh SV
Atherosclerosis (Netherlands) Jan-Feb 1975, 21 (1) p15-9

Summary: The effect of garlic and onion on alimentary hyperlipemia, induced by feeding 100 g butter, has been studied in 10 healthy subjects. The freshly extracted juice of 50 g of garlic or onion, as well as an equivalent amount of their ether-extracted essential oils, was administered randomly on four different days during a one-week period. Garlic and onion have a significant protective action against fat-induced increases in serum cholesterol and plasma fibrinogen and decreases in coagulation time and fibrinolytic activity. The essential oil fraction, which contains all the taste and odour, exactly duplicated the beneficial effects of whole garlic and onion. It is, therefore, concluded that the active principle of garlic and onion is the essential oil, which chemically is a combination of sulphur-containing compounds, mainly allyl propyl disulphide and diallyl disulphide.

Garlic extract therapy in children with hypercholesterolemia

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Archives of Pediatrics and Adolescent Medicine (United States), 1998, 152/11 (1089-1094)

Objective: To determine whether garlic extract therapy is efficacious and safe in children with hypercholesterolemia.

Design: Randomized, double- blind, placebo-controlled clinical trial.

Setting: Specialized pediatric lipid disorders ambulatory clinic.

Participants: Thirty pediatric patients, aged 8 to 18 years, who had familial hyperlipidemia and a minimum fasting total cholesterol level greater than 4.8 mmol/L (>185 mg/dL).

Intervention: An 8-week course of a commercially available garlic extract (Kwai [Lichtwer Phanna, Berlin, Germany], 300 mg, 3 times a day) or an identical placebo.

Main Outcome Measures: Absolute and relative changes in fasting lipid profile parameters. Results: The groups were equivalent at baseline and compliance was similar in the 2 groups (P = .45). There was no significant relative attributable effect of garlic extract on fasting total cholesterol (+0.6% [95% confidence interval, -5.8% to +6.9%]) or low-density lipoprotein cholesterol (-0.5% [95% confidence interval, -8.7% to +7.6%]). The lower limits of the confidence intervals did not include -10%, the minimum relative attributable effect believed to be clinically important. Likewise, no significant effect was seen on the levels of high-density lipoprotein, triglycerides, apolipoprotein B-100, lipoprotein (a), fibrinogen, homocysteine, or blood pressure. There was a small effect on apolipoprotein A-I (+10.0% [95% confidence interval, + 1.2% to + 16.5%] P=.03). There were no differences in adverse effects between groups.

Conclusion: Garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.

Changes in platelet function and susceptibility of lipoproteins to oxidation associated with administration of aged garlic extract

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Journal of Cardiovascular Pharmacology (United States), 1998, 31/6 (904-908)

Garlic and some of its organosulfur components have been found to be potent inhibitors of platelet aggregation in vitro. Demonstration of their efficacy in vivo, however, especially when administered over extended periods, is sparse. We recently performed a 10-month study comparing the effect of aged garlic extract (AGE) with placebo on the lipid profiles of moderately hypercholesterolemic men. In the course of the intervention trial, we examined platelet functions and susceptibility of lipoproteins to oxidation in a subgroup of this study population. Study subjects supplemented with 7.2 AGE per day showed a significant reduction of epinephrine- and, to a lesser degree, collagen-induced platelet aggregation but failed to demonstrate an inhibition of adenosine diphosphate (ADP)-induced aggregation. Platelet adhesion to fibrinogen, measured in a laminar flow chamber at moderately high shear rate, was reduced by similar30% in subjects taking AGE compared with placebo supplement. A trend toward decreased susceptibility of lipoproteins to oxidation also was noted during AGE administration compared with the placebo period. We conclude that the beneficial effect of garlic preparations on lipids and blood pressure extends also to platelet function, thus providing a wider potential protection of the cardiovascular system.

Dietary therapy for preventing and treating coronary artery disease

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American Family Physician (United States), 1998, 57/6 (1299-1306)

Nearly one half of Americans die of cardiovascular disease. The morbidity and mortality associated with coronary artery disease is strongly related to abnormal lipid levels, oxidation of lipids and intra-arterial clot formation. Nutrition powerfully influences each of these factors. There is growing evidence that patients can improve lipid levels and decrease the rate of cardiovascular events by 'adding' specific foods to their diets and switching from saturated and polyunsaturated to monounsaturated fats and n-3 fatty acids. Appropriate dietary changes decrease arteriosclerotic plaque formation, improve endothelial vasomotor dynamics, reduce oxidation of low- density lipoproteins and enhance

thrombolytic activity. Brief discussions between physicians and patients can influence patients' food choices. Changes in diet can reduce the premature mortality and morbidity associated with coronary artery disease.

Effect of garlic on some blood lipids and hmgcoa reductase activity

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Iranian Journal of Medical Sciences (Iran), 1996, 21/3-4 (141-146)

Triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, lipoprotein (a), free fatty acids and glucose levels were measured in the serum or plasma of 86 normal male human subjects, aged 25 to 50 years, before and after one month of garlic powder consumption (one 400 mg garlic tablet, 3 times daily). Levels of total cholesterol, LDL cholesterol and triglycerides were significantly decreased after garlic consumption (by 10.7%, 11.5% and 14.2% respectively, $p < 0.05$). Furthermore, this decrease was significantly greater ($p < 0.05$) for initial cholesterol levels of > 200 mg/dl and triglyceride levels of > 150 mg/dl/(14.7% and 15% respectively), and less pronounced for cholesterol levels of less than or equal to200 mg/dl and triglyceride levels of less than or equal to150 mg/dl/(7.3% and 6% respectively). The reduction in LDL cholesterol was also significantly greater ($p < 0.05$) for initial levels of > 135 mg/dl/(16.7%)as compared with levels of less than or equal to135 mg/dl/(10.0%). No significant differences existed in the levels of glucose, free fatty acids, lipoprotein (a) and HDL cholesterol measured before and after consumption of garlic . Measurements of cholesterol and triglycerides were also carried out in 15 normal male rats, weighing 250 to 300g, after receiving a diet containing 2.5% garlic powder for 10 days. Total cholesterol and triglyceride levels were significantly lower ($p < 0.05$) in these rats as compared to a control group receiving regular stock powder without garlic . The specific activity of HMGCoA reductase in the liver microsomal fraction of 12 normal male rats receiving the garlic powder (2.5% of the diet) for 10 days, was also significantly decreased ($p < 0.05$) as compared to a control group on the stock diet without garlic .

Physical performance support with combined phytotherapy. Ginseng, whitethorn and mixed pollen combination against stress

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Therapiewoche (Germany), 1996, 46/25 (1421-1425)

In a randomized, double-blind, clinically-controlled study, BNK 04, a combination of active ingredients containing ginseng, hawthorn, and micronized mixed polled as its main ingredients, was administered to 18 stressed and

untrained patients (test group: 9 female, 9 male subjects; mean age = 56,9 years) for 40 days (first treatment phase). A significant increase in physical performance ($p < 103$) as compared to the control group (10 female, 8 male patients; mean age = 59,2 years) was detected by means of bicycle ergometry. The difference between groups was 20,0%, expressed as the Watt-minute product (Delta = 207 W x min). Sixteen patients of the test group underwent a second treatment phase with BNK 04 (single-blind) following a 4-week washout phase, during which patients received placebo. At the onset of the second treatment phase, physical performance continued to be significantly increased ($p = 0,008$) compared to baseline (11,7%). At the end of treatment, the enhancement of physical performance was 20,6% combpared to baseline ($p = 0,006$). Adverse drug reactions were not observed. These results demonstrate the conditioning effect on physical performance of the active ingredient combination, BNK 04, upon repeated administration.

Antioxidant of the coronary diet and disease

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Clinica Cardiovascular (Spain), 1996, 14/2 (29-38)

High levels of cholesterol and Low Density Lipoproteins (LDL) in plasma are related to high risk to develop Coronary Heart Disease (CHD). LDL-chosterol is a primary ingredient of the atherosclerotic plaque; its accumulation in the subendothelial space is due to peroxidative reactions. Natural antioxidants such as carotenes, polyphenolic flavonoids, vitamin E and C show defensive properties against lipid peroxidation, hence it is possible to apply these molecules in clinical therapy in the prevention of the CHD. On the other hand, alcohol, and special red wine, as well as the intake of selenium can afford a cardioprotective effect. Blood cholesterol reduction, dietary and/or due to pharmacological interventions, could modulate lipid peroxidation through a decreased production of O2.-, pivotal step in the peroxidative chain of reactions. The importance of other dietary components (fresh fruits, nuts, garlic and other vegetables as well as olive oil) have been analyzed to assess its influence and protective action in the prevention of CHD.

Satellite symposium 'International Garlic Research'

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Zeitschrift fur Phytotherapie (Germany), 1996, 17/1 (13-25)

The reports of the satellite symposium 'International Garlic Research' presented recent results of garlic research. Pharmacological investigations showed that the

vessel-dilatating effect of garlic powder extracts, allicin and ajoen is mediated by opening K+-channels and by membrane hyperpolarization. It could be shown that garlic powder directly affects cholesterol -accumulation by LDL and that there exists an inverse correlation between LDL-atherogenicity and sialic acid content of LDL. By garlic powder in hyperlipidemic patients the decreased sialic acid level could be normalized. Garlic constituents influence cholesterol biosynthesis on several levels. With respect to the late steps of cholesterol biosynthesis the inhibition of lanosterol 14-demethylase by allicin and ajoene was most important. Garlic also influences nitric oxide metabolism by increasing the blood levels of NO. Insufficient synthesis of NO in the blood may result in hypertension, angina pectoris and impotentia. A metaanalysis of clinical trials with garlic powder preparations proves their effects on blood pressure and lipid levels. A comparative trial of the effects of garlic powder and garlic oil bas shown, that powder preparations have a stronger lipid-lowering effect than oil-preparations, while blood pressure is affected by powder preparations only. Another study showed that supplementation of a fish oil medication with garlic abolishes the fish-oil-induced increase of LDL-cholesterol levels and lowers the LDL-cholesterol levels. Finally the preliminary evaluation of an epidemiological study indicates that there are hints of a decreased stiffness of the aorta in humans with regular intake of a garlic powder preparation while another trial reveals a significant reduction of the extention of atheromateous plaques by garlic powder.

Garlic in hyperlipidemia. Influence of a garlic preparation on the lipid serum levels of patients with primary hyperlipidaemia

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Zeitschrift fur Phytotherapie (Germany), 1995, 16/6 (343-348)

The lipid lowering effect of an enteric coated garlic /cyclodextrine preparation (Tegra (R)) was investigated. 97 patients with known primary hyperlipidaemia (serum levels of total cholesterol exceeding 260 mg/100 ml) took part in this trial. Patients received 10 mg/day of essential garlic oil obtained by steam distillation of garlic . The trial was carried out of 3 months and for 6 months in those cases in which the aim of the treatment (reduction of serum levels of total cholesterol to values less than 260 mg/100 ml) had not been reached after 3 months. Most of the patients did not alter their diet, though they were advised to do so. In 28 of 97 patients the treatment was successful after 3 months. The total cholesterol (TC) decreased by 7.8% from 287 to 264 mg/100 ml in the mean, the triglycerides (TG) by 2.2% from 205 to 180 mg/100 ml, the low-density lipoprotein cholesterol (LDL-C) by 10.2% from 207 to 186 mg/100 ml. The high-density lipoprotein cholesterol (HDL-C) increased by 10% from 38.8 to 42.6 mg/100 ml. Continuing the trial for a further three months in 69 patients resulted in an overall reduction of TC by 14.1% to 246 mg/100 ml, of TG by 20.2% to 164 mg/100 ml, and of LDL-C by 18.8% to 168 mg/100 ml. HDL-C values in the same time increased by 17.6% to 45.6 mg/100 ml. All changes were statistically significant ($p < 0.001$). The aim of the treatment was reached by 90% of the patients (87 of 97). All

patients had a reduction of TC, TG and LDL-C and an increase in HDL-C. No severe side effects were observed. The results of the study demonstrate the efficacy of essential garlic oil/beta-cyclodextrine complexes in the treatment of hyperlipidaemia.

Therapeutic actions of garlic constituents

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Medicinal Research Reviews (USA), 1996, 16/1 (111-124)

Most studies on garlic during the past 15 years have been primarily in the fields of cardiovascular and cancer research. Cardiovascular studies have been mainly related to atherosclerosis, where effects were examined on serum cholesterol, LDL, HDL, and triglycerides. Although the studies were not consistent in relation to the dosage, standardization of garlic preparations, and period of treatment, most findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. Lowering of serum lipids by garlic ingestion may decrease the atherosclerosis process. The other major beneficial effect of garlic is due to its antithrombotic actions. This field of garlic research has been extensively studied. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents of garlic because of their in vitro effects. Since both allicin and adenosine are rapidly metabolized in human blood and other tissues, it is doubtful that these compounds contribute to any antithrombotic actions in the body. In addition, ajoene also seems not to be an active antiplatelet principle, because it is not naturally present in garlic, garlic powders, or other commercial garlic preparations. Only a small amount of ajoene can be found in garlic oil-macerates; however, ajoene is being developed as a drug for treatment of thromboembolic disorders. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts are interesting, and may have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory, and anticancer actions. Epidemiological studies have suggested that garlic plays a significant role in the reduction of deaths caused by malignant diseases. This had led many investigators to examine garlic and garlic constituents for their antitumor and cytotoxic actions both in vitro and in laboratory animals. The data from these investigations suggest that garlic contains several potentially important agents that possess antitumor and anticarcinogenic properties. In summary, the epidemiological, clinical, and laboratory data have proved that garlic contains many biologically and pharmacologically important compounds, which are beneficial to human health from cardiovascular, neoplastic, and several other diseases. Numerous studies are in progress all over the world to develop effective

and odorless garlic preparations, as well as to isolate the active principles that may be therapeutically useful.

Towards the control of the hypertension epidemic. The Philippine experience

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Philippine Journal of Internal Medicine (Philippines), 1995, 33/2 (33-35)

As of 1990 the Philippines is 2nd to Indonesia in hypertensive-related mortality. To reverse this trend, hypertension control strategies involve health provider and client perceptions of the issues. A recent Philippine Society of Hypertension (PSH) survey which included pooled historical data of 25,427 respondents showed 15% clinical practice hypertension prevalence. Most initial work-up includes ECG, urinalysis, cholesterol and sugar blood levels and chest x-ray examinations. Antihypertensive monotherapy preferences were calcium antagonists (25%), betablockers (8%), and diuretics (7%). Client awareness of being hypertensive is 52% with only 23% admitting good BP control. Almost 60% are asymptomatic at hypertension discovery. Role of diabetes, pregnancy, renal and eye problems in hypertension obtained low perception. Use of garlic and cleansing diet were perceived to be beneficial in BP control despite lack of documentation. Antihypertensive medication compliance was 33% in industrial patients compared to 51% in the general population. From this pooled survey data, programs and strategies will emerge in order to control the hypertension epidemic. A clear message seems obvious - it is wrong to assume that a patient understands a doctor's explanation readily.

How does garlic exert its hypocholesterolaemic action? The tellurium hypothesis

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Medical Hypotheses (United Kingdom), 1995, 44/4 (295-297)

The efficacy of garlic as a lipid-lowering agent is being increasingly recognized, but the biochemical mechanisms underlying this action are currently unknown. It is proposed that organic tellurium compounds, which are found in high concentration in fresh garlic buds, may contribute to this action by inhibiting squalene epoxidase, the penultimate enzyme in the synthetic pathway of cholesterol . Weanling rats fed a diet rich in tellurium develop a demyelinating polyneuropathy due to inhibition of this enzyme in peripheral nerves. Chronic exposure to small amounts of tellurium found in garlic might reduce endogenous cholesterol production through inhibition of hepatic squalene epoxidase and so reduce cholesterol levels. Tellurium may also contribute to the characteristic

odour of garlic since the most obvious clinical sign of tellurium poisoning is a garlic -like odour.

Efficacy of dietary recommendations and phytotherapy with Allium sativum in mild and moderate hypercholesterinemia

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Med. Welt (Germany), 1994, 45/7-8 (327-323)

Within a primary lipid screening including 9251 persons a group of 8001 subjects (65% women, 35% men) with a serum level of 221 -300 mg/dl total cholesterol are recommended a diet with low fat and cholesterol content during 6-8 weeks. The 'nonresponder' received by continuous diet 600 mg/die of Allium sativum. After the period with diet alone the mean serum cholesterol level decrease was 3 mg/dl, after the next weeks with additional application of garlic powder a decrease of 6 mg/dl was measured. Short time dietary recommendations alone are not as succesful as a diet connected with application of standardized garlic powder. With a good compliance the effect of diet on serum cholesterol level is supported by phytotherapy.

Effect of garlic powder tablets on blood lipids and blood pressure - A six month placebo controlled, double blind study

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Br. J. Clin. Res. (United Kingdom), 1993, 4/- (37-44)

In a double blind, placebo controlled randomised study the effects of a standardised garlic powder tablet (Kwai(*), Lichtwer Pharma) on blood lipids and blood pressure was investigated. A total of 52 out-patients with total cholesterol values over 6.5 mmol/l took part in the study. Patients were randomly allocated to take tablets containing a total of 900 mg garlic powder (standardised to 1.3% alliin) daily or the same number of placebo tablets for six months. All patients were advised to follow a low fat/ cholesterol diet. Blood lipids were measured at baseline and after three and six months treatment. Blood pressure and well-being were assessed in monthly intervals. The baseline mean for serum total cholesterol of 6.92 mmol/l was reduced to 6.31 mmol/l after six months of garlic powder tablet treatment. Corresponding values for placebo were 7.05 mmol/l before and 6.74 mmol/l after placebo treatment. The difference between active treatment and placebo is statistically significant ($p < 0.05$). The mean values for low density lipoprotein cholesterol (LDL-C) was reduced by nearly 10% by garlic and by 6% by placebo. Mean systolic blood pressure (SBP) remained unchanged in the placebo group and was reduced in the active treated group by 17% from 145 to 120 mmHg ($p < 0.001$). Mean diastolic blood pressure (DBP) remained

unchanged in the placebo group and was reduced in the active treated group from 90 mmHg to 80 mmHg ($p < 0.01$). The differences between active and placebo treatment were significant after two months of treatment for DBP and after four months for SBP. Well-being, as analysed by a five-point score system, remained unchanged in the placebo group and was improved in the active treated group by 20% ($p < 0.001$).

Garlic supplementation and lipoprotein oxidation susceptibility

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Lipids (USA), 1993, 28/5 (475-477)

Interventions which make serum lipoproteins less susceptible to oxidation may be antiatherogenic. The antioxidant properties of garlic which have been demonstrated in vitro led us to investigate the effects of garlic supplements on lipoprotein oxidation susceptibility in humans. Ten healthy volunteers were given 600 mg/d of garlic powder (6 tablets of Kwai (R)) for two weeks in a placebo-controlled, randomized, double-blind crossover trial. We found that although serum lipid and lipoprotein levels were not lowered in this short time period, the ex vivo susceptibility of apolipoprotein B-containing lipoproteins to oxidation was significantly decreased (-34%). Because garlic has been reported to beneficially affect serum lipid levels, platelet function, fibrinolysis and blood pressure, this additional effect of retarding lipoprotein oxidation may contribute to the potential antiatherosclerotic effect of garlic .

Garlic as a phytogenic lipid-lowering drug - A review of clinical trails with standardized garlic powder preparations

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Fortschr. Med. (Germany, Federal Republic of), 1990, 108/36 (49-54)

Garlic (Allium sativum L.) is a commonplace drug. It is now available in the form of dragees made of garlic powder, standardized to 1.3% alliin. The lipid-lowering potential of such preparations has not been reviewed yet. In 7 out of 8 studies, including over 500 patients, a daily dose of 0.6 g to 0.9 g garlic powder reduced plasma cholesterol and triglyceride levels by 5 to 20 percent. The metabolic mechanisms of these reductions are not known.

Effect of an odor-modified garlic preparation on blood lipids

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Nutr. Res. (USA), 1987, 7/2 (139-149)

The effect of an odor-modified liquid garlic extract on blood lipids was evaluated in human subjects over a six month period. Lowering of cholesterol , triglycerides, low density and very low density lipoproteins (LDL, VLDL) with rise of high density lipoprotein (HDL) was observed in the majority of subjects who took garlic extract; the effect was clearly more significant than with subjects taking placebo. Garlic extract did not significantly influence the levels of cholesterol and triglycerides in subjects whose initial cholesterol levels were relatively low. Of special interest was the initial rise of cholesterol , triglycerides, and LDL/VLDL with garlic supplementation, suggesting possible mobilization of tissue lipids into the circulation during this phase of garlic ingestion. This study confirms previous reports of lowering cholesterol and triglycerides using various garlic preparations. Furthermore, it suggests that odor-modified garlic extract may be used in conjunction with dietary modification for control of hyperlipidemia.

Oral guar gum treatment of intrahepatic cholestasis and pruritus in pregnant women: effects on serum cholestanol and other non- cholesterol sterols.

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Eur J Clin Invest (England) May 1998, 28 (5) p359-63

BACKGROUND: Our aim was to investigate whether intestinal binding of bile acids by guar gum, a dietary fibre, relieves cholestasis and pruritus in intrahepatic cholestasis of pregnancy.

METHODS: Forty-eight pregnant women with cholestasis and pruritus were randomized double-blind to guar gum and placebo until the time of delivery, and 20 healthy pregnant women were used as control subjects. The pruritus score and serum bile acids, lipids and non-cholesterol sterols were measured at baseline, at least 2 weeks after treatment, just before delivery and up to 4 weeks after delivery.

RESULTS: The increase in serum bile acids and worsening of pruritus were prevented by guar gum in relation to placebo ($P < 0.05$). Serum cholesterol was unchanged, but increased cholesterol precursor sterol values suggested that cholesterol synthesis was increased by guar gum. Serum cholestanol proportion, an indicator of cholestasis, was related to pruritus but was unaffected by guar gum.

CONCLUSION: We conclude that in intrahepatic cholestasis of pregnancy and pruritus, guar gum treatment is beneficial in relieving pruritus, even although indicators of cholestasis are only partially reduced.

Increasing amounts of dietary fiber provided by foods normalizes physiologic response of the large bowel without altering calcium balance or fecal steroid excretion.

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Am J Clin Nutr (United States) Sep 1998, 68 (3) p615-22

Nine healthy, young men consumed constant diets to determine selected large-bowel, serum cholesterol and triacylglycerol, and calcium balance responses to 3 amounts of fiber provided by a mixture of fruit, vegetables, and grains. The diets, each consumed for 1 mo, contained 16, 30, and 42 g total fiber /d, of which 2.9, 4.8, and 7.7 g, respectively, was soluble. Mean daily wet and dry stool weights increased with each fiber addition. The first fiber addition increased defecation frequency and decreased fecal pH, bile acid concentration, and neutral steroid concentration; the second addition had no further effect. Mean weight of each defecation and stool moisture did not increase and serum cholesterol and triacylglycerol concentrations, calcium balance, and gastrointestinal transit time did not decrease as fiber intake increased. We conclude that 1) fiber provided by a mixed-food diet increases stool weight as effectively as does wheat or oat bran; 2) even high amounts of dietary fiber do not change transit time or defecation frequency if they are already approximately 1 and 2-3 d, respectively; 3) food patterns consistent with the food pyramid and incorporating legumes and whole grains are necessary to achieve recommended fiber intakes of 20-35 g/d, even if energy intake is > 12.55 MJ (3000 kcal); 4) soluble fiber provided by a mixture of whole foods has no effect on serum cholesterol concentrations or output of fecal bile acids; and 5) mixed-food fiber has little effect on calcium balance when calcium intakes are high (> or = 1.5 g/d).

[The use of dietary fiber as natural enterosorbents in diseases of the hepatobiliary system]

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Lik Sprava (Ukraine) Mar-Apr 1998, (2) p80-2

Intensity was studied of sorption of cholesterol , bile acids, and phospholipids by cereals food fibre in samples of vesicular and hepatic bile. Intensive absorption has been shown of these fractions by food fibres. Clinical observation over 92 patients with chronic noncalculous cholecystitis confirmed the beneficial effect of cereals food fibre.

Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City.

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Salud Publica Mex (Mexico) Mar-Apr 1998, 40 (2) p133-40

OBJECTIVE: To assess the reproducibility and validity of a 116 item semi-quantitative food frequency questionnaire (FFQ), designed to assess the relation between dietary intake and chronic diseases.

MATERIAL AND METHODS: To test the reproducibility of the FFQ questionnaire, the FFQ was administered twice to 134 women residing in Mexico City at an interval of approximately one year; to assess the validity we compared results obtained by the FFQs with those obtained by four 4-day 24-hour recalls at three month intervals. Validity and reproducibility were evaluated using regression analysis and Pearson and intraclass correlation coefficients of log-e and calorie-adjusted nutrient scores.

RESULTS: Mean values for intake of most nutrients assessed by the two food frequency questionnaires were similar. However, means for the 24-hr recall were significantly lower. Intraclass correlation coefficients for nutrient intakes, assessed by questionnaires, administered one year apart, ranged from 0.38 for cholesterol to 0.54 for crude fiber. Correlation coefficients between energy-adjusted nutrient intakes, measured by diet recalls, and the first FFQ ranged from 0.12 for polyunsaturated fatty acids to 0.67 for saturated fatty acids. Regression coefficients between 24-hr recall and FFQ,s were all significant were significant for all nutrients, except for polyunsaturated fat, folic acid, vitamin E and Zinc.

CONCLUSIONS: These data indicate that this semi-quantitative FFQ is reproducible and provides a useful estimate by which to categorize individuals by level of past nutrient intake. However, its application outside Mexico City or in different age and gender populations will require additional modifications and validation efforts.

Definition of healthy eating in the Spanish adult population: a national sample in a pan-European survey.

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Public Health (England) Mar 1998, 112 (2) p95-101

A national survey was carried out to find out how the Spanish adult population defined 'healthy eating'. Consumers were asked to describe in their own words what 'healthy eating' means to them. The sample included 1009 Spanish subjects over 15 y of age selected by a multietapic procedure. This study belongs to the Spanish partnership in a pan-European survey about attitudes to food, nutrition and health coordinated by the Institute of European Food Studies of Dublin. The results were shown as the percentages of the sample who gave one of the five most frequently mentioned descriptions ('more vegetables', 'balanced diet', 'more fruit', 'less fat' and 'more fish') and the distribution of responses by age, sex, region, socio-economic level and education level. A multivariable logistic regression model was fitted to assess the characteristics independently related to the use of the definition 'balance and variety' for healthy eating. The majority of the Spanish people defined 'healthy eating' as a diet with 'more vegetables' as the main description. Other descriptions commonly mentioned were 'less fat', 'more fruit', 'more fish', and 'more lean meat'. A higher age was associated with a lower likelihood of mentioning the concept of balanced diet. A higher educational level was also independently and strongly related to a higher prevalence of this definition. Differences between men and women showed only borderline significance. Our results suggest the need to improve nutritional education about fiber, low fat and cholesterol. It would be interesting to develop strategies in Spain to educate people on a definition of 'healthy eating' based upon 'balance and variety'.

Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk.

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Am J Clin Nutr (United States) Mar 1998, 67 (3) p421-30

Zinc absorption, mineral balance, and blood lipid concentrations were measured in 21 women aged 33 +/- 7 y (range: 20-42 y) consuming controlled lactoovovegetarian and nonvegetarian diets for 8 wk each in a crossover design. The lactoovovegetarian and nonvegetarian diets, respectively, provided (by analysis) 973 and 995 mg Ca, 1.8 and 1.3 mg Cu, 367 and 260 mg Mg, 5.9 and 2.5 mg Mn, 1457 and 1667 mg P, 9.1 and 11.1 mg Zn, and (by calculation) 40 and 16 g dietary fiber , 2.5 and 0.8 mmol phytic acid, molar ratios of phytate to Zn of 14 and 5, and millimolar ratios of (phytate x Ca) to Zn of 344 and 111. Dietary zinc absorption was measured by extrinsic isotopic labeling and whole-body counting. Plasma cholesterol , cholesterol fractions, and lipoproteins were reduced 7-12% with the lactoovovegetarian diet, consistent with predictions based on dietary cholesterol and fat. Blood pressure was unaffected. Calcium, copper, magnesium, and phosphorus balances were not different between diets; manganese balance tended to be greater with the lactoovovegetarian diet ($P < 0.07$). The lactoovovegetarian diet was associated with a 21% reduction in absorptive efficiency that, together with a 14% reduction in dietary zinc, reduced

the amount of zinc absorbed by 35% (2.4 compared with 3.7 mg/d) and reduced plasma zinc by 5% within the normal range. Zinc balance was maintained with both diets. Although there is a greater risk of zinc deficiency in persons consuming lactoovovegetarian compared with omnivorous diets, with inclusion of whole grains and legumes zinc requirements can be met and zinc balance maintained.

Long-term effects of consuming foods containing psyllium seed husk on serum lipids in subjects with hypercholesterolemia.

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The effects of consuming foods containing 0 (control), 3.4, 6.8, or 10.2 g psyllium seed husk (PSH)/d for 24 wk on the serum lipid profile were assessed in this randomized, double-blind controlled study. Men and women (n = 286) with LDL-cholesterol concentrations between 3.36 and 5.68 mmol/L (130 and 220 mg/dL) were randomly assigned to one of four treatment groups after following a low-fat diet for > or = 8 wk. At week 24, LDL cholesterol was 3% above baseline in the control group. In the group consuming 10.2 g PSH/d, LDL cholesterol remained below baseline during treatment, with a value 5.3% below that of the control group at week 24 ($P < 0.05$ compared with the control group). No significant differences were observed in HDL cholesterol or triacylglycerol. Although modest, the effect of 10.2 g PSH/d on LDL cholesterol (relative to the control) persisted throughout the 24-wk treatment period, indicating potential for long-term benefit.

Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women.

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J Nutr (United States) Feb 1998, 128 (2) p209-13

The relationship between soy product intake and serum total cholesterol concentration was examined in 1242 men and 3596 women who participated in an annual health check-up program in Takayama City, Japan, provided by the municipality in 1992. The intake of soy products and various foods and nutrients was assessed by a semiquantitative food-frequency questionnaire. Blood samples were collected from fasting subjects to measure the serum total cholesterol concentration. A significant trend (P for trend = 0. 0001) was observed for

decreasing total cholesterol concentration with an increasing intake of soy products in men after controlling for age, smoking status and intake of total energy, total protein and total fat. This negative trend (P for trend = 0.0001) was also noted in women after controlling for age, menopausal status, body mass index and intake of total energy and vitamin C. An additional adjustment for physical activity, coffee and tea consumption, and intake of cholesterol , carbohydrates, fiber and vitamin E did not change the results. These data suggest a role for soy products in human cholesterol homeostasis.

Cholesterol , phospholipid, and protein changes in focal opacities in the human eye lens.

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Invest Ophthalmol Vis Sci (United States) Jan 1998, 39 (1) p94-103

PURPOSE: Focal opacities are signs of early cataractogenesis in the human lens. They progress slowly over a lifetime and may be precursors of mature cataracts. The authors analyzed changes in proteins, phospholipids, and cholesterol in these opacities using in situ techniques: Raman microspectroscopy, filipin cytochemistry for cholesterol , and transmission electron microscopy (TEM).

METHODS: Human lenses with verified focal opacities were fixed in 1% paraformaldehyde. Slabs with opacities were analyzed using confocal Raman spectroscopy, then filipin Raman analysis of cholesterol , and finally TEM.

RESULTS: Compared with normal fibers, opacities consistently showed elevated levels of cholesterol and aliphatic chains, increased phospholipid acyl chain disorder, and changes in phospholipid lateral packing. Disulfide bridges of specific geometry (trans-gauche-trans) were found. Although protein content was unchanged, compared with normal fibers, aromatic amino acid content was significantly lower. The hydrophobicity of tyrosine residues showed a significant decrease, and a change in the tryptophan indole ring angle was found. The changes were abrupt and sharply delineated focal opacities. TEM confirmed this sharp boundary and showed that the opacities were densely packed with vesicles of varying size and electron density embedded in a homogenous matrix.

CONCLUSIONS: The Raman and TEM analyses of opacities showed that early cataractogenic events led to disruption of fiber membranes, formation of vesicles from the membrane constituents, and protein changes. The aberrant morphology of the membranes enveloping the focal opacities may have segregated the affected fibers from the surrounding normal tissue, thus explaining the stationary or slowly progressing character of these opacities.

Food and nutrient intake of premenopausal female vegetarians and omnivores in Finland

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Scandinavian Journal of Nutrition/Naringsforskning (Sweden), 1998, 42/3 (98-103)

We have investigated the food and nutrient intake of five demi-vegans, six lacto-vegetarians and fourteen omnivores, all females and aged 22-45 years, collecting a total of 42 dietary records per person in 2-day periods during one year. The yearly mean intakes of cereals, vegetables, fruits and berries, dietary fibre and vitamin C were higher and that of sugar, eggs, saturated fat and cholesterol lower in the vegetarians than in the omnivores. The intake of iron was higher in the vegetarians, but their serum ferritin levels were lower throughout the year than in the omnivores indicating lower iron status in vegetarians. The vegetarian diets provided practically no vitamin D, which was reflected in a low serum 25-hydroxyvitamin-D concentration during spring, but during summer concentrations increased to the adequate level. Furthermore, the mean iodine intake of vegetarians using minor amounts of dairy products was below the recommended level. Thus, the vegetarians had lower cholesterol , saturated fat and higher carbohydrates and fibre intakes than omnivores. However, seven of the eleven vegetarians were iron deficient throughout the year and six had serum 25-hydroxyvitamin-D concentrations below reference values in the winter.

Functional food science and the cardiovascular system

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Cardiovascular disease has a multifactorial aetiology, as is illustrated by the existence of numerous risk indicators, many of which can be influenced by dietary means. It should be recalled, however, that only after a cause-and-effect relationship has been established between the disease and a given risk indicator (called a risk factor in that case), can modifying this factor be expected to affect disease morbidity and mortality. In this paper, effects of diet on cardiovascular risk are reviewed, with special emphasis on modification of the plasma lipoprotein profile and of hypertension. In addition, dietary influences on arterial thrombotic processes, immunological interactions, insulin resistance and hyperhomocysteinaemia are discussed. Dietary lipids are able to affect lipoprotein metabolism in a significant way, thereby modifying the risk of cardiovascular disease. However, more research is required concerning the possible interactions

between the various dietary fatty acids, and between fatty acids and dietary cholesterol. In addition, more studies are needed with respect to the possible importance of the postprandial state. Although in the aetiology of hypertension the genetic component is definitely stronger than environmental factors, some benefit in terms of the development and coronary complications of atherosclerosis in hypertensive patients can be expected from fatty acids such as alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. This particularly holds for those subjects where the hypertensive mechanism involves the formation of thromboxane A2 and/or alpha1-adrenergic activities. However, large-scale trials are required to test this contention. Certain aspects of blood platelet function, blood coagulability, and fibrinolytic activity are associated with cardiovascular risk, but causality has been insufficiently proven. Nonetheless, well-designed intervention studies should be initiated to further evaluate such promising dietary components as the various n-3 and n-6 fatty acids and their combination, antioxidants, fibre, etc. for their effect on processes participating in arterial thrombus formation. Long-chain polyenes of the n-3 family and antioxidants can modify the activity of immunocompetent cells, but we are at an early stage of examining the role of immune function on the development of atherosclerotic plaques. Actually, there is little, if any, evidence that dietary modulation of immune system responses of cells participating in atherogenesis exerts beneficial effects. Although it seems feasible to modulate insulin sensitivity and subsequent cardiovascular risk factors by decreasing the total amount of dietary fat and increasing the proportion of polyunsaturated fatty acids, additional studies on the efficacy of specific fatty acids, dietary fibre, and low-energy diets, as well as on the mechanisms involved are required to understand the real function of these dietary components. Finally, dietary supplements containing folate and vitamins B6 and/or B12 should be tested for their potential to reduce cardiovascular risk by lowering the plasma level of homocysteine.

Lipid- and glucose-lowering efficacy of Plantago Psyllium in type II diabetes

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Journal of Diabetes and its Complications (United States), 1998, 12/5 (273-278)

The beneficial effect of dietary fiber in the management of type II diabetes is still controversial and has not been totally demonstrated. The purpose of this study was to determine the plasma-lowering effects of 5 g t.i.d. of Plantago Psyllium, as an adjunct to dietary therapy, on lipid and glucose levels, in patients with type II diabetes. Patients were randomly selected from an outpatient clinic of primary care to participate in a double-blind placebo-controlled study in which Plantago Psyllium or placebo was given in combination with a low fat diet. One hundred twenty-five subjects were included in the study that consisted in a 6-week period of diet counseling followed by a 6-week treatment period. Fasting plasma glucose, total plasma cholesterol , LDL cholesterol , HDL cholesterol and triglyceride levels were measured every 2 weeks. The test products (Psyllium or placebo) were supplied to subjects in identically labeled foil packets containing a

5-g dose of product, to consume three doses per day (of 5 g each one), before regular meals. There was an excellent tolerance to Psyllium, without significant adverse effects. No significant changes were observed in the patient's weight for both groups (not significant). Fasting plasma glucose, total cholesterol , LDL cholesterol , and triglycerides levels, showed a significant reduction ($p < 0.05$), whereas HDL cholesterol increased significantly ($p < 0.01$) following Psyllium treatment. Our results show that 5 g t.i.d. of Psyllium is useful, as an adjunct to dietary therapy, in patients with type II diabetes, to reduce plasma lipid and glucose levels, resolving the compliance conflict associated with the ingest of a great amount of fiber in customary diet.

Whole flaxseed consumption lowers serum LDL- cholesterol and lipoprotein(a) concentrations in postmenopausal women

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Nutrition Research (United States), 1998, 18/7 (1203-1214)

We conducted a double-blind cross-over study to compare the effects of whole flaxseed and sunflower seed, as part of the daily diet, on the lipid profile of postmenopausal women. During two 6-wk periods, thirty-eight mild, moderate, or severely (5.85-9.05 mmol/L) hypercholesterolemic postmenopausal women were randomly assigned to one of the two regimens: flaxseed or sunflower seed. The subjects were provided with 38 g of either treatment in the forms of breads and muffins. The first treatment period lasted six weeks and was followed by a two-wk washout phase. After the washout phase, subjects switched regimens and treatments continued for another 6 weeks. Blood samples were collected at baseline, 6, 8, and 14th wk of the study periods. Significant ($p<0.01$) reductions in total cholesterol were observed for both treatments (6.9 and 5.5% for flaxseed and sunflower seed, respectively). However only flaxseed regimen was able to significantly ($p<0.001$) lower LDL- cholesterol (14.7%). Serum HDL- cholesterol and triglyceride concentrations were unaffected by either of the treatments. Most interestingly, lipoprotein(a) [Lp(a)], a strong predictor of cardiovascular disease, concentrations were significantly ($p<0.05$) lowered by the flaxseed treatment (7.4% compared to baseline values). Regression analyses showed the strongest association between age and both total and LDL- cholesterol concentrations. Among the dietary variables, total and soluble fiber intakes were negatively correlated with serum total and LDL-cholesterol concentrations. The cholesterol lowering effects of flaxseed and sunflower seed may be due to the activity of single or multiple components, including alpha-linolenic or linoleic acids, total and soluble fiber , and non-protein constituents present in these seeds.

The potential role of soluble fibre in the treatment of hypercholesterolaemia

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Postgraduate Medical Journal (United Kingdom), 1998, 74/873 (391-394)

The three major modifiable coronary risk factors are smoking, hypertension, and hypercolesterolaemia. Serum cholesterol levels are above the desirable level of 5.2 mmol/l in 79% of men and 65% of women aged between 35 and 50 years and thus are an important target for intervention. In this paper, the role of nonpharmacological intervention with soluble fibre in treating mild to moderate primary hypercholesterolaemia is reviewed. Evidence from controlled studies shows that soluble fibre can be effective in lowering cholesterol by clinically significant amounts. It is stressed, however, that risk factors for coronary heart disease are interactive and attention is shifting to addressing multiple rather that individual factors.

Nutrition and coronary heart disease

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Modification of the nutritional risk factors, along with moderate amount of fiber content in food, fresh fruits and vegetables, necessary mineral supplements, smoking reduction and routine physical exercise, is an important strategy for the prevention and reduction of adverse outcome in coronary heart disease.

Dietary fiber , the evolution of the human diet and coronary heart disease

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Speculation on the evolution of the human diet together with comparative studies with the diet of other primates suggest that the human gastrointestinal tract and metabolism are adapted to high fiber diets. Epidemiological studies support a negative association between dietary fiber intake and risk of coronary heart diseases (CHD). For the most part, the association has been with insoluble fiber , especially wheat bran. However, viscous fiber sources are likely to play a role since they reduce lipid rink factors for CHD including total and low-density-

lipoprotein cholesterol and apolipoprotein B by increasing fecal bile acid losses. In addition, soluble fiber may reduce the rate of nutrient absorption so altering chylomicron synthesis and reducing postprandial glucose and insulin levels and other risk factors for CHD. There is also evidence that soma insoluble fibers might alter serum lipids and improve carbohydrate tolerance but these phenomena need to be confirmed and other mechanisms explored including improved clothing and thrombolytic factors and increased antioxidant status. Epidemiology, clinical and laboratory studies support increased consumption of high fiber foods as part of the strategy to reduce the risk of CHD.

Managing hypercholesterolaemia: What role for dietary fibre?

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Although there is now general agreement that lowering blood cholesterol levels brings about a reduction in the incidence of coronary heart disease (CHD), there is no consensus as to how and on whom lipid lowering should be attempted. With millions of people likely to benefit from cholesterol lowering, many of them with no overt signs or symptoms of CHD, managing hypercholesterolaemia needs to be effective, inexpensive, and highly acceptable to patients. This review looks briefly at the need to manage hypercholesterolaemia, and then considers the methods available for management. In particular, it explores the potential role of the addition of soluble fibre to the diet.

Human fatty acid synthesis is reduced after the substitution of dietary starch for sugar

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Using new nonisotopic and isotopic methods, we showed previously that fatty acid synthesis was markedly stimulated in weight-stable normal volunteers by a very-low-fat formula diet with 10% of energy as fat and 75% as short glucose polymers. In this study, we determined whether fatty acid synthesis was equally stimulated by a very-low-fat solid diet made with foods consumed typically. Four normal volunteers consumed the same very-low-fat formula diet for 25 d and then an isoenergetic solid food diet with 10% of energy as fat and 75% as starch, simple sugars, and fiber for 25 d. To measure fatty acid synthesis, the fatty acid compositions of the diets were matched to the composition of each subject's

adipose tissue and compared with the composition of VLDL-triacylglycerol. In all subjects, the large increases in newly formed palmitate and decreases in linoleate in VLDL-triacylglycerol were quickly reversed by the solid food diet, and the fraction of de novo synthesized fatty acids in fasting VLDL-triacylglycerol decreased from 30- 54% to 0-1%. In a second group of subjects, the stimulation of fatty acid synthesis by the formula diet with 75% glucose polymers was similarly reduced by a formula diet with amounts of fat, starch, and sugar chosen to mimic those of the solid food diet, but persisted after the addition of fiber or a diet with 75% sugar. In conclusion, an increase in fatty acid synthesis and palmitate-rich, linoleate-poor VLDL-triacylglycerol induced by very-low-fat, high-sugar diets may be reduced by the substitution of dietary starch for sugar with potentially beneficial effects on cardiovascular health.

Influence of vitamin C status on ethanol metabolism in guinea-pigs.

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Physiol Res (Czech Republic) 1998, 47 (2) p137-41

Guinea-pigs were maintained for 5 weeks on a diet containing three different concentrations of vitamin C : a) traces (none added), b) medium (0.05% w/w) and high (0.5% w/w). Twenty-four hours before killing the animals received one i.p. dose of 3 g ethanol per kg body weight (a model of short-term acute intoxication). In a parallel experiment which lasted 5 weeks, the animals were treated every week with two i.p. doses of 1 g ethanol per kg body weight followed by the final acute intoxication (3g ethanol/kg) (a model of long-term chronic alcoholization). In both experiments, the guinea-pigs with the highest tissue concentration of vitamin C proved to have significantly decreased residual levels of ethanol and acetaldehyde in the liver and the brain, a decreased activity of alanine- and aspartate aminoacyl transferases in the serum and decreased contents of triacylglycerols and cholesterol in the serum and liver in comparison with the vitamin C -unsupplemented group. The regression curve expressing vitamin C levels versus residual ethanol and acetaldehyde concentrations in the liver confirmed the highly significant negative correlation between them. Administration of the guinea-pigs with large amounts of vitamin C appears to accelerate ethanol and acetaldehyde metabolism and reduce some of their adverse health effects.

Dietary antioxidants inhibit development of fatty streak lesions in the LDL receptor-deficient mouse.

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Arterioscler Thromb Vasc Biol (United States) Sep 1998, 18 (9) p1506-13

Oxidized low density lipoprotein (LDL) promotes atherogenesis. Although pharmacological antioxidants such as probucol inhibit both LDL oxidation and atherosclerosis in hyperlipidemic animals, the effects of natural antioxidants such as vitamin E are inconclusive. To further determine the effects of supplemental dietary antioxidants in vivo, we evaluated whether combined dietary antioxidants (0.1% vitamin E, 0.5% beta-carotene, and 0.05% vitamin C) inhibit LDL oxidation and fatty streak lesion development in homozygous LDL receptor-null (LDLR-/-) mice fed a high-fat, high- cholesterol diet. An additional group of mice were fed black tea, which has been shown to inhibit LDL oxidation in vitro. After receiving a high-fat, high- cholesterol diet for 8 weeks, the combined antioxidant-supplemented (antioxidant) group (n=18), tea group (n=19), and control group (n=17) had equivalent plasma cholesterol levels. LDL oxidation, as measured by the lag phase of conjugated diene formation, was markedly inhibited in the antioxidant group compared with the tea or control groups [mean lag phases=143+/-7 (antioxidant), 100+/-5 (tea), and 84+/-4 (control) minutes; P<0.0001 antioxidant versus tea or control]. The cross-sectional surface area of fatty streak lesions in the aortic sinus was reduced by 60% in the antioxidant group compared with both the tea and control groups (P<0.0001 antioxidant versus tea or control). There was no difference in lesion area between tea and control groups. Although both LDL oxidation and atherosclerosis were significantly inhibited in the antioxidant group, no correlation between lag phase values and lesion size was observed among individual animals. Furthermore, black tea did not inhibit fatty streak development in LDLR-/- mice. These data suggest that combined natural dietary antioxidants inhibit both LDL oxidation and atherogenesis in animals with elevated LDL but that inhibition of LDL oxidation alone may not prevent the development of atherosclerosis.

Vitamin E combined with selenium inhibits atherosclerosis in hypercholesterolemic rabbits independently of effects on plasma cholesterol concentrations.

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Circ Res (United States) Aug 24 1998, 83 (4) p366-77

Several antioxidants inhibit atherosclerosis. This study investigated the hypothesis that combining vitamin E, a lipophilic antioxidant, with vitamin C , a hydrophilic antioxidant, and/or selenium, a cofactor of peroxidases that detoxify lipid peroxides, would inhibit atherosclerosis more effectively than vitamin E alone. We also considered whether regional variation in inhibition of atherosclerosis by antioxidants would be associated with regional variation in aortic lipophilic antioxidants. Rabbits were fed an atherogenic diet (control) or an atherogenic diet supplemented with vitamin E, vitamins E and C, vitamin E+selenium, vitamins E and C+selenium, or probucol (positive control). Supplements were as follows: vitamin E, 146 IU/d; vitamin C , 791 mg/d; selenium, 22 microg/d; or probucol,

406 mg/d. Vitamin C did not influence atherosclerosis. After 22 weeks of treatment, rank order of aortic atherosclerosis was control>vitamin E (with or without vitamin C)>vitamin E+selenium (with or without vitamin C)>probucol. Antioxidant treatment reduced aortic cholesterol concentrations 21% to 56%, 29% to 86%, and 19% to 75% for the aortic arch, descending thoracic aorta, and abdominal aorta, respectively (P<0.025 to P<0.0003 by ANOVA), with slightly greatly reductions for areas of atherosclerotic lesions. Some treatments reduced plasma cholesterol concentrations, but none altered the distribution of cholesterol among lipoproteins. Corrected for differences in plasma cholesterol concentrations, aortic cholesterol concentrations were reduced up to 72% (P<0.02) by the antioxidant treatments, with equal reductions by vitamin E+selenium and by probucol. Aortic alpha-tocopherol standardized by aortic cholesterol as a measure of aortic lipids was lower in the abdominal aorta than in the aortic arch of rabbits not given alpha-tocopherol and increased relatively more in the abdominal aorta than in the aortic arch with alpha-tocopherol supplementation. The results of this study suggest that vitamin E+ selenium inhibited atherosclerosis as effectively as an equally hypocholesterolemic dose of probucol by a mechanism(s) that is in part independent of effects on plasma and lipoprotein cholesterol concentrations. The tendency for greater efficacy of antioxidant treatments in the abdominal aorta than aortic arch may relate to the lower concentrations of alpha-tocopherol in the abdominal aorta of unsupplemented rabbits.

Regulation of apolipoprotein B-containing lipoproteins by vitamin C level and dietary fat saturation in guinea pigs.

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Metabolism (United States) Jul 1998, 47 (7) p883-91

Effects of suboptimal and adequate vitamin C , with varying dietary fat saturation, on hepatic cholesterol and plasma lipoprotein concentrations and metabolism were studied in guinea pigs fed 15% (wt/wt) fat/0.04% cholesterol diets. Fat mixtures were either 49% saturated (SFA) (24% lauric acid) or 53% polyunsaturated fatty acid (PUFA) linoleic acid with vitamin C at 50 (suboptimal) or 500 (adequate) mg/kg diet. Guinea pigs fed suboptimal vitamin C had 15% lower hepatic active 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and 25% lower low-density lipoprotein (LDL; apolipoprotein [apo] B/E) receptor number, 20% higher acyl-CoA:cholesterol acyltransferase (ACAT) activity, 28% higher triacylglycerol (TAG) and cholesteryl ester concentrations, and increased very-low-density lipopoprotein (VLDL) apo B secretion rates in comparison to animals fed adequate vitamin C. Intake of suboptimal vitamin C lowered plasma high-density lipoprotein (HDL) cholesterol concentrations by 45% and increased plasma TAG, total and VLDL/LDL cholesterol , and cholesteryl ester transfer protein (CETP) activity by 40%, 50%, and 30%, respectively. The hyperlipidemic effects of suboptimal vitamin C were

more pronounced with intake of the SFA diet. These data demonstrate that low vitamin C intake results in a pattern of changes in whole-body cholesterol and lipoprotein metabolism that are related to increased risk of cardiovascular disease (CVD).

The nutritional health of New Zealand vegetarian and non-vegetarian Seventh-day Adventists: selected vitamin, mineral and lipid levels.

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N Z Med J (New Zealand) Mar 27 1998, 111 (1062) p91-4

AIM: To determine whether adult non-vegetarian Seventh-day Adventists differ in selected nutrition related health aspects from adult vegetarian Seventh-day Adventists.

METHODS: One hundred and forty-one Seventh-day Adventist church members responded to a general health questionnaire. Forty-seven sex and age matched subjects (23 non-vegetarians and 24 vegetarians) were selected for further investigation. Blood lipids, serum vitamin B12, folate, haemoglobin and ferritin levels were measured along with stature, weight and blood pressure. A quantitative 7-day diet record was also completed.

RESULTS: Body mass index was similar between the non-vegetarian and vegetarian groups but diastolic blood pressure was higher for non-vegetarian than vegetarian males. Even though the dietary vitamin B12 intake was significantly lower ($p < 0.01$) in the vegetarian group both vegetarians and non-vegetarians recorded similar serum vitamin B12 levels. The vegetarian and non-vegetarian groups had similar haemoglobin concentrations. While dietary iron intake was higher in the female vegetarian group, though predominantly in the non-haem form, the difference was not significant. Low serum ferritin levels were found in both female dietary groups even though the vegetarian group had a significantly ($p < 0.05$) higher vitamin C intake. Blood lipid levels were similar in the two diet groups even though the vegetarian group had a lower percentage energy contribution from total and saturated fat ($p < 0.01$) and consumed significantly less cholesterol.

CONCLUSION: Both non-vegetarian and vegetarian Seventh-day Adventists appear likely to enjoy a lower risk of nutrition related chronic degenerative disease than the average New Zealander and have a satisfactory iron and vitamin B12 status.

Low-density lipoprotein oxidation and vitamins E and C in sustained and white-coat hypertension.

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Hypertension (United States) Feb 1998, 31 (2) p621-6

Low-density lipoprotein oxidation and antioxidant vitamins E and C were investigated in white-coat hypertension in comparison with sustained hypertension and normotension. We selected 21 sustained hypertensive subjects, 21 white-coat hypertensive subjects, and 21 normotensive subjects matched for gender, age, and body mass index. White-coat hypertension was defined as clinical hypertension and daytime ambulatory blood pressure <139/90 (subjects were also reclassified using 134/90 and 135/85 mm Hg as cutoff points for daytime blood pressure). Blood samples were drawn for lipid profile determination, assessment of fluorescent products of lipid peroxidation in native LDL, evaluation of susceptibility to LDL oxidation in vitro (lag phase and propagation rate), and determination of LDL vitamin E and plasma vitamins E and C contents. Compared with sustained hypertensive subjects, white-coat hypertensives had significantly lower fluorescent products of lipid peroxidation (15.4+/-3.4 versus 10.2+/-3 units of relative fluorescence/mg LDL protein, P<.05), longer lag phase (54+/-10 versus 88+/-10 minutes, P<.05), lower propagation rate (8.2+/-2.5 versus 5.95+/-2.1 nmol diene/min per mg LDL cholesterol , P<.05), higher LDL vitamin E content (8.3+/-1.1 versus 10.1+/-1.8 nmol/mg LDL cholesterol , P<.05), and plasma vitamin C content (40+/-13 versus 57+9 micromol/L, P<. 05). No significant difference was observed between white-coat hypertensive and normotensive subjects. The results did not change after reclassification of subjects. Our data show that white-coat hypertensive subjects do not show an enhanced propensity to LDL oxidation or reduction in antioxidant vitamins. Given the role of LDL oxidation in the development of atherosclerosis and that of vitamin E and C in protecting against it, these findings suggest that white-coat hypertension per se carries a low atherogenic risk.

Citrus fruit supplementation reduces lipoprotein oxidation in young men ingesting a diet high in saturated fat: presumptive evidence for an interaction between vitamins C and E in vivo.

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Lipid Research Laboratory, Sheba Hospital, Tel Hashomer, Israel.
Am J Clin Nutr (United States) Feb 1998, 67 (2) p240-5

To determine the effects of vitamin C on cardiovascular risk factors, we studied dietary vitamin C enrichment in 36 healthy male students consuming a diet high in saturated fatty acids. After a 1-mo run-in period during which the subjects consumed approximately 50 mg ascorbic acid/d (low-C diet), half of the subjects were randomly assigned to receive 500 mg ascorbic acid/d for an additional 2 mo (high-C diet). Plasma ascorbic acid increased from 13.5 micromol/L with the low-

C diet to 51.7 micromol/L with the high-C diet. Plasma cholesterol increased slightly with the high-C diet, but not above baseline concentrations. This increase was offset by an increase in the lag period of in vitro LDL oxidation, which correlated with plasma ascorbic acid concentrations ($r = 0.735$, $P = 0.0012$). Lipoprotein vitamin E concentrations were unchanged with the two diets. There were no effects on concentrations of fibrinogen or factor VII. The fact that ascorbic acid reduced the in vitro susceptibility of lipoproteins to oxidation provides presumptive evidence for an interaction between aqueous and lipophilic antioxidants (vitamins C and E) in maintaining the integrity of LDL particles.

Diet, antioxidant status, and smoking habits in French men

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Am J Clin Nutr (United States) Feb 1998, 67 (2) p231-9

The aim of this study was to assess the association between smoking, food consumption, and antioxidant vitamin intake and plasma indexes of oxidative stress and antioxidant defenses in French adults. Food and nutrient intakes of 459 healthy men aged 23-57 y were estimated by the diet history method and analyzed by smoking status. Plasma alpha-tocopherol, ascorbic acid, and carotenoids were measured as antioxidants and malondialdehyde, protein Schiff bases, and autoantibodies against malondialdehyde-protein adducts as oxidative stress indexes. Smokers ate less fruit and vegetables than nonsmokers, leading to lower vitamin E, vitamin C , and carotene intakes, even after adjustment for age, education, and marital status. Unlike vitamin E, plasma ascorbic acid and beta-carotene concentrations were reduced in smokers compared with nonsmokers and were inversely related to cigarette consumption. This difference remained significant after adjustment for alcohol and dietary intakes. Among the measured oxidative stress indexes, only Schiff base concentration was positively related to the number of cigarettes smoked. In our sample of French men, smoking had an adverse effect on antioxidant status; vitamin intakes were reduced in smokers and plasma antioxidant indexes were altered independently of dietary intakes. As in other countries, in France smokers require particular attention in terms of public health intervention.

Vitamin C supplementation restores the impaired vitamin E status of guinea pigs fed oxidized frying oil.

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J Nutr (United States) Jan 1998, 128 (1) p116-22

To investigate the effect of dietary oxidized frying oil (OFO) on tissue retention of vitamin C , and to explore the effect of vitamin C supplementation on tissue vitamin E concentrations and lipid peroxidation, male weanling guinea pigs were divided into four groups. Guinea pigs were fed 15% OFO diets supplemented with vitamin C at 300, 600 or 1500 mg/kg diet. Control animals were fed a diet containing 15% fresh untreated soybean oil with 300 mg/kg of vitamin C. After 60 d of feeding, body weight gain, food intake, feed efficiency and plasma triglyceride concentration were significantly lower in guinea pigs fed OFO diets than in controls ($P < 0.05$). However, plasma cholesterol concentration was highest in guinea pigs fed the OFO diet supplemented with 300 mg/kg vitamin C. Increasing vitamin C in OFO diets significantly reduced plasma cholesterol concentration. Plasma and tissue vitamins C and E concentrations were significantly lower in the OFO-fed guinea pigs receiving 300 mg/kg vitamin C than in controls. Greater levels of supplemental vitamin C increased tissue vitamins C and E. Guinea pigs fed OFO diets had significantly higher tissue levels of thiobarbituric acid reactive substances (TBARS) ($P < 0.05$) than controls. Our results demonstrated that OFO feeding, which impaired alpha-tocopherol retention and increased TBARS, could be alleviated somewhat by vitamin C supplementation.

Antioxidant vitamins and coronary artery disease risk in South African males

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Clinica Chimica Acta (Netherlands), 1998, 278/1 (55-60)

Decreased antioxidant-vitamin nutritional status may increase lipid peroxidation and susceptibility of low-density lipoprotein (LDL) to oxidative modification. The aim of this study was to evaluate the vitamin nutritional status of coronary artery disease (CAD) patients and to assess the risk of CAD related to each individual antioxidant vitamin. The study was performed as a case-control study with 41 patients with angiographically demonstrated CAD and 41 apparently healthy age- and smoking status-matched controls. Plasma vitamin E, C and A concentrations were significantly decreased in CAD patients compared with controls ($p<0.001$) after correcting for significant covariates. Per quartile decrease in vitamin A and E concentrations was associated with increased risk of CAD, even after adjusting for CAD risk factors, while per quartile decrease in vitamin C concentrations was not associated with significant CAD risk after adjusting for CAD risk factors. Decreased vitamin A and E concentrations are independently associated with increased risk of CAD independent from other CAD risk factors in white male South Africans and dietary intervention strategies are advocated.

Vitamins E plus C and interacting conutrients required for optimal health

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BioFactors (Netherlands), 1998, 7/1-2 (113-174)

Antioxidants are crucial components of fruit/vegetable-rich diets preventing cardiovascular disease (CVD) and cancer: - plasma vitamins C, E, carotenoids from diet correlate prevalence of CVD and cancer inversely, low levels predict an increased risk of individuals which is potentiated by combined inadequacy (e.g., vitamins C+E, C+carotene, A+carotene); - self-prescribed rectification of vitamins C and E at adequacy of other micronutrients reduce forthcoming CVD, of vitamins A, C, E, carotene and conutrients also cancer; - randomized exclusive supplementation of beta-carotene plus or minus vitamin A or E lack benefits except prostate cancer reduction by vitamin E, and overall cancer reduction by selenium; - randomized intervention with synchronous rectification of vitamins A+C+E+B + minerals reduces CVD and counteracts precancerous lesions; - high vitamin E supplements reveal potentials in secondary CVD prevention. Plasma values desirable for primary prevention: less than or equal to30 micromol/l lipid-standardized vitamin E alpha-tocopherol/cholesterol less than or equal to 5.0 micromol/mmol); less than or equal to 50 micromol/l vitamin C aiming at vitamin C /vitamin E ratio >1.3-1.5; less than or equal to 0.4 micromol/l beta- (less than or equal to 0.5 micromol/l alpha+beta-) carotene. Conclusions: - in CVD vitamin E acts as first risk discriminator, vitamin C as second one; - optimal health requires synchronously optimized vitamins C+E, A, carotenoids and vegetable conutrients.

Hypolipidemic effects of synthetic gugulsterones in normal rats and assessment of its long-term toxicity at cellular levels in various organs.

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Indian J Med Sci (India) Mar 1996, 50 (3) p63-7

Synthetic gugulsterones when administered to rats for a period of 3 weeks in dose of 5.0 mg/kg body weight/day caused a reduction in levels of total cholesterol by 30%, LDL-chol. by 40%, Tg by 40%. VLDL-chol. by 40% and HDL-chol. by 35%. The drug when administered to rats for a period of 16 weeks with increasing dose upto 1150 mg/kg body weight/day, reduced VLDL-chol. and Tg. by 55% and 50% respectively ($P < 0.001$) and LDL-chol by 33% ($P < 0.05$), whereas HDL-chol. was increased by 25% ($P < 0.001$). Histopathological studies on liver, spleen, intestine, lung, kidney, stomach and adrenal gland revealed drug related changes in a few animals upon exposure to high dose of the drug.

Effects of S-allyl cysteine sulfoxide isolated from Allium sativum Linn and gugulipid on some enzymes and fecal excretions of bile acids and sterols in cholesterol fed rats.

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Department of Bio-Chemistry, University of Kerala, Thiruvananthapuram, India.
Indian J Exp Biol (India) Oct 1995, 33 (10) p749-51

S-allyl cysteine sulfoxide, isolated from garlic, A. sativum, is more or less as active as gugulipid in controlling hypercholestermia, obesity and derangement of enzyme activities in cholesterol diet fed rats. The beneficial effects of the drugs are partly due to their inhibitory effects on transaminases, alkaline phosphatase, lipogenic enzymes and HMG CoA reductase and partly due to their stimulatory effects on plasma lecithin- cholesterol acyl transferase lipolytic enzymes and fecal excretion of sterols and bile acids.

Antiperoxide effects of S-allyl cysteine sulphoxide isolated from Allium sativum Linn and gugulipid in cholesterol diet fed rats.

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Indian J Exp Biol (India) May 1995, 33 (5) p337-41

Cholesterol containing diet significantly increased not only the body weight, but also the weight of liver and adipose tissue of rats. This is accompanied by a significant increase in blood lipids, atherogenic index and lipid peroxidation and a significant decrease in reduced glutathione level, superoxide dismutase and catalase activities in tissues. Treatment with S-allyl cysteine sulphoxide reverses the deleterious effects of cholesterol diet significantly and almost as effectively as gugulipid.

Clinical trials with gugulipid. A new hypolipidaemic agent

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J Assoc Physicians India (India) May 1989, 37 (5) p323-8

Multicentric clinical trials of the efficacy of gugulipid conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknow, Nagpur and Varanasi have been reported. Two hundred and five patients completed 12 week open trial with gugulipid in a dose of 500 mg tds after 8 week diet and placebo therapy. One patient showed gastrointestinal symptoms which did not necessitate withdrawal of the drug. A significant lowering of serum cholesterol (av. 23.6%) and serum triglycerides (av. 22.6%) was observed in 70-80% patients Double-blind, crossover study was

completed in 125 patients with gugulipid therapy and in 108 patients with clofibrate therapy. Two patients had flu-like syndrome with clofibrate and opted out from the study. With gugulipid the average fall in serum cholesterol and triglycerides was 11 and 16.8% respectively and with clofibrate 10 and 21.6% respectively. The lipid lowering effect of both drugs became evident 3-4 week after starting the drug and had no relationship with age, sex, and concomitant drug intake. Hypercholesterolaemic patients responded better to gugulipid therapy than hypertriglyceridaemic patients who responded better to clofibrate therapy. In mixed hyperlipidaemic patients response to both drugs was comparable. HDL-cholesterol was increased in 60% cases who responded to gugulipid therapy. Clofibrate had no effect on HDL- cholesterol. A significant decrease in LDL-cholesterol was observed in the responder group to both drugs.

Nicotinic acid treatment shifts the fibrinolytic balance favourably and decreases plasma fibrinogen in hypertriglyceridaemic men

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J Cardiovasc Risk, 1997 Jun, 4:3, 165-71

BACKGROUND: Nicotinic acid in gram doses decreases cholesterol and triglyceride concentrations in plasma, but the effect on haemostatic function is not known.

METHODS: Twenty-three men with hypertriglyceridaemia were treated with 4 g nicotinic acid daily for 6 weeks. Tests for haemostatic function and serum lipoproteins were performed before and at the end of the period of treatment.

RESULTS: Treatment with nicotinic acid had the expected effect on lipoprotein concentrations: it reduced the serum concentrations of triglyceride and the three major density fractions of triglyceride (very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL)). The VLDL cholesterol concentration was reduced, but that of HDL cholesterol was increased (all $P<0.0001$). The lipoprotein(a) (Lp(a)) concentration decreased significantly ($P<0.01$). The total fibrinolytic activity was increased by nicotinic acid treatment as indicated by decreases in plasminogen activator inhibitor-1 activity from 34.3 to 23.8 U/ml ($P<0.01$) and in alpha2-antiplasmin activity from 1.10 to 0.97 U/ml ($P<0.01$). The plasma fibrinogen concentration decreased from 3.55 to 3.01 U/ml ($P<0.01$). Multvariate analysis showed that the changes in alpha2-antiplasmin and Lp(a) concentrations could explain 53% of the change in plasma fibrinogen, suggesting that increased plasmin mobilization could be responsible for the decrease in plasma fibrinogen.

CONCLUSION: This study of hypertriglyceridaemic men has shown that long-term treatment with nicotinic acid not only corrects serum lipoprotein

abnormalities, but also reduces the fibrinogen concentration in plasma and stimulates fibrinolysis.

Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study.

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Am J Cardiol, 1998 Dec 17, 82:12A, 35U-38U; discussion 39U-41U

Niacin is a useful lipid-modifying drug because it (1) decreases low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein(a), and (2) raises high-density lipoprotein (HDL) cholesterol. Its use tends to be limited by side effects and inconvenient dosing regimens. The availability of an extended-release preparation (Niaspan-which has safety and efficacy similar to immediate-release niacin but which can be given once a day) provides an opportunity to increase the use of this effective lipid-modifying agent. To study the safety and efficacy of escalating doses of extended-release niacin, hyperlipidemic patients were randomly assigned to placebo or Niaspan. A forced dose-titration was done with the dosage increasing by 500 mg every 4 weeks to a maximum of 3,000 mg/day. Niaspan showed dose-related changes in total, LDL, and HDL cholesterol levels, triglycerides, cholesterol/HDL ratio, and lipoprotein(a). At a dosage of 2,000 mg/day, total cholesterol decreased by 12.1%, LDL cholesterol by 16.7%, triglycerides by 34.5%, and lipoprotein(a) by 23.6%; HDL cholesterol increased by 25.8%. Flushing was the most commonly reported side effect; flushing episodes tended to decrease with time despite an increasing dose of niacin. Of the reported side effects, only pruritus and rash were significantly different between the 2 groups. Aspartate aminotransferase, lactate dehydrogenase, and uric acid increased in a dose-dependent fashion, but fasting blood sugar increased by about 5% across most dosages. Two subjects had aspartate aminotransferase levels greater than twice the upper limit of normal, but there were no subjects in whom transaminases increased to 3 times the upper limit of normal. Women tended to have a greater LDL cholesterol response to the medication and also experienced more side effects, especially at higher dosages. Thus, the use of lower dosages of niacin may be desirable in women. The results of this dose-escalation study show beneficial effects of Niaspan on the entire lipid profile. At the maximum recommended dosage of 2,000 mg/day, all lipid and lipoprotein levels changed in desirable directions. Side effects (other than flushing) and blood chemistries were comparable to those seen with immediate-release niacin.

Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats

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Molecular and Cellular Biochemistry (Netherlands), 1997, 166/1-2 (169-175)

Streptozotocin-induced diabetic rats were maintained on 0.5% curcumin containing diet for 8 weeks. Blood cholesterol was lowered significantly by dietary curcumin in these diabetic animals. Cholesterol decrease was exclusively from LDL-VLDL fraction. Significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin in diabetic rats. In a parallel study, wherein diabetic animals were maintained on a high cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were still higher compared to those maintained on control diet. Curcumin exhibited lowering of cholesterol and phospholipid in these animals also. Liver cholesterol, triglyceride and phospholipid contents were emin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on high cholesterol diet. Dietary curcumin also showed significant countering of renal cholesterol and triglycerides elevated in diabetic rats. In order to understand the mechanism of hypocholesterolemic action of dietary curcumin, activities of hepatic cholesterol-7a-hydroxylase and HMG CoA reductase were measured. Hepatic cholesterol-7a-hydroxylase activity was markedly higher in curcumin fed diabetic animals suggesting a higher rate of cholesterol catabolism.

Effects of S-allyl cysteine sulfoxide isolated from Allium sativum Linn and gugulipid on some enzymes and fecal excretions of bile acids and sterols in cholesterol fed rats

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Indian Journal of Experimental Biology (India), 1995, 33/10 (749-751)

S-allyl cysteine sulfoxide, isolated from garlic, A. sativum, is more or less as active as gugulipid in controlling hypercholesterolemia, obesity and derangement of enzyme activities in cholesterol diet fed rats. The beneficial effects of the drugs are partly due to their inhibitory effects on transaminases, alkaline phosphatase, lipogenic enzymes and HMG CoA reductase and partly due to their stimulatory effects on plasma lecithin-cholesterol acyl transferase lipolytic enzymes and fecal excretion of sterols and bile acids.

Antiperoxide effects of S-allyl cysteine sulphoxide isolated from Allium sativum Linn and gugulipid in cholesterol diet fed rats

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Indian Journal of Experimental Biology (India), 1995, 33/5 (337-341)

Cholesterol containing diet significantly increased not only the body weight, but also the weight of liver and adipose tissue of rats. This is accompanied by a significant increase in blood lipids, atherogenic index and lipid peroxidation and a significant decrease in reduced glutathione level, superoxide dismutase and catalase activities in tissues. Treatment with S-allyl cysteine sulphoxide reverses the deleterious effects of cholesterol diet significantly and almost as effectively as gugulipid.

Cholesterol biosynthesis inhibitory component from Zingiber officinale Roscoe

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Chem Pharm Bull (Tokyo) (Japan) Apr 1993, 41 (4) p710-3

We previously reported on the isolation and identification of (E)-8 beta,17-epoxylabd-12-ene-15,16-dial (ZT) from ginger (rhizome of Zingiber officinale Roscoe, Zingiberaceae). In this paper, the pharmacological effects of ZT are reported. The experimental mouse hypercholesterolemia induced by Triton WR-1339 was treated after oral administration of ZT. In homogenated rat liver with ZT, cholesterol biosynthesis was decreased. In addition, the same activity was observed in the homogenated rat liver which was resected after the oral administration of ZT. According to the results of general pharmacological screening, no remarkable activity of ZT was observed except for an inhibitory effect on the cholesterol biosynthesis.

Effect of psyllium in hypercholesterolemia at two monounsaturated fatty acid intakes.

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We performed two studies to determine whether the lipid-lowering effect of viscous soluble fiber was modified by monounsaturated fatty acid (MUFA). First, psyllium (1.4 g/MJ) was compared with wheat bran (control) in 1-mo metabolic diets by using a randomized crossover design (n = 32 hyperlipidemic subjects). The background diet contained approximately 6% of energy as MUFA (20% of total fat). The second study (n = 27 hyperlipidemic subjects) was similar to the first but the background diet contained approximately 12% MUFA (29% of total fat) because of the addition of canola oil. At both fat intakes, psyllium resulted in

significant reductions in total, low-density-lipoprotein (LDL), and high-density-lipoprotein (HDL) cholesterol compared with the wheat bran control. For the psyllium diet at 6% compared with 12% MUFA, the decreases in LDL cholesterol were 12.3 +/- 1.5% ($P < 0.001$) and 15.3 +/- 2.4% ($P < 0.001$), respectively. With the higher-MUFA diet triacylglycerol fell significantly over the control phase (16.6 +/- 5.5%, $P = 0.006$) and the ratio of LDL to HDL cholesterol fell significantly over the psyllium phase (7.3 +/- 2.8%, $P = 0.015$). Psyllium and MUFA intakes were negatively related to the percentage change in the ratio of LDL to HDL cholesterol ($r = -0.34$, $P = 0.019$ and $r = -0.44$, $P = 0.002$, respectively). Chenodeoxycholate synthesis rate increased (30 +/- 13%, $P = 0.038$) with the psyllium diet in the 12 subjects in whom this was assessed. We conclude that psyllium lowered LDL- and HDL-cholesterol concentrations similarly at both MUFA intakes. However, there may be some advantage in combining soluble fiber and MUFA to reduce the ratio of LDL to HDL cholesterol.

Wheat bread supplemented with depolymerized guar gum reduces the plasma cholesterol concentration in hypercholesterolemic human subjects.

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Am J Clin Nutr (United States) Jan 1997, 65 (1) p107-13

Recent human studies have shown that the physiologic effects of guar gum are not diminished by partial depolymerization of its galactomannan fraction. We evaluated the effect of depolymerized guar galactomannan on fasting plasma cholesterol and triacylglycerol concentrations in healthy volunteers with moderately raised plasma cholesterol concentrations (range: 5.2-8.0 mmol/L). This study was designed as a randomized, double-blind crossover of two 3-wk feeding periods separated by a 4-wk washout period. Control and guar wheat breads were prepared by a commercial bread-making process. Subjects ($n = 11$) were asked to replace their normal bread with that provided, receiving control bread for one 3-wk period and guar bread for the other period, without altering their baseline diet. Subjects recorded their intake of foods for 6 consecutive days on three occasions during the study. Fasting venous blood samples (10 mL) were taken from subjects on two consecutive mornings at the start and end of each feeding period. No significant changes in body weight or dietary intake were recorded in the control and guar bread periods. There was a significant reduction (10%) in total plasma cholesterol concentration after the guar treatment ($P < 0.001$), mainly because of a reduction in the low-density-lipoprotein-cholesterol fraction. No changes in plasma high-density-lipoprotein-cholesterol or triacylglycerol concentrations were seen. The cholesterol-lowering effect of partially depolymerized guar gum appears to be of a magnitude similar to that of high-molecular-weight guar gum used in earlier studies.

Eicosapentaenoic acid, but not docosahexaenoic acid, increases mitochondrial fatty acid oxidation and upregulates 2,4-dienoyl-CoA reductase gene expression in rats.

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Lipids (United States) Jun 1996, 31 (6) p579-92

The aim of the present study was to investigate whether eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) was responsible for the triglyceride-lowering effect of fish oil. In rats fed a single dose of EPA as ethyl ester (EPA-EE), the plasma concentration of triglycerides was decreased at 8 h after acute administration. This was accompanied by an increased hepatic fatty acid oxidation and mitochondrial 2,4-dienoyl-CoA reductase activity. The steady-state level of 2,4-dienoyl-CoA reductase mRNA increased in parallel with the enzyme activity. An increased hepatic long-chain acyl-CoA content, but a reduced amount of hepatic malonyl-CoA, was obtained at 8 h after acute EPA-EE treatment. On EPA-EE supplementation, both EPA (20:5n-3) and docosapentaenoic acid (DPA, 22:5n-3) increased in the liver, whereas the hepatic DHA (22:6n-3) concentration was unchanged. On DHA-EE supplementation retroconversion to EPA occurred. No statistically significant differences were found, however, for mitochondrial enzyme activities, malonyl-CoA, long-chain acyl-CoA, plasma lipid levels, and the amount of cellular fatty acids between DHA-EE treated rats and their controls at any time point studied. In cultured rat hepatocytes, the oxidation of [1-14C]palmitic acid was reduced by DHA, whereas it was stimulated by EPA. In the in vivo studies, the activities of phosphatidate phosphohydrolase and acetyl-CoA carboxylase were unaffected after acute EPA-EE and DHA-EE administration, but the fatty acyl-CoA oxidase, the rate-limiting enzyme in peroxisomal fatty acid oxidation, was increased after feeding these n-3 fatty acids. The hypocholesterolemic properties of EPA-EE may be due to decreased 3-hydroxy-3-methylglutaryl-CoA reductase activity. Furthermore, replacement of the ordinary fatty acids, i.e., the monoenes (16:1n-7, 18:1n-7, and 18:1n-9) with EPA and some conversion to DPA concomitant with increased fatty acid oxidation is probably the mechanism leading to changed fatty acid composition. In contrast, DHA does not stimulate fatty acid oxidation and, consequently, no such displacement mechanism operates. In conclusion, we have obtained evidence that EPA, and not DHA, is the fatty acid primarily responsible for the triglyceride-lowering effect of fish oil in rats.

Soy protein concentrate and isolated soy protein similarly lower blood serum cholesterol but differently affect thyroid hormones in hamsters.

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J Nutr (United States) Aug 1996, 126 (8) p2007-11

There is a wide variation in the hypocholesterolemic response to ingestion of soy protein in humans. One possible explanation is that the different soy protein preparations used contain different spectra of biologically active components. This could affect a number of indices including thyroid hormone status. An increased level of thyroxine has been proposed as an underlying mechanism of the hypocholesterolemic effect of soy protein. The objective of this study was to determine if serum cholesterol and thyroid hormone concentrations differed because of feeding soy protein from different sources. Twenty-nine male weanling golden Syrian hamsters were fed rations containing 25 g/100 g protein from either isolated soy protein (ISP), soy protein concentrate (SPC) or casein for 35 d. Serum total cholesterol concentrations were lower in hamsters fed ISP and SPC compared with those fed casein ($P < 0.05$). No differences in cholesterol concentrations were observed in lipoprotein fractions. Serum thyroxine and free thyroxine were greater only in hamsters fed ISP than in those fed casein ($P < 0.05$), whereas triiodothyronine concentrations were higher in casein-fed than in SPC-fed hamsters ($P < 0.05$). Results indicate that protein from ISP and SPC are both effective in lowering blood cholesterol concentrations, whereas only ISP increases thyroxine concentrations. Therefore, it appears unlikely that modulation of thyroid hormone status is responsible for the cholesterol-lowering effect of soy protein.

Ascorbate administration to normal and cholesterol-fed rats inhibits in vitro TBARS formation in serum and liver homogenates.

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Life Sci (England) 1996, 58 (14) p1101-8

We have recently shown that ascorbate has a hypocholesterolemic and hypotriglyceridemic effect on rats fed a diet enriched with 1.5% cholesterol and 25% hydrogenated coconut oil (Nath diet). In this study we evaluated the effect of intraperitoneal ascorbate administration on susceptibility to lipoperoxidation either in rats fed standard or Nath diet. In normal rats ascorbate treatment decreased ($p<0.05$) the susceptibility to lipoperoxidation induced by incubation of serum for 24 hours with 2.2 mM Cu++, without altering the normal serum fatty acid profile. In rats fed Nath diet we observed a reduced susceptibility of serum to CU++-induced lipoperoxidation (36%), according with their low levels of serum unsaturated fatty acids (40% less than rats fed standard diet). In these animals ascorbate administration affects serum fatty acid profile leading to a decrease of S/U ratio from 1.6 to 1.2 without significantly modifying the susceptibility of serum to lipoperoxidation. Moreover, the production of spontaneous lipid peroxides in liver homogenates, measured as TBARS levels, was strongly inhibited by ascorbate ($p<0.01$) in rats fed either standard or Nath diet. These data indicate that ascorbate administration exerts an antioxidant effect and that in hypercholesterolemic rats, in addition to a lipid lowering effect, ascorbate exerts a protective role against the peroxidative damage of lipids.

Cholesterol-lowering effect of soyabean lecithin in normolipidaemic rats by stimulation of biliary lipid secretion.

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Br J Nutr (England) Mar 1996, 75 (3) p471-8

The purpose of the present study was to assess the role of the liver in the plasma-cholesterol-lowering effect of soyabean lecithin. Normolipidaemic rats were fed on lecithin-enriched or control diets with the same amount of protein. The lecithin diets contained 200 g/kg high-fat commercial semi-purified soyabean lecithin (230 g/kg total lipids as soyabean phosphatidylcholine) or 200 g/kg high-fat purified soyabean lecithin (930 g/kg total lipids as soyabean phosphatidylcholine). The control diets were a lowfat diet (40 g fat/kg) and a high-fat triacylglycerol-rich diet (200 g fat/kg). The high-fat diets were isoenergetic. The cholesterol-lowering effect of the lecithin-enriched diets was associated with significantly lower levels of plasma total- and HDL-cholesterol and significantly higher levels of bile phosphatidylcholine (PC), bile salts and cholesterol. These findings suggest that the liver plays a major role in the reduction of plasma cholesterol, the increased biliary lipid being provided by both HDL and the hepatic microsomal pools of PC and cholesterol.

Effect of a combination of gemfibrozil and niacin on lipid levels.

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J Clin Pharmacol (United States) Aug 1996, 36 (8) p696-700

To determine the effect of the combination of niacin and gemfibrozil on the lipid profile, a retrospective review was conducted of 161 patients who were prescribed a combination of gemfibrozil and niacin for 6 to 12 months at a community-based lipid clinic. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, ratio of total cholesterol to HDL, alanine aminotransferase (ALT), and weight were measured at entry to the clinic, 2 months after dietary instruction, during single-agent therapy, and during combination therapy. Mean doses of niacin and gemfibrozil were 1,229 mg/day and 1,200 mg/day, respectively. Patient weight decreased significantly after dietary instruction and after institution of combination therapy. There were no significant changes in ALT levels with either single-agent therapy or with combination therapy. The combination of niacin and gemfibrozil produced marked and significant changes in lipid levels: total cholesterol and LDL decreased by 14%, HDL increased by 24%, the ratio of total cholesterol to HDL

decreased by 30%, and triglycerides decreased by 52%. The combination of niacin and gemfibrozil in the setting of dietary instruction has a marked beneficial effect on serum lipid levels, and was most effective in patients with initial levels of HDL < 40 mg/dL, triglycerides > 250 mg/dL, and LDL > 160 mg/dL. No episodes of ALT elevation or symptomatic myositis were seen.

New developments in the use of niacin for treatment of hyperlipidemia: new considerations in the use of an old drug.

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Coron Artery Dis (United States) Apr 1996, 7 (4) p321-6

Niacin has been used for many years to treat hyperlipidemia. It has been shown to reduce coronary death and non-fatal myocardial infarction and, in a separate analysis of long-term (15-year) follow-up, all cause mortality. It reduces total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglycerides and increases high density lipoprotein cholesterol (HDL-C). Sustained-release niacin may be associated with more dramatic changes in LDL-C and triglyceride, whereas the short acting preparation causes greater increases in HDL-C. The increase of HDL-C occurs at a lower dose (1500 mg/day) than the reduction of LDL-C (> 1500 mg/day). Niacin also favorably influences other lipid parameters including lipoprotein(a) [Lp(a)], alimentary lipemia, familial defective apolipoprotein B-100 and small dense LDL. Combination of niacin with a bile acid sequestrant or a reductase inhibitor represents a powerful lipid-altering regimen. Whereas the reductase inhibitors and bile acid binding resins primarily affect LDL-C, the combined therapy has a synergistic effect to reduce LDL-C and, in addition, the niacin reduces triglycerides and increases HDL-C. The major drawback in the use of niacin is associated side effects (flushing and palpitations) and toxicity (worsening of diabetes control, exacerbation of peptic ulcer disease, gout, hepatitis). Niacin has a long history of use as a lipid lowering agent and has several attractive features. Unfortunately, the side effect profile of this agent warrants its use only in patients with marked dyslipidemia in whom side effects and potential toxicity are closely monitored. (47 Refs.)

Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering.

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Circulation (United States) Nov 15 1996, 94 (10) p2369-72

BACKGROUND: There is accumulating experimental, epidemiological, and clinical evidence of an association between anti-oxidant vitamin intake and

reduced risk of coronary heart disease. Using data from the Cholesterol Lowering Atherosclerosis Study (CLAS), we explored the association of self-selected supplementary antioxidant vitamin intake on the rate of progression of early preintrusive atherosclerosis.

METHODS AND RESULTS: CLAS was an arterial imaging trial in which nonsmoking 40- to 59-year-old men with previous coronary artery bypass graft surgery were randomized to colestipol/niacin plus diet or placebo plus diet. The rate of progression of early preintrusive atherosclerosis was determined in 146 subjects using high-resolution B-mode ultrasound quantification of the distal common carotid artery far wall intima-media thickness (IMT). From the nutritional supplement database, 22 subjects had an on-trial average supplementary vitamin E intake of > or = 100 IU per day (high users) and 29 subjects had an average on-trial supplementary vitamin C intake of > or = 250 mg per day (high users). Within the placebo group, less carotid IMT progression was found for high supplementary vitamin E users when compared with low vitamin E users (0.008 versus 0.023 mm/y, P = .03). No effect of vitamin E within the drug group was found. No effect of vitamin C within the drug or placebo group was found.

CONCLUSIONS: Supplementary vitamin E intake appears to be effective in reducing the progression of atherosclerosis in subjects not treated with lipid-lowering drugs while the process is still confined to the arterial wall (early preintrusive atherosclerosis).

Clinical trial of wax-matrix sustained-release niacin in a Russian population with hypercholesterolemia.

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Arch Fam Med (United States) Nov-Dec 1996, 5 (10) p567-75

OBJECTIVE: To assess the clinical effectiveness and tolerability of wax-matrix, controlled-release nicotinic acid (CNA) in persons with hypercholesterolemia.

DESIGN: Randomized, double-blind, placebo controlled, crossover trial.

SETTING: Ambulatory clinic at an academic cardiology center in Moscow, Russia.

PATIENTS: A volunteer sample of 135 men and women, aged 20 to 70 years, with hypercholesterolemia greater than 5.82 mmol/L (225 mg/dL) (70th-95th percentile for age and sex) who otherwise met study inclusion and exclusion criteria, were initially recruited into the study. Cholesterol levels were reduced to less than 5.82 mmol/L (225 mg/dL) in 46 subjects who participated in the initial diet intervention and were excluded from the drug intervention. Eighty-nine

subjects were randomized into the clinical trial; 4 subjects (4.5%) dropped out of the study because of intolerance of CNA.

INTERVENTION: Eight weeks of diet alone (American Heart Association Step I Diet) was followed by randomization to 2 treatment groups (1500 mg/d CNA [ENDURACIN] or placebo) for 2 months followed by a crossover of treatments for 2 months, followed by all subjects taking 2000 mg/d of CNA for 2 months.

MAIN OUTCOME MEASURES: Significant improvements in baseline measures for total serum cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were observed after initial diet (TC, 6%; LDL-C, 6%; P < .001, t test), after 1500 mg/d CNA (TC, 14%; LDL-C, 18%; P < .001, t test), and after 2000 mg/d CNA (TC, 16%; LDL-C, 21%; P < .001, t test). Triglyceride, high-density lipoprotein cholesterol, and lipoprotein(a) levels also improved. No serious toxic reactions were encountered, and 4 subjects withdrew from the study because of intolerance of cutaneous and gastrointestinal adverse effects.

CONCLUSION: Wax-matrix CNA is an effective and well-tolerated pharmacological treatment for hypercholesterolemia.

Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin.

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Pharmacotherapy (United States) May-Jun 1996, 16 (3) p419-23

STUDY OBJECTIVES. To determine if low-dose lovastatin in combination with niacin causes a greater percentage reduction in low-density lipoprotein (LDL) cholesterol than lovastatin alone, and to determine if the combination increases the risk of serious adverse effects. design. Prospective, randomized, open-label, clinical trial. setting. Family medicine clinic of a university-affiliated hospital. Patients. Patients with fasting LDL cholesterol concentrations of at least 150 mg/dl after 4 weeks of dietary stabilization and washout of any cholesterol-lowering drugs.

INTERVENTIONS. Twenty-eight patients received lovastatin 20 mg/day for 4 weeks after dietary stabilization and washout. If LDL cholesterol remained above 130 mg/dl (100 mg/dl in patients with coronary artery disease), they were randomized to receive either lovastatin 40 mg/day or a combination of lovastatin 20 mg/day and niacin 500 mg 3 times/day.

MEASUREMENTS AND MAIN RESULTS. There was no difference in actual or percentage reductions of LDL cholesterol, total cholesterol, and triglycerides between the groups. A greater increase in high-density lipoprotein (HDL) cholesterol occurred with combination therapy (p = 0.024). There was no

difference in liver function tests, glucose, or uric acid between the therapies. Based on drug-acquisition cost, combination therapy is approximately 40% less expensive than monotherapy.

CONCLUSION. Low-dose niacin plus low-dose lovastatin was as effective as higher-dose lovastatin in lowering total cholesterol, LDL cholesterol, and triglyceride levels. The combination may offer benefit in raising HDL cholesterol levels.

Clinical trials with gugulipid. A new hypolipidaemic agent

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J Assoc Physicians India (India) May 1989, 37 (5) p323-8

Multicentric clinical trials of the efficacy of gugulipid conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknow, Nagpur and Varanasi have been reported. Two hundred and five patients completed 12 week open trial with gugulipid in a dose of 500 mg tds after 8 week diet and placebo therapy. One patient showed gastrointestinal symptoms which did not necessitate withdrawal of the drug. A significant lowering of serum cholesterol (av. 23.6%) and serum triglycerides (av. 22.6%) was observed in 70-80% patients Double-blind, crossover study was completed in 125 patients with gugulipid therapy and in 108 patients with clofibrate therapy. Two patients had flu-like syndrome with clofibrate and opted out from the study. With gugulipid the average fall in serum cholesterol and triglycerides was 11 and 16.8% respectively and with clofibrate 10 and 21.6% respectively. The lipid lowering effect of both drugs became evident 3-4 week after starting the drug and had no relationship with age, sex, and concomitant drug intake. Hypercholesterolaemic patients responded better to gugulipid therapy than hypertriglyceridaemic patients who responded better to clofibrate therapy. In mixed hyperlipidaemic patients response to both drugs was comparable. HDL-cholesterol was increased in 60% cases who responded to gugulipid therapy. Clofibrate had no effect on HDL-cholesterol. A significant decrease in LDL-cholesterol was observed in the responder group to both drugs.

Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia

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Cardiovasc Drugs Ther (United States) Aug 1994, 8 (4) p659-64

The effects of the administration of 50 mg of guggulipid or placebo capsules twice daily for 24 weeks were compared as adjuncts to a fruit- and vegetable-enriched prudent diet in the management of 61 patients with hypercholesterolemia

(31 in the guggulipid group and 30 in the placebo group) in a randomized, double-blind fashion. Guggulipid decreased the total cholesterol level by 11.7%, the low density lipoprotein cholesterol (LDL) by 12.5%, triglycerides by 12.0%, and the total cholesterol/high density lipoprotein (HDL) cholesterol ratio by 11.1% from the postdiet levels, whereas the levels were unchanged in the placebo group. The HDL cholesterol level showed no changes in the two groups. The lipid peroxides, indicating oxidative stress, declined 33.3% in the guggulipid group without any decrease in the placebo group. The compliance of patients was greater than 96%. The combined effect of diet and guggulipid at 36 weeks was as great as the reported lipid-lowering effect of modern drugs. After a washout period of another 12 weeks, changes in blood lipoproteins were reversed in the guggulipid group without such changes in the placebo group. Side effects of guggulipid were headache, mild nausea, eructation, and hiccup in a few patients.

Beneficial effects of Allium sativum (garlic), Allium cepa and Commiphora mukul on experimental hyperlipidemia and atherosclerosis--a comparative evaluation.

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J Postgrad Med (India) Jul 1991, 37 (3) p132-5

Oral administration of petroleum ether extract of Allium sativum, Allium cepa and ethylacetate extract of Commiphora mukul in albino rats significantly prevented rise in serum cholesterol and serum triglyceride level, caused by atherogenic diet. All the three agents were also found to confer significant protection against atherogenic diet induced atherosclerosis.

Curcumin, a major component of food spice turmeric (Curcuma longa) inhibits aggregation and alters eicosanoid metabolism in human blood platelets

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Prostaglandins Leukotrienes and Essential Fatty Acids (United Kingdom), 1995, 52/4 (223-227)

In traditional medicine, Ayurveda, several spices and herbs are held to possess medicinal properties. Earlier we have reported that extracts from several spices, including turmeric, inhibit platelet aggregation and modulate eicosanoid biosynthesis. Due to their eicosanoid-modulating property, it was suggested that the spices may serve to provide clues to drugs directed to arachidonic acid (AA) pathway enzymes as pharmacological targets. Curcumin, a major component of turmeric, inhibited platelet aggregation induced by arachidonate, adrenaline and

collagen. This compound inhibited thromboxane B2 (TXB2) production from exogenous (14C) arachidonate in washed platelets with a concomitant increase in the formation of 12-lipoxygenase products. Moreover, curcumin inhibited the incorporation of (14C)AA into platelet phospholipids and inhibited the deacylation of AA-labelled phospholipids (liberation of free AA) on stimulation with calcium ionophore A23187. Curcumin's anti-inflammatory property may, in part, be explained by its effects on eicosanoid biosynthesis.

Influence of capsaicin, eugenol, curcumin and ferulic acid on sucrose-induced hypertriglyceridemia in rats

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Nutr. Rep. Int. (USA), 1988, 38/3 (571-581)

The spice active principles, capsaicin, eugenol curcumin and 'ferulic acid' a common plant constituent were found to counter many of the metabolic changes caused by a high sucrose diet fed to rats. The compounds tested at high and low levels were mostly found to lower or tend to lower liver weight, liver triglycerides, free fatty acids, phospholipids, serum total, VLDL+LDL and HDL triglycerides, VLDL+LDL cholesterol, free fatty acids and also elevate serum total and HDL cholesterol.

Inhibitory effect of curcumin, an anti-inflammatory agent, on vascular smooth muscle cell proliferation

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Eur. J. Pharmacol. (Netherlands), 1992, 221/2-3 (381-384)

The effects of curcumin, an anti-inflammatory agent from Curcuma longa, on the proliferation of blood mononuclear cells and vascular smooth muscle cells were studied. Proliferative responses were determined from the uptake of tritiated thymidine. In human peripheral blood mononuclear cells, curcumin dose dependently inhibited the responses to phytohemagglutinin and mixed lymphocyte reaction at the dose ranges of 10-6 to 3 x 10-5 and 3 x 10-6 to 3 x 10-5 M, respectively. Curcumin (10-6 to 10-4 M) dose dependently inhibited the proliferation of rabbit vascular smooth muscle cells stimulated by fetal calf serum. Curcumin had a greater inhibitory effect on platelet-derived growth factor-stimulated proliferation than on serum-stimulated proliferation. Cinnamic acid, coumaric acid and ferulic acid were much less effective than curcumin as inhibitors of serum-induced smooth muscle cell proliferation, suggesting that the cinnamic acid and ferulic acid moieties alone are not sufficient for activity, and

that the characteristics of the diferuloylmethane molecule itself are necessary for activity. Curcumin may be useful as a new template for the development of better remedies for the prevention of the pathological changes of atherosclerosis and restenosis.

Polyphenols as cancer chemopreventive agents.

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J Cell Biochem Suppl (United States) 1995, 22 p169-80

This article summarizes available data on the chemopreventive efficacies of tea polyphenols, curcumin and ellagic acid in various model systems. Emphasis is placed upon the anticarcinogenic activity of these polyphenols and their proposed mechanism(s) of action. Tea is grown in about 30 countries and, next to water, is the most widely consumed beverage in the world. Tea is manufactured as either green, black, or oolong; black tea represents approximately 80% of tea products. Epidemiological studies, though inconclusive, suggest a protective effect of tea consumption on human cancer. Experimental studies of the antimutagenic and anticarcinogenic effects of tea have been conducted principally with green tea polyphenols (GTPs). GTPs exhibit antimutagenic activity in vitro, and they inhibit carcinogen-induced skin, lung, forestomach, esophagus, duodenum and colon tumors in rodents. In addition, GTPs inhibit TPA-induced skin tumor promotion in mice. Although several GTPs possess anticarcinogenic activity, the most active is (-)-epigallocatechin-3-gallat e (EGCG), the major constituent in the GTP fraction. Several mechanisms appear to be responsible for the tumor-inhibitory properties of GTPs, including enhancement of antioxidant (glutathione peroxidase, catalase and quinone reductase) and phase II (glutathione-S-transferase) enzyme activities; inhibition of chemically induced lipid peroxidation; inhibition of irradiation- and TPA-induced epidermal ornithine decarboxylase (ODC) and cyclooxygenase activities; inhibition of protein kinase C and cellular proliferation; antiinflammatory activity; and enhancement of gap junction intercellular communication. Curcumin is the yellow coloring agent in the spice tumeric. It exhibits antimutagenic activity in the Ames Salmonella test and has anticarcinogenic activity, inhibiting chemically induced preneoplastic lesions in the breast and colon and neoplastic lesions in the skin, forestomach, duodenum and colon of rodents. In addition, curcumin inhibits TPA-induced skin tumor promotion in mice. The mechanisms for the anticarcinogenic effects of curcumin are similar to those of the GTPs. Curcumin enhances glutathione content and glutathione-S-transferase activity in liver; and it inhibits lipid peroxidation and arachidonic acid metabolism in mouse skin, protein kinase C activity in TPA-treated NIH 3T3 cells, chemically induced ODC and tyrosine protein kinase activities in rat colon, and 8-hydroxyguanosine formation in mouse fibroblasts. Ellagic acid is a polyphenol found abundantly in various fruits, nuts and vegetables. Ellagic acid is active in antimutagenesis assays, and has been

shown to inhibit chemically induced cancer in the lung, liver, skin and esophagus of rodents, and TPA-induced tumor promotion in mouse skin.

Anti-tumour and antioxidant activity of natural curcuminoids.

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Cancer Lett (Ireland) Jul 20 1995, 94 (1) p79-83

Matural curcuminoids, curcumin, I, II and III isolated from turmeric (Curcuma longa) were compared for their cytotoxic, tumour reducing and antioxidant activities. Curcumin III was found to be more active than the other two as a cytotoxic agent and in the inhibition of Ehrlich ascites tumour in mice (ILS 74.1%). These compounds were also checked for their antioxidant activity which possibly indicates their potential use as anti-promoters. The amount of curcuminoids (I, II and III) needed for 50% inhibition of lipid peroxidation was 20, 14 and 11 g/m. Concentrations needed for 50% inhibition of superoxides were 6.25, 4.25 and 1.9 micrograms/ml and those for hydroxyl radical were 2.3, 1.8 and 1.8 micrograms/ml, respectively. The ability of these compounds to suppress the superoxide production by macrophages activated with phorbol-12-myristate-13-acetate (PMA) indicated that all the three curcuminoids inhibited superoxide production and curcumin III produced maximum effect. These results indicate that curcumin III is the most active of the curcuminoids present in turmeric. Synthetic curcumin I and III had similar activity to natural curcumins.

Phospholipid epitopes for mouse antibodies against bromelain-treated mouse erythrocytes.

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Immunology (England) Sep 1987, 62 (1) p11-6

The reactivity of mouse antibodies against bromelain-treated mouse erythrocytes (BrMRBC) with phospholipid epitopes was assessed by ELISA, using four clones of monoclonal anti-BrMRBC antibodies that had idiotypes distinct from one another. The four antibodies could bind to low-density lipoproteins (LDL) from human and chicken, but not to LDL from mouse and rat. As to liposomes of natural phospholipids, all the clones reacted with liposomes of phosphatidylcholine, and some of them could react with liposomes of sphingomyelin, phosphatidylglycerol, phosphatidylic acid or cardiolipin. For liposomes of synthetic phosphatidylcholine with different fatty acids, the length of carbon chains and the number of unsaturated carbon chains of the fatty acids markedly affected the binding of each monoclonal antibody to the liposomes. The addition of dicetyl phosphate or stearylamine to phosphatidylcholine liposomes

changed the reactivity of the liposomes. These results support the view that mouse anti-BrMRBC antibodies can recognize appropriately spaced phosphorylcholine residues on the surface of phospholipid liposomes, LDL and cells. The four clones had similar capacities for binding to LDL as well as to BrMRBC, but they had obviously different capacities for binding to phospholipid liposomes; the epitopes on phospholipid liposomes used in the present study were not so perfect as to react well with every anti-BrMRBC antibody.

The effect of spices on cholesterol 7 alpha-hydroxylase activity and on serum and hepatic cholesterol levels in the rat.

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Department of Food Chemistry, Central Food Technological Research Institute, Mysore, India.
Int J Vitam Nutr Res (Switzerland) 1991, 61 (4) p364-9

The effect of feeding curcumin, capsaicin, ginger, mustard, black pepper and cumin on cholesterol and bile acid metabolism was studied in rats. The activity of hepatic cholesterol-7 alpha-hydroxylase, the rate-limiting enzyme of bile acid biosynthesis, was significantly elevated in curcumin (turmeric), capsaicin (red pepper), ginger and mustard treated animals. The enzyme activity was comparable to controls in black pepper and cumin fed rats. Serum and liver microsomal cholesterol contents were significantly higher in the curcumin and capsaicin treated animals. Thus, this study has suggested that the spices--turmeric, red pepper, ginger and mustard can stimulate the conversion of cholesterol to bile acids, an important pathway of elimination of cholesterol from the body. However, simultaneous stimulation of cholesterol synthesis by the spice principles--curcumin and capsaicin suggests that there may not be any significant contribution of stimulation of bile acid biosynthesis to the hypocholesterolemic action of these spices, and the latter action may solely be due to interference with exogenous cholesterol absorption.

Effect of gugulipid on bioavailability of diltiazem and propranolol.

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J Assoc Physicians India (India) Jun 1994, 42 (6) p454-5

The effect of single oral dose of 1 gm gugulipid was studied on bioavailability of single oral dose of propranolol (40 mg) and diltiazem (60 mg) in 10 and 7 normal healthy male volunteers respectively. It was a randomised within group crossover study. Blood samples were collected at hourly intervals upto 8 hrs. Gugulipid significantly reduced ($P < .01$) peak plasma concentration (Cmax) and area under curve (AUC 0-8 hrs) of both the drugs in normal volunteers. Such interaction in

patients receiving propanolol or diltiazem with gugulipid may lead to diminished efficacy or nonresponsiveness due to significant reduction in bioavailability.

Biological effects of isoflavones in young women: Importance of the chemical composition of soyabean products

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British Journal of Nutrition (United Kingdom), 1995, 74/4 (587-601)

To examine the hormonal effects of isoflavones, of which soyabean is a rich source, fifteen healthy non-vegetarian premenopausal women were studied over 9 months. They lived in a metabolic suite for between 4 and 6 months where their diet and activity levels were kept constant and their hormonal status was measured over two or three menstrual cycles. During one (control) menstrual cycle a normal but constant diet containing no soyabean products was fed. Then, over a second complete cycle six subjects consumed a similar diet into which 60 g textured vegetable protein (TVP)/d, containing 45 mg conjugated isoflavones, had been incorporated. Three participants had 50 g miso (a fermented soyabean paste), containing 25 mg unconjugated isoflavones, added daily to their diet over a menstrual cycle, and six others consumed 28 g TVP/d, containing 23 mg conjugated isoflavones. Five participants completed a third diet period where they were randomly assigned to consume either the control diet over a cycle, or a similar diet incorporating 60 g of a soyabean product which had had the isoflavones chemically extracted (Arcon F). Follicular phase length was significantly ($P < 0.01$) increased and peak progesterone concentrations were delayed with 60 g TVP but no effects were observed with Arcon F. The increase in menstrual cycle length did not reach statistical significance in the three subjects who ate 50 g miso/d, but peak progesterone levels were significantly ($P < 0.05$) delayed. Mid-cycle peaks of luteinizing hormone (LH) and follicle stimulating hormone CFSH) were suppressed with 45 mg conjugated isoflavones as 60 g TVP ($P < 0.05$ and $P < 0.01$ respectively). No other changes in sex-steroid hormone levels were observed on any of the other diets. A significant reduction in total cholesterol was found with 45 mg conjugated isoflavones ($P < 0.05$), but not with 23 mg conjugated isoflavone-free Arcon F. There was no effect of menstrual cycle phase on transit time.

Overview of proposed mechanisms for the hypocholesterolemic effect of soy

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Journal of Nutrition (USA), 1995, 125/3 Suppl. (606S-611S)

A large body of literature indicates that protein from soybeans reduces blood cholesterol concentrations in experimental animals as well as in humans. The mechanism and component of soy responsible has not been established fully. Some suggest that when soy protein is fed, cholesterol absorption and/or bile acid reabsorption is impaired. This is observed in some animal species, such as rabbits and rats, but not in humans nor when amino acids replace intact soy protein. Others propose that changes in endocrine status, such as alteration in insulin:glucagon ratio and thyroid hormone concentrations, are responsible. The metabolic changes that have been observed on soy protein feeding in a variety of animal models, and in some cases humans, include increased cholesterol synthesis, increased bile acid synthesis (or fecal bile acid excretion), increased apolipoprotein B or E receptor activity and decreased hepatic lipoprotein secretion and cholesterol content, which are associated with an increased clearance of cholesterol from the blood. One hypothesis suggests amino acid composition or proportionality of soy causes changes in cholesterol metabolism (possibly via the endocrine system). Others have proposed that nonprotein components (such as saponins, fiber, phytic acid, minerals and the isoflavones) associated with soy protein affect cholesterol metabolism either directly or indirectly.

Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women

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Am. J. Clin. Nutr. (USA), 1994, 60/3 (333-340)

The influence of a diet containing soy protein on the hormonal status and regulation of the menstrual cycle was examined in six premenopausal women with regular ovulatory cycles. Soy protein (60 g containing 45 mg isoflavones) given daily for 1 mo significantly ($P < 0.01$) increased follicular phase length and/or delayed menstruation. Midcycle surges of luteinizing hormone and follicle-stimulating hormone were significantly suppressed during dietary intervention with soy protein. Plasma estradiol concentrations increased in the follicular phase and cholesterol concentrations decreased 9.6%. Similar responses occur with tamoxifen, an antiestrogen undergoing clinical trial as a prophylactic agent in women at high risk for breast cancer. These effects are presumed to be due to nonsteroidal estrogens of the isoflavone class, which behave as partial estrogen agonists/antagonists. The responses to soy protein are potentially beneficial with respect to risk factors for breast cancer and may in part explain the low incidence of breast cancer and its correlation with a high soy intake in Japanese and Chinese women.

A review of the clinical effects of phytoestrogens

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Obstetrics and Gynecology (USA), 1996, 87/5 II Suppl. (897-904)

Objective: To review the sources, metabolism, potencies, and clinical effects of phytoestrogens on humans.

Data Sources: The MEDLINE data base for the years 1980-1995 and reference lists of published articles were searched for relevant English-language articles concerning phytoestrogens, soy products, and diets with high-phytoestrogen content.

Methods of Study Selection: We identified 861 articles as being relevant. Human cell line studies, human epidemiologic studies (case-control or cohort), randomized trials, and review articles were included. Animal studies regarding phytoestrogens were included when no human data were available concerning an important clinical area.

Tabulation, Integration, and Results: Included were studies containing information considered pertinent to clinical practice in the areas of growth and development, menopause, cancer, and cardiovascular disease. When findings varied, those presented in this study reflect consensus. All studies concurred that phytoestrogens are biologically active in humans or animals. These compounds inhibit the growth of different cancer cell lines in cell culture and animal models. Human epidemiologic evidence supports the hypothesis that phytoestrogens inhibit cancer formation and growth in humans. Foods containing phytoestrogens reduce cholesterol levels in humans, and cell line, animal, and human data show benefit in treating osteoporosis.

Conclusion: This review suggests that phytoestrogens are among the dietary factors affording protection against cancer and heart disease in vegetarians. With this epidemiologic and cell line evidence, intervention studies are now an appropriate consideration to assess the clinical effects of phytoestrogens because of the potentially important health benefits associated with the consumption of foods containing these compounds.

Nutritional interest of flavonoids

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Medecine et Nutrition (France), 1996, 32/1 (17-27)

Polyphenols represent a complex group of compounds including several categories such as 4-oxo-flavonoids, anthocyanins and tannins. Some of these molecules are present in substantial amounts in various beverages and in plant

foods (fruits, vegetables...), and several investigations have established that they were liable to cross the intestinal barrier in mammals. Significant concentrations of flavonoid or polyphenol metabolites are likely to circulate in blood plasma in humans, and it appears thus important to assess their potential biological effects. Some interesting properties have already been reported, especially as to 4-oxo-flavonoids: they have antioxidizing and metal-complexing properties, and they are liable to modulate the activity of enzymes governing important cell functions. By protecting L.D.L. from oxidative alterations and by affecting platelet functions and plasma cholesterol, flavonoids might play a protective role against atherosclerosis. Some 4-oxo-flavonoids (quercetin, genistein...) show antiproliferative properties in vitro and inhibit the development of chimio-induced cancers in animal models. Thus, together with other micronutriments, their occurence in fruits and legumes could explain the preventive effects towards cancer risk of plant foods. Isoflavones which present a phytoestrogenic activity could be more specifically involved in the prevention of breast cancer risk. Further investigations are required to determine the actual bioavailability of the different classes of flavonoids, and to fully understand the underlying mechanisms of their biological effects.

Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat

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Molecular and Cellular Biochemistry (USA), 1995, 152/1 (13-21)

Effect of feeding 0.5% curcumin diet or 1% cholesterol diet was examined in albino rats rendered diabetic with streptozotocin injection. Diabetic rats maintained on curcumin diet for 8 weeks excreted Comparatively less amounts of albumin, urea, creatinine and inorganic phosphorus. Urinary excretion of the electrolytes sodium and potassium were also significantly lowered under curcumin treatment. Dietary curcumin also partially reversed the abnormities in plasma albumin, urea, creatinine and inorganic phosphorus in diabetic animals. On the other hand, glucose excretion or the fasting sugar level was unaffected by dietary curcumin and so also the body weights were not improved to any significant extent. Diabetic rats fed curcumin diet had a lowered relative liver weight at the end of the study compared to other diabetic rat groups. Diabetic rats fed a curcumin diet also showed lowered lipid peroxidation in plasma and urine when compared to other diabetic groups. The extent of lipid peroxidation on the other hand, was still higher in cholesterol fed diabetic groups compared to diabetic rats fed with control diet. Thus, the study reveals that curcumin feeding improves the metabolic status in diabetic condition, despite no effect on hyperglycemic status or the body weights. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence, antioxidant nature and free radical scavenging property.

Effect of retinol deficiency and curcumin or turmeric feeding on brain Na+-K+ adenosine triphosphatase activity

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Mol. Cell. Biochem. (USA), 1994, 137/2 (101-107)

The effect of retinol deficiency and curcumin and turmeric feeding on brain microsomal Na+-K+ ATPase activity was investigated. The brain Na+- K+ ATPase activity registered an increase of 148.5% as compared to the control group. Upon treating retinol deficient rats with curcumin or turmeric, the abnormally elevated activity showed a decrease of 36.9 and 47.1%, respectively, when compared to the retinol deficient group. An increase in V(max) by 67% and K(m) by 66% for ATP was observed in the retinol deficient group. Curcumin or turmeric fed retinol-deficient groups reduced the V(max) by 25 and 33%, while K(m) was reduced by 25 and 31%, respectively, compared to the retinol deficient group. Arrhenius plot of Na+-K+ ATPase showed a typical bi-phasic pattern in all the groups. Cholesterol:Phospholipid ratio showed a decrease in the retinol-deficient group by 67.8%, which showed a marked increase in curcumin or turmeric treated groups. Detergents could increase the Na+-K+ ATPase activity more in the control group than in the retinol deficient groups. Curcumin or turmeric improved the detergent action on the enzyme. Subsequent freezing and thawing over a period of 30 min decreased the enzyme activity by 22.8% in the retinol deficient group compared to 15.9% decrease in the control group. Curcumin or turmeric treated groups showed a decrease in the enzyme activity by 22.0 and 19.2%, respectively, when compared to the zero time in each group. In the presence of concanavalin-A (Con-A) there was only 52.4% stimulation in the enzyme activity in retinol deficient groups, compared to 108.0% in the control group. Curcumin or turmeric treated retinol-deficient groups showed a stimulation in the presence of con-A by 70 and 99.5%, respectively.

Bioactive substances in food: Identification and potential uses

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Can. J. Physiol. Pharmacol. (Canada), 1994, 72/4 (423-434)

Bioactive substances in foods can represent 'extranutritional' constituents naturally present in small quantities in the food matrix, produced upon either in vivo or industrial enzymatic digestion, the latter being a result of food-processing activities. Bioactive constituents of food evoke physiological, behavioral, and immunological effects. Evidence from both epidemiological and animal studies has suggested chemopreventative roles for phytochemicals in certain forms of

cancers and in the control of hyperlipidemia. Secondary products of plant metabolism can modulate xenobiotic metabolizing and cholesterol synthetic enzymes. Unique physicochemical properties of food-derived peptides with characteristic amino acid composition and sequences have been reported to influence intestinal transit, modify nutrient absorption and excretion, and exhibit immunostimulating and antihypertensive activity. Biologically active peptides derived from casein, fish muscle, and plant protein hydrolysates have been isolated, purified, and identified in peptide sequence studies. Therapeutic proteins (e.g., specific antibodies) derived from animal products such as milk may offer the potential for developing specialized food products with prophylactic as well as nutritive quality. This paper discusses the physicochemical mechanism of action of specific bioactive substances naturally present in or derived from foods. The biotechnologies employed to develop these products and the issues concerning acceptance by consumer and regulatory bodies are also addressed.

Mechanism of antiinflammatory actions of curcumine and boswellic acids

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J. Ethnopharmacol. (Ireland), 1993, 38/2-3 (113-119)

Curcumine from Curcuma longa and the gum resin of Boswellia serrata, which were demonstrated to act as antiinflammatories in in vivo animal models, were studied in a set of in vitro experiments in order to elucidate the mechanism of their beneficial effects. Curcumine inhibited the 5-lipoxygenase activity in rat peritoneal neutrophils as well as the 12-lipoxygenase and the cyclooxygenase activities in human platelets. In a cell free peroxidation system curcumine exerted strong antioxidative activity. Thus, its effects on the dioxygenases are probably due to its reducing capacity. Boswellic acids were isolated from the gum resin of Boswellia serrata and identified as the active principles. Boswellic acids inhibited the leukotriene synthesis via 5-lipoxygenase, but did not affect the 12-lipoxygenase and the cyclooxygenase activities. Additionally, boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. The data suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting directly with 5-lipoxygenase or blocking its translocation.

Influence of dietary spices on adrenal steroidogenesis in rats

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Nutr. Res. (USA), 1993, 13/4 (435-444)

Experiments were carried on adult rats which were fed the following diets for 2 months: Control, Curcumin (0.5%), Capsaicin (15mg%), Ginger (50mg%), Black pepper (0.5%), Cumin (1.25%), Mustard (250mg%), Fenugreek (2%) and Onion (3%). Adrenal weights in the various experimental groups were comparable to controls. Adrenal cholesterol was found to be significantly lower in all the spice fed animals except mustard suggesting a higher rate of cholesterol turnover to corticosteroid hormones. Cholesterol depletion was accompanied by reduced ascorbic acid content in the adrenals of curcumin, capsaicin, fenugreek and onion fed rats. Urinary excretion of 17-oxo and 17- hydroxy steroids which are the metabolites of corticosteroids was significantly higher in these spice fed groups. These data are indicative of the stimulatory influence of dietary spices on adrenal steroidogenesis.

Differential effects of dietary lipids and curcumin on kidney microsomal fatty acids and Na+, K+ - ATPase activity in rat

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Dept. of Food Chemistry, Central Food Technol. Research Inst., Mysore - 570013 India
Nutr. Res. (USA), 1992, 12/7 (893-904)

The effect of dietary lipids and spice principle curcumin on kidney microsomal lipids, Na+, K+ - ATPase activity and serum lipid levels were studied. Rats were fed a diet containing either coconut oil, safflower oil or menhaden oil for 8 weeks. Safflower oil and menhaden oil feeding resulted in the accumulation of n-6 polyunsaturated fatty acids (PUFA) and n-3 PUFA respectively in the kidney microsomes. The specific activity of Na+, K+ - ATPase was higher by 26% in animals fed safflower oil when compared to animals fed coconut oil or menhaden oil. Supplementation of curcumin in the diets containing different lipids did not affect either the kidney microsomal fatty acid profiles or Na+, K+ - ATPase activity. However, dietary curcumin reduced the serum triglyceride level by 44% in safflower oil fed animals and serum cholesterol levels by 24% and 31% in animals fed safflower oil and menhaden oil respectively. These studies indicated that dietary lipids and curcumin differentially affect membrane fatty acid composition, Na+, K+ - ATPase activity and serum lipids.

12. Constipation

Preventative and curative options include:

Ascorbic acid, magnesium oxide, pantothenic acid, green tea, chitosan, guar gum, pectin, psyllium, l-arginine, ferrous gluconate.

Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group.

Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Registre Bourguignon des Tumeurs Digestives, Faculte de Medecine de Dijon, France.

Lancet 2000 Oct 14;356(9238):1300-6

BACKGROUND: Some epidemiological studies have suggested that high dietary intake of calcium and fibre reduces colorectal carcinogenesis. Available data are not sufficient to serve as a basis for firm dietary advice. We undertook a multicentre randomised trial to test the effect of diet supplementation with calcium and fibre on adenoma recurrence. METHODS: We randomly assigned 665 patients with a history of colorectal adenomas to three treatment groups, in a parallel design: calcium gluconolactate and carbonate (2 g elemental calcium daily), fibre (3.5 g ispaghula husk), or placebo. Participants had colonoscopy after 3 years of follow-up. The primary endpoint was adenoma recurrence. Analyses were by intention to treat. FINDINGS: 23 patients died, 15 were lost to follow-up, 45 refused repeat colonoscopy, and five developed severe contraindications to colonoscopy. Among the 552 participants who completed the follow-up examination, 94 stopped treatment early. At least one adenoma developed in 28 (15.9%) of 176 patients in the calcium group, 58 (29.3%) of 198 in the fibre group, and 36 (20.2%) of 178 in the placebo group. The adjusted odds ratio for recurrence was 0.66 (95% CI 0.38-1.17; p=0.16) for calcium treatment and 1.67 (1.01-2.76, p=0.042) for the fibre treatment. The odds ratio associated with the fibre treatment was significantly higher in participants with baseline dietary calcium intake above the median than in those with intake below the median (interaction test, p=0.028) INTERPRETATION: Supplementation with fibre as ispaghula husk may have adverse effects on colorectal adenoma recurrence, especially in patients with high dietary calcium intake. Calcium supplementation was associated with a modest but not significant reduction in the risk of adenoma recurrence.

A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation.

Dettmar PW, Sykes J. Reckitt & Colman Products Ltd, Hull, UK.

Curr Med Res Opin 1998;14(4):227-33

An open, multi-centre study in general practice compared with efficacy, speed of action and acceptability of ispaghula husk (Fybogel Orange, Reckitt & Colman Products, UK), lactulose and other laxatives in the treatment of patients with simple constipation. A total of 65 GPs recruited 394 patients, of whom 224 (56.9%) were assigned to treatment with ispaghula and 170 (43.1%) to other laxatives (mainly lactulose) for up to four weeks. Thirteen patients withdrew before treatment started, so that 381 entered the study. Patients were assessed by their GP before entry and after two and four weeks of treatment. Patients also kept daily records of their bowel movements. After four weeks' treatment, ispaghula husk was assessed by the GPs to be superior to the other treatments in improving bowel function and in overall effectiveness, palatability and acceptability. Patients' reports of time to first bowel movement showed little difference between the treatments. Over 60% of patients in each treatment group passed a first motion within 24 hours, and over 80% within 36 hours. Ispaghula husk produced a higher percentage of normal, well-formed stools and fewer hard stools than other laxatives. Incidences of soiling, diarrhoea and abdominal pain were lower in the group receiving ispaghula husk. Overall, ispaghula husk was an effective treatment for simple constipation, and was associated with better stool consistency and a lower incidence of adverse events compared with lactulose or with other laxatives.

The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig.

Hills JM, Aaronson PI. Smith Kline Beecham Pharmaceuticals Ltd., Welwyn, Herts, England.

Gastroenterology 1991 Jul;101(1):55-65

An investigation of the mechanism of peppermint oil action was performed using isolated pharmacological preparations from guinea pig large intestine and patch clamp electrophysiology techniques on rabbit jejunum. Peppermint oil relaxed carbachol-contracted guinea pig taenia coli (IC50, 22.1 micrograms/mL) and inhibited spontaneous activity in the guinea pig colon (IC50, 25.9 micrograms/mL) and rabbit jejunum (IC50, 15.2 micrograms/mL). Peppermint oil markedly attenuated contractile responses in the guinea pig taenia coli to acetylcholine, histamine, 5-hydroxytryptamine, and substance P. Peppermint oil reduced contractions evoked by potassium depolarization and calcium contractions evoked in depolarizing Krebs solutions in taenia coli. Potential-dependent calcium currents recorded using the whole cell clamp configuration in rabbit jejunum smooth muscle cells were inhibited by peppermint oil in a concentration-dependent manner. Peppermint oil both reduced peak current amplitude and increased the rate of current decay. The effect of peppermint oil resembled that of the dihydropyridine calcium antagonists. It is concluded that peppermint oil relaxes gastrointestinal smooth muscle by reducing calcium influx.

The osmotic and intrinsic mechanisms of the pharmacological laxative action of oral high doses of magnesium sulphate. Importance of the release of digestive polypeptides and nitric oxide.

Izzo AA; Gaginella TS; Capasso F Department of Experimental Pharmacology, University of Naples Federico II, Italy.

Magnes Res (England) Jun 1996, 9 (2) p133-8

A common use for high doses of oral magnesium salts is to produce a laxative effect to treat constipation. In the intestinal lumen the poorly absorbable magnesium ions (and other ions such as sulphate) exert an osmotic effect and cause water to be retained in the intestinal lumen. This increases the fluidity of the intraluminal contents and results in a laxative action. Although the laxative action of magnesium is thought to be due to a local effect in the intestinal tract, it is also possible that released hormones such as cholecystokinin or activation of constitutive nitric oxide synthase might contribute to this pharmacological effect. Under normal circumstances the pharmacological administration of high doses of oral magnesium salts is safe and some salts--such as magnesium hydroxide--also have an antacid effect to neutralize stomach acid. However, high doses of magnesium or prolonged use may allow sufficient absorption into the systemic circulation to cause renal or other organ toxicity.

Chitosan And Fat Absorption

Kanauchi O; Deuchi K; Imasato Y; Shizukuishi M; Kobayashi E Applied Bioresearch Center, Kirin Brewery Co. Ltd., Gunma, Japan. Biosci Biotechnol Biochem (JAPAN) May 1995, 59 (5) p786-90 We investigated the mechanism for the inhibition of fat digestion by chitosan, and the synergistic effect of ascorbate. The important inhibition characteristics of fat digestion by chitosan from observations of the ileal contents were that it dissolved in the stomach and then changed to a gelled form, entrapping fat in the intestine. The synergistic effect of ascorbate (AsA) on the inhibition of fat digestion by chitosan is thought not to be acid-dependent but due to the specificity of AsA itself, according to the data resulting from using preparations supplemented with sodium ascorbate (AsN). The mechanism for the synergistic effect is considered to be 1) viscosity reduction in the stomach, which implies that chitosan mixed with a lipid is better than chitosan alone, 2) an increase in the oil-holding capacity of the chitosan gel, and 3) the chitosan-fat gel being more flexible and less likely to leak entrapped fat in the intestinal tract.

[Magnesium: current concepts of its physiopathology, clinical aspects and therapy]

Mancinella A, Bartolucci E.

Acta Vitaminol Enzymol (Italy) 1982, 4 (1-2) p87-97

Functional constipation is not a life-threatening disease, but as a chronic state it worries the patient and causes him discomfort and often leads him to self-medication with potentially dangerous drugs. Ro 01-4709 contains as active substance dexpanthenol, which is the alcohol of pantothenic acid, a vitamin of the B-complex. In the cells, dexpanthenol is readily oxidized to pantothenic acid, which stimulates peristalsis when administered in therapeutically effective doses.

Ro 01-4709 has already proven its efficacy in the prevention and treatment of adynamic ileus. Recently, several open and two double-blind studies have been carried out, investigating the efficacy of oral Ro 01-4709 in the treatment of chronic functional constipation. The two double-blind studies showed Ro 01-4709 to be superior to placebo in all parameters measured. The studies with an open design also demonstrated a favourable effect of Ro 01-4709 in the treatment of chronic functional constipation. Owing to its physiological action-which is in a favourable contrast to that of normal laxatives. Ro 01-4709 can be recommended for the treatment of functional constipation in pregnant women, children and the elderly.

Fat binder: a study of safety in obese patients.

Rossner S, Abelin J:

MATS Medical AB, Stockholm, Sweden, 1995.

Abstract: L112 Biopolymer (L112 Fat Blocker) is an investigational drug extracted from shellfish. L112 Biopolymer has unique properities in its ability of binding fat from the food in the stomach and in the intestines. This leads to a correction and normalization of the LDL cholesterol and triglyceride levels in the blood. The HDL-cholesterol level in the blood increases. The fat sucked out of the food and remains in the digestional canal. Thus the blood takes up less fat which leads to less fat deposits in the body. The body absorbs fewer calories from the fat and the cholesterol and triglyceride levels in the blood are reduced, all in one natural process. L112 Fat Blocker is made of a special fibre-like substance derived from the shells of shrimps, crabs and ohter shellfishes. After chemical extraction the substances has got electrostatic properties and has unique fat binding properties. It has been tested by a Norwegian research laboratory. When given orally together with the food it immediately disperse into tiny particles. These have great affinity to fat and starts binding themselves to fat particles in the stomach and upper intestines. With increasing pH in the lower intestines the binding occurs probably through precipitation and the body cannot any longer absorb the fat through the intestinal wall or dispense the into the blood stream. The substances has been tested in clinical trials and shows a remarkable effect in reducing total cholesterol while allowing the HDL-cholesterol to increase. In one randomized double-blind study with placebo-control the weight reduction was 2.5 times better than diet alone. A preliminary review on L112 Biopolymer has been published elsewhere. When fat contents in the bowel increases, it makes the feces soft and smooth. This may be particularly positive for those who suffer from obstipation. In this unicentre trial the fat content in feces and laboratory parameters, during treatment with L112 twice daily, will be investigated.

[A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy]

Signorelli P; Croce P; Dede A Divisione di Ostetricia e Ginecologia, Ospedale di Codogno, Regione Lombardia, USL n. 25, Lodi.

Minerva Ginecol (Italy) Dec 1996, 48 (12) p577-82

RATIONAL: Constipation is a problem frequently encountered during pregnancy as is excessive weight gain. Treatments of common use to control constipation are endowed with some drawbacks and they are not active in controlling weight increase. A preparation of lactulose and glucomannan in previous studies proved very effective and well tolerated in patients affected by stypsis and evidentiated also activity both in controlling excessive food intake and in correcting some metabolic imbalances regarding lipids and urea.

MATERIAL AND METHODS: 50 pregnant females affected by constipation were treated with sachets containing a preparation of glucomannan (1.45 g) and lactulose (4.2 g) in a posology of 2 (1-4) sachets a day for 1-3 months.

RESULTS: Treatment induced a return to normal frequency of weekly number of evacuations (4.9-5.8/week) and a parallel control of weight gain (within 20% of initial body weight). The latter finding seems to be related to hunger control induced by glucomannan at the gastric level which prevents an excessive food intake.

Analysis of two novel classes of plant antifungal proteins from radish (Raphanus sativus L.) seeds.

Terras FR, Schoofs HM, De Bolle MF, Van Leuven F, Rees SB, Vanderleyden J, Cammue BP, Broekaert WF. F. A. Janssens Laboratory of Genetics, Catholic University of Leuven, Heverlee, Belgium.

J Biol Chem 1992 Aug 5;267(22):15301-9

Two novel classes of antifungal proteins were isolated from radish seeds. The first class consists of two homologous proteins (Rs-AFP1 and Rs-AFP2) that were purified to homogeneity. They are highly basic oligomeric proteins composed of small (5-kDa) polypeptides that are rich in cysteine. Both Rs-AFPs have a broad antifungal spectrum and are among the most potent antifungal proteins hitherto characterized. In comparison with many other plant antifungal proteins, the activity of the Rs-AFPs is less sensitive to the presence of cations. Moreover, their antibiotic activity shows a high degree of specificity to filamentous fungi. The amino-terminal regions of the Rs-AFPs show homology with the derived amino acid sequences of two pea genes specifically induced upon fungal attack, to gamma-thionins and to sorghum alpha-amylase inhibitors. The radish 2S storage albumins were identified as the second novel class of antifungal proteins. All isoforms inhibit growth of different plant pathogenic fungi and some bacteria. However, their antimicrobial activities are strongly antagonized by cations.

Physiological role of dietary fiber: a ten-year review.

Trowell H, Burkitt D.

ASDC J Dent Child 1986 Nov-Dec;53(6):444-7

It is accepted nowadays that dietary fiber is an important constituent of the diet. There is growing evidence that the low fiber Western diets and the low

consumption of whole grain products are important factors in several common diseases of the large bowel. Cereal fiber differs from that present in vegetables and fruit. A low intake of cereal fiber has been implicated in cancer of the large bowel, diverticular disease of the colon and coronary heart disease. High fiber diets are often prescribed for diabetes. Although fiber consumption by British and American consumers has decreased over the past century, consumption of whole wheat breads and fiber-rich breakfast cereals has received new attention during the past ten years.

Clinical response to dietary fiber treatment of chronic constipation.

Voderholzer WA; Schatke W; Muhldorfer BE; Klauser AG; Birkner B; Muller-Lissner SA Medizinische Klinik, Klinikum Innenstadt, University of Munich, Germany.

Am J Gastroenterol (United States) Jan 1997, 92 (1) p95-8

OBJECTIVES: To determine the clinical outcome of dietary fiber therapy in patients with chronic constipation.

METHODS: One hundred, forty-nine patients with chronic constipation (age 53 yr, range 18-81 yr, 84% women) at two gastroenterology departments in Munich, Germany, were treated with Plantago ovata seeds, 15-30 g/day, for a period of at least 6 wk. Repeated symptom evaluation, oroanal transit time measurement (radiopaque markers), and functional rectoanal evaluation (proctoscopy, manometry, defecography) were performed. Patients were classified on the basis of the result of dietary fiber treatment: no effect, n = 84; improved, n = 33; and symptom free, n = 32.

RESULTS: Eighty percent of patients with slow transit and 63% of patients with a disorder of defecation did not respond to dietary fiber treatment, whereas 85% of patients without a pathological finding improved or became symptom free.

CONCLUSION: Slow GI transit and/or a disorder of defecation may explain a poor outcome of dietary fiber therapy in patients with chronic constipation. A dietary fiber trial should be conducted before technical investigations, which are indicated only if the dietary fiber trial fails.

Mechanisms of constipation in older persons and effects of fiber compared with placebo.

Cheskin LJ, Kamal N, Crowell MD, Schuster MM, Whitehead WE Division of Digestive Diseases, Johns Hopkins Bayview Medical Center, Baltimore, MD 21224, USA. J Am Geriatr Soc 1995 Jun;43(6):666-9

OBJECTIVE: To investigate the mechanisms of constipation and the effect of fiber supplementation on physiology, mechanisms, stool parameters, and colonic transit times in a group of constipated older patients.

DESIGN: Single-blind, randomized, placebo-controlled fiber intervention with crossover.

SETTING: A university-based outpatient center.

PATIENTS: Ten community-living older men and women, healthy except for chronic constipation.

INTERVENTIONS: Patients were given either 24 g psyllium fiber or placebo fiber daily for 1 month, then crossed over to the other arm for an additional month. Structured testing, including total gut transit time and rectal and colonic manometry, was performed at the end of each intervention month. Patients recorded stool frequency, consistency, and weights daily.

RESULTS: The predominant mechanism for constipation in these patients was outlet delay caused by pelvic dyssynergia. Fiber decreased total gut transit time from 53.9 hours (placebo condition) to 30.0 hours (< .05). stool weights and consistency were not significantly improved by fiber, though there was a trend toward an increase in stool frequency (1.3 vs 0.8 bowel movements per day.) Pelvic floor dyssynergia was not remedied by fiber, even when constipation was clinically improved.

CONCLUSIONS: Fiber supplementation appeared to benefit constipated older patients clinically, and it improved colonic transit time, but it did not rectify the most frequent underlying abnormality, pelvic floor dyssynergia.

[Intake of dietary fiber and other nutrients by children with and without functional chronic constipation]

de Morais MB; Vitolo MR; Aguirre AN; Medeiros EH; Antoneli EM; Fagundes-Neto U Departamento de Pediatrica da Universidade Federal de Sao-Paulo-Escola Paulista de Medicina (UNIFESP-EPM).

Arq Gastroenterol (Brazil) Apr-Jun 1996, 33 (2) p93-101

The aim of this study was to evaluate the dietary fiber intake and the dietary habits of children with and without functional chronic constipation. We enrolled 58 children with functional chronic constipation and 58 controls without constipation matched for sex and age. Food and fiber intake were evaluated by 24 hour dietary recall and a complete clinical history was performed. The age of onset of constipation occurred during the first year of life in 55.4% of the patients while the median age of evaluation was 78 months. Soiling was found in 41.7% of patients. The median period of exclusive breast feeding was shorter (P = 0.002) in the constipation group (one month) than in the control group (three month). The proportion of constipation was similar for mothers of children of both groups as well as for siblings in both groups. The fathers of children with constipation presented higher frequency of constipation (12.3%) than the fathers of children in control group (1.8%), but the difference did not reach statistical significance (P = 0.06). The amount of food measured by 24 hour recall was similar in both groups.

The calorie intake of constipated children (1526 +/- 585 calories/day) was lower (P = 0.07) than in the control group (1712 +/- 513 calories/day) but the difference did not reach statistical significance. The intake of protein, fat and iron was lower in the constipation group than in the control group. The volume of cow's milk intake was similar in both groups. The median of total dietary fiber intake in the constipation group (13.5 g/day) was statistically (P = 0.009) lower than in the control group (16.8 g/day). The daily intake of insoluble dietary fiber was also statistically lower (P = 0.001) in the constipation group (6.3 g) than in the control group (9.4 g). The intake of soluble dietary fiber was similar in both groups. The intake of dietary fiber per 1,000 calories of diet was 10.3 g in the constipation group and 10.4 in the control group (P = 0.41). There was a considerable intersection of individual values in fiber intake of the constipation and control groups, suggesting that low fiber intake acts in association with others factors on the genesis of constipation in children. However, the low intake of insoluble fiber, suggests that it plays an important role on the pathogenesis of chronic constipation in children.

Effectiveness of bran supplement on the bowel management of elderly rehabilitation patients.

Gibson CJ; Opalka PC; Moore CA; Brady RS; Mion LC

J Gerontol Nurs (United States) Oct 1995, 21 (10) p21-30

1. Constipation is a common problem in the elderly that affects up to 20% of those 65 years and older.

2. Patients receiving the fiber supplement had a significantly lower number of bowel agents per day as compared to the control patients.

3. Side effects from the additional fiber occurred in a subgroup of patients; thus, institution of additional fiber to the diets of ill, physically dependent patients is best done gradually and with close monitoring.

Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the treatment of constipation.

Kinnunen O, Salokannel J Department of Internal Medicine, Health Centre Hospital, Oulu, Finland.

J Int Med Res 1989 Sep-Oct;17(5):442-54

In a crossover study the effects of magnesium hydroxide on serum lipids, carbohydrates, vitamins A and E, uric acid and whole blood minerals were compared with those of a bulk laxative containing plantago rind and sorbitol in 64 constipated, elderly long-stay patients, 55 of whom were receiving diuretics. Hypomagnesaemia occurred in 11 (17%) patients after bulk laxative and in two (2%) patients after magnesium hydroxide treatment. There was a slight reduction in low values of high-density lipoprotein cholesterol and high values of

triglycerides after magnesium hydroxide treatment. There were no significant differences in plasma lipids, whole blood minerals or vitamins A and E using either laxative. Negative p correlations were found between the increase in serum concentrations of magnesium and glycosylated haemoglobin A1 (P less than 0.02) and the serum level of uric acid (P less than 0.01). These results suggest that the long-term effects of magnesium hydroxide and bulk laxative on the absorption of nutrients may not be significantly different. Magnesium hydroxide, however, may have beneficial effects on lipid disorders, impaired glucose tolerance and hyperuricaemia in magnesium deficiency due to diuretics and thus may be a favourable laxative for use in bedridden geriatric patients receiving diuretics.

The connection between dietary fibre intake and chronic constipation in children

Mooren G.C.A.H.C.M.; Van Der Plas R.N.; Bossuyt P.M.M.; Taminiau J.A.J.M. ; Buller H.A. Academisch Medisch Centrum, Kinder AMC, Afd. Kindergastroenterologie/Voed ing, Meibergdreef 9, 1105 AZ Amsterdam Netherlands

Nederlands Tijdschrift voor Geneeskunde (Netherlands), 1996, 140/41 (2036-2039)

Objective. Evaluation of the feeding patterns of children with chronic constipation, in particular dietary fibres, energy and fluid intake and their influence on colonic transit time. In addition, the effect of dietary recommendations regarding fibres was assessed.

Design. Prospective randomized study.

Setting. Department of Paediatric Gastroenterology and Nutrition, Academic Medical Centre, Amsterdam, the Netherlands.

Method. Children with at least 2 months of complaints related to constipation were enrolled and both dietary intake and colonic transit time were evaluated. After dietary and laxative treatment, in some combined with biofeedback training, and a follow-up of 6 months, a randomized sample were again evaluated regarding their transit times and dietary patterns.

Results. In 73 consecutive children mean fibre intake was the same as in healthy controls, although energy and fluid intake were lower. Colonic transit time was increased compared with healthy controls and no relationship was established between fibre intake and transit time. At 6 months no significant increase in mean fibre intake was observed and no relationship was found between either transit time and change in fibre intake or cure and change in fibre intake. In the cured patients no increase of their mean fibre intake could be observed.

Conclusion. The amount of dietary fibres played no pathogenic part in chronic constipation. Dietary advice did not change the mean fibre content of the diet. In addition, changes in fibre intake had no effect on colonic transit time or cure.

Dietary fiber and laxation in postop orthopedic patients.

Ouellet LL; Turner TR; Pond S; McLaughlin H; Knorr S Clin Nurs Res (United States) Nov 1996, 5 (4) p428-40

The addition of wheat fiber in the diet of post-surgical orthopedic patients as a means of preventing constipation was studied using a quasi-experimental design. It was hypothesized that a 20 gm supplement of All Bran and natural bran would promote spontaneous bowel movements, reduce the incidence of constipation, and thus decrease the need for elimination interventions. The results show that the study group had more spontaneous bowel movements and required fewer elimination interventions than did the control group.

[Intake of dietary fiber and other nutrients by children with and without functional chronic constipation]

de Morais MB; Vitolo MR; Aguirre AN; Medeiros EH; Antoneli EM; Fagundes-Neto U
Departamento de Pediatrica da Universidade Federal de Sao-Paulo-Escola Paulista de Medicina (UNIFESP-EPM).
Arq Gastroenterol (Brazil) Apr-Jun 1996, 33 (2) p93-101

The aim of this study was to evaluate the dietary fiber intake and the dietary habits of children with and without functional chronic constipation. We enrolled 58 children with functional chronic constipation and 58 controls without constipation matched for sex and age. Food and fiber intake were evaluated by 24 hour dietary recall and a complete clinical history was performed. The age of onset of constipation occurred during the first year of life in 55.4% of the patients while the median age of evaluation was 78 months. Soiling was found in 41.7% of patients. The median period of exclusive breast feeding was shorter (P = 0.002) in the constipation group (one month) than in the control group (three month). The proportion of constipation was similar for mothers of children of both groups as well as for siblings in both groups. The fathers of children with constipation presented higher frequency of constipation (12.3%) than the fathers of children in control group (1.8%), but the difference did not reach statistical significance (P = 0.06). The amount of food measured by 24 hour recall was similar in both groups. The calorie intake of constipated children (1526 +/- 585 calories/day) was lower (P = 0.07) than in the control group (1712 +/- 513 calories/day) but the difference did not reach statistical significance. The intake of protein, fat and iron was lower in the constipation group than in the control group. The volume of cow's milk intake was similar in both groups. The median of total dietary fiber intake in the constipation group (13.5 g/day) was statistically (P = 0.009) lower than in the control group (16.8 g/day). The daily intake of insoluble dietary fiber was also statistically lower (P = 0.001) in the constipation group (6.3 g) than in the control group (9.4 g). The intake of soluble dietary fiber was similar in both groups. The intake of dietary fiber per 1,000 calories of diet was 10.3 g in the constipation group and 10.4 in the control group (P = 0.41). There was a considerable intersection of individual values in fiber intake of the constipation and control groups, suggesting that low fiber intake acts in association with others factors on the genesis of constipation in children. However, the low intake of insoluble fiber,

suggests that it plays an important role on the pathogenesis of chronic constipation in children.

[A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy]

Signorelli P; Croce P; Dede A
Divisione di Ostetricia e Ginecologia, Ospedale di Codogno, Regione Lombardia, USL n. 25, Lodi.
Minerva Ginecol (Italy) Dec 1996, 48 (12) p577-82

RATIONAL: Constipation is a problem frequently encountered during pregnancy as is excessive weight gain. Treatments of common use to control constipation are endowed with some drawbacks and they are not active in controlling weight increase. A preparation of lactulose and glucomannan in previous studies proved very effective and well tolerated in patients affected by stypsis and evidentiated also activity both in controlling excessive food intake and in correcting some metabolic imbalances regarding lipids and urea.

MATERIAL AND METHODS: 50 pregnant females affected by constipation were treated with sachets containing a preparation of glucomannan (1.45 g) and lactulose (4.2 g) in a posology of 2 (1-4) sachets a day for 1-3 months.

RESULTS: Treatment induced a return to normal frequency of weekly number of evacuations (4.9-5.8/week) and a parallel control of weight gain (within 20% of initial body weight). The latter finding seems to be related to hunger control induced by glucomannan at the gastric level which prevents an excessive food intake.

Dietary fiber and laxation in postop orthopedic patients.

Ouellet LL; Turner TR; Pond S; McLaughlin H; Knorr S
Clin Nurs Res (United States) Nov 1996, 5 (4) p428-40

The addition of wheat fiber in the diet of post-surgical orthopedic patients as a means of preventing constipation was studied using a quasi-experimental design. It was hypothesized that a 20 gm supplement of All Bran and natural bran would promote spontaneous bowel movements, reduce the incidence of constipation, and thus decrease the need for elimination interventions. The results show that the study group had more spontaneous bowel movements and required fewer elimination interventions than did the control group.

[The relationship between intake of dietary fiber and chronic constipation in children]

Mooren GC; van der Plas RN; Bossuyt PM; Taminiau JA; Buller HA
Academisch Medisch Centrum-Het Kinder AMC, afd Kindergastroenterologie en Voeding, Amsterdam.
Ned Tijdschr Geneeskd (Netherlands) Oct 12 1996, 140 (41) p2036-9

OBJECTIVE: Evaluation of the feeding patterns of children with chronic constipation, in particular dietary fibres, energy and fluid intake and their influence on colonic transit time. In addition, the effect of dietary recommendations regarding fibres was assessed.

DESIGN: Prospective randomized study.

SETTING: Department of Paediatric Gastroenterology and Nutrition, Academic Medical Centre, Amsterdam, the Netherlands.

METHOD: Children with at least 2 months of complaints related to constipation were enrolled and both dietary intake and colonic transit time were evaluated. After dietary and laxative treatment, in some combined with biofeedback training, and a follow-up of 6 months, a randomized sample were again evaluated regarding their transit times and dietary patterns.

RESULTS: In 73 consecutive children mean fibre intake was the same as in healthy controls, although energy and fluid intake were lower. Colonic transit time was increased compared with healthy controls and no relationship was established between fibre intake and transit time. At 6 months no significant increase in mean fibre intake was observed and no relationship was found between either transit time and change in fibre intake or cure and change in fibre intake. In the cured patients no increase of their mean fibre intake could be observed.

CONCLUSION: The amount of dietary fibres played no pathogenic part in chronic constipation. Dietary advice did not change the mean fibre content of the diet. In addition, changes in fibre intake had no effect on colonic transit time or cure.

Assessment of the effect of increased dietary fibre intake on bowel function in patients with spinal cord injury.

Cameron KJ; Nyulasi IB; Collier GR; Brown DJ
Spinal Injuries Unit, Austin Hospital, Heidelberg, Victoria, Australia.
Spinal Cord (England) May 1996, 34 (5) p277-83

It is common for constipation to occur following severe spinal cord injury (SCI). Although a bowel management program including a high fibre diet is an integral part of rehabilitation, the effect of a high fibre diet on large bowel function in SCI has not been examined. The aims of this study were to assess the nutrient intake of SCI patients, to determine baseline transit time, stool weight and evacuation

time and to assess the effect of addition of bran on large bowel function. Eleven subjects, aged 32 +/- 10.5 years participated in the study. The level of injury ranged from C4 to T12; only one patient had an incomplete injury. Baseline mean energy intake was 7823 +/- 1443 kJ/d, protein intake 93 +/- 21 g/d, carbohydrate intake 209 +/- 39 g/d and mean dietary fibre intake 25 +/- 8 g/d. Mean baseline stool weight was 128 +/- 55 g/d and bowel evacuation time was 13 +/- 7.4 min/d. Three subjects who consumed < 18 g dietary fibre/d had low stool weights of 60-70 g/d and two had very delayed transit times that were too slow to enable quantitation. Mean mouth to anus transit time was 51.3 +/- 31.2 h, mean colonic transit time 28.2 +/- 3.5 h, right colonic transit time 5.9 +/- 4.5 h, left colonic transit time 14.5 +/- 5.2 h and rectosigmoid colonic transit time 7.9 +/- 5.6 h. Following the addition of bran, dietary fibre intake significantly increased from 25 g/d to 31 g/d ($P < 0.001$). However, the mean colonic transit time increased from 28.2 h to 42.2 h ($P < 0.05$) and rectosigmoid colon transit time increased from 7.9 to 23.3 h ($P < 0.02$). Stool weight, mouth to anus, left and right colon transit time and evacuation time did not change significantly. Results of this study suggest that increasing dietary fibre in SCI patients does not have the same effect on bowel function as has been previously demonstrated in individuals with 'normally functioning' bowels. Indeed the effect may be the opposite to that desired. This preliminary study highlights the need for further research to examine the optimal level of dietary fibre intake in SCI patients.

Therapeutic availability of iron administered orally as the ferrous gluconate together with magnesium-L-aspartate hydrochloride.

Disch G; Classen HG; Spatling L; Leifert U; Schumacher E
Department of Pharmacology and Toxicology of Nutrition, University of Hohenheim, Stuttgart-Hohenheim, Germany.
Arzneimittelforschung (Germany) Mar 1996, 46 (3) p302-6

Since in vitro experiments had excluded interactions between Fe-gluconate (Fe-gluc) and magnesium-L-aspartate hydrochloride (MAH) in aqueous solutions the present in vivo studies seemed to be justified. Animal studies: Rats were kept on magnesium-(Mg)- and iron-(Fe)- sufficient and deficient diets. The intragastral administration of Fe-gluc significantly increased plasma Fe after 3 h, either given alone, or in combination with MAH (inducing hypermagnesemia). Same results were obtained when fortified diets were offered to Fe/Mg-deficient animals. Human studies: The combination of Fe-gluc (2 x 50 mg Fe per day, per os) plus MAH (2 x 7.5 mmol Mg per day, p.o.) was well tolerated by healthy volunteers. Single dose experiments revealed that Fe-gluc alone and in combination with MAH increased plasma Fe levels during 3 h to the same extent. Two groups of pregnant women with moderately reduced hemoglobin levels either received Fe-gluc (out-patients) or its combination with MAH (at least temporarily hospitalised because of preterm labor). Treatments were well tolerated. Hemoglobin levels did not further decrease, as expected without Fe supplements, during the course of pregnancy, thus indicating the therapeutic availability of the electrolytes in both study groups. Progesterone-induced constipation is frequently observed during

pregnancy; hence stool softening reported by 50% of the women receiving Fe-gluc plus MAH (versus 33% in the Fe-gluc group) can be regarded as desirable effect. It is concluded that MAH does not interfere with the enteral absorption of Fe-gluc when both electrolytes are orally administered together. Taking both electrolytes together instead of 2 to 3 h apart from each other, as actually recommended, means a less complicated dosage regimen and probably improves compliance.

The osmotic and intrinsic mechanisms of the pharmacological laxative action of oral high doses of magnesium sulphate. Importance of the release of digestive polypeptides and nitric oxide.

Izzo AA; Gaginella TS; Capasso F
Department of Experimental Pharmacology, University of Naples Federico II, Italy.
Magnes Res (England) Jun 1996, 9 (2) p133-8

A common use for high doses of oral magnesium salts is to produce a laxative effect to treat constipation. In the intestinal lumen the poorly absorbable magnesium ions (and other ions such as sulphate) exert an osmotic effect and cause water to be retained in the intestinal lumen. This increases the fluidity of the intraluminal contents and results in a laxative action. Although the laxative action of magnesium is thought to be due to a local effect in the intestinal tract, it is also possible that released hormones such as cholecystokinin or activation of constitutive nitric oxide synthase might contribute to this pharmacological effect. Under normal circumstances the pharmacological administration of high doses of oral magnesium salts is safe and some salts--such as magnesium hydroxide--also have an antacid effect to neutralize stomach acid. However, high doses of magnesium or prolonged use may allow sufficient absorption into the systemic circulation to cause renal or other organ toxicity. (35

Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the eatment of constipation.

Kinnunen O, Salokannel J
Department of Internal Medicine, Health Centre Hospital, Oulu, Finland.
J Int Med Res 1989 Sep-Oct;17(5):442-54

In a crossover study the effects of magnesium hydroxide on serum lipids, carbohydrates, vitamins A and E, uric acid and whole blood minerals were compared with those of a bulk laxative containing plantago rind and sorbitol in 64 constipated, elderly long-stay patients, 55 of whom were receiving diuretics. Hypomagnesaemia occurred in 11 (17%) patients after bulk laxative and in two (2%) patients after magnesium hydroxide treatment. There was a slight reduction in low values of high-density lipoprotein cholesterol and high values of

triglycerides after magnesium hydroxide treatment. There were no significant differences in plasma lipids, whole blood minerals or vitamins A and E using either laxative. Negative p correlations were found between the increase in serum concentrations of magnesium and glycosylated haemoglobin A1 (P less than 0.02) and the serum level of uric acid (P less than 0.01). These results suggest that the long-term effects of magnesium hydroxide and bulk laxative on the absorption of nutrients may not be significantly different. Magnesium hydroxide, however, may have beneficial effects on lipid disorders, impaired glucose tolerance and hyperuricaemia in magnesium deficiency due to diuretics and thus may be a favourable laxative for use in bedridden geriatric patients receiving diuretics.

[Magnesium: current concepts of its physiopathology, clinical aspects and therapy]

Acta Vitaminol Enzymol (Italy) 1982, 4 (1-2) p87-97

Functional constipation is not a life-threatening disease, but as a chronic state it worries the patient and causes him discomfort and often leads him to self-medication with potentially dangerous drugs. Ro 01-4709 contains as active substance dexpanthenol, which is the alcohol of pantothenic acid, a vitamin of the B-complex. In the cells, dexpanthenol is readily oxidized to pantothenic acid, which stimulates peristalsis when administered in therapeutically effective doses. Ro 01-4709 has already proven its efficacy in the prevention and treatment of adynamic ileus. Recently, several open and two double-blind studies have been carried out, investigating the efficacy of oral Ro 01-4709 in the treatment of chronic functional constipation. The two double-blind studies showed Ro 01-4709 to be superior to placebo in all parameters measured. The studies with an open design also demonstrated a favourable effect of Ro 01-4709 in the treatment of chronic functional constipation. Owing to its physiological action-which is in a favourable contrast to that of normal laxatives. Ro 01-4709 can be recommended for the treatment of functional constipation in pregnant women, children and the elderly.

Endogenous nitric oxide modulates morphine-induced constipation.

Calignano A, Moncada S, Di Rosa M
Department of Experimental Pharmacology, University of Naples Federico II, Italy.
Biochem Biophys Res Commun 1991 Dec 16;181(2):889-93

Administration of morphine in mice causes inhibition of the gastrointestinal transit of a charcoal meal. Morphine-induced constipation in mice seems to depend predominantly on action(s) on the central nervous system since N-methyl morphine, a quaternary derivative, inhibits intestinal transit only when administered intracerebroventricularly (i.c.v.). L- but not D-arginine, given intraperitoneally, reversed the constipation induced by both morphine and its

quaternary analogue. L-arginine was ineffective when given i.c.v. and did not reverse atropine-induced constipation. These results suggest that L-arginine preferentially modulates opioid-induced constipation through a stereospecific and peripheral action(s). It is possible that the effect of L-arginine is achieved by increasing the amount of nitric oxide released by non-adrenergic, non-cholinergic nerves in the gut. Thus, L-arginine may represent a useful agent for the treatment of undesirable constipation associated with the use of narcotic analgesics.

13. Depression

Preventative and curative options include:

SAMe, DHEA, pregnenolone, *dl*-phenylalanine, DMAE, vitamin B5, tyrosine, l-carnitine, NADH, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B12, choline, folic acid, vitamin C, potassium, St. John's wort, ginseng, ginkgo biloba, fish oil.

Nutrition and depression: the role of folate.

Alpert JE, Fava M. Department of Psychiatry, Harvard Medical School, Boston, MA 02114, USA.

Nutr Rev 1997 May;55(5):145-9

A relationship between folate and neuropsychiatric disorders has been inferred from clinical observation and from the enhanced understanding of the role of folate in critical brain metabolic pathways. Depressive symptoms are the most common neuropsychiatric manifestation of folate deficiency. Conversely, borderline low or deficient serum or red blood cell folate levels have been detected in 15-38% of adults diagnosed with depressive disorders. Recently, low folate levels have been linked to poorer antidepressant response to selective serotonin reuptake inhibitors. Factors contributing to low serum folate levels among depressed patients as well as the circumstances under which folate and its derivatives may have a role in antidepressant pharmacotherapy must be further clarified.

Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction.

Bell IR, Edman JS, Morrow FD, Marby DW, Perrone G, Kayne HL, Greenwald M, Cole JO. Department of Psychiatry, Harvard Medical School.

J Am Coll Nutr 1992 Apr;11(2):159-63

This was a 4-week randomized placebo-controlled double-blind study to assess augmentation of open tricyclic antidepressant treatment with 10 mg each of vitamins B1, B2, and B6 in 14 geriatric inpatients with depression. The active vitamin group demonstrated significantly better B2 and B6 status on enzyme activity coefficients and trends toward greater improvement in scores on ratings of depression and congnitive function, as well as in serum nortriptyline levels compared with placebo-treated subjects (Ss). Without specific supplementation, B12 levels increased in Ss receiving B1/B2/B6 and decreased in placebo Ss.

These findings offer preliminary support for further investigation of B complex vitamin augmentation in the treatment of geriatric depression.

Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine

Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H Special Studies Clinic, Mexican Institute of Psychiatry, Tlalpan. Psychiatry Res 1992 Dec;44(3):257-62

A double-blind clinical trial was carried out to evaluate the efficacy of S-adenosyl-L-methionine (SAMe) in speeding the onset of action of imipramine (IMI). SAMe is a naturally occurring substance that has been shown to possess antidepressant activity with a rapid mode of onset and minimal side effects. Sixty-three outpatients with moderate to severe depression were included in the study. After an initial 1-week placebo period, only 40 patients entered the active treatment phase. During the first 2 weeks of the trial, half of these patients received 200 mg/day of SAMe intramuscularly, while the other half received placebo. Simultaneously, oral IMI was administered to all patients at a fixed dose of 150 mg/day. The onset of clinical response was determined by evaluating patients every second day. By the end of week 2, the parenteral treatment was suppressed and IMI was adjusted according to individual needs. Depressive symptoms decreased earlier in the patients who were receiving the SAMe-IMI combination than in those who were receiving the placebo-IMI combination.

5-Hydroxytryptophan: a clinically-effective serotonin precursor.

Birdsall TC. 73541.2166@compuserve.com

Altern Med Rev 1998 Aug;3(4):271-80

5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. Unlike LT, 5-HTP cannot be shunted into niacin or protein production. Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behaviour, and pain sensation. Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia.

L-deprenyl plus L-phenylalanine in the treatment of depression.

Birkmayer W, Riederer P, Linauer W, Knoll J.

J Neural Transm 1984;59(1):81-7

The antidepressive efficacy of 1-deprenyl (5-10 mg daily) plus 1-phenylalanine (250 mg/day) has been evaluated in 155 unipolar depressed patients. Both oral and intravenous administration showed beneficial effects in 90% of outpatients and 80.5% of inpatients. It is concluded that this combined treatment has a potent antidepressive action based on the accumulation of 1-phenylethylamine in the brain.

Dehydroepiandrosterone treatment of midlife dysthymia.

Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Behavioral Endocrinology Branch, National Institute of Mental Health, Bethesda, MD 20892-1276, USA.

Biol Psychiatry 1999 Jun 15;45(12):1533-41

BACKGROUND: This study evaluated the efficacy of the adrenal androgen, dehydroepiandrosterone, in the treatment of midlife-onset dysthymia.

METHODS: A double-blind, randomized crossover treatment study was performed as follows: 3 weeks on 90 mg dehydroepiandrosterone, 3 weeks on 450 mg dehydroepiandrosterone, and 6 weeks on placebo. Outcome measures consisted of the following. Cross-sectional self-ratings included the Beck Depression Inventory, and visual analogue symptom scales. Cross-sectional objective ratings included the Hamilton Depression Rating Scale, the Cornell Dysthymia Scale and a cognitive test battery. Seventeen men and women aged 45 to 63 years with midlife-onset dysthymia participated in this study. Response to dehydroepiandrosterone or placebo was defined as a 50% reduction from baseline in either the Hamilton Depression Rating Scale or the Beck Depression Inventory.

RESULTS: In 15 patients who completed the study, a robust effect of dehydroepiandrosterone on mood was observed compared with placebo. Sixty percent of the patients responded to dehydroepiandrosterone at the end of the 6-week treatment period compared with 20% on placebo. A significant response was seen after 3 weeks of treatment on 90 mg per day. The symptoms that improved most significantly were anhedonia, loss of energy, lack of motivation, emotional "numbness," sadness, inability to cope, and worry. Dehydroepiandrosterone showed no specific effects on cognitive function or sleep disturbance, although a type II error could not be ruled out.

CONCLUSIONS: This pilot study suggests that dehydroepiandrosterone is an effective treatment for midlife-onset dysthymia.

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders

Bottiglieri T, Hyland K, Reynolds EH Metabolic Disease Center, Baylor Research Institute, Dallas, Texas.

Drugs 1994 Aug;48(2):137-52

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; SAMe). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAMe is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAMe concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

Homocysteine, folate, methylation, and monoamine metabolism in depression.

Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Department of Neurology, King's College Hospital, London, UK.

J Neurol Neurosurg Psychiatry 2000 Aug;69(2):228-32

OBJECTIVES: Previous studies suggest that folate deficiency may occur in up to one third of patients with severe depression, and that treatment with the vitamin may enhance recovery of the mental state. There are, however, difficulties in interpreting serum and red cell folate assays in some patients, and it has been suggested that total plasma homocysteine is a more sensitive measure of functional folate (and vitamin B12) deficiency. Other studies suggest a link between folate deficiency and impaired metabolism of serotonin, dopamine, and noradrenaline (norepinephrine), which have been implicated in mood disorders. A study of homocysteine, folate, and monoamine metabolism has, therefore, been undertaken in patients with severe depression.

METHODS: In 46 inpatients with severe DSM III depression, blood counts, serum and red cell folate, serum vitamin B12, total plasma homocysteine, and, in 28 patients, CSF folate, S-adenosylmethionine, and the monoamine neurotransmitter metabolites 5HIAA, HVA, and MHPG were examined. Two control groups comprised 18 healthy volunteers and 20 patients with neurological disorders, the second group undergoing CSF examination for diagnostic purposes.

RESULTS: Twenty four depressed patients (52%) had raised total plasma homocysteine. Depressed patients with raised total plasma homocysteine had significant lowering of serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls.

CONCLUSIONS: Utilising total plasma homocysteine as a sensitive measure of functional folate deficiency, a biological subgroup of depression with folate deficiency, impaired methylation, and monoamine neurotransmitter metabolism has been identified. Detection of this subgroup, which will not be achieved by routine blood counts, is important in view of the potential benefit of vitamin replacement.

Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study.

Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. St. John's Episcopal Hospital, Far Rockaway, New York 11691, USA.

Clin Ther 2000 Apr;22(4):411-9

BACKGROUND: Hypericum (St. John's wort) has been shown to be as efficacious and well tolerated as standard antidepressants in the treatment of depression but has not been compared with selective serotonin reuptake inhibitors (SSRIs).

OBJECTIVE: This study compared hypericum and the SSRI sertraline in the treatment of depression.

METHODS: In a double-blind, randomized study conducted in a community hospital, 30 male and female outpatients (19 women, 11 men; mean age, 45.5 years) with mild to moderate depression received 600 mg/d of a standardized extract of hypericum (LI 160) or 50 mg/d sertraline for I week, followed by hypericum 900 mg/d or sertraline 75 mg/d for 6 weeks.

RESULTS: The severity of symptoms, as assessed by scores on the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression scale, was significantly reduced in both treatment groups (< 0.01). Clinical response (defined as a < or =50% reduction in HAM-D scores) was noted in 47% of patients receiving hypericum and 40% of those receiving sertraline. The difference was not statistically significant. Both agents were well tolerated. A post hoc power analysis indicated that failure to reach statistical significance between treatments resulted primarily from an absence of clinical differences rather than the small sample size.

CONCLUSION: The hypericum extract was at least as effective as sertraline in the treatment of mild to moderate depression in a small group of outpatients.

S-adenosyl-l-methionine (SAMe) as antidepressant: Meta-analysis of clinical studies

Bressa GM Department of Psychiatry, University Cattolica Sacro Cuore School of Medicine, Rome, Italy.

Acta Neurol Scand Suppl 1994;154:7-14

Introduction - S-adenosyl-l-methionine (SAMe) is a naturally-occurring substance which is a major source of methyl groups in the brain. Material and methods - We conducted a meta-analysis of the studies on SAMe to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants. Results - Our meta-analysis showed a greater response rate with SAMe when compared with placebo, with a global effect size ranging from 27% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants. Conclusion - The efficacy of SAMe in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since SAMe is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

[Effect of pyridoxine on the psychopathology and pathochemistry of involutional depressions] [Article in Russian]

Bukreev VI.

Zh Nevropatol Psikhiatr Im S S Korsakova 1978;78(3):402-8

In agreement with the catecholamine hypotheses of affective disorders the main role in the pathogenesis of depressive states is allocated to the central "noradrenergic insufficiency". The author thinks it feasible to use pyridoxine (vit. B6) in the treatment of depressive states, inasmuch as it is involved in the process of catecholamine synthesis as a cofactor of DOPA-decarboxylase. The author examined 48 patients among which 31 were with involutional melancholia and 17 with manic-depressive psychoses, manifesting after 40 years. Along with a positive therapeutical effect there was an increase in the noradrenaline excretion and a drop in the relative adrenaline content.

Neuropsychiatric disorders associated with nutritional deficiencies. Incidence and therapeutic implications

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CNS Drugs (CNS DRUGS) (New Zealand) 1995, 3/4 (279-290) Deficiencies of various vitamins are associated with a variety of neuropsychiatric manifestations. Depression is a feature of deficiencies of folic acid, vitamin B 2 (riboflavin) and vitamin B 6 (pyridoxine), while vitamin B 1 (thiamine) deficiency is associated with several psychosyndromes including alcoholism and schizophrenia. Data

from recent studies of vitamin deficiency reveal that gross manifestations such as beri-beri (characteristics include Wernicke's encephalopathy and Korsakoff's syndrome) and pellagra (characteristics include fatigue, insomnia and encephalopathy) are now relatively rare in the Western world. However, milder and subclinical syndromes are still common. For example, the prevalence of low levels of vitamin B 12 (cyanocobalamin) is has been estimated to be 5.8 to 26.1% in psychiatric patients, while that of folic acid is higher at 15 to 51% (derived from various studies). Despite these apparent associations, whether deficiencies of vitamins are causal in neuropsychiatric disorders or a result of them is difficult to determine. For example, there is little direct evidence of a causal role for folic acid in neuropsychiatric disorders, except in the rare in-born errors of metabolism that present with neuropsychiatric abnormalities. It is known that folic acid deficiency is associated with the use of many therapeutic drugs, concomitant physical illnesses and chronicity of psychiatric illness. However, retrospective studies of the effects of folic acid replacement therapy in deficient patients, employing clinical and social outcome criteria, have shown an improvement in psychiatric symptoms over a period of 6 to 12 months in most patients. Controlled studies of folic acid replacement therapy are also encouraging. In 1 double-blind, placebo-controlled add-on trial involving patients with endogenous depression and schizophrenia, the majority of folic acid treated patients improved compared with placebo recipients. The situation with regard to a causal role for other vitamins in neuropsychiatric disorders is even less clear. Obviously, more data are needed in this area to assist clinicians in determining the aetiology of episodes of depression and other neuropsychiatric disorders and, ultimately, their treatment.

Red cell folate concentrations in psychiatric patients

Carney M.W.P.; Chary T.K.N.; Laundy M.; Bottiglieri T.; Chanarin I.; Reynolds E.H.; Toone B. Department of Psychiatry, Clinical Research Centre, Northwick Park Hospital, Watford Road,Harrow HA1 3UJ United Kingdom

Journal of Affective Disorders (J. AFFECT. DISORD.) (Netherlands) 1990, 19/3 (207-213) Red cell folate and vitamin B12 estimations were performed on 243 successively admitted in-patients at a District General Hospital Psychiatric Unit and 42 out-patients (29 attending a lithium clinic). Patients were classified into five diagnostic groups. The mean ages of the manic and schizophrenic patients were lower than of the depressed or euthymic patients but age was not correlated with red cell folate or serum B12 levels in any group. There were 89 (31%) patients with red cell folate below 200 ng/ml and 35 (12%) with concentrations below 150 ng/ml. Significantly more of these low-folate patients were in-patients than outpatients. The mean red cell folate in the depressed patients was significantly lower than in the euthymic, manic and schizophrenic groups. Alcoholics had a similar mean red cell folate to depressed patients which was not quite significantly lower than the other groups. The mean serum B12 level in the alcoholics was, however, significantly raised. There were no significant differences in red cell folate or serum B12 between lithium-treated and untreated euthymic patients. The highest proportions of values below 200 ng/ml and 150 ng/ml were found in depressed and alcoholic patients. Endogenous depressives had the highest percentage of values below 150 ng/ml (folate-deficient) of all

psychiatric groups and alcoholic patients. The significance of these findings is discussed.

A controlled clinical trial of L-tryptophan in acute mania.

Chouinard G, Young SN, Annable L.

Biol Psychiatry 1985 May;20(5):546-57

In a 2-week study, 24 newly admitted manic patients were treated for 1 week with L-tryptophan (12 g/day); during the second week, half the patients, chosen at random, continued to receive tryptophan, while placebo was substituted in the other half under double-blind conditions. In the open phase of the study, there was a clinically and statistically (p less than 0.001) significant reduction in manic symptom scores, with little need for haloperidol prn. Patients who continued to be treated with tryptophan showed no significant change in mean scores during the second week, but those who were switched to placebo tended (p less than 0.10) to show an increase in the mean scores for manic symptoms. There was a significant (p less than 0.05) increase in the geometric mean of morning fasting total and free plasma tryptophan concentrations in men, but not in women. These results suggest that increasing the synthesis of 5-hydroxytryptamine has some therapeutic effect in mania.

Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial.

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J Affect Disord 2000 Nov;60(2):121-30

BACKGROUND: A consistent finding in major depression has been a low plasma and red cell folate which has also been linked to poor response to antidepressants. The present investigation was designed to investigate whether the co-administration of folic acid would enhance the antidepressant action of fluoxetine.

METHODS: 127 patients were randomly assigned to receive either 500 microg folic acid or an identical looking placebo in addition to 20 mg fluoxetine daily. All patients met the DSM-III-R criteria for major depression and had a baseline Hamilton Rating Scale (17 item version) score for depression of 20 or more. Baseline and 10-week estimations of plasma folate and homocysteine were carried out.

RESULTS: Patients receiving folate showed a significant increase in plasma folate.This was less in men than in women. Plasma homocysteine was significantly decreased in women by 20.6%, but there was no significant change in men. Overall there was a significantly greater improvement in the fluoxetine plus folic acid group. This was confined to women where the mean Hamilton

Rating Scale score on completion was 6.8 (S.D. 4. 1) in the fluoxetine plus folate group, as compared to 11.7 (S.D. 6. 7) in the fluoxetine plus placebo group (< 0.001).A percentage of 93. 9 of women, who received the folic acid supplement, showed a good response (< 50% reduction in score) as compared to 61.1% of women who received placebo supplement (< 0.005). Eight (12.9%) patients in the fluoxetine plus folic acid group reported symptoms possibly or probably related to medication, whereas in the fluoxetine plus placebo group 19 (29.7%) patients reported such symptoms (< 0.05).

LIMITATIONS AND CONCLUSIONS: Folic acid is a simple method of greatly improving the antidepressant action of fluoxetine and probably other antidepressants. Folic acid should be given in doses sufficient to decrease plasma homocysteine. Men require a higher dose of folic acid to achieve this than women, but more work is required to ascertain the optimum dose of folic acid.

S-Adenosyl-Methionine improves depression in patients with Parkinson's disease in an open-label clinical trial.

Di Rocco A, Rogers JD, Brown R, Werner P, Bottiglieri T.

Department of Neurology, Beth Israel Medical Center-Albert Einstein College of Medicine, New York, NY 10003, USA.

Mov Disord 2000 Nov;15(6):1225-9

We report a pilot study of S-adenosyl-methionine (SAM) in 13 depressed patients with Parkinson's disease. All patients had been previously treated with other antidepressant agents and had no significant benefit or had intolerable side effects. SAM was administered in doses of 800 to 3600 mg per day for a period of 10 weeks. Eleven patients completed the study, and 10 had at least a 50% improvement on the 17-point Hamilton Depression Scale (HDS). One patient did not improve. Two patients prematurely terminated participation in the study because of increased anxiety. One patient experienced mild nausea, and another two patients developed mild diarrhea, which resolved spontaneously. The mean HDS score before treatment was 27.09 +/- 6.04 (mean +/- standard deviation) and was 9.55 +/- 7.29 after SAM treatment (< 0.0001). Although uncontrolled and preliminary, this study suggests that SAM is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease.

Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients.

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J Affect Disord 1998 Mar;48(2-3):149-55

BACKGROUND: There is a hypothesis that lack of n-3 polyunsaturated fatty acids (PUFAs) is of aetiological importance in depression. Docosahexaenoic acid, a member of the n-3 PUFA family, is a crucial component of synaptic cell membranes. The aim of this study was to measure RBC membrane fatty acids in a group of depressed patients relative to a well matched healthy control group. METHOD: Red blood cell (RBC) membrane levels, and dietary PUFA intake were measured in 10 depressed patients and 14 matched healthy control subjects. RESULTS: There was a significant depletion of RBC membrane n-3 PUFAs in the depressed subjects which was not due to reduced calorie intake. Severity of depression correlated negatively with RBC membrane levels and with dietary intake of n-3 PUFAs. CONCLUSION: Lower RBC membrane n-3 PUFAs are associated with the severity of depression. LIMITATIONS: Although patient numbers were small, confounding factors were well controlled for and the results were highly significant. Results of the dietary data would tend to be weakened due to the limitations associated with dietary assessment. CLINICAL RELEVANCE: The findings raise the possibility that depressive symptoms may be alleviated by n-3 PUFA supplementation.

Effect of vitamin B complex on neurotransmission and neurite outgrowth.

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Gen Pharmacol 1996 Sep;27(6):995-1000

1. The effect of vitamin B complex (vitamin B1, B6 and B12) was studied on nerve conduction velocity in acrylamide-neuropathy rats maintained on refined semisynthetic complete vitamin and vitamin B-deficient diets in vivo and on neurite outgrowth in vitro using cells obtained from dorsal root ganglions of mice. 2. Acrylamide neuropathy was clearer in the group maintained on a refined semisynthetic vitamin B-deficient diet than in those on a refined semisynthetic complete vitamin diet. The neurotoxicity was lowest in the group given vitamin B complex prophylactic-therapeutically, next higher following therapeutic administration and last with no vitamin B complex administration in both groups maintained on a refined semisynthetic vitamin B-deficient diet and a refined semisynthetic complete vitamin diet. 3. The nerve conduction velocity tended to decrease by treatment with acrylamide. The decrement of nerve conduction velocity was partially inhibited by vitamin B complex. No significant difference was found in the groups treated with acrylamide and given vitamin B complex prophylactic-therapeutically and the control (no acrylamide treatment) in the group maintained on a refined semisynthetic vitamin B-deficient diet. 4. The greatest neurite outgrowth was found in the group treated with vitamins B1, B6 and B12-enriched medium, followed by the group of vitamin B12-enriched and vitamin B1-enriched media. All groups treated with a vitamin B-enriched medium had significantly greater (< 0.01) outgrowth than the controls.

St John's wort for depression: a systematic review.

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Arch Intern Med 2000 Jan 24;160(2):152-6

To address whether St John's wort is useful for the treatment of depression we attempted to retrieve all English-language articles with data on the efficacy, safety, and availability of St John's wort. Randomized, controlled, double-blind trials were selected and assessed for methodological quality using a standardized checklist, and data on pharmacology, cost, regulation, and safety were extracted. Eight studies were identified, found to be of generally good methodological quality, and determined to provide a modest amount of data to suggest that St John's wort is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of St John's wort ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. More data are required to assess both its use in severe depression and its efficacy compared with other antidepressants. Rates of side effects were low. As a dietary supplement, St John's wort is currently largely unregulated, but the Food and Drug Administration is reviewing plans to tighten its regulatory oversight.

St. John's Wort extract: efficacy for menopausal symptoms of psychological origin.

Grube B, Walper A, Wheatley D. Lichtwer Pharma AG, Berlin, Germany.

Adv Ther 1999 Jul-Aug;16(4):177-86

Herbal remedies such as St. John's Wort preparations can be used successfully to relieve the psychological and vegetative symptoms of menopause. This drug-monitoring study investigated 12 weeks of treatment with St. John's Wort, one tablet three times daily (900 mg Hypericum, Kira), in 111 women from a general medical practice. The patients, who were between 43 and 65 years old, had climacteric symptoms characteristic of the pre- and postmenopausal state. Treatment outcome was evaluated by the Menopause Rating Scale, a self-designed questionnaire for assessing sexuality, and the Clinical Global Impression scale. The incidence and severity of typical psychological, psychosomatic, and vasomotor symptoms were recorded at baseline and after 5, 8, and 12 weeks of treatment. Substantial improvement in psychological and psychosomatic symptoms was observed. Climacteric complaints diminished or disappeared completely in the majority of women (76.4% by patient evaluation and 79.2% by physician evaluation). Of note, sexual well-being also improved after treatment with St. John's Wort extract.

Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine.

Harrer G, Schmidt U, Kuhn U, Biller A. Institut fur Forensische Psychiatrie der Universitat Salzburg, Germany.

Arzneimittelforschung 1999 Apr;49(4):289-96

In a randomised double-blind comparative trial, the antidepressant efficacy of a daily dose of 800 mg of the St. John's wort extract LoHyp-57 (dry extract of St. John's wort, drug extrakt ratio 5-7:1, solvent, ethanol 60% [w/w]) was shown to be equivalent to that of 20 mg fluoxetine (CAS 54910-89-3) in elderly patients with mild or moderate depressive episodes according to ICD 10 (International Statistical Classification of Diseases and Related Health Problems). Treatment was given for six weeks. 149 out-patients (129 females and 20 males) were included in the intention-to-treat analysis. 72 of these patients were assigned to the ICD 10 diagnostic criterion F32.0 (mild depressive episode), while 77 patients were suffering from moderate depressive episodes, corresponding to F32.1. The principal target criterion was the patient's global score on the HAMILTON Depression Scale (items 1-17). During the six-week course of treatment with LoHyp-57, the HAMILTON global score fell from 16.60 points at entry to 7.91 points, and in the fluoxetine sample it fell from 17.18 to 8.11 points. In the group of patients with mild depressive episodes, the score showed a mean fall from 14.21 to 6.21 points on LoHyp-57, and from 15.21 to 7.46 points on fluoxetine. In patients with moderate depressive episodes, the score showed a mean fall from 18.73 to 9.43 points on LoHyp-57 and from 19.10 to 8.75 points on fluoxetine. The efficacy of both medications was found to be equivalent both in mild and moderate depressive episodes. Both treatment groups showed adverse drug reactions (ADRs). Twelve ADRs with a possible relationship to the study medication were reported during treatment with LoHyp-57. Six patients were prematurely withdrawn from treatment with the study medication for this reason. On fluoxetine 17 ADRs occurred with a possible relationship to the study medication. These led to abandonment of treatment and therefore premature withdrawal from the study in 8 cases.

Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy.

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Am J Clin Nutr 1995 Jul;62(1):1-9

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and post-partum depression. We postulate that

adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Decreased cerebral 5-HT1A receptors during ageing: reversal by Ginkgo biloba extract (EGb 761).

Huguet F, Drieu K, Piriou A. Institut des Xenobiotiques, Faculte de Medecine et de Pharmacie, Poitiers, France.

J Pharm Pharmacol 1994 Apr;46(4):316-8

Investigation of [3H]8-hydroxy-2(di-n-propylamino)tetralin binding to 5-HT1A receptors in cerebral cortex membranes of Wistar rats showed that the maximal number of binding sites (Bmax) was reduced significantly (22%) in aged (24-month-old) as compared with young (4-month-old) animals. Chronic treatment with Ginkgo biloba extract did not alter binding in young rats but increased binding density significantly (33%) in aged rats. These results confirm previously described age-related 5-hydroxytryptaminergic alterations. Together with data in the literature, they also suggest a restorative effect in aged rats, associated with decreased receptor density resulting from the protective action of Ginkgo biloba extract treatment on neuronal membrane.

Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial.

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J Clin Endocrinol Metab 2000 Dec;85(12):4650-6

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are adrenal precursors of steroid biosynthesis and centrally acting neurosteroids. Glucocorticoid and ineralocorticoid deficiencies in Addison's disease require life-long hormone replacement, but the associated failure of DHEA synthesis is not corrected. We conducted a randomized, double blind study in which 39 patients with Addison's disease received either 50 mg oral DHEA daily for 12 weeks, followed by a 4-week washout period, then 12 weeks of placebo, or vice versa. After DHEA treatment, levels of DHEAS and Delta(4)-androstenedione rose from subnormal to within the adult physiological range. Total testosterone increased from subnormal to low normal with a fall in serum sex hormone-binding globulin in females, but with no change in either parameter in males. In both sexes, psychological assessment showed significant enhancement of self-esteem with a tendency for improved overall well-being. Mood and fatigue also improved significantly, with benefit being evident in the evenings. No effects on cognitive or sexual function, body composition, lipids, or bone mineral density were observed. Our results indicate that DHEA replacement corrects this steroid deficiency effectively and improves some aspects of psychological function.

Beneficial effects in males, independent of circulating testosterone levels, suggest that it may act directly on the central nervous system rather than by augmenting peripheral androgen biosynthesis. These positive effects, in the absence of significant adverse events, suggest a role for DHEA replacement therapy in the treatment of Addison's disease.

Effect of acute and chronic administration of dehydroepiandrosterone on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-induced wet dog shaking behavior in rats.

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J Neural Transm 1999;106(1):23-33

It has been reported that dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEA-S) is associated with affective disorders and that pathology of affective disorders are related with dysfunction of serotonin(5-HT)-2A receptor-mediated responses. In this study, we investigated the effect of DHEA on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane (DOI), 5-HT-2A receptor agonist, -induced wet dog shaking behavior (WDS) in rats. Acute treatment with DHEA inhibited the DOI-induced WDSs dose dependently. This inhibition was recovered by opioid receptor antagonist, naltrexone. 5-HT-2A receptor-mediated WDSs were desensitized after chronic treatment with DOI, however chronic treatment with DHEA had no effect on this desensitization. Chronic treatment with DHEA had no facilitating effect of chronic dexamethasone treatment on DOI-induced WDSs. These findings may lead the possibility that DHEA has the inhibitory effect of 5-HT-2A mediated signaling pathway via non-genomic action.

Treatment of seasonal affective disorder (SAD) with hypericum extract.

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Pharmacopsychiatry 1997 Sep;30 Suppl 2:89-93

Seasonal affective disorder (SAD) is a subgroup of major depression and characterized by a regular occurrence of symptoms in autumn/winter and full remission or hypomania in spring/summer. Light therapy (LT) and recently pharmacotherapy with specific antidepressants have been shown to be beneficial. Within the array of pharmacotherapy hypericum extract has also been found to be effective in a single-blind study (Martinez et al., 1994). In this 4 weeks treatment study 900 mg of hypericum was associated with a significant reduction in the total score of the Hamilton Depression Rating Scale. There was no significant difference when bright light therapy was combined with hypericum, compared to the situation without bright light therapy. Overall, hypericum was well tolerated and therefore the data suggest that pharmacological treatment with hypericum may be an efficient therapy in patients with SAD, which needs to be substantiated in further controlled studies.

Folates: supplemental forms and therapeutic applications.

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Altern Med Rev 1998 Jun;3(3):208-20

Folates function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides form purine precursors, indirectly in the synthesis of transfer RNA, and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine. Oral folates are generally available in two supplemental forms, folic and folinic acid. Administration of folinic acid bypasses the deconjugation and reduction steps required for folic acid. Folinic acid also appears to be a more metabolically active form of folate, capable of boosting levels of the coenzyme forms of the vitamin in circumstances where folic acid has little to no effect. Therapeutically, folic acid can reduce homocysteine levels and the occurrence of neural tube defects, might play a role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis, appears to be a rational aspect of a nutritional protocol to treat vitiligo, and can increase the resistance of the gingiva to local irritants, leading to a reduction in inflammation. Reports also indicate that neuropsychiatric diseases secondary to folate deficiency might include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.

Vitamin D3 enhances mood in healthy subjects during winter.

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Psychopharmacology (Berl) 1998 Feb;135(4):319-23

Mood changes synchronised to the seasons exist on a continuum between individuals, with anxiety and depression increasing during the winter months. An extreme form of seasonality is manifested as the clinical syndrome of seasonal affective disorder (SAD) with carbohydrate craving, hypersomnia, lethargy, and changes in circadian rhythms also evident. It has been suggested that seasonality and the symptoms of SAD may be due to changing levels of vitamin D3, the hormone of sunlight, leading to changes in brain serotonin. Forty-four healthy subjects were given 400 IU, 800 IU, or no vitamin D3 for 5 days during late winter in a random double-blind study. Results on a self-report measure showed that vitamin D3 significantly enhanced positive affect and there was some evidence of a reduction in negative affect. Results are discussed in terms of their implications for seasonality, SAD, serotonin, food preference, sleep, and circadian rhythms.

Controlled trials of inositol in psychiatry.

Levine J. Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel.

Eur Neuropsychopharmacol 1997 May;7(2):147-55

Inositol is a simple polyol precursor in a second messenger system important in the brain. Cerebrospinal fluid inositol has been reported as decreased in depression. A double-blind controlled trial of 12 g daily of inositol in 28 depressed patients for four weeks was performed. Significant overall benefit for inositol compared to placebo was found at week 4 on the Hamilton Depression Scale. No changes were noted in hematology, kidney or liver function. Since many antidepressants are effective in panic disorder, twenty-one patients with panic disorder with or without agoraphobia completed a double-blind, placebo-controlled, four week, random-assignment crossover treatment trial of inositol 12 g per day. Frequency and severity of panic attacks and severity of agoraphobia declined significantly with inositol compared to placebo. Side-effects were minimal. Since serotonin re-uptake inhibitors benefit obsessive compulsive disorder (OCD) and inositol is reported to reverse desensitization of serotonin receptors, thirteen patients with OCD completed a double-blind controlled crossover trial of 18 g inositol or placebo for six weeks each. Inositol significantly reduced scores of OCD symptoms compared with placebo. A controlled double-blind crossover trial of 12 g daily of inositol for a month in twelve anergic schizophrenic patients, did not show any beneficial effects. A double-blind controlled crossover trial of 6 g of inositol daily vs. glucose for one month each was carried out in eleven Alzheimer patients, with on clearly significant therapeutic effects. Antidepressant drugs have been reported to improve attention deficit disorder (ADDH) with hyperactivity symptomatology. We studied oral inositol in children with ADDH in a double-blind, crossover, placebo-controlled manner. Eleven children, mean age 8.9 +/- 3.6 years were enrolled in an eight week trial of inositol or placebo at a dose of 200 mg/kg body weight. Results show a trend for aggravation of the syndrome with myo-inositol as compared to placebo. Recent studies suggest that serotonin re-uptake inhibitors are helpful in at least some symptoms of autism. However a controlled double-blind crossover trial of inositol 200 mg/kg per day showed no benefit in nine children with autism. Cholinergic agonists have been reported to ameliorate electroconvulsive therapy (ECT)-induced memory impairment. Inositol metabolism is involved in the second messenger system for several muscarinic cholinergic receptors. Inositol 6 g daily was given in a crossover-double-blind manner for five days before the fifth or sixth ECT to a series of twelve patients, without effect. These results suggest that inositol has therapeutic effects in the spectrum of illness responsive to serotonin selective re-uptake inhibitors, including depression, panic and OCD, and is not beneficial in schizophrenia, Alzheimer's ADDH, autism or ECT-induced cognitive impairment.

Double-blind, controlled trial of inositol treatment of depression.

Levine J, Barak Y, Gonzalves M, Szor H, Elizur A, Kofman O, Belmaker RH. Yehuda Abarbanel Mental Health Center, Bat Yam, Israel.

Am J Psychiatry 1995 May;152(5):792-4

OBJECTIVE: CSF levels of inositol have been reported to be lower than normal in depressed subjects. The authors administered inositol to depressed patients in a double-blind, controlled trial. METHOD: Under double-blind conditions, 12 g/day of inositol (N = 13) or placebo (N = 15) was administered to depressed patients for 4 weeks. RESULTS: The overall improvement in scores on the Hamilton Depression Rating Scale was significantly greater for inositol than for placebo at week 4. No changes were noted in hematology or in kidney or liver function. CONCLUSIONS: This may be the first use of the precursor strategy for a second messenger rather than a neurotransmitter in treating depression. Although inositol had a significant antidepressant effect in this study, replication is crucial.

Follow-up and relapse analysis of an inositol study of depression.

Levine J, Barak Y, Kofman O, Belmaker RH. Abarbanel Mental Health Center, Bat Yam, Israel.

Isr J Psychiatry Relat Sci 1995;32(1):14-21

A recent controlled double-blind study of 28 patients treated with 12 gm daily of inositol or placebo revealed significant antidepressant effect for this second messenger precursor. Patients were followed-up by interview and Hamilton Depression Scale 10-12 months after the end of the study. Half of the patients who had responded well to inositol relapsed rapidly after inositol discontinuation whereas none of those who responded to placebo relapsed rapidly after placebo cessation. Klein suggested that true drug responders to tricyclic antidepressants respond slowly and gradually whereas placebo responders improve early in an abrupt fashion. However, in the recent study both inositol and placebo responders improved at similar rates. Hamilton Depression Scale Scores 10-12 months after completion of the study were not significantly different between those who had responded and those who had not responded to inositol or to placebo.

St John's wort for depression--an overview and meta-analysis of randomised clinical trials.

Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. Projekt Munchener Modell, Ludwig-Maximilians-Universitat, Munich, Germany.

BMJ 1996 Aug 3;313(7052):253-8

OBJECTIVE--To investigate if extracts of Hypericum perforatum (St John's wort) are more effective than placebo in the treatment of depression, are as effective as standard antidepressive treatment, and have fewer side effects than standard antidepressant drugs. DESIGN-Systematic review and meta-analysis of trials revealed by searches. TRIALS--23 randomised trials including a total of 1757 outpatients with mainly mild or moderately severe depressive disorders: 15 (14 testing single preparations and one a combination with other plant extracts) were placebo controlled, and eight (six testing single preparations and two combinations) compared hypericum with another drug treatment. MAIN

OUTCOME MEASURES--A pooled estimate of the responder rate ratio (responder rate in treatment group/responder rate in control group), and numbers of patients reporting and dropping out for side effects. RESULTS--Hypericum extracts were significantly superior to placebo (ratio = 2.67; 95% confidence interval 1.78 to 4.01) and similarly effective as standard antidepressants (single preparations 1.10; 0.93 to 1.31, combinations 1.52; 0.78 to 2.94). There were two (0.8%) drop outs for side effects with hypericum and seven (3.0%) with standard antidepressant drugs. Side effects occurred in 50 (19.8%) patients on hypericum and 84 (52.8%) patients on standard antidepressants. CONCLUSION--There is evidence that extracts of hypericum are more effective than placebo for the treatment of mild to moderately severe depressive disorders. Further studies comparing extracts with standard antidepressants in well defined groups of patients and comparing different extracts and doses are needed.

Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial.

Lingaerde O, Foreland AR, Magnusson A. Department of Research and Education, Aker Hospital, Oslo, Norway.

Acta Psychiatr Scand 1999 Jul;100(1):62-6

OBJECTIVE: The aim was to test the hypothesis that the Ginkgo biloba extract PN246, in tablet form (brand name Bio-Biloba), may prevent the symptoms of winter depression (WD) in patients with seasonal affective disorder (SAD). METHOD: A total of 27 SAD patients were randomized to receive double-blind placebo or Bio-Biloba for 10 weeks or until they developed symptoms of WD, starting in a symptom-free phase about 1 month before expected WD symptoms. An extended Montgomery-Asberg Depression Rating Scale was completed before and immediately after termination of medication. The patients also self-rated some key symptoms on a visual analogue scale every 2 weeks during the trial. RESULTS: There were no significant differences between the treatment groups in the number of patients who developed treatment-requiring WD, or in the development of single key symptoms during the trial. CONCLUSION: We did not find that Ginkgo biloba was able to prevent the development of the symptoms of winter depression.

Effect of St. John's wort (Hypericum perforatum) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers.

Markowitz JS, DeVane CL, Boulton DW, Carson SW, Nahas Z, Risch SC. Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston 29425, USA. markowij@musc.edu

Life Sci 2000 Jan 21;66(9):PL133-9

The effects of the herb St. John's wort (Hypericum perforatum), a purported antidepressant, on the activity of cytochrome P-450 (CYP) 2D6 and 3A4 was assessed in seven normal volunteers. Probe substrates dextromethorphan (2D6

activity) and alprazolam (3A4 activity) were administered orally with and without the co-administration of St. John's wort. Urinary concentrations of dextromethorphan and dextrorphan were quantified and dextromethorphan metabolic ratios (DMRs) determined. Plasma samples were collected (0-60 hrs) for alprazolam pharmacokinetic analysis sufficient to estimate tmax, Cmax, t 1/2, and AUC. Validated HPLC methods were used to quantify all compounds of interest. No statistically significant differences were found in any estimated pharmacokinetic parameter for alprazolam or DMRs. These results suggest that St. John's wort, when taken at recommended doses for depression, is unlikely to inhibit CYP 2D6 or CYP 3A4 activity.

EGG phosphatidylcholine combined with vitamin B12 improved memory impairment following lesioning of nucleus basalis in rats.

Masuda Y, Kokubu T, Yamashita M, Ikeda H, Inoue S. Q.P. Corporation, Department of Neuropsychiatry, Kochi Medical School, Tokyo, Japan.

Life Sci 1998;62(9):813-22

We investigated the effects of egg phosphatidylcholine (PC) combined with vitamin B12 on memory in the Morris water maze task, and on choline and acetylcholine (ACh) concentrations in the brain of rats. Animals with nucleus basalis Magnocellularis (NBM) lesion received intragastric administration of egg PC or vitamin B12, or both for 18 days. Memory acquisition and retention were remarkably impaired in NBM lesioned rats compared with in sham-operated control. NBM lesioned group had lower choline and ACh concentrations than control group in the frontal cortex. High dose of egg PC alone significantly increased choline concentration, but did not change ACh concentration in the frontal cortex. High dose of vitamin B12 alone did not change choline and ACh concentrations in the brain. Either egg PC or vitamin B12 did not improve memory acquisition and retention. However, low dose of egg PC combined with vitamin B12 significantly increased ACh concentration and improved memory acquisition and retention in the NBM lesioned rats. We concluded that egg PC combined with vitamin B12 improved the memory impairment of NBM lesioned rats through the action on the cholinergic neurons.

Evaluation of the relative potency of individual competing amino acids to tryptophan transport in endogenously depressed patients.

Moller, Svend E.

Psychiatry Research 3(2):141-150, 1980

The relative potency of the individual amino acids as competitive inhibitors of tryptophan transport into the human brain was evaluated retrospectively; the combination of competitors that yields the highest predictive value of the plasma tryptophan ratio for the course of treatment of depressed patients with L-tryptophan was also examined. Phenylalanine consistently reduced, and isoleucine slightly reduced the predictive value of the plasma tryptophan ratio. The ratio of

tryptophan to the sum of valine, leucine, and tyrosine was identified as most predictive for the therapeutic response to tryptophan. L-tryptophan responders showed a normal plasma total tryptophan concentration as did the nonresponders, whereas the concentration of the three competitors was significantly elevated. It is concluded that while the plasma ratio of tryptophan to the sum of valine, leucine, and tyrosine is a useful predictor of the course of depressives on L-tryptophan, it does not definitely separate out the L-tryptophan responders from the control subjects.

Relationship between plasma ratio of tryptophan to competing amino acids and the response to L-tryptophan treatment in endogenously depressed patients.

Moller SE, Kirk L, Honore P.

J Affect Disord 1980 Mar;2(1):47-59

The ratio of the plasma of total tryptophan to those amino acids that compete with tryptophan during transport into the brain was determined in 60 control subjects and 87 patients suffering from endogenous depression, all females. The plasma ratio in the control subjects showed a significant negative correlation with age. There was no significant difference in the distribution of the biochemical data between the control subjects and the depressed patients. There was a significant higher proportion of bipolar depressed subjects compared to unipolar depressives and patients of uncertain polarity who showed a plasma ratio in the lower normal range. Thirty-two patients were subsequently treated with L-tryptophan. In the patients who showed a particularly low plasma ratio of tryptophan to competing amino acids a remission frequency of 80% was observed on day 14. The efficacy of L-tryptophan in the patients who showed a plasma ratio within the upper normal range was extremely poor. The results suggest that the ratio in the plasma of tryptophan to competing amino acids is a useful predictor of the course of treatment of depressed subjects with L-tryptophan.

St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor.

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Proc Natl Acad Sci U S A 2000 Jun 20;97(13):7500-2

St. John's wort (Hypericum perforatum) is an herbal remedy used widely for the treatment of depression. Recent clinical studies demonstrate that hypericum extracts increase the metabolism of various drugs, including combined oral contraceptives, cyclosporin, and indinavir. In this report, we show that hyperforin, a constituent of St. John's wort with antidepressant activity, is a potent ligand (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that

regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with hypericum extracts or hyperforin results in a marked induction of CYP3A4 expression. Because CYP3A4 is involved in the oxidative metabolism of >50% of all drugs, our findings provide a molecular mechanism for the interaction of St. John's wort with drugs and suggest that hypericum extracts are likely to interact with many more drugs than previously had been realized.

The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women.

Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. Department of Reproductive Medicine, School of Medicine, University of California San Diego, La Jolla, USA.

Clin Endocrinol (Oxf) 1998 Oct;49(4):421-32

OBJECTIVE: The biological role of the adrenal sex steroid precursors--DHEA and DHEA sulphate (DS) and their decline with ageing remains undefined. We observed previously that administration of a 50 daily dose of DHEA for 3 months to age-advanced men and women resulted in an elevation (10%) of serum levels of insulin-like growth factor-I (IGF-I) accompanied by improvement of self-reported physical and psychological well-being. These findings led us to assess the effect of a larger dose (100 mg) of DHEA for a longer duration (6 months) on circulating sex steroids, body composition (DEXA) and muscle strength (MedX).

SUBJECTS AND DESIGN: Healthy non-obese age-advanced (50-65 yrs of age) men (n = 9) and women (n = 10) were randomized into a double-blind placebo-controlled cross-over trial. Sixteen subjects completed the one-year study of six months of placebo and six months of 100 mg oral DHEA daily.

MEASUREMENTS: Fasting early morning blood samples were obtained. Serum DHEA, DS, sex steroids, IGF-I, IGFBP-1, IGFBP-3, growth hormone binding protein (GHBP) levels and lipid profiles as well as body composition (by DEXA) and muscle strength (by MedX testing) were measured at baseline and after each treatment.

RESULTS: Basal serum levels of DHEA, DS, androsternedione (A), testosterone (T) and dihydrotestosterone (DHT) were at or below the lower range of young adult levels. In both sexes, a 100 mg daily dose of DHEA restored serum DHEA levels to those of young adults and serum DS to levels at or slightly above the young adult range. Serum cortisol levels were unaltered, consequently the DS/cortisol ratio was increased to pubertal (10:1) levels. In women, but not in men, serum A, T and DHT were increased to levels above gender-specific young adult ranges. Basal SHBG levels were in the normal range for men and elevated in women, of whom 7 of 8 were on oestrogen replacement therapy. While on DHEA, serum SHBG levels declined with a greater (P < 0.02) response in women (-40 +/- 8%; P = 0.002) than in men (-5 +/- 4%; P = 0.02). Relative to

baseline, DHEA administration resulted in an elevation of serum IGF-I levels in men (16 +/- 6%, P = 0.04) and in women (31 +/- 12%, P = 0.02). Serum levels of IGFBP-1 and IGFBP-3 were unaltered but GHBP levels declined in women (28 +/- 6%; P = 0.02) not in men. In men, but not in women, fat body mass decreased 1.0 +/- 0.4 kg (6.1 +/- 2.6%, P = 0.02) and knee muscle strength 15.0 +/- 3.3% (P = 0.02) as well as lumbar back strength 13.9 +/- 5.4% (P = 0.01) increased. In women, but not in men, an increase in total body mass of 1.4 +/- 0.4 kg (2.1 +/- 0.7%; P = 0.02) was noted. Neither gender had changes in basal metabolic rate, bone mineral density, urinary pyridinoline cross-links, fasting insulin, glucose, cortisol levels or lipid profiles. No significant adverse effects were observed.

CONCLUSIONS: A daily oral 100 mg dose of DHEA for 6 months resulted in elevation of circulating DHEA and DS concentrations and the DS/cortisol ratio. Biotransformation to potent androgens near and slightly above the range of their younger counterparts occurred in women with no detectable change in men. Given this hormonal milieu, an increase in serum IGF-I levels was observed in both genders but dimorphic responses were evident in fat body mass and muscle strength in favour of men. These differences in response to DHEA administration may reflect a gender specific response to DHEA and/or the presence of confounding factor(s) in women such as oestrogen replacement therapy.

Tryptophan depletion and risk of depression relapse: a prospective study of tryptophan depletion as a potential predictor of depressive episodes.

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Biol Psychiatry 2000 Aug 15;48(4):327-9

BACKGROUND: This study investigated the relationship between depressive symptom response during tryptophan depletion and future depressive episodes. METHODS: Twelve subjects with prior major depressive episodes in remission and medication-free for > or =3 months (patients), and 12 matched healthy (control) subjects received two tryptophan depletion tests 1 week apart. During follow-up the Hamilton Depression Rating Scale was administered weekly for 1 month, monthly for 3 months, and once at 6 and 12 months. RESULTS: With results from both tests, tryptophan depletion has a sensitivity of 78%, specificity of 80%, positive predictive value of 70%, and negative predictive value of 86% to identify future depressive episodes. Survival analysis shows that mood response to tryptophan depletion reliably predicts major depressive episodes during the follow-up year (r =.2725, p =.014). CONCLUSIONS: Tryptophan depletion may be clinically useful in identifying individuals at risk for future major depressive episodes.

Cognitive behavior therapy, relaxation training, and tricyclic antidepressant medication in the treatment of depression.

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Psychol Rep 1995 Oct;77(2):403-20

Outcomes of seven treatment trials comparing cognitive behavioral therapy to treatment with tricyclic antidepressant medication in major depressive disorder have been quite similar to one another. This led us to question whether treatment outcome in time-limited studies reflected a unique effect of cognitive behavioral therapy. To test the uniqueness hypothesis, relaxation training, a nonpharmacologic, noncognitive treatment, was chosen as a comparison for cognitive behavioral therapy as well as drug therapy. Treatment duration was 16 weeks. The sample of 37 patients treated for major depressive disorder was less depressed than those previously studied. For both cognitive behavioral therapy and relaxation training, outcome of depression was superior to that of tricyclic antidepressant medication by endpoint analysis. The posttreatment scores on the Beck Depression Inventory of 82% of the group receiving cognitive behavioral therapy improved to a Beck Depression Inventory score < or = 9 which was not significantly greater than that for the group receiving relaxation training (73%), so a unique effect was not demonstrated for cognitive behavioral therapy. The outcome for tricyclic antidepressant medication (29% improved to criteria) was significantly worse than that for cognitive behavioral therapy. The patient's pretreatment initial expectancy was not predictive.

[Neuropsychic effects of dehydroepiandrosterone]. [Article in French]

Rigaud AS, Pellerin J. Service de Medecine Interne et de Gerontologie, Hopital Broca, CHU Cochin Port-Royal, Universite Rene-Descartes - Paris-V, 54-56, rue Pascal, 75013 Paris.

Ann Med Interne (Paris) 2001 Apr;152 Suppl 3:43-9

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) are secreted primarily by the adrenal glands. DHEA could also be a neuroactive steroidal hormone. Because basal levels of DHEA and DHEA-S in humans decrease significantly with age, these hormones have been assumed to be involved in the aging process and in a number of pathologies which develop with aging: immunosenescence, increased mortality, increased incidence of cancer, osteoporosis and cardiovascular diseases. However, its role is still unknown. In humans, cross sectional and longitudinal studies have shown that DHEA might be associated with global measures of well-being and functioning, but positive effects on measures of memory and attention could not be found. Studies investigating DHEA and DHEA-S levels in dementia have produced controversial results. Short-term experimental studies have not shown significant improvement in global measures of well-being and functioning in healthy subjects but have revealed preliminary evidence for mood enhancing and antidepressant effects of DHEA. There is no evidence that DHEA could induce addiction in human beings.

Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women.

Salmaggi P, Bressa GM, Nicchia G, Coniglio M, La Greca P, Le Grazie C. Obstetrics and Gynecology Department, University La Sapienza School of Medicine, Rome, Italy.

Psychother Psychosom 1993;59(1):34-40

S-adenosyl-L-methionine (SAMe) is a naturally occurring substance which is a major source of methyl groups in the brain and has been found in previous studies to be an effective antidepressant. The aim of this study was to assess the efficacy of oral SAMe in the treatment of depressed postmenopausal women in a 30-day double-blind placebo-controlled randomized trial. During the course of the study, 80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAMe 1,600 mg/day or placebo. There was a significantly greater improvement in depressive symptoms in the group treated with SAMe compared to the placebo group from day 10 of the study. Side effects were mild and transient.

Plasma vitamin C concentrations in patients in a psychiatric hospital.

Schorah CJ, Morgan DB, Hullin RP.

Hum Nutr Clin Nutr 1983 Dec;37(6):447-52

Plasma vitamin C was measured in 885 patients in a psychiatric hospital and in 110 healthy controls. The average value was lower in the patients (0.51 mg/100 ml) than in the controls (0.87 mg/100 ml). Length of stay in hospital had little effect on plasma vitamin C in the patients, but the values were marginally lower in males, females on iron therapy and in those with senile dementia. In the patients, many of whom had been offered a similar diet for several years, age was not associated with a change in plasma vitamin C and this suggests that changes in vitamin C with age that have been reported reflect differences in intake. Few patients had values as low as those found in clinical scurvy (less than 0.1 mg/100 ml), but many (32 per cent) had concentrations below the threshold (0.35 mg/100 ml) at which some detrimental effects on health have been reported.

Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression.

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Int Clin Psychopharmacol 2000 Mar;15(2):61-8

Treatment with St John's wort extract tablets (hypericum Ze 117) and the commonly used slow serotonin reuptake inhibitor (SSRI) fluoxetine was

compared in patients with mild-moderate depression with entry Hamilton Depression Scale (HAM-D) (21-item) in the range 16-24, in a randomized, double-blind, parallel group comparison in 240 subjects; fluoxetine: 114 (48%), hypericum: 126 (52%). After 6 weeks' treatment, mean HAM-D at endpoint decreased to 11.54 on hypericum and to 12.20 on fluoxetine (P < 0.09), while mean Clinical Global Impression (CGI) item I (severity) was significantly (P < 0.03) superior on hypericum, as was the responder rate (P = 0.005). Hypericum safety was substantially superior to fluoxetine, with the incidence of adverse events being 23% on fluoxetine and 8% on hypericum. The commonest events on fluoxetine were agitation (8%), GI disturbances (6%), retching (4%), dizziness (4%), tiredness, anxiety/nervousness and erectile dysfunction (3% each), while on hypericum only GI disturbances (5%) had an incidence greater than 2%. We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is safety. Hypericum was superior to fluoxetine in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported.

Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial.

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Arch Gen Psychiatry 1999 May;56(5):407-12

BACKGROUND: Omega3 fatty acids may inhibit neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate, 2 effective treatments for bipolar disorder. The present study was performed to examine whether omega3 fatty acids also exhibit mood-stabilizing properties in bipolar disorder. METHODS: A 4-month, double-blind, placebo-controlled study, comparing omega3 fatty acids (9.6 g/d) vs placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder. RESULTS: A Kaplan-Meier survival analysis of the cohort found that the omega3 fatty acid patient group had a significantly longer period of remission than the placebo group (P = .002; Mantel-Cox). In addition, for nearly every other outcome measure, the omega3 fatty acid group performed better than the placebo group. CONCLUSION: Omega3 fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes.

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Int J Gynaecol Obstet 1999 Dec;67(3):169-74

OBJECTIVE: To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them. METHODS: ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG. RESULTS: CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG. CONCLUSIONS: Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio.

Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10.

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Pharmacopsychiatry 1997 Sep;30 Suppl 2:81-5

The special extract of St. John's wort, LI 160, exhibited a superior antidepressant efficacy compared to placebo in several controlled trials. Two further trials demonstrated a similar reduction of depressive symptomatology under LI 160 compared to tricyclics. All these trials were performed in mildly to moderately depressed patients. The present investigation was a randomized, controlled, multicentre, 6-week trial comparing 1800 mg LI 160/die to 150 mg imipramine/die in severely depressed patients according to ICD-10. The main efficacy parameter, a reduction of the total score of the Hamilton Depression Scale, proved both treatment regimens very effective at the end of the 6 week treatment period (mean values 25.3 to 14.5 in the LI 160 group and 26.1 to 13.6 in the imipramine group), but not statistically equivalent within a a-priori defined 25% interval of deviation. The analysis of subgroups with more than a 33% and 50% reduction of the HAMD total score justified the assumption of equivalence

within a 25% deviation interval. This view was also supported by the global efficacy ratings from patients and investigators. Regarding adverse events, the nonrejection of the nonequivalence hypothesis denotes a superiority of the herbal antidepressant. These main result indicate that LI 160 might be a treatment alternative to the synthetic tricyclic antidepressant imipramine in the majority of severe forms of depressions. However, more studies of this type must be performed before a stronger recommendation can be made.

Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group.

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Int J Clin Pharmacol Res 1999;19(3):89-99

A randomized, multicenter, double-blind, parallel group study was performed to assess the effects of a standardized ginseng extract compared with those of a placebo on quality of life (QoL) and on physiological parameters in symptomatic postmenopausal women. Validated questionnaires [Psychological General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ)] and Visual Analogue (VA) scales were used to assess the effects of the extract on QoL at baseline and after 16 weeks' treatment with either the ginseng extract or placebo. To assess the efficacy of ginseng on postmenopausal symptoms, physiological parameters [follicle-stimulating hormone (FSH) and estradiol levels, endometrial thickness, maturity index and vaginal pH] were recorded at the same time points. Of the 384 randomized patients (mean age 53.5 +/- 4.0 years), the questionnaires were completed by 193 women treated with ginseng and 191 treated with placebo. With regard to the primary endpoint (total score of the PGWB index) the extract showed only a tendency for a slightly better overall symptomatic relief (p < 0.1). Exploratory analysis of PGWB subsets, however, reported p-values < 0.05 for depression, well-being and health subscales in favor of ginseng compared with placebo. No statistically significant effects were seen for the WHQ and the VA scales or the physiological parameters, including vasomotor symptoms (hot flushes). The positive effects of ginseng on health-related QoL in menopausal women should be further investigated. This study shows, however, that the beneficial effects of ginseng are most likely not mediated by hormone replacement-like effects, as physiological parameters such as FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH were not affected by the treatment.

Comparison of St John's wort and imipramine for treating depression: randomised controlled trial.

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BMJ 2000 Sep 2;321(7260):536-9

OBJECTIVES: To compare the efficacy and tolerability of Hypericum perforatum (St John's wort extract) with imipramine in patients with mild to moderate depression. DESIGN: Randomised, multicentre, double blind, parallel group trial. SETTING: 40 outpatient clinics in Germany. Participants: 324 outpatients with mild to moderate depression. INTERVENTION: 75 mg imipramine twice daily or 250 mg hypericum extract ZE 117 twice daily for 6 weeks. MAIN OUTCOME MEASURES: Hamilton depression rating scale, clinical global impression scale, and patient's global impression scale. RESULTS: Among the 157 participants taking hypericum mean scores on the Hamilton depression scale decreased from 22.4 at baseline to 12.00 at end point; among the 167 participants taking imipramine they fell from 22.1 to 12.75. Mean clinical global impression scores at end point were 2.22 out of 7 for the hypericum group and 2.42 for the imipramine group. On the 7 point self assessments of global improvement completed by participants (score of 1 indicating "very much improved" and 7 indicating "very much deteriorated") mean scores were 2.44 in the hypericum group and 2.60 in the imipramine group. None of the differences between treatment groups were significant. However, the mean score on the anxiety-somatisation subscale of the Hamilton scale (3.79 in the hypericum group and 4.26 in the imipramine group) indicated a significant advantage for hypericum relative to imipramine. Mean scores on the 5 point scale used by participants to assess tolerability (score of 1 indicating excellent tolerability and 5 indicating very poor tolerability) were better for hypericum (1.67) than imipramine (2.35). Adverse events occurred in 62/157 (39%) participants taking hypericum and in 105/167 (63%) taking imipramine. 4 (3%) participants taking hypericum withdrew because of adverse events compared with 26 (16%) taking imipramine. CONCLUSIONS: This Hypericum perforatum extract is therapeutically equivalent to imipramine in treating mild to moderate depression, but patients tolerate hypericum better.

Dehydroepiandrosterone (DHEA) treatment of depression.

Wolkowitz OM; Reus VI; Roberts E; Manfredi F; Chan T; Raum WJ; Ormiston S ; Johnson R; Canick J; Brizendine L; Weingartner H Department of Psychiatry, University of California, San Francisco, School of Medicine 94143-0984, USA.

Biol Psychiatry (United States) Feb 1 1997, 41 (3) p311-8

Dehydroepiandrosterone (DHEA) and its sulfate, DHEA-S, are plentiful adrenal steroid hormones that decrease with aging and may have significant neuropsychiatric effects. In this study, six middle-aged and elderly patients with major depression and low basal plasma DHEA f1p4or DHEA-S levels were openly administered DHEA (30-90 mg/d x 4 weeks) in doses sufficient to achieve circulating plasma levels observed in younger healthy individuals. Depression ratings, as well as aspects of memory performance significantly improved. One treatment-resistant patient received extended treatment with DHEA for 6 months: her depression ratings improved 48-72% and her semantic memory performance improved 63%. These measures returned to baseline after treatment ended. In

both studies, improvements in depression ratings and memory performance were directly related to increases in plasma levels of DHEA and DHEA-S and to increases in their ratios with plasma cortisol levels. These preliminary data suggest DHEA may have antidepressant and promemory effects and should encourage double-blind trials in depressed patients.

Double-blind treatment of major depression with dehydroepiandrosterone.

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Am J Psychiatry 1999 Apr;156(4):646-9

OBJECTIVE: This study was designed to assess possible antidepressant effects of dehydroepiandrosterone (DHEA), an abundant adrenocortical hormone in humans.

METHOD: Twenty-two patients with major depression, either medication-free or on stabilized antidepressant regimens, received either DHEA (maximum dose = 90 mg/day) or placebo for 6 weeks in a double-blind manner and were rated at baseline and at the end of the 6 weeks with the Hamilton Depression Rating Scale. Patients previously stabilized with antidepressants had the study medication added to that regimen; others received DHEA or placebo alone.

RESULTS: DHEA was associated with a significantly greater decrease in Hamilton depression scale ratings than was placebo. Five of the 11 patients treated with DHEA, compared with none of the 11 given placebo, showed a 50% decrease or greater in depressive symptoms.

CONCLUSIONS: These results suggest that DHEA treatment may have significant antidepressant effects in some patients with major depression. Further, larger-scale trials are warranted.

Replacement of DHEA in aging men and women. Potential remedial effects.

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Ann N Y Acad Sci (UNITED STATES) Dec 29 1995, 774 p128-42

DHEA in appropriate replacement doses appears to have remedial effects with respect to its ability to induce an anabolic growth factor, increase muscle strength and lean body mass, activate immune function, and enhance quality of life in aging men and women, with no significant adverse effects. Further studies are needed to confirm and extend our current results, particularly the gender differences.

The use of diet and dietary components in the study of factors controlling affect in humans: a review.

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J Psychiatry Neurosci 1993 Nov;18(5):235-44

Although one of the first biological treatments of a major psychiatric disorder was the dietary treatment of pellagra, the use of diet and dietary components in the study of psychopathology has not aroused much interest. This article reviews three areas in which the dietary approach has provided interesting information. The tryptophan depletion strategy uses a mixture of amino acids devoid of tryptophan to lower brain tryptophan in order to study the symptoms that can be elicited. One effect of tryptophan depletion is a lowering of mood, the magnitude of which seems to depend on the baseline state of the subject. Therefore, recovered depressed patients often undergo an acute relapse, while normal subjects show more moderate changes of mood. Totally euthymic subjects show no lowering of mood, but subjects with high normal depression scale scores or subjects with a family history of depression show a moderate lowering of mood. These data indicate that low serotonin levels alone cannot cause depression. However, serotonin does have a direct effect on mood, and low levels of serotonin contribute to the etiology of depression in some depressed patients. Folic acid deficiency causes a lowering of brain serotonin in rats, and of cerebrospinal fluid 5-hydroxyindoleacetic acid in humans. There is a high incidence of folate deficiency in depression, and there are indications in the literature that some depressed patients who are folate deficient respond to folate administration. Folate deficiency is known to lower levels of S-adenosylmethionine, and S-adenosylmethionine is an antidepressant that raises brain serotonin levels. These data suggest that low levels of serotonin in some depressed patients may be a secondary consequence of low levels of S-adenosylmethionine. They also suggest that the dietary intake and psychopharmacological action of methionine, the precursor of S-adenosylmethionine, should be studied in patients with depression. Normal meals have definite effects on mood and performance in humans. The composition of the meal, in terms of protein and carbohydrate content, can influence these behaviors. Because protein and carbohydrate meals can influence brain serotonin in rats, these effects in humans have usually been interpreted in terms of altered serotonin functioning. However, the current balance of evidence is against the involvement of serotonin in the acute effects of protein and carbohydrate meals in humans. The underlying mechanisms involved are unknown, but there are a variety of possibilities.(ABSTRACT TRUNCATED AT 400 WORDS)

Folic acid and psychopathology.

Young SN, Ghadirian AM. Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Prog Neuropsychopharmacol Biol Psychiatry 1989;13(6):841-63

1. The incidence of folic acid deficiency is high in patients with various psychiatric isorders including depression, dementia and schizophrenia. 2. In epileptics on anticonvulsants, folate deficiency often occurs because anticonvulsants inhibit folate absorption. In these patients folate deficiency is often associated with psychiatric symptoms. 3. In medical patients psychiatric symptoms occur more frequently, and in psychiatric patients symptoms are more severe, in those with folate deficiency than in those with normal levels. 4. Many open studies have demonstrated therapeutic effects of folate administration on psychiatric symptoms in folate deficient patients. 5. Several placebo-controlled studies have not demonstrated therapeutic effects, possibly because the doses they used (15-20 mg/day) are known to be toxic and to cause mental symptoms. 6. Two placebo-controlled studies have demonstrated beneficial effects of folic acid administration, one in patients with a syndrome of psychiatric and neuropsychological changes associated with folate deficiency and the other in patients on long-term lithium therapy. In the latter study the dose was only 0.2 mg/day. 7. Folic acid deficiency is known to lower brain S-adenosylmethionine and 5-hydroxytryptamine. S-Adenosylmethionine, which has antidepressant properties, raises brain 5-hydroxytryptamine. Thus, depression associated with folate deficiency is probably related to low brain 5HT. 8. S-Adenosylmethionine is involved in many methylation reactions, including methylation of membrane phospholipids, which influences membrane properties. This may explain the wide variety of symptoms associated with folate deficiency. 9. Because the costs and risks associated with low doses of folic acid (up to 0.5 mg/day) are small, folic acid should be given as an adjunct in the treatment of patients with unipolar or bipolar affective disorders and anorexia, epileptics on anticonvulsants, geriatric patients with mental symptoms and patients with gastrointestinal disorders who exhibit psychiatric symptoms. 10. Although the majority of the patients listed above will probably not be helped by folic acid therapy, a significant minority are likely to have folate-responsive symptoms.

Relationship between dopamine-stimulated phospholipid methylation and the single-carbon folate pathway.

Zhao R, Chen Y, Tan W, Waly M, Sharma A, Stover P, Rosowsky A, Malewicz B, Deth RC. Department of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts 02115, USA.

J Neurochem 2001 Aug;78(4):788-96

In a previous study we demonstrated the ability of dopamine (DA) to stimulate phospholipid methylation (PLM) via a novel mechanism involving the D4 dopamine receptor (D4R) in which single-carbon folates appeared to be the primary source of methyl groups. To further understand the relationship between D4R-mediated PLM and folate metabolism, we examined the effect of several folate pathway interventions on the level of basal and DA-stimulated incorporation of [14C]-labeled formate into phospholipids in cultured SH-SY5Y neuroblastoma cells. These interventions included: (i) Overexpression of methenyltetrahydrofolate synthetase (MTHFS). (ii) Treatment with 5-formylTHF. (iii) Treatment with the MTHFS inhibitor 5-formyltetrahydrohomofolic acid (5-

formylTHHF). (iv) Growth in nucleoside-free media. 31P-NMR was also used to follow DA-induced changes in cell phospholipid composition. MTHFS overexpression and 5-formylTHHF treatment, both of which lower 5-methylTHF levels, each reduced basal PLM and its stimulation by DA. In contrast, 5-formylTHF, which increases 5-methylTHF, caused a dose-dependent increase in both basal and DA-stimulated PLM. Growth in nucleoside-free media caused time-dependent changes in PLM, which were due to the absence of purine nucleosides. While basal PLM was maintained at a reduced level, DA-stimulated PLM was initially increased followed by a later decrease. Together, these findings indicate a close functional relationship between single-carbon folate metabolism and DA-stimulated PLM, consistent with a role for 5-methylTHF as the methyl donor for the D4R-mediated process.

Antidepressive effectiveness of a highly dosed hypericum extract

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Munchener Medizinische Wochenschrift (Germany), 1996, 138/3 (35-39)

Study objective: Clinical effectiveness of the hypericum extract LI 160 in cases of mild and moderate depression.

Design: Randomized, double-blind placebo-controlled study with subsequent active medication in both patient groups. Patients: 102 outpatients with major depression in mild or moderate form according to DSM-IIIR. Intervention: Daily dosage 3 x 1 coated tablet LI 160 (equivalent to 900 mg hypericum extract) or placebo for four weeks with subsequent two weeks active medication in both medication groups. Endpoint: Changes of depressive symptoms according to psychometric tests.

Main results: The total Hamilton score in the active treatment group fell significantly ($p < 0.001$) further (from 21.0 to 8.9) after four weeks than in the placebo group (from 20.4 to 14.4). Significant differences were also shown for v. Zerssen's depressivity scale (D-S) and when evaluating the level of symptoms ($p < 0.01$). The four-week placebo phase was followed by a two week active medication phase in both groups. This also led to a reduction in symptoms in the placebo group that correlated with the changes observed in the verum group during the first two weeks of treatment. Side ffects, in the form of slight sleep disturbances, were only reported by one patient in the verum group.

Conclusion: On account of its antidepressive effectiveness and very good tolerability, the hypericum extract LI 160 can be recommended for treating patients with mild to moderate depression.

St. John's Wort in the treatment of depression

Ernst E.
Fortschritte der Medizin (Germany), 1995, 113/25 (32-33)

St. John's Wort (Hypericum perforatum) has been used to treat a variety of complaints since ancient times. Recent studies have shown that it is clinically effective for the treatment of the symptoms of depression. It has proved superior to placebo, equally as effective as standard medication and has a clear advantage over the latter in terms of side-effects. It follows that, on the basis of our present knowledge, St. John's Wort can be recommended for use as an anti-depressant.

Hypericum perforatum

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Fitoterapia (Italy), 1995, 66/1 (43-68)

H. perforatum is a medicinal plant which has been known in traditional medicine as antiinflammatory and healing agent. Nowadays purified extracts of its aerial parts are used for their antidepressant activity. Furthermore the antiviral activity of hypericin is currently under investigation. This review deals with the botany, chemistry, pharmacology and the clinical efficacy of H. perforatum extracts and of their active constituents, namely hypericin and pseudohypericin.

Psychomotoric performance improvement: Antidepressant therapy with St John's wort

Schmidt U.; Maisenbacher J.; Harrer G.; Kuhn U.
Therapiewoche (Germany), 1995, 45/2 (106+108+110+112)

The following study investigated the influence of a herbal antidepressant containing Hypericum extract, on the cognitive performance in patients with anxiety depression. In the course of the 4-week treatment, the patients showed a reduction in both the state of anxiety and depression. The responder rate determined with the Hamilton Depression Scale was nearly 70%. Tolerance was very good. There weren't observed any adverse drug effects. The psychometric tests well established in traffic medicine could show, in comparison with the untreated control group, that the antidepressant therapy did not impair concentration nor reactivity. The data from the responder group indicates that the antidepressant therapy even caused an increase in complex cognitive performances which exceed the known training effect of these tests.

Hypericum in the treatment of seasonal affective disorders

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S29-S33)

Seasonal affective disorder (SAD) represents a subgroup of major depression with a regular occurrence of symptoms in autumn/winter and full remission in spring/summer. Light therapy (LT) has become the standard treatment of this type of depression. Apart from this, pharmacotherapy with antidepressants also seems to provide an improvement of SAD symptoms. The aim of this controlled, single-blind study was to evaluate if hypericum, a plant extract, could be beneficial in treating SAD patients and whether the combination with LT would be additionally advantageous. Patients who fulfilled DSM-III-R criteria for major depression with seasonal pattern were randomized in a 4-week treatment study with 900 mg of hypericum per day combined with either bright (3000 lux, n = 10) or dim (< 300 lux, n = 10) light condition. Light therapy was applied for 2 hours daily. We found a significant (MANOVA, P < .001) reduction of the Hamilton Depression Scale score in both groups but no significant difference between the two groups. Our data suggest that pharmacologic treatment with hypericum may be an efficient therapy in patients with seasonal affective disorder.

Effectiveness and tolerance of the hypericum extract LI 160 compared to maprotiline: A multicenter double-blind study

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S24-S28)

A randomized, double-blind study examining the effectiveness and tolerance of a standardized hypericum preparation when compared to maprotiline was performed in a group of 102 patients with depression, in accordance with ICD-10, F 32.1. The study was conducted in the offices of neurology and psychiatry specialists. The patients received, over a period of 4 weeks, either 3 x 300 mg of the hypericum extract or 3 x 25 mg maprotiline pills of identical appearance. Effectiveness was determined using the Hamilton Depression Scale (HAMD), the Depression Scale according to von Zerssen (D-S), and the Clinical Global Impression Scale (CGI). The total score of the HAMD scale dropped during the 4 weeks of therapy in both treatment groups by about 50%. The mean values of the D-S scale and the CGI scale showed similar results, and after 4 weeks of therapy, no significant differences in either treatment group were noticed. The onset of the effects occurred up to the second week of treatment, but were observed earlier with maprotiline than with the hypericum extract. On the other hand, maprotiline treatment resulted in more cases of tiredness, mouth dryness, and heart complaints.

Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine: Randomized double-blind study with 135 outpatients

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S19-S23)

In a double-blind comparative study, 135 depressed patients were treated in 20 centers. Inclusion diagnoses were typical depressions with single episode (296.2), several episodes (296.3), depressive neurosis (300.4), and adjustment disorder with depressed mood (309.0) in accordance with DSM-III-R. The dosage was 3 x 300 mg hypericum extract LI 160 or 3 x 25 mg imipramine daily. The treatment lasted for 6 weeks. Main assessment criteria were the Hamilton Depression Scale (HAMD), the Depression Scale according to von Zerssen (D-S) and the Clinical Global Impressions (CGI). In both treatment groups, a parallel reduction of the Hamilton score from 20.2 to 8.8 (LI 160, n = 67) or from 19.4 to 10.7 (imipramine, n = 68), and the transformed D-S point values from 39.6 to 27.2 (LI 160) and 39.0 to 29.2 (imipramine) were found. The analysis of CGI revealed comparable results in both treatment groups. Clinically relevant changes of the safety parameters were not found. In the LI 160 group fewer and milder side effects were found as compared to imipramine.

Multicenter double-blind study examining the antidepressant effectiveness of the hypericum extract LI 160

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S15-S18)

Seventy-two depressive patients of 11 physicians' practices were treated in a double-blind study for a period of 6 weeks either with hypericum extract LI 160 or with placebo. Inclusion criterion was a major depression in accordance with DSM-III-R. The changes were assessed using four psychometric scales (HAMD, D-S, BEB, CGI). After 4 weeks of therapy, the statistical evaluation revealed a significant improvement in all four psychometric tests in the active group as compared to the placebo group. After switching the placebo group to active treatment (5th to 6th week of therapy), significant improvements were found in the original placebo group. No serious side effects were observed.

Hypericum treatment of mild depressions with somatic symptoms

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J. Geriatr. Psychiatry Neurol. (Canada), 1994, 7/Suppl. 1 (S12-S14)

In a randomized, placebo-controlled, double-blind study, 39 patients with depression with somatic symptoms were treated with hypericum extract LI 160. The therapy lasted for 4 weeks; the dosage was 300 mg three times daily. At the onset of the study as well as after 2 and 4 weeks, the following criteria were analyzed: HAMD, B-L, CGI, and vegetative symptoms. The results show a significant improvement in the active treatment group at the 5% level as compared to placebo. Seventy percent of the patients treated with LI 160 were free of symptoms after 4 weeks. Typical symptoms of the depression such as lack of activity, tiredness, fatigue, and disturbed sleep, were especially responsive. In no case were any undesirable side effects observed.

St. Johns' wort: A prescription from nature against depressions

Sattler S.; Schutt H.
Therapiewoche (Germany), 1994, 44/14 (808+811-815)

The various use of St. Johns' wort, especially for depressive disorders, is based on the specific pattern of ingredients. Characteristic constituents for this plant are hypericins, hyperforine and flavonoids. These flavonoids are inhibitors of type A monoamino-oxidase in vitro. An improved utilisation of light is due to hypericin. In agreement of common experiences clinical studies prove the effectiveness of Hypericum perforatum on minor and moderate depressive disorders comparable to tricyclic antidepressants used in therapy. Therefore Hypericum perforatum represents a high potent drug for phytotherapy including good compatibility and low risk of side effects.

Extract of St. John's wort in the treatment of depression - Attention and reaction remain unimpaired

Schmidt U.; Sommer H.
Fortschr. Med. (Germany), 1993, 111/19 (37-40)

Method: In a placebo-controlled, randomized, double-blind trial involving outpatients with mild to moderately severe depression, an extract of St. John's wort (Hypericum), LI 160, a herbal antidepressant was tested for efficacy and tolerability, as well as for possible negative effects on cognitive performance.

Results: The responder rate to treatment with the extract was 66,6% as compared with only 26,7% with placebo. The treatment was very well tolerated; only in two patients did transient minor side effects occur under LI 160. No impairment of cognitive performance was observed: during the trial, Hypericum did not lead to any impairment of attention, concentration or reaction.

Investigations of the antidepressive effects of St. Johns Wort

Sparenberg B.; Demisch L.; Holzl J.
Pz Wiss. (Germany), 1993, 138/2 (50-54)

Extracts from Hypericum perforatum are used in the treatment of symptoms related to depressive disorders, although the active principle is not yet elucidated. Recent investigations showed a significant inhibition of MAO type-A in vitro by extracts from Hypericum. Therefore a number of Hypericum components have been tested for their MAO-inhibitory potency in vitro. The results revealed flavonoidaglyca as the active substances. The glycosides are less active, only quercitrin shows inhibition of MAO. Furthermore 1,3,6,7-tetrahydroxyxanthone was found to be a strong inhibitor of MAO A in vitro.

Experimental animal studies of the psychotropic activity of a Hypericum extract

Okpanyi S.N.; Weischer M.L.
Arzneim.-Forsch./Drug Res. (Germany, West), 1987, 37/1 (10-13)

Extracts of Hypericum perforatum (Psychotonin(Reg.trademark) M) (St. John's wort) with known concentrations of hypericin were tested in several models generally accepted as screening methods in experimental animal studies for the recognition of psychotropic, and in particular of antidepressant activity. Hypericum extract enhanced the exploratory activity of mice in a foreign environment, significantly prolonged the narcotic sleeping time dose-dependently, and within a narrow dose range exhibited reserpine antagonism. Similar to most other antidepressants, hypericum extract enhanced significantly the activity of mice in the water wheel test and after a prolonged daily administration decreased aggressiveness in socially isolated male mice. The presented data in addition to the already proven clinical efficacy justify the use of standardised Hypericum extract in the treatment of mild to moderate depression.

Plasma tryptophan and five other amino acids in depressed and normal subjects.

DeMyer, Marian K.; Shea, Philip A.; Hendrie, Hugh C.; Yoshimura,
Archives of General Psychiatry 38(6):642-646, 1981

The ratio of plasma tryptophan (TRP) to five other neutral amino acids (TRP/5aa ratio) was examined in depressed Ss and normal controls. Plasma TRP (free and total), phenylalanine (PHE), tyrosine (TYR), leucine, isoleucine, and valine were measured on three days. When depression was most severe, depressed patients

had lower TRP/5aa ratios and total TRP levels and higher PHE and TYR levels. As Hamilton depression scores improved, the plasma TRP/5aa ratios increased significantly. The finding tends to support the idea that changes in brain serotonin level reflect changes in depression severity. 41 references.

Trace amine deficit in depressive illness: the phenylalanine connexion.

Sandler, M.; Ruthven, C. R. J.; Goodwin, B. L.; Reynolds, G. P.; Rao, V. A. R.; Coppen, A.
Acta Psychiatrica Scandinavica 61(Suppl. 280):29-39, 1980

Preliminary studies of deficiencies of three trace amines (phenylethylamine, tyramine, and octopamine) in patients with depressive illness are described. Data from two groups of depressed Ss and control Ss indicate that the mean output of p-hydroxyphenylacetic acid and p-hydroxymandelic acid in urine is significantly lower in depressed patients than in control Ss. Both the patients as a whole and the male patients as a subset possessed significantly lower cerebrospinal fluid phenylacetic acid concentrations than did control Ss. Three patients characterized by severe endogenous depression features and who responded poorly to tricyclic drugs had very low excretion values of p-hydroxymandelic acid and p-hydroxyphenylacetic acid, although the other metabolites were normal. A panel discussion of these findings is appended. 40 references.

Phenylalanine levels in endogenous psychoses.

Uebelhack, Ralf; Franke, Leonora; Kitzrow, Werner; Seidel, Karl.
Psychiatrie, Neurologie und Medizinische Psychologie 32(10):631-633, 1980

The effects of phenylalanine levels on 65 depressive and psychotic patients were made over a period of 14 days. Patients were kept on a protein free diet for 24 hours prior to the test. Patients received doses of L-phenylalanine at a rate of 100mg/kg. Blood samples drawn hourly were analyzed for amino acid content. Phenylalanine doses were found to be effective for 48 hours. EEG examinations were given to 29 patients both before and after the test. Four female patients experienced hallucinations during the first 4 hours. No conclusions were reached regarding the relation of deviant phenylalanine levels to psychoses. Six patients experienced a remission of psychotic symptoms beginning 2 to 3 weeks after the experiment. A decrease in psychotic symptomatology was seen in 16 depressive patients. 11 references.

Evaluation of the relative potency of individual competing amino acids to tryptophan transport in endogenously depressed patients.

Moller, Svend E.
Psychiatry Research 3(2):141-150, 1980

The relative potency of the individual amino acids as competitive inhibitors of tryptophan transport into the human brain was evaluated retrospectively; the combination of competitors that yields the highest predictive value of the plasma tryptophan ratio for the course of treatment of depressed patients with L-tryptophan was also examined. Phenylalanine consistently reduced, and isoleucine slightly reduced the predictive value of the plasma tryptophan ratio. The ratio of tryptophan to the sum of valine, leucine, and tyrosine was identified as most predictive for the therapeutic response to tryptophan. L-tryptophan responders showed a normal plasma total tryptophan concentration as did the nonresponders, whereas the concentration of the three competitors was significantly elevated. It is concluded that while the plasma ratio of tryptophan to the sum of valine, leucine, and tyrosine is a useful predictor of the course of depressives on L-tryptophan, it does not definitely separate out the L-tryptophan responders from the control subjects.

Amino acids in mental illness.

Yaryura-Tobias, J. A.
Biological psychiatry today. Vol. B Amsterdam, Elsevier/North Holland, 1979, p1581-4

Research on the influence of several aromatic amino acids in psychiatric disturbances is reviewed, with emphasis on phenylalanine, tyrosine, and tryptophan. The principles of a dopaminergic theory of schizophrenia and of levodopa therapy in neuropsychiatric disorders are treated, along with the role of phenylalanine in phenylketonuria, depression, and schizophrenia. The relation of tryptophan to Hartnup disease, schizophrenia, depression, manic-depression, manic-depressive illness, insomnia, and obsessive-compulsive disorders is also treated. It is concluded that these compounds have important roles in brain physiology and may be involved in the physiopathology of certain mental disorders and/or their treatment.

Depression, pregnancy and phenylalanine.

Portnoy, Mario Ernesto.
Neuropisiquiatria (Buenos Aires) 8(1):60-64, 1977

A case study of a mentally depressed pregnant woman who was successfully treated with phenylalanine is reported. The subject was a 34-year-old Argentine woman, married for 5 years and childless. Once the subject was administered phenylalanine, her condition improved. It is noted that a heightened dosage of the drug is required during pregnancy, and that this has no complicating effect on the mother or the child. To check this, the subject's baby was observed for a year after

birth. The physiological action of the drug is analyzed, and the progress of the treatment through pregnancy is charted. 17 references.

Phenylethylamine and glucose in true depression.

Journal of Orthomolecular Psychiatry (Regina) 5(3):199-202, 1976

The relationship between urinary phenylethylamine (PEA) and oral glucose tolerance tests in true depression was investigated in 12 depressives who were resistant to psychotherapy, chemotherapy, and electroconvulsive shock therapy. All medication was discontinued 72 hours prior to testing. Urinary PEA was measured 24 hours before and 72 hours after patients were placed on a 350g carbohydrate load diet. Clinical psychiatric examinations were also performed before, during, and after this treatment. Results revealed severely depressed PEA levels in all patients and disturbed glucose metabolism in 10 of the 12. Improvement was shown by the fifth day of the diet, and good remission of symptoms began by the second week. Side effects, which included mild headache, low blood pressure, and agitation,were few. It is concluded that D-phenylalanine and DL-phenylalanine are thus shown to be antidepressants in true depressives whose illness is caused by biochemical deficiencies, and that the presence of a glucose imbalance in the patients studied may suggest a monoamine disorder as the cause of depression. 28 references.

Therapeutic action of D-phenylalanine in Parkinson's disease.

Heller B, Fischer E, Martin R
Arzneimittelforschung 1976 Apr;26(4):577-9

An open field trial of D-phenylalanine was made in 15 patients with Parkinson's disease of 6 months' to 13 years' duration. All medication was suspended 10 days before the trial, and the patients received only 200mg-500mg D-phenylalanine daily, divided into 2 doses, for 4 weeks. Positive results were highly significant in relation to rigidity, walking disabilities, speech difficulties, and mental depression, but no significant therapeutic results were obtained in regard to tremor. The therapeutic action on the total development of the disease may be considered highly significant. The results suggest a special cholinergic origin of tremor in Parkinson's disease, and in these cases a combination of the amino acid with anticholinergic agents should be tried.

Effects of D-phenylalanine on clinical picture and phenethylaminuria in depression.

Biological Psychiatry 10(2):235-239, 1975

The administration of D-phenylalanine in 11 cases of depression with low urinary phenethylamine output was studied. It was found that the administration of D-phenylalanine to depressed patients in daily oral doses of 100-200mg produced an improvement of the clinical state associated with an increase in the daily urinary phenethylamine output.

Phenylalanine Effective Against Depression

Treatment of endogenous depression with d,1-phenylalanine and d-phenylalanine is reported. Ss all had long-term endogenous depression, and all had been treated unsucessfully with imipramine like drugs and/or inhibitors of monoamineoxidase. Ss were given daily oral doses of 50mg or 100mg of either drug over a period of 15 days. Complete euthymia was obtained in 74% of the Ss between 1 and 13 days of treatment. Side-effects were minimal and in no case required termination of treatment. 13 references. (Author abstract modified)

Phenylalanine for endogenous depression.

Yaryura Tobias J.A.; Heller B.; Spatz H.; Fischer E.
North Nassau Ment. Hlth Cent., Manhasset, Long Island, N.Y. 11030 United States
Journal of Orthomolecular Psychiatry 1974, 3/2 (80-81)

Phenylalanine was administered to patients suffering from endogenous depression. Although the experimental trial was short and the dosage small, it seems that some forms of endogenous depression responded well to phenylalanine therapy, mainly with the dextrorotatory form.

Rapidity of onset of the antidepressant effect of parenteral S-adenosyl-L-methionine

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Psychiatry Res 1995 Apr 28;56(3):295-7

A possible method of reducing the delay in antidepressant response is to use S-adenosyl-L-methionine (SAMe), a naturally occurring compound that appears to have a rapid onset of effect in the treatment of depression. In this open, multicenter study, 195 patients were given 400 mg of SAMe, and no serious adverse events were reported. Further studies with a double-blind design are needed to confirm this preliminary indication that SAMe is a relatively safe and fast-acting antidepressant.

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders

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Metabolic Disease Center, Baylor Research Institute, Dallas, Texas.
Drugs 1994 Aug;48(2):137-52

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; SAMe). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAMe is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAMe concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

Primary fibromyalgia is responsive to S-adenosyl-L-methionine

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/7 (797-806)

Forty-seven patients with primary fibromyalgia were treated with S-adenosyl-L-methionine (SAMe) 200 mg intramuscularly once daily, plus SAMe 400 mg orally twice daily, for 6 weeks. The treatment was preceded by a 7-day drug-free run-in washout period. SAMe significantly decreased tenderness of painful sites, significantly improved general well-being, and significantly reduced the mean scores (baseline vs day 42) for the Hamilton Rating Scale for Depression, the Zung SelRating Scale, the Hamilton Rating Scale for Anxiety, and Lorish and Maisiak's Face Scale. SAMe was well tolerated in all patients and no adverse side effects were reported.

S-adenosyl-L-methionine in Sjogren's syndrome and fibromyalgia

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (699-706)

The subjects were 30 patients aged 25 to 60 years (mean, 51 years) with primary Sjogren's syndrome, both Sjogren's syndrome and primary fibromyalgia, or fibromyalgia only. Each patient received 200 mg of S-adenosyl-L-methionine (SAMe) by intramuscular injection daily. After 4 weeks of treatment, in the 10 patients with Sjogren's syndrome, disease symptoms and scores on Zung's SelRating Scale for Depression showed a nonsignificant decrease; a reduction in mean scores on Hamilton's Rating Scale for Depression, however, was statistically significant ($P < 0.05$). In the 10 patients with both Sjogren's syndrome and fibromyalgia, no significant changes in symptoms, depression scale scores, or scores on a pain-severity scale were found; however, the numbers of tender points and painful areas were reduced significantly ($P < 0.01$). In the 10 patients with fibromyalgia, symptoms of fibromyalgia, numbers of tender points and painful areas, pain severity scores, and scores on both depression scales were reduced significantly ($P < 0.01$). No adverse side effects were reported. The results indicate that SAMe can reduce the symptoms of fibromyalgia and improve mood; further studies are warranted.

Effects of S-adenosyl-L-methionine on cognitive and vigilance functions in the elderly

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Teaching Department of Neurology, General Hospital,Venice Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (682-689)

Forty elderly patients with impaired cognition and vigilance functions associated with primary or secondary organic brain syndrome were treated with S-adenosyl-L-methionine (SAMe) for 2 months. Patients scoring 17 or higher on Hamilton's Rating Scale for Depression (HRSD) were excluded from the study. The SAMe dosing schedule was 400 mg intravenously during the first 20 days, and 200 mg intramuscularly plus 400 mg orally twice daily for another 40 days. Examinations were performed using the Mini-Mental State Examination (MMSE) and the Sandoz Clinical Assessment Geriatric Scale (SCAG) at time 0 (baseline) and on days 20 and 60 of treatment. Statistically significant differences ($P < 0.01$) were observed in MMSE and SCAG total scores on day 60 versus baseline. Significant improvements were observed in 4 out of 19 items on the SCAG versus baseline on day 20, and in 13 out of 19 items versus baseline on day 60. No adverse side effects were reported.

Results of treatment with s-adenosyl-l-methionine in patients with major depression and internal illnesses

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/6 (666-674)

Forty-eight patients with major depression associated with internal illnesses of various origins were enrolled for 4 weeks of treatment with S-adenosyl-L-methionine (SAMe). The medication was administered parenterally (400 mg daily either intravenously or intramuscularly) in inpatients and orally (800 mg daily) in outpatients. Evaluations were performed via Beck's Depression Inventory (BDI) by comparing the scores on day 28 with baseline values. Statistically significant differences were observed ($P < 0.01$). Although minor adverse side effects were reported, they were not severe enough to withdraw medication. SAMe treatment proved to be effective and relatively safe in depressed patients with associated internal illnesses.

S-adenosyl-l-methionine (SAMe) as antidepressant: Meta-analysis of clinical studies

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Acta Neurol Scand Suppl 1994;154:7-14

Introduction - S-adenosyl-l-methionine (SAMe) is a naturally-occurring substance which is a major source of methyl groups in the brain. Material and methods - We conducted a meta-analysis of the studies on SAMe to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants. Results - Our meta-analysis showed a greater response rate with SAMe when compared with placebo, with a global effect size ranging from 27% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants. Conclusion - The efficacy of SAMe in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since SAMe is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

S-adenosyl-L-methionine in the treatment of major depression complicating chronic alcoholism

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Current Therapeutic Research - Clinical and Experimental (United States) 1994, 55/1 (83-92)

S-adenosyl-L-methionine (SAMe) is a methyl donor endowed with both antidepressant and detoxifying activity. In a 4-week trial, 40 alcoholic patients with major depression received 200 mg of SAMe daily administered intravenously and 400 mg BID administered orally. After a 1-week placebo period during which placebo responders were eliminated, patients were evaluated with the Hamilton Rating Scale for Depression, the Zung Sel Rating Scale for depression, the Hamilton Rating Scale for Anxiety, and the Lorish and Maisiak face scale at baseline and at days 7, 14, 21, and 28. Standard laboratory values were measured at baseline and at the completion of the trial. Significant improvements were seen in most psychometric scores beginning on day 14 and continuing through the end of the study. Baseline values for gamma-glutamyltranspeptidase, alkaline phosphatase, bilirubin, and mean corpuscular volume dropped dramatically and, in some cases, returned to normal. No adverse reactions were reported. Although standard antidepressant therapy has very often been unsuccessful in treating depression in these patients, SAMe proved to be well tolerated at the study dosage and was effective in reducing depression.

Clinical evaluation of S-adenosyl-L-methionine versus transcutaneous electrical nerve stimulation in primary fibromyalgia

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Current Therapeutic Research - Clinical and Experimental (United States) 1993, 53/2 (222-229)

The effects of S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) were evaluated in a 6-week controlled trial of 30 patients with primary fibromyalgia. Unlike TENS, SAMe significantly decreased the total number of tender points, had a significant beneficial effect on the subjective symptoms of pain and fatigue, and significantly reduced the scores on the Hamilton Depression and Anxiety Rating Scales and Zung's SelRating Scale for Depression. At the end of treatment, patients in the TENS group exhibited significantly reduced scores on the Hamilton Anxiety Scale only.

Double blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women

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Psychother Psychosom 1993;59(1):34-40

S-adenosyl-L-methionine (SAMe) is a naturally occurring substance which is a major source of methyl groups in the brain and has been found in previous studies to be an effective antidepressant. The aim of this study was to assess the efficacy of oral SAMe in the treatment of depressed postmenopausal women in a 30-day double-blind placebo-controlled randomized trial. During the course of the study, 80 women, between the ages of 45 and 59, who were diagnosed as having DSM-III-R major depressive disorder or dysthymia between 6 and 36 months following either natural menopause or hysterectomy, underwent 1 week of single-blind placebo washout, followed by 30 days of double-blind treatment with either SAMe 1,600mg/day or placebo. There was a significantly greater improvement in depressive symptoms in the group treated with SAMe compared to the placebo group from day 10 of the study. Side effects were mild and transient.

S-Adenosyl-methionine (SAMe) as antidepressant

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Psychiatric Department, Ospedale San Giovanni,Soave-Verona Italy
New Trends in Clinical Neuropharmacology (Italy) 1992, 6/1-4 (11-18)

In 1971 S-Adenosylmethionine (SAMe) entered in clinical research. The clinical trial as well as an extensive clinical practice in Europe and more recently in the United States have shown that SAMe, related to depressive syndromes, is effective as tricyclic, but it has some characteristics which distinguish it from other antidepressant drugs. They are: - absence of side effects particularly at liver level; - rapid effect and therefore short period of latency between administration and therapeutic activity.

Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine

Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H
Special Studies Clinic, Mexican Institute of Psychiatry, Tlalpan.
Psychiatry Res 1992 Dec;44(3):257-62

A double-blind clinical trial was carried out to evaluate the efficacy of S-adenosyl-L-methionine (SAMe) in speeding the onset of action of imipramine (IMI). SAMe is a naturally occurring substance that has been shown to possess antidepressant activity with a rapid mode of onset and minimal side effects. Sixty-three outpatients with moderate to severe depression were included in the study. After an initial 1-week placebo period, only 40 patients entered the active treatment phase. During the first 2 weeks of the trial, half of these patients received 200 mg/day of SAMe intramuscularly, while the other half received placebo. Simultaneously, oral IMI was administered to all patients at a fixed dose of 150 mg/day. The onset of clinical response was determined by evaluating patients every second day. By the end of week 2, the parenteral treatment was

suppressed and IMI was adjusted according to individual needs. Depressive symptoms decreased earlier in the patients who were receiving the SAMe-IMI combination than in those who were receiving the placebo-IMI combination.

Oral S-adenosyl-L-methionine in depression

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Current Therapeutic Research - Clinical and Experimental (United States) 1992, 52/3 (478-485)

The antidepressant activity of oral S-adenosyl-L-methionine (SAMe) was evaluated in a randomized, double-blind, imipramine-controlled trial in 30 patients with major depression. The results suggest that oral SAMe is a safe, effective antidepressant with negligible side effects and a rapid onset of action. Only one patient became hypomanic but did not drop out of the study. SAMe may be useful for patients who cannot tolerate other antidepressant agents or for patients with other risk factors. These findings suggest a role for methylation in the pathophysiology of depression.

Neuroendocrine effects of S-adenosyl-(L)-methionine, a novel putative antidepressant

Fava M, Rosenbaum JF, MacLaughlin R, Falk WE, Pollack MH, Cohen LS, Jones L, Pill L
Clinical Psychopharmacology Unit, Massachusetts General Hospital, Harvard Medical School, Boston 02114.
J Psychiatr Res 1990;24(2):177-84

S-adenosyl-L-methionine (SAMe), a putative antidepressant, is a naturally occurring substance whose mechanism of action is still a matter of speculation. It has been recently postulated that SAMe may increase the dopaminergic tone in depressed patients. Since dopamine inhibits both thyrotropin (TSH) and prolactin secretion, we investigated the effects of treatment with SAMe on the TSH and prolactin response to thyrotropin-releasing-hormone (TRH) stimulation in 7 depressed outpatient women (mean age: 46.1 plus or minus7.2 years) and 10 depressed outpatient men (mean age: 38.0 plus or minus 10.0 years) participating in a six-week open study of oral SAMe in the treatment of major depression. At the end of the study, there was a significant reduction after treatment with SAMe in the response of both prolactin and TSH to TRH stimulation in the group of derpressed men compared to pre-treatment values. On the other hand, in the group of depressed women, the posttreatment prolactin response to TRH did not appear to change when compared to pre-treatment and the TSH response to TRH challenge tended even to augment slightly after treatment with SAMe. Our

results, at least in depressed men, seem to support the hypothesis of a stimulating effect of SAMe on the dopaminergic system.

The antidepressant potential of oral S-adenosyl-l-methionine

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Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston 02114.
Acta Psychiatr Scand 1990 May;81(5):432-6

S-adenosyl-l-methionine (SAMe), a naturally occurring brain metabolite, has previously been found to be effective and tolerated well in parenteral form as a treatment of major depression. To explore the antidepressant potential of oral SAMe, we conducted an open trial in 20 outpatients with major depression, including those with (n = 9) and without (n = 11) prior history of antidepressant nonresponse. The group as a whole significantly improved with oral SAMe: 7 of 11 non-treatment-resistant and 2 of 9 treatment-resistant patients experienced full antidepressant response. Side effects were mild and transient.

S-Adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism

Friedel HA, Goa KL, Benfield P
ADIS Drug Information Services, Auckland, New Zealand.
Drugs 1989 Sep;38(3):389-416

S-Adenosyl-L-methionine (SAMe) is a naturally occurring molecule distributed to virtually all body tissues and fluids. It is of fundamental importance in a number of biochemical reactions involving enzymatic transmethylation, contributing to the synthesis, activation and/or metabolism of such compounds as hormones, neurotransmitters, nucleic acids, proteins, phospholipids and certain drugs. The administration of a stable salt of SAMe, either orally or parenterallly, has been shown to restore normal hepatic function in the presence of various chronic liver diseases (including alcoholic and non-alcoholic cirrhosis, oestrogen-induced and other forms of cholestasis), to prevent or reverse hepatotoxicity due to several drugs and chemicals such as alcohol, paracetamol (acetaminophen), steroids and lead, and to have antidepressant properties. In all of these studies SAMe has been very well tolerated, a finding of great potential benefit given the well-known adverse effects of tricyclic antidepressants with which it has been compared in a few trials. Thus, with its novel mechanisms of action and good tolerability, SAMe is an interesting new therapeutic agent in several diverse disease conditions, but its relative value remains to be determined in appropriate comparisons with other treatment modalities in current use.

Neuropharmacology of S-adenosyl-L-methionine

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Am J Med 1987 Nov 20;83(5A):95-103

The metabolite S-adenosyl-L-methionine (SAMe), when prepared as the stable p-toluene-sulfonate complex of its sulfate salt and given parenterally in high doses, appears to have mood-elevating effects in depressed adults. The material is remarkably well tolerated when given by injection or intravenous infusion for this purpose, even in elderly or demented patients. Assuming that the toluene sulfonate component is inert, SAMe appears to have central neuropharmacologic effects after systemic injection in high doses. Nevertheless, the functional consequences of these remain unclear and, indeed, the ability of exogenous SAMe to reach the brain, and especially neuronal cytoplasm, is limited. SAMe has small effects on monoamine metabolism and, after injection, appears to have effects on the microviscosity of cell membranes that may be related to stimulation of phospholipid synthesis. The recent introduction of an orally administered form of SAMe for use in the treatment of osteoarthritis promises to stimulate further study of SAMe in disease-associated depression, major depressive disorder, and other neuropsychiatric conditions.

Vitamins in psychiatry. Do they have a role?

Petrie WM, Ban TA
Drugs 1985 Jul;30(1):58-65

Deficiencies of specific vitamins produce consistent symptoms of psychiatric disorder. Thiamine deficiency, which is common in alcoholism, can produce confusion and psychotic symptoms, in addition to neurological signs. Vitamin Bsub 1sub 2 and folate deficiency may contribute symptoms of disorientation, depression or psychosis; their measurement is a part of routine dementia work-ups. Pyridoxine deficiency results in seizures, although the effects of exogenously administered pyridoxine are not clearly understood in depression and anxiety - the disorders in which it is most frequently used clinically. The use of vitamins has been most prominent in psychiatry in the treatment of schizophrenia, where large doses of nicotinic acid were initially given alone and later combined with other vitamins and minerals. Several theoretical models were described to support the use of vitamins in schizophrenia. These included: the parallels of schizophrenia to the psychiatric symptoms of pellagra; hypotheses of a defect in adrenaline metabolism; and the accumulation of psychotoxic substances which produce psychotic symptoms. Initially, positive results were reported over 30 years ago, but have not been replicated by thorough investigations. An extensive series of comprehensive placebo-controlled trials failed to show efficacy for any of the vitamin therapies tested. Although clearly less effective than antipsychotic drug

treatment, vitamin therapy is not without risks - adverse effects have been reported with nicotinic acid, pyridoxine and vitamin C. Although the possible role of vitamins has played an important part in the development of biological psychiatry, vitamin therapy is no longer extensively practised, and claims for its efficacy have not been supported by objective scientific evidence.

S-adenosyl-L-methionine (SAMe) in clinical practice: Preliminary report on 75 minor depressives

De Leo D.
University of Padua, School of Medicine, Department of Psychiatry, Padua Italy
Current Therapeutic Research - Clinical and Experimental (United States) 1985, 37/4 (658-661)

An open trial was performed on a population of 75 patients suffering from minor depression. The subjects were administered 100 mg/die of S-adenosyl-L-methionine intramuscularly for 30 days. Modifications occurring were evaluated with the Zung SelRating Depression Scale and with the Clinical Global Impression and Patient Global Impression. The trial showed SAMe to have good clinical efficacy and to be virtually devoid of side effects.

S-Adenosyl-L-Methionine (SAMe) treatment in psychogeriatry: a controlled clinical trial in depressed patients

G.Gerontol. (Italy), 1977, 25/3

The authors report some results obtained by treatment with S-Adenosyl-L-Methionine (135 mg/day given intramuscularly for 15 days) in senile depressed patients (17 subjects). The evaluation was performed using the Hamilton Rating Scale for depression (HRS) and the scale by Overall and Gorham (BPRS). The items considering the depressive state improved significantly by treatment.

A methyl donor, adenosylmethionine, in depression

Folia Neuropsychiat.(Lecce) (Italy), 1973, 16/4

Because of the excellent results obtained by Fazio et al. in depressive syndromes with S adenosyl L methionine (SAM), the same drug was administered in the present trial. It was given intravenously in doses of 45 mg per day, for periods of 10 to 20 days to 8 patients suffering from depressive syndromes. Five patients (62%) were cured. Normalization occurred rapidly (in 5 days) and appeared to be lasting (still good at followup 5 months after the end of the treatment). Since SAM readily gives off methyl groups and since it passes the blood brain barrier, it

probably influences the biochemistry of the brain, especially its catecholamine metabolism which is probably subnormal in depressive psychoses. Consequently, it may be regarded as a highly useful drug in the treatment of hypothermic syndromes; further trials on a larger scale are advocated.

Therapeutic effects and mechanism of action of S adenosyl l methionine in depressive syndromes

Fazio C, Andreoli V, Agnoli A, Casacchia M, Cerbo R
Minerva Med 1973 Apr 30;64(29):1515-29

S-adenosyl methionine (SAM) is physiologically synthesised in the CNS and present in various concentrations in the different areas of the brain. The donor substance is activated by methyls and is involved in neurotransmitter synthesis and catabolism process. SAM injected into the systemic circulation rapidly crosses the blood brain barrier and is thus a potential nerve drug in the management of depression in the present crisis surrounding neuropharmacological theory. An open and double blind clinical trial was run on 49 patients. The drug manifested a rapid and intense antidepressive action, with positive results in over 80% of cases. A specific rating scale (Hamilton's scale) for depression was used in evaluating the experiment and the effect of the drug on certain target symptoms is discussed.

Monitoring S-adenosyl-methionine blood levels and antidepressant effect

Del Vecchio M, Amati A, Vacca L, Zizolfi S
Acta Neurol (Napoli) 1980 Dec;2(6):488-95

Seven depressed inpatients, classified according to the Multi-Aspect Classification Model, were treated with S-adenosyl-methionine (SAMe), 200 mg pro die i.v. for three weeks, in a single blind trial. Blood SAMe levels were determined in samples collected in a basal condition and after drug administration on the 7th, 14th and 21st day of the treatment. Computerized spectral frequency analysis of bioelectric brain activity has been performed before and after the treatment using some geometrical spectral parameters. The Hamilton Rating Scale for Depression (HRS), Comprehensive Psychopathological Rating Scale and Zung's Scale were rated before, during and after the treatment on the days of blood collection. At the end of the treatment, the improvement, according to HRS total scores, varied from 12.8 to 42.8 per cent (mean + or - SD: 21.8 + or - 4). No side effects were noted. A negative linear correlation was found between HRS total scores and blood SAMe levels ($r = -0.3641$; $p<0.05$). EEG spectral computerized analysis shows some differences after the treatment, which might indicate that SAMe interacts with brain tissues. Further studies are required to clarify the relationship between blood SAMe levels, therapeutic response and EEG recordings.

Clinic and psychometric effects of S adenosyl methionine on chronically L Dopa treated parkinsonians

Acta Neurol. (Napoli) (Italy), 1977, 32/2 (204-217)

S adenosyl methionine was administered for 15 days i.v. by glucose, at a daily dosage of 60 mg, to 15 subjects affected by idiopathic parkinsonism in chronic treatment with L-Dopa. SAM: favors the remission of akinesia; has an antidepressive effect; increases the anxious valencies; is a manageable drug, well tolerated with secondary side effects of minute importance.

14. Diabetes

Preventative and curative options include:

Alpha lipoic acid, american ginseng, aminoguanidine, bilberry, biotin carnitine, carnosine, CoQ10, chromium, CLA, DHEA, essential fatty acids, garlic, ginkgo biloba, gymnema sylvestre, magnesium, n-acetyl-L-cysteine, niacin, silymarin, vanadyl sulphate, vitamin C, vitamin E, vitamin K.

[Antiplatelet properties of nitrogen monoxide] [Article in French]

Adrie C. Service de reanimation medicale, hopital Saint-Louis, Paris.

Arch Mal Coeur Vaiss 1996 Nov;89(11 Suppl):1527-32

Nitric (correction of nitrous) oxide (NO) plays a fundamental part in the haemostatic equilibrium between the endothelium and platelets, an equilibrium of established clinical importance in cardiovascular disease. NO stimulates the enzyme guanylate cyclase which is responsible for synthesis of GMPc, the increase of which results in platelet inhibition. Synthesis of NO may have endogenous auto or paracrine origine from platelets or endothelial cells and participates in the local regulation of platelet function in association with other products of endothelial or platelet synthesis. Exogenous administration is common in therapeutics either in molecules which release NO (nitrate derivatives, sodium nitropruside, molsidomine, etc) or by NO gas administered by inhalation. The antiplatelet effect of NO has been clearly demonstrated in vitro, in vivo or ex vivo, in animals and humans, and probably explains, at least partially, the efficacy of nitrate derivatives in ischaemic coronary artery disease. Nevertheless, the platelet inhibition observed with intravenous NO releasing drugs is associated with potentially harmful systemic hypotension. Platelet inhibition by inhalation of NO could be an alternative means of avoiding this unwanted effect.

Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes.

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Diabetes 1997 Nov;46(11):1786-91

Chromium is an essential nutrient involved in normal carbohydrate and lipid metabolism. The chromium requirement is postulated to increase with increased glucose intolerance and diabetes. The objective of this study was to test the

hypothesis that the elevated intake of supplemental chromium is involved in the control of type 2 diabetes. Individuals being treated for type 2 diabetes (180 men and women) were divided randomly into three groups and supplemented with: 1) placebo, 2) 1.92 micromol (100 microg) Cr as chromium picolinate two times per day, or 3) 9.6 micromol (500 microg) Cr two times per day. Subjects continued to take their normal medications and were instructed not to change their normal eating and living habits. HbA1c values improved significantly after 2 months in the group receiving 19.2 pmol (1,000 microg) Cr per day and was lower in both chromium groups after 4 months (placebo, 8.5 +/- 0.2%; 3.85 micromol Cr, 7.5 +/- 0.2%; 19.2 micromol Cr, 6.6 +/- 0.1%). Fasting glucose was lower in the 19.2-micromol group after 2 and 4 months (4-month values: placebo, 8.8 +/- 0.3 mmol/l; 19.2 micromol Cr, 7.1 +/- 0.2 mmol/l). Two-hour glucose values were also significantly lower for the subjects consuming 19.2 micromol supplemental Cr after both 2 and 4 months (4-month values: placebo, 12.3 +/- 0.4 mmo/l; 19.2 micromol Cr, 10.5 +/- 0.2 mmol/l). Fasting and 2-h insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased after 4 months in the subjects receiving 19.2 micromol/day Cr. These data demonstrate that supplemental chromium had significant beneficial effects on HbA1c, glucose, insulin, and cholesterol variables in subjects with type 2 diabetes. The beneficial effects of chromium in individuals with diabetes were observed at levels higher than the upper limit of the Estimated Safe and Adequate Daily Dietary Intake.

The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes.

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Saudi Med J 2000 Sep;21(9):831-7

OBJECTIVE: To study the effects of supplementation with organic and inorganic chromium on glucose tolerance, serum lipids, and drug dosage in type 2 diabetes patients, in the hope of finding a better and more economical method of control. METHODS: Seventy eight type 2 diabetes patients were divided randomly into two groups and given Brewer's yeast (23.3ug Cr/day), and CrCl3 (200ug Cr/day) sequentially with placebo in between, in a double blind cross-over design of four stages, each lasting 8 weeks. At the beginning and end of each stage, subjects were weighed, their dietary data and drug dosage recorded, and blood and urine samples were collected for analysis of glucose (fasting and 2 hour post 75g glucose load) fructosamine, triglycerides, total and HDL-cholesterol, and serum and urinary chromium. RESULTS: Both supplements caused a significant decrease in the means of glucose (fasting and 2 hour post glucose load), fructosamine and triglycerides. The means of HDL-cholesterol, and serum and urinary chromium were all increased. The mean drug dosage decreased slightly (and significantly in case of Glibenclamide) after both supplements and some patients no longer required insulin. No change was noted in dietary intakes or Body Mass Index. A higher percentage of subjects responded positively to

Brewer's yeast chromium, which was retained more by the body, with effects on fructosamine, triglycerides, and HDL-cholesterol maintained in some subjects when placebo followed it, and mean urinary chromium remaining significantly higher than zero time mean. CONCLUSION: Chromium supplementation gives better control of glucose and lipid variables while decreasing drug dosage in type 2 diabetes patients. A larger scale study is needed to help decide on the convenient chemical form, and dosage required to achieve optimal response.

Dehydroepiandrosterone prevents lipid peroxidation and cell growth inhibition induced by high glucose concentration in cultured rat mesangial cells.

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J Endocrinol 2000 Aug;166(2):401-6

The oxidative stress induced by high glucose concentration contributes to tissue damage associated with diabetes, including renal injury. Dehydroepiandrosterone (DHEA), the major secretory product of the human adrenal gland, has been shown to possess a multi-targeted antioxidant activity which is also effective against lipid peroxidation induced by high glucose. In this study we evaluated the effect of DHEA on the growth impairment which high glucose concentration induces in cultured rat mesangial cells. Primary cultures of rat mesangial cells were grown for 10 days in media containing either normal (i.e. 5.6 mmol/l) or high (i.e. 30 mmol/l) concentrations of glucose, without or with DHEA at different concentrations. The impairment of cell growth induced by high glucose was reversed by 100 nmol/l and 500 nmol/l DHEA, which had no effect on mesangial cells cultured in media containing glucose at the normal physiological concentration (5.6 mmol/l). In high-glucose cultured mesangial cells, DHEA also attenuated the lipid peroxidation, as measured by thiobarbituric acid reactive substances (TBARS) generation and 4-hydroxynonenal (HNE) concentration, and preserved the cellular content of reduced glutathione as well as the membrane Na+/K+ ATPase activity. The data further support the protective effect of DHEA against oxidative damage induced by high glucose concentrations, and bring into focus its possible effectiveness in preventing chronic complications of diabetes.

Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus.

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N Engl J Med 2000 May 11;342(19):1392-8

BACKGROUND: The effect of increasing the intake of dietary fiber on glycemic control in patients with type 2 diabetes mellitus is controversial. METHODS: In a

randomized, crossover study, we assigned 13 patients with type 2 diabetes mellitus to follow two diets, each for six weeks: a diet containing moderate amounts of fiber (total, 24 g; 8 g of soluble fiber and 16 g of insoluble fiber), as recommended by the American Diabetes Association (ADA), and a high-fiber diet (total, 50 g; 25 g of soluble fiber and 25 g of insoluble fiber), containing foods not fortified with fiber (unfortified foods). Both diets, prepared in a research kitchen, had the same macronutrient and energy content. We compared the effects of the two diets on glycemic control and plasma lipid concentrations. RESULTS: Compliance with the diets was excellent. During the sixth week, the high-fiber diet, as compared with the the sixth week of the ADA diet, mean daily preprandial plasma glucose concentrations were 13 mg per deciliter [0.7 mmol per liter] lower (95 percent confidence interval, 1 to 24 mg per deciliter [0.1 to 1.3 mmol per liter]; P=0.04) and mean median difference, daily urinary glucose excretion 1.3 g (0.23; 95 percent confidence interval, 0.03 to 1.83 g; P= 0.008). The high-fiber diet also lowered the area under the curve for 24-hour plasma glucose and insulin concentrations, which were measured every two hours, by 10 percent (P=0.02) and 12 percent (P=0.05), respectively. The high-fiber diet reduced plasma total cholesterol concentrations by 6.7 percent (P=0.02), triglyceride concentrations by 10.2 percent (P=0.02), and very-low-density lipoprotein cholesterol concentrations by 12.5 percent (P=0.01). CONCLUSIONS: A high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA, improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations in patients with type 2 diabetes.

Novel lipid-lowering properties of Vaccinium myrtillus L. leaves, a traditional antidiabetic treatment, in several models of rat dyslipidaemia: a comparison with ciprofibrate.

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Thromb Res 1996 Dec 1;84(5):311-22

Vaccinium myrtillus L. (blueberry) leaf infusions are traditionally used as a folk medicine treatment of diabetes. To further define this therapeutical action, a dried hydroalcoholic extract of the leaf was administered orally to streptozotocin-diabetic rats for 4 days. Plasma glucose levels were consistently found to drop by about 26% at two different stages of diabetes. Unexpectedly, plasma triglyceride (TG) were also decreased by 39% following treatment. Subsequent to the latter observation, possible lipid-lowering properties of the extract were investigated on other models of hyperlipidaemia and ciprofibrate, a well-established hypolipidaemic drug, was used as a reference compound. Both drug reduced TG levels of rats on hyperlipidaemic diet in a dose-dependent fashion. When administered at single doses over the same experimental period, blueberry and ciprofibrate were effective in lowering TG concentrations in ethanol-treated normolipidaemic animals and in genetically hyperlipidaemic Yoshida rats. Unlike ciprofibrate, however, blueberry failed to prevent the rise in plasma TG elicited by fructose and did not affect free fatty acid levels in any of the above experimental conditions. In rats treated with Triton WR-1339, blueberry feeding

induced an hypolipidaemic activity one hour after injection but proved to be ineffective at later time points, thus suggesting that its hypolipidaemic action may reflect improved TG-rich lipoprotein catabolism. In addition, ciprofibrate and the extract were tested for antithrombotic activity using a collagen-triggered model of venous thrombosis in diabetic and Yoshida rats. Only ciprofibrate, however, significantly reduced thrombus formation in diabetics, possibly because of its effects on free fatty acid metabolism, whereas no effect was observed in Yoshida rats. In conclusion, the present findings indicate that active consituent(s) of Vaccinium myrtillus L. leaves may prove potentially useful for treatment of dyslipidaemiae associated with impaired TG-rich lipoprotein clearance.

Nitric oxide synthase: role in the genesis of vascular disease.

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Annu Rev Med 1997;48:489-509

The product of nitric oxide (NO) synthase is the most potent endogenous vasodilator known. No not only is a potent vasodilator, it also inhibits platelet adherence and aggregation, reduces adherence of leukocytes to the endothelium, and suppresses proliferation of vascular smooth muscle cells. A number of disorders are associated with reduced synthesis and/or increased degradation of vascular NO. These include hypercholesterolemia, diabetes mellitus, hypertension, and tobacco use. The endothelial dysfunction caused by these disorders contributes to the alterations in vascular function and structure observed in these conditions. A reduction in the activity of vascular NO likely plays a significant role in the development of atherosclerosis. Insights into the mechanisms by which NO production or activity is altered in these states will lead to new therapeutic strategies in the treatment of a number of vascular disorders, including hypertension, atherosclerosis, restenosis, and thrombosis.

Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation.

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Metabolism 1994 Dec;43(12):1558-62

The urinary excretion of zinc in individuals with insulin-dependent diabetes mellitus (IDDM) is approximately doubled. In the absence of a compensatory mechanism, this hyperzincuria should induce a deficient or marginal Zn status. We examined parameters of Zn status in plasma and in blood cells with respect to urinary Zn losses and Zn supplementation. We measured Zn levels in the urine, plasma, and erythrocytes of 14 IDDM subjects and 15 nondiabetics who kept dietary records for 3 consecutive days. Subsequently, six IDDM subjects and seven nondiabetics were supplemented with 50 mg Zn daily for 28 days. We measured the above parameters, as well as mononuclear leukocyte Zn (MNL-Zn)

and the plasma subfraction of albumin-bound Zn (alb-Zn). The total plasma Zn-binding capacity was also assessed. Plasma copper and erythrocyte Cu were monitored as indicators of potential Zn toxicity. Individuals with IDDM displayed the expected hyperzincuria, but had normal blood Zn parameters. Zincuria increased by a similar amount in both groups during supplementation, as did the MNL-Zn content. However, erythrocyte Zn (e-Zn) was refractory, so a trend toward lower e-Zn among IDDM subjects persisted during Zn supplementation. Hemoglobin A1c (HbA1c) increased markedly in the Zn-supplemented IDDM group. Despite their chronic hyperzincuria, individuals with IDDM appear not to be Zn-deficient. Large-dose Zn supplementation increases MNL-Zn and induces an undesirable elevation of HbA1c in all individuals. This is especially disconcerting for those with IDDM, and may reflect an exacerbation of a chronic "Zn diabetes." These data suggest a potential for toxicity from large-dose Zn supplementation.

Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effect of alpha-tocopherol supplementation.

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Circulation 2000 Jul 11;102(2):191-6

BACKGROUND: Although diabetes confers an increased propensity toward accelerated atherogenesis, data are lacking on monocyte activity in type 2 diabetic patients with (DM2-MV) and without (DM2) macrovascular disease compared with control subjects. Thus, we tested whether (1) postsecretory modifications of LDL (glycation and oxidation), monocyte proatherogenic activity, and circulating levels of soluble cell adhesion molecules (sCAMs) are more pronounced in DM2-MV than in DM2 and control subjects and (2) RRR-alpha-tocopherol (AT) therapy, 1200 IU/d for 3 months, has a similar effect in the 3 groups (n=25 per group). METHODS AND RESULTS: Although LDL glycation was increased in both diabetic groups compared with control subjects, AT therapy had no significant effect on glycation. AT therapy significantly decreased LDL oxidizability in all 3 groups. Diabetic monocytes released significantly more superoxide anion (O(2)(-)) and interleukin-1beta (IL-1beta) and exhibited greater adhesion to endothelium than control subjects. AT therapy significantly decreased the release of O(2)(-), IL-1beta, tumor necrosis factor-alpha, and monocyte-endothelium adhesion in all 3 groups. There was no significant difference between the 2 diabetic groups for any of the above parameters. sICAM levels were significantly elevated in both diabetic groups compared with controls. AT therapy resulted in a significant decrease in sCAMs. CONCLUSIONS: This is the first demonstration of increased IL-1beta secretion and increased adhesion of monocytes to endothelium from normotriglyceridemic diabetic subjects and of decreased monocyte activity and sCAMs with AT therapy in diabetic subjects with and without macrovasculopathy.

Diabetes-induced nitrative stress in the retina, and correction by aminoguanidine.

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J Neurochem 2002 Mar;80(5):771-9

Aminoguanidine inhibits the development of retinopathy in diabetic animals, but the mechanism remains unclear. Inasmuch as aminoguanidine is a relatively selective inhibitor of the inducible isoform of nitric oxide synthase (iNOS), we have investigated the effects of hyperglycemia on the retinal nitric oxide (NO) pathway in the presence and absence of aminoguanidine. In vivo studies utilized retinas from experimentally diabetic rats treated or without aminoguanidine for 2 months, and in vitro studies used bovine retinal endothelial cells and a transformed retinal glial cell line (rMC-1) incubated in 5 mm and 25 mm glucose with and without aminoguanidine (100 microg/mL). NO was detected as nitrite and nitrate, and nitrotyrosine and iNOS were detected using immunochemical methods. Retinal homogenates from diabetic animals had greater than normal levels of NO and iNOS (< 0.05), and nitrotyrosine was greater than normal, especially in one band immunoprecipitated from retinal homogenates. Oral aminoguanidine significantly inhibited all of these increases. Nitrotyrosine was detected immunohistochemically only in the retinal vasculature of non-diabetic and diabetic animals. Retinal endothelial and rMC-1 cells cultured in high glucose increased NO and NT, and aminoguanidine inhibited both increases in rMC-1 cells, but only NT in endothelial cells. Hyperglycemia increases NO production in retinal cells, and aminoguanidine can inhibit this abnormality. Inhibition of diabetic retinopathy by aminoguanidine might be mediated in part by inhibition of sequelae of NO production.

Magnesium and insulin-dependent diabetes mellitus.

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Diabetes Res Clin Pract 1990 Nov-Dec;10(3):203-9

There is accumulating evidence that the changes which occur in the metabolism of some micronutrients in diabetes mellitus might have a specific role in the pathogenesis and complications of this disease. Magnesium deficiency is the most evident disturbance of metal metabolism in insulin-dependent diabetes mellitus. Hypomagnesemia has been linked both to the acute metabolic and late chronic complication of diabetes. Of particular concern, is the association between hypomagnesemia and ischemic heart disease and severe retinopathy in humans with diabetes mellitus. Appropriate magnesium supplementation might prove beneficial in normalizing the low plasma and tissue magnesium levels and prevent or retard the development of vascular complications in diabetic patients.

However, well designed and documented experiments need to be performed before the rationales for such therapy are well established.

Zinc and insulin sensitivity.

Faure P, Roussel A, Coudray C, Richard MJ, Halimi S, Favier A. Laboratoire de Biochimie C, Hopital A. Michallon, Grenoble, France.

Biol Trace Elem Res 1992 Jan-Mar;32:305-10

Many studies have shown that zinc deficiency could decrease the response to insulin. In genetically diabetic animals, a low zinc status has been observed contrary to induced diabetic animals. The zinc status of human patients depends on the type of diabetes and the age. Zinc supplementation seems to have beneficial effects on glucose homeostasis. However, the mechanism of insulin resistance secondary to zinc depletion is yet unclear. More studies are therefore necessary to document better zinc metabolism in diabetes mellitus, and the antioxidant activity of zinc on the insulin receptor and the glucose transporter.

Cross-talk between iron metabolism and diabetes.

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Diabetes 2002 Aug;51(8):2348-54

Emerging scientific evidence has disclosed unsuspected influences between iron metabolism and type 2 diabetes. The relationship is bi-directional--iron affects glucose metabolism, and glucose metabolism impinges on several iron metabolic pathways. Oxidative stress and inflammatory cytokines influence these relationships, amplifying and potentiating the initiated events. The clinical impact of these interactions depends on both the genetic predisposition and the time frame in which this network of closely related signals acts. In recent years, increased iron stores have been found to predict the development of type 2 diabetes while iron depletion was protective. Iron-induced damage might also modulate the development of chronic diabetes complications. Iron depletion has been demonstrated to be beneficial in coronary artery responses, endothelial dysfunction, insulin secretion, insulin action, and metabolic control in type 2 diabetes. Here, we show that iron modulates insulin action in healthy individuals and in patients with type 2 diabetes. The extent of this influence should be tested in large-scale clinical trials, searching for the usefulness and cost-effectiveness of therapeutic measures that decrease iron toxicity. The study of individual susceptibility and of the mechanisms that influence tissue iron deposition and damage are proposed to be valuable in anticipating and treating diabetes complications.

Aminoguanidine prolongs survival in azotemic-induced diabetic rats.

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Am J Kidney Dis 1997 Aug;30(2):253-9

Toxic effects of hyperglycemia-induced advanced glycosylated end products (AGEs) may explain some vasculopathic complications of diabetes. Aminoguanidine, a known inhibitor of AGE formation, was administered by gavage to Sprague-Dawley streptozotocin-induced diabetic rats made azotemic by surgical reduction of renal mass. All rats became hyperglycemic. Renal ablation caused renal insufficiency, as evidenced by markedly reduced endogenous creatinine clearances at days 7 and 14. Aminoguanidine-treated rats had significantly (< 0.04) superior survival to that of untreated azotemic diabetic rats. We infer from the extended life in a rat model of uremia in diabetic nephropathy that aminoguanidine may prove beneficial in human diabetes.

Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress?

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Metabolism 1995 Mar;44(3):363-8

Accelerated atherosclerotic vascular disease is the leading cause of mortality in patients with diabetes mellitus. Endothelium-derived nitric oxide (NO) is a potent endogenous nitrovasodilator and plays a major role in modulation of vascular tone. Selective impairment of endothelium-dependent relaxation has been demonstrated in aortas of both nondiabetic animals exposed to elevated concentrations of glucose in vitro and insulin-dependent diabetic animals. The impaired NO release in experimentally induced diabetes may be prevented by a number of antioxidants. It has been hypothesized that oxygen-derived free radicals (OFR) generated during both glucose autoxidation and formation of advanced glycosylation end products may interfere with NO action and attenuate its vasodilatory activity. The oxidative injury may also be increased in diabetes mellitus because of a weakened defense due to reduced endogenous antioxidants (vitamin E, reduced glutathione [GSH]). A defective endothelium-dependent vascular relaxation has been found in animal models of hypertension and in hypertensive patients. An imbalance due to reduced production of NO or increased production of free radicals, mainly superoxide anion, may facilitate the development of an arterial functional spasm. Treatment with different antioxidants increases blood flow in the forearm and decreases blood pressure and viscosity in normal humans; vitamin E inhibits nonenzymatic glycosylation, oxidative stress, and red blood cell microviscosity in diabetic patients. Long-term randomized clinical trials of adequate size in secondary and primary prevention could support the free-radical hypothesis for diabetic diabetic vascular complications and the use of antioxidants to reduce the risk of coronary heart disease.

Clinical and experimental study on the long-term effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation, thromboxane formation, and prostacyclin production.

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Prostaglandins Leukot Essent Fatty Acids 1994 Nov;51(5):311-6

Effects of a dietary intake of the polyunsaturated omega-6 essential fatty acids (EFAs) linoleic and gamma-linolenic acids (GLA) on blood lipids, platelet function, and vascular prostacyclin production were studied 12 hyperlipidemic patients (doses of 3 g/day) and 12 male Wistar rats (doses of 3 mg/kg/day) for 4 months. In humans, GLA supplementation decreased plasma triglyceride (TG) levels by 48% (< 0.001) and increased HDL-cholesterol concentration by 22% (< 0.01). Total cholesterol and LDL-cholesterol levels were significantly decreased by omega-6 EFAs. Platelet aggregation induced by low concentrations of adenosine diphosphate (ADP) and epinephrine, and serum thromboxane B2 decreased by 45% both in humans and animals after GLA supplementation. Bleeding time increased 40% (p , 0.01). In rats, vascular prostacyclin production measured by radioimmunoassay of 6-keto-PGF1 alpha was enhanced by GLA intake. These effects of omega-6 EFAs may contribute to cardiovascular protection and prevention of the atherosclerotic disease.

DHEA treatment reduces fat accumulation and protects against insulin resistance in male rats.

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J Gerontol A Biol Sci Med Sci 1998 Jan;53(1):B19-24

The purpose of this study was to determine whether administration of dehydroepiandrosterone (DHEA) protects male rats against the accumulation of body fat the development of insulin resistance with advancing age. We found that supplementation of the diet with 0.3% DHEA between the ages of 5 months and approximately 25 months resulted in a significantly lower final body weight (DHEA, 593 +/- 18 g vs control, 668 +/- 12 g, < 0.02), despite no decrease in food intake. Lean body mass was unaffected by the DHEA, and the lower body weight was due to a approximately 25% reduction in body fat. The rate of glucose disposal during a euglycemic, hyperinsulinemic clamp was 30% higher in the DHEA group than in the sedentary controls due to a greater insulin responsiveness. The DHEA administration was as effective in reducing body fat content and maintaining insulin responsiveness as exercise in the form of voluntary wheel running. The DHEA had no significant effect on muscle GLUT4 content. A preliminary experiment provided evidence suggesting that muscle insulin signaling, as reflected in binding of phosphatidylinositol 3-kinase to the insulin receptor substrate-1, was enhanced in the DHEA-treated and wheel running groups as compared to controls. These results provide evidence that

DHEA, like exercise, protects against excess fat accumulation and development of insulin resistance in rats.

A possible new role for the anti-ageing peptide carnosine.

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Cell Mol Life Sci 2000 May;57(5):747-53

The naturally occurring dipeptide carnosine (beta-alanyl-L-histidine) is found in surprisingly large amounts in long-lived tissues and can delay ageing in cultured human fibroblasts. Carnosine has been regarded largely as an anti-oxidant and free radical scavenger. More recently, an anti-glycating potential has been discovered whereby carnosine can react with low-molecular-weight compounds that bear carbonyl groups (aldehydes and ketones). Carbonyl groups, arising mostly from the attack of reactive oxygen species and low-molecular-weight aldehydes and ketones, accumulate on proteins during ageing. Here we propose, with supporting evidence, that carnosine can react with protein carbonyl groups to produce protein-carbonyl-carnosine adducts ('carnosinylated' proteins). The various possible cellular fates of the carnosinylated proteins are discussed. These proposals may help explain anti-ageing actions of carnosine and its presence in non-mitotic cells of long-lived mammals.

Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat.

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Biochem Biophys Res Commun 1998 Mar 27;244(3):678-82

Conjugated linoleic acid (CLA) is a naturally occurring fatty acid which has anti-carcinogenic and anti-atherogenic properties. CLA activates PPAR alpha in liver, and shares functional similarities to ligands of PPAR gamma, the thiazolidinediones, which are potent insulin sensitizers. We provide the first evidence that CLA is able to normalize impaired glucose tolerance and improve hyperinsulinemia in the pre-diabetic ZDF rat. Additionally, dietary CLA increased steady state levels of aP2 mRNA in adipose tissue of fatty ZDF rats compared to controls, consistent with activation of PPAR gamma. The insulin sensitizing effects of CLA are due, at least in part, to activation of PPAR gamma since increasing levels of CLA induced a dose-dependent transactivation of PPAR gamma in CV-1 cells cotransfected with PPAR gamma and PPRE X 3-luciferase reporter construct. CLA effects on glucose tolerance and glucose homeostasis indicate that dietary CLA may prove to be an important therapy for the prevention and treatment of NIDDM.

Diet, lifestyle, and the risk of type 2 diabetes mellitus in women.

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N Engl J Med 2001 Sep 13;345(11):790-7

BACKGROUND: Previous studies have examined individual dietary and lifestyle factors in relation to type 2 diabetes, but the combined effects of these factors are largely unknown. METHODS: We followed 84,941 female nurses from 1980 to 1996; these women were free of diagnosed cardiovascular disease, diabetes, and cancer at base line. Information about their diet and lifestyle was updated periodically. A low-risk group was defined according to a combination of five variables: a bodymass index (the weight in kilograms divided by the square of the height in meters) of less than 25; a diet high in cereal fiber and polyunsaturated fat and low in trans fat and glycemic load (which reflects the effect of diet on the blood glucose level); engagement in moderate-to-vigorous physical activity for at least half an hour per day; no current smoking; and the consumption of an average of at least half a drink of an alcoholic beverage per day. RESULTS: During 16 years of follow-up, we documented 3300 new cases of type 2 diabetes. Overweight or obesity was the single most important predictor of diabetes. Lack of exercise, a poor diet, current smoking, and abstinence from alcohol use were all associated with a significantly increased risk of diabetes, even after adjustment for the body-mass index. As compared with the rest of the cohort, women in the low-risk group (3.4 percent of the women) had a relative risk of diabetes of 0.09 (95 percent confidence interval, 0.05 to 0.17). A total of 91 percent of the cases of diabetes in this cohort (95 percent confidence interval, 83 to 95) could be attributed to habits and forms of behavior that did not conform to the low-risk pattern. CONCLUSIONS: Our findings support the hypothesis that the vast majority of cases of type 2 diabetes could be prevented by the adoption of a healthier lifestyle.

Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid.

Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, Jung WI, Augustin HJ, Dietze GJ. Department of Internal Medicine, City Hospital, Baden-Baden, Germany.

Arzneimittelforschung 1995 Aug;45(8):872-4

Insulin resistance of skeletal muscle glucose uptake is a prominent feature of Type II diabetes (NIDDM); therefore pharmacological interventions should aim to improve insulin sensitivity. Alpha-lipoic acid (CAS 62-46-4, thioctic acid, ALA), a natural occurring compound frequently used for treatment of diabetic polyneuropathy, enhances glucose utilization in various experimental models. To see whether this compound also augments insulin mediated glucose disposal in NIDDM, 13 patients received either ALA (1000 mg/Thioctacid/500 ml NaCl, n = 7) or vehicle only (500 ml NaCl, n = 6) during a glucose-clamp study. Both groups were comparable in age, body-mass index and duration of diabetes and

had a similar degree of insulin resistance at baseline. Acute parenteral administration of ALA resulted in a significant increase of insulin-stimulated glucose disposal; metabolic clearance rate (MCR) for glucose rose by about 50% (3.76 ml/kg/min = pre vs. 5.82 ml/kg/min = post, p < 0.05), whereas the control group did not show that alpha-lipoic acid increases insulin stimulated glucose disposal in NIDDM. The mode of action of ALA and its potential use as an antihyperglycemic agent require further investigation.

The antioxidant alpha-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle.

Jacob S, Streeper RS, Fogt DL, Hokama JY, Tritschler HJ, Dietze GJ, Henriksen EJ. Department of Physiology, University of Arizona College of Medicine, Tucson, AZ, USA.

Diabetes 1996 Aug;45(8):1024-9

Insulin resistance of muscle glucose metabolism is a hallmark of NIDDM. The obese Zucker (fa/fa) rat--an animal model of muscle insulin resistance--was used to test whether acute (100 mg/kg body wt for 1 h) and chronic (5-100 mg/kg for 10 days) parenteral treatments with a racemic mixture of the antioxidant alpha-lipoic acid (ALA) could improve glucose metabolism in insulin-resistant skeletal muscle. Glucose transport activity (assessed by net 2-deoxyglucose [2-DG] uptake), net glycogen synthesis, and glucose oxidation were determined in the isolated epitrochlearis muscles in the absence or presence of insulin (13.3 nmol/l). Severe insulin resistance of 2-DG uptake, glycogen synthesis, and glucose oxidation was observed in muscle from the vehicle-treated obese rats compared with muscle from vehicle-treated lean (Fa/-) rats. Acute and chronic treatments (30 mg.kg-1.day-1, a maximally effective dose) with ALA significantly (P < 0.05) improved insulin-mediated 2-DG uptake in epitrochlearis muscles from the obese rats by 62 and 64%, respectively. Chronic ALA treatment increased both insulin-stimulated glucose oxidation (33%) and glycogen synthesis (38%) and was associated with a significantly greater (21%) in vivo muscle glycogen concentration. These adaptive responses after chronic ALA administration were also associated with significantly lower (15-17%) plasma levels of insulin and free fatty acids. No significant effects on glucose transporter (GLUT4) protein level or on the activities of hexokinase and citrate synthase were observed. Collectively, these findings indicate that parenteral administration of the antioxidant ALA significantly enhances the capacity of the insulin-stimulatable glucose transport system and of both oxidative and nonoxidative pathways of glucose metabolism in insulin-resistant rat skeletal muscle.

Lipoic acid (LA) decreases protein glycation and increases (NA++K+)- and Ca++ATPases activities in high glucose (G)-treated red blood cells (RBC)

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Free Radical Biol. Med. 1998; 25: S94 (Abstr. 268)

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na+ + K+)-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na+ + K+)- and Ca++-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R sterioisomers) in a shaking water bath at 37°C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na+ + K+)- and Ca++-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na+ + K+)- and Ca++-ATPases in high glucose- treated RBC. There were no differences in lipid peroxidation, GHb and (Na+ + K+)- and Ca++-ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na+ + K+)- and Ca++-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-treated human erythrocytes.

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Free Radic Biol Med 2000 Dec;29(11):1122-8

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na(+) + K(+))-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R sterioisomers) in a shaking water bath at 37 degrees C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na(+) + K(+))- and Ca(++)-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na(+) + K(+))- and Ca(++)-ATPases in high glucose- treated RBC. There were no differences in lipid peroxidation, GHb and (Na(+) + K(+))- and Ca(++)-

ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na(+) + K(+))- and Ca(++)-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes.

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J Am Coll Nutr 2001 Aug;20(4):327-36

OBJECTIVES: These studies investigated the ability of a hydroxychalcone from cinnamon to function as an insulin mimetic in 3T3-LI adipocytes. METHODS: Comparative experiments were performed with the cinnamon methylhydroxychalcone polymer and insulin with regard to glucose uptake, glycogen synthesis. phosphatidylinositol-3-kinase dependency, glycogen synthase activation and glycogen synthase kinase-3beta activity. The phosphorylation state of the insulin receptor was also investigated. RESULTS: MHCP treatment stimulated glucose uptake and glycogen synthesis to a similar level as insulin. Glycogen synthesis was inhibited by both wortmannin and LY294002, inhibitors directed against the PI-3-kinase. In addition, MHCP treatment activated glycogen synthase and inhibited glycogen synthase kinase-3beta activities, known effects of insulin treatment. Analysis of the insulin receptor demonstrated that the receptor was phosphorylated upon exposure to the MHCP. This supports that the insulin cascade was triggered by MHCP. Along with comparing MHCP to insulin, experiments were done with MHCP and insulin combined. The responses observed using the dual treatment were greater than additive, indicating synergism between the two compounds. CONCLUSION: Together, these results demonstrate that the MHCP is an effective mimetic of insulin. MHCP may be useful in the treatment of insulin resistance and in the study of the pathways leading to glucose utilization in cells.

Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity.

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Diabetes 1999 Dec;48(12):2398-406

Oxidative stress is produced under diabetic conditions and possibly causes various forms of tissue damage in patients with diabetes. The aim of this study was to examine the involvement of oxidative stress in the progression of pancreatic beta-

cell dysfunction in type 2 diabetes and to evaluate the potential usefulness of antioxidants in the treatment of type 2 diabetes. We used diabetic C57BL/KsJ-db/db mice, in whom antioxidant treatment (N-acetyl-L-cysteine [NAC], vitamins C plus E, or both) was started at 6 weeks of age; its effects were evaluated at 10 and 16 weeks of age. According to an intraperitoneal glucose tolerance test, the treatment with NAC retained glucose-stimulated insulin secretion and moderately decreased blood glucose levels. Vitamins C and E were not effective when used alone but slightly effective when used in combination with NAC. No effect on insulin secretion was observed when the same set of antioxidants was given to nondiabetic control mice. Histologic analyses of the pancreases revealed that the beta-cell mass was significantly larger in the diabetic mice treated with the antioxidants than in the untreated mice. As a possible cause, the antioxidant treatment suppressed apoptosis in beta-cells without changing the rate of beta-cell proliferation, supporting the hypothesis that in chronic hyperglycemia, apoptosis induced by oxidative stress causes reduction of beta-cell mass. The antioxidant treatment also preserved the amounts of insulin content and insulin mRNA, making the extent of insulin degranulation less evident. Furthermore, expression of pancreatic and duodenal homeobox factor-1 (PDX-1), a beta-cell-specific transcription factor, was more clearly visible in the nuclei of islet cells after the antioxidant treatment. In conclusion, our observations indicate that antioxidant treatment can exert beneficial effects in diabetes, with preservation of in vivo beta-cell function. This finding suggests a potential usefulness of antioxidants for treating diabetes and provides further support for the implication of oxidative stress in beta-cell dysfunction in diabetes.

Lipoic acid acutely induces hypoglycemia in fasting nondiabetic and diabetic rats.

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Metabolism 1999 Apr;48(4):504-10

Lipoic acid (LA) is a unique antioxidant that increases peripheral glucose utilization in diabetic patients. This study was conducted to investigate whether the inhibition of glucose production could be an additional mechanism for the action of LA. Intravenous (i.v.) LA injection (100 or 60 mg/kg body weight) to fasting nondiabetic or streptozotocin (STZ)-induced diabetic rats caused a rapid reduction in blood glucose with no effect on circulating insulin levels. In vivo conversion of fructose to glucose was not inhibited by LA, whereas the gluconeogenesis flux from alanine was completely prevented. Reduced liver pyruvate carboxylase (PC) activity in vivo is suggested by the finding that LA induced a decrease in liver coenzyme A (CoA) content (44% and 28% reduction in nondiabetic and diabetic rats, respectively, compared with vehicle-treated animals) and liver acetyl CoA content (80% and 67% reduction in nondiabetic and diabetic rats, respectively). A reduction in plasma free carnitine (42% and 22% in nondiabetic and diabetic rats, respectively) was observed in LA-treated animals, and acylcarnitine levels were increased twofold. This could be attributed

to elevated levels of C16 and C18 acylcarnitine, without a detectable accumulation of lipoylcarnitine. Under such conditions, a significant increase in the plasma free fatty acid (FFA) concentration (204% in nondiabetic and 151% in diabetic animals) with no elevation in beta-hydroxybutyrate levels was noted. In conclusion, this study suggests that short-term administration of LA at high dosage to normal and diabetic rats causes an inhibition of gluconeogenesis secondary to an interference with hepatic fatty acid oxidation. This may render LA an antihyperglycemic agent for the treatment of diabetic subjects, who display glucose overproduction as a major metabolic abnormality.

Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.

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Int J Dev Neurosci 1999 Dec;17(8):765-75

Dehydroepiandrosterone (DHEA) is a native neurosteroid with immunomodulating activity. DHEA effectively protects animals from several viral, bacterial and parasitic infections and it was suggested that its age-associated decline is related with immunosenescence. In the present study we examined the ability of DHEA to inhibit the production of inflammatory mediators by mycoplasma-stimulated glial cells and to change the course of acute central nervous system (CNS) inflammatory disease in vivo. Addition of DHEA (10 microg/ml) markedly inhibited tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) production (98 and 95%, respectively), whereas nitric oxide (NO) and prostaglandin E2 (PGE2) production was not affected. However, daily administration of 0.5 mg DHEA to mice or 5 mg to rats did not change the clinical outcome of experimental autoimmune encephalomyelitis (EAE).

Biotin for diabetic peripheral neuropathy.

Koutsikos D, Agroyannis B, Tzanatos-Exarchou H. University of Athens, Aretaieon University Hospital, Greece.

Biomed Pharmacother 1990;44(10):511-4

Biotin in high doses was given for 1-2 years to three diabetic patients suffering from severe diabetic peripheral neuropathy. Within 4-8 weeks there was a marked improvement in clinical and laboratory findings. It is suggested that in diabetes may exist a deficiency, inactivity or unavailability of Biotin, resulting in disordered activity of biotin-dependent enzyme, pyruvate carboxylase, leading to accumulation of pyruvate and/or depletion of aspartate, both of which play a significant role in nervous system metabolism. Based on our good results, regular biotin administration could be suggested for every diabetic patient for the prevention and management of peripheral neuropathy although extensive randomised clinical trials are required.

Activation of acetyl-CoA carboxylase by a glutamate- and magnesium-sensitive protein phosphatase in the islet beta-cell.

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Diabetes 2001 Jul;50(7):1580-7

Acetyl-CoA carboxylase (ACC) catalyzes the formation of malonyl-CoA, a precursor in the biosynthesis of long-chain fatty acids, which have been implicated in physiological insulin secretion. The catalytic function of ACC is regulated by phosphorylation (inactive)-dephosphorylation (active). In this study we investigated whether similar regulatory mechanisms exist for ACC in the pancreatic islet beta-cell. ACC was quantitated in normal rat islets, human islets, and clonal beta-cells (HIT-15 or INS-1) using a [(14)C]bicarbonate fixation assay. In the beta-cell lysates, ACC was stimulated by magnesium in a concentration-dependent manner. Of all the dicarboxylic acids tested, only glutamate, albeit ineffective by itself, significantly potentiated magnesium-activated ACC in a concentration-dependent manner. ACC stimulation by glutamate and magnesium was maximally demonstrable in the cytosolic fraction; it was markedly reduced by okadaic acid (OKA) in concentrations (<50 nmol/l) that inhibited protein phosphatase 2A (PP2A). Furthermore, pretreatment of the cytosolic fraction with anti-PP2A serum attenuated the glutamate- and magnesium-mediated activation of ACC, thereby suggesting that ACC may be regulated by an OKA-sensitive PP2A-like enzyme. Streptavidin-agarose chromatography studies have indicated that glutamate- and magnesium-mediated effects on ACC are attributable to activation of ACC's dephosphorylation; this suggests that the stimulatory effects of glutamate and magnesium on ACC might involve activation of an OKA-sensitive PP2A-like enzyme that dephosphorylates and activates ACC. In our study, 5-amino-imidazolecarboxamide (AICA) riboside, a stimulator of AMP kinase, significantly inhibited glucose-mediated activation of ACC and insulin secretion from isolated beta-cells. Together, our data provide evidence for a unique regulatory mechanism for the activation of ACC in the pancreatic beta-cell, leading to the generation of physiological signals that may be relevant for physiological insulin secretion.

C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease.

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Am J Cardiol 2001 Nov 15;88(10):1139-42

The acute-phase reactant C-reactive protein (CRP) has emerged as an independent risk factor for coronary artery disease. Experimental and clinical studies provide evidence of anti-inflammatory effects of n-3 polyunsaturated fatty acids (PUFA)

derived from fish. We have studied the effect of marine n-3 PUFA on CRP levels in 269 patients referred for coronary angiography because of clinical suspicion of coronary artery disease. All patients filled out a food questionnaire regarding fish intake. The n-3 PUFA content of granulocyte membranes was determined and the concentration of CRP in serum was measured using a highly sensitive assay. The results were related to angiographic findings. CRP was significantly higher in patients with significant coronary stenoses than in those with no significant angiographic changes (p <0.001), but the CRP levels were not associated with the number of diseased vessels. Subjects with CRP levels in the lower quartile had a significantly higher content of docosahexaenoic acid (DHA) in granulocytes than subjects with CRP levels in the upper quartile (p = 0.02), and in a multivariate linear regression analysis, DHA was independently correlated to CRP (R(2) = 0.179; p = 0.003). The inverse correlation between CRP and DHA may reflect an anti-inflammatory effect of DHA in patients with stable coronary artery disease and suggest a novel mechanism by which fish consumption may decrease the risk of coronary artery disease.

Therapeutic evaluation of the effect of biotin on hyperglycemia in patients with non-insulin dependent diabetes mellitus.

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Journal of Clinical Biochemistry and Nutrition 1993 14 (3): p 211-218

The therapeutic efficacy of biotin was evaluated in 43 patients with non-insulin dependent diabetes mellitus. The serum biotin concentration in the patients was significantly lower than that in the 64 healthy control subjects and inversely correlated with the fasting blood glucose level. The oral administration of biotin, 9 mg daily, corrected the hyperglycemia in the patients with no change in their serum insulin level. The serum levels of pyruvate and lactate decreased to their normal ranges after the administration. These observations suggest that the biotin administration ameliorates abnormal glucose metabolism in diabetic patients, presumably by enhancing the activity of the biotin-dependent enzyme, pyruvate carboxylase, with a subsequent promotion of glucose utilization for the entry into the tricarboxylic acid cycle. The administration also enhanced the response to glibenclamide in patients who had been resistant to the agent, suggesting a significant increase in the potency of the endogenous insulin action. The result demonstrates that biotin administration is effective for the treatment of the patients. Neither a relapse of clinical symptoms nor an occurrence of undesirable side effects has been observed.

Diabetic cardiomyopathy and carnitine deficiency.

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J Diabetes Complications 1999 Mar-Apr;13(2):86-90

This study was designed to study the pathogenesis of cardiomyopathy in animals with longstanding (6 months) diabetes mellitus. Male Wistar rats were made diabetic by the injection of streptozotocin (35 mg/kg) intraperitoneal at 6 months of age. Myocardial contractility was evaluated at 1 year of age by an echocardiogram. Blood was collected at that time to measure blood glucose and hemoglobin A1c as an indicator of metabolic control. Serum carnitine was also measured on the same sample to evaluate the availability of this substance so essential for fatty acid metabolism in the myocardium. Myocardial anatomy was evaluated by both light and electron microscopy after the animals had diabetes for 6 months. It was found that the left ventricular volume was greater at the end of systole and diastole. There was the suggestion of left ventricular fractional shortening and calculated reduced ejection fraction indicating decreased contractility consistent with cardiomyopathy. The hearts had no evidence of coronary vascular occlusion, and the serum cholesterol was normal. Myocardial ultrastructure revealed abnormal-appearing mitochondria consistent with carnitine deficiency. Serum and myocardial carnitine levels in the animals with diabetes and reduced myocardial function were low. Carnitine levels and metabolism could be important in the pathogenesis of diabetic cardiomyopathy.

Can correction of sub-optimal coenzyme Q status improve beta-cell function in type II diabetics?

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Med Hypotheses 1999 May;52(5):397-400

A stimulus to mitochondrial respiratory activity is a crucial component of the signal transduction mechanism whereby increased plasma glucose evokes insulin secretion by beta-cells. Efficient function of the glycerol-3-phosphate shuttle is important in this regard, and the rate-limiting enzyme in this shuttle--the mitochondrial glycerol-3-phosphate dehydrogenase (G3PD)--is underexpressed in the beta cells of human type II diabetics as well of rodents that are models for this disorder. Suboptimal tissue levels of coenzyme Q10 (CoQ) could be expected to further impair G3PD activity. Clinical reports from Japan suggest that supplemental CoQ may often improve beta-cell function and glycemic control in type II diabetics. Thus, it is proposed that correction of suboptimal CoQ status, by aiding the efficiency of G3PD and of respiratory chain function, will improve the glucose-stimulated insulin secretion of diabetic beta-cells.

Toward a wholly nutritional therapy for type 2 diabetes.

McCarty MF. Helicon Foundation, San Diego, CA, USA.

Med Hypotheses 2000 Mar;54(3):483-7

It may now be feasible to target specific supplemental nutrients to each of the key dysfunctions which conspire to maintain hyperglycemia in type 2 diabetes:

bioactive chromium for skeletal muscle insulin resistance, conjugated linoleic acid for adipocyte insulin resistance, high-dose biotin for excessive hepatic glucose output, and coenzyme Q(10) for beta cell failure. Nutritional strategies which disinhibit hepatic fatty acid oxidation (involving hydroxycitrate, carnitine, pyruvate, and other adjuvants) may likewise prove beneficial - in the short term, by decreasing serum free fatty acids and, in the longer term, by promoting regression of visceral obesity. The nutrients and food factors recommended here appear to be safe and well tolerated, and thus may have particular utility for diabetes prevention.

Effects of dietary supplementation of alpha-lipoic acid on early glomerular injury in diabetes mellitus.

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J Am Soc Nephrol 2001 Jan;12(1):124-33

Antioxidants, in particular vitamin E (VE), have been reported to protect against diabetic renal injury. alpha-Lipoic acid (LA) has been found to attenuate diabetic peripheral neuropathy, but its effects on nephropathy have not been examined. In the present study, parameters of glomerular injury were examined in streptozotocin diabetic rats after 2 mo on unsupplemented diets and in diabetic rats that received the lowest daily dose of dietary LA (30 mg/kg body wt), VE (100 IU/kg body wt), or vitamin C (VC; 1 g/kg body wt), which detectably increased the renal cortical content of each antioxidant. Blood glucose values did not differ among the diabetic groups. At 2 mo, inulin clearance, urinary albumin excretion, fractional albumin clearance, glomerular volume, and glomerular content of immunoreactive transforming growth factor-beta (TGF-beta) and collagen alpha1 (IV) all were significantly increased in unsupplemented D compared with age-matched nondiabetic controls. With the exception of inulin clearance, LA prevented or significantly attenuated the increase in all of these glomerular parameters in D, as well as the increases in renal tubular cell TGF-beta seen in D. At the dose used, VE reduced inulin clearance in D to control levels but failed to alter any of the other indices of glomerular injury or to suppress renal tubular cell TGF-beta in D. VC suppressed urinary albumin excretion, fractional albumin clearance, and glomerular volume but not glomerular or tubular TGF-beta or glomerular collagen alpha1 (IV) content. LA but not VE or VC significantly increased renal cortical glutathione content in D. These data indicate that LA is effective in the prevention of early diabetic glomerular injury and suggest that this agent may have advantages over high doses of either VE or VC.

Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia.

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Br J Nutr 2002 Feb;87(2):157-62

The purpose of the present study was to test whether hyperlipidaemia and insulin resistance in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats can be improved by dietary supplementation with purified eicosapentaenoic acid (EPA) or oleic acid (OA). Male OLETF rats were fed powdered chow (510 g fat/kg) alone (n 8) or chow supplemented with 10 g EPA- (n 8) or OA- (n 8) rich oil/kg per d from 5 weeks until 30 weeks of age. An oral glucose tolerance test and hyperinsulinaemic euglycaemic clamp was performed at 25 and 30 weeks of age. EPA supplementation resulted in significantly (P<0.05) reduced plasma lipids, hepatic triacylglycerols, and abdominal fat deposits, and more efficient in vivo glucose disposal compared with OA supplementation and no supplementation. OA supplementation was associated with significantly increased insulin response to oral glucose compared with EPA supplementation and no supplementation. Inverse correlation was noted between glucose uptake and plasma triacylglycerol levels (r -086, P<0.001) and abdominal fat volume (r -0.80, P<0.001). The result of oral glucose tolerance test study showed that the rats fed EPA tended to improve glucose intolerance, although this was not statistically significant. Levels of plasma insulin at 60 min after glucose was significantly increased in rats fed OA compared with the other two groups. The results indicate that long-term feeding of EPA might be effective in preventing insulin resistance in diabetes-prone rats, at least in part, due to improving hypertriacylglycerolaemia.

L-carnitine improves glucose disposal in type 2 diabetic patients.

Mingrone G, Greco AV, Capristo E, Benedetti G, Giancaterini A, De Gaetano A, Gasbarrini G. Istituto di Medicina Interna, Catholic University, Rome, Italy.

J Am Coll Nutr 1999 Feb;18(1):77-82

OBJECTIVE: Aim of the present study is to evaluate the effects of L-carnitine on insulin-mediated glucose uptake and oxidation in type II diabetic patients and compare the results with those in healthy controls. DESIGN: Fifteen type II diabetic patients and 20 healthy volunteers underwent a short-term (2 hours) euglycemic hyperinsulinemic clamp with simultaneous constant infusion of L-carnitine (0.28 micromole/kg bw/minute) or saline solution. Respiratory gas exchange was measured by an open-circuit ventilated hood system. Plasma glucose, insulin, non-esterified fatty acids (NEFA) and lactate levels were analyzed. Nitrogen urinary excretion was calculated to evaluate protein oxidation. RESULTS: Whole body glucose uptake was significantly (p<0.001) higher with L-carnitine than with saline solution in the two groups investigated (48.66+/-4.73 without carnitine and 52.75+/-5.19 micromoles/kg(ffm)/minute with carnitine in healthy controls, and 35.90+/-5.00 vs. 38.90+/-5.16 micromoles/kg(ffm)/minute in diabetic patients). Glucose oxidation significantly increased only in the diabetic group (17.61+/-3.33 vs. 16.45+/-2.95 micromoles/kg(ffm)/minute, p<0.001). On the contrary, glucose storage increased in both groups (controls: 26.36+/-3.25 vs. 22.79+/-3.46 micromoles/kg(ffm)/minute, p<0.001; diabetics: 21.28+/-3.18 vs. 19.66+/-3.04

micromoles/kg(ffm)/minute, p<0.001). In type II diabetic patients, plasma lactate significantly decreased during L-carnitine infusion compared to saline, going from the basal period to the end-clamp period (0.028+/-0.0191 without carnitine and 0.0759+/-0.0329 with carnitine, p<0.0003). CONCLUSIONS: L-carnitine constant infusion improves insulin sensitivity in insulin resistant diabetic patients; a significant effect on whole body insulin-mediated glucose uptake is also observed in normal subjects. In diabetics, glucose, taken up by the tissues, appears to be promptly utilized as fuel since glucose oxidation is increased during L-carnitine administration. The significantly reduced plasma levels of lactate suggest that this effect might be exerted through the activation of pyruvate dehydrogenase, whose activity is depressed in the insulin resistant status.

Polyol pathway hyperactivity is closely related to carnitine deficiency in the pathogenesis of diabetic neuropathy of streptozotocin-diabetic rats.

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J Pharmacol Exp Ther 1998 Dec;287(3):897-902

To investigate the relationship between polyol pathway hyperactivity and altered carnitine metabolism in the pathogenesis of diabetic neuropathy, the effects of an aldose reductase inhibitor, [5-(3-thienyl) tetrazol-1-yl]acetic acid (TAT), and a carnitine analog, acetyl-L-carnitine (ALC), on neural functions and biochemistry and hemodynamic factors were compared in streptozotocin-diabetic rats. Significantly delayed motor nerve conduction velocity, decreased R-R interval variation, reduced sciatic nerve blood flow and decreased erythrocyte 2, 3-diphosphoglycerate concentrations in diabetic rats were all ameliorated by treatment with TAT (administered with rat chow containing 0.05% TAT, approximately 50 mg/kg/day) or ALC (by gavage, 300 mg/kg/day) for 4 weeks. Platelet hyperaggregation activity in diabetic rats was diminished by TAT but not by ALC. TAT decreased sorbitol accumulation and prevented not only myo-inositol depletion but also free-carnitine deficiency in diabetic nerves. On the other hand, ALC also increased the myo-inositol as well as the free-carnitine content without affecting the sorbitol content. These observations suggest that there is a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy and that an aldose reductase inhibitor, TAT, and a carnitine analog, ALC, have therapeutic potential for the treatment of diabetic neuropathy.

Metabolism and actions of dehydroepiandrosterone in humans.

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J Steroid Biochem Mol Biol 1991;40(4-6):599-605

Dehydroepiandrosterone (3 beta-hydroxy-5-androsten-17-one; DHA) and DHA-sulfate are abundantly produced adrenal steroids, whose serum concentrations exceed those of other adrenal steroids. Serum concentrations of DHA and DHA-sulfate, in contrast to other adrenal steroids, exhibit a progressive age-related decline. The mechanism(s) for this selective decline in serum DHA and DHA-sulfate levels and the biologic function of these steroids remain unknown. Studies examining insulin's regulation of adrenal androgens are reviewed. These studies show that experimentally-induced hyperinsulinemia lowers serum DHA and DHA-sulfate levels, and suggest that insulin reduces serum concentrations of these steroids by inhibiting production rather than by increasing clearance. Studies examining the actions of short-term pharmacologic DHA administration to young nonobese and obese men are also reviewed. These studies suggest that DHA may possess hypolipidemic and, possibly, anti-obesity properties. They have failed, however, to demonstrate any effect of DHA on tissue insulin sensitivity.

Dietary magnesium supplements improve B-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects.

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Acta Endocrinol (Copenh) 1989 Jul;121(1):16-20

Hypomagnesemia and low erythrocyte magnesium content are both common findings in non-insulin-dependent diabetic subjects. Moreover, intracellular magnesium may play a crucial role in modulating B-cell response to glucose by interfering with potassium permeability. Eight elderly, moderately obese, non-insulin-dependent diabetic subjects were treated with either magnesium supplementation (3 g/day) to the diet or placebo. Both treatment schemes lasted 4-weeks and were separated by a 'wash-out' of 3 weeks. At the end of each treatment period, in glucose test (0.33 g/kg for 3 min) and an iv arginine (5 g) test were performed to determine the B-and A-cell responses. Dietary magnesium supplementation vs placebo produced a slight but significant decrease in basal plasma glucose (8.6 +/- 0.3 vs 8.0 +/- 0.1 mmol/l, p less than 0.05) and an increase in acute insulin response after iv glucose (3.7 +/- 2.3 vs - 14.7 +/- 0.9 pmol.l 1. (10 min)-1, p less than 0.01) and after iv arginine (151 +/- vs 81 +/- 15 pmol.l-1. (10 min)-1, p less than 0.01), respectively. Plasma glucagon levels were unaffected by chronic dietary magnesium supplementation as well under basal conditions as in response to arginine. Net increase in acute insulin response after iv glucose and after iv arginine was significantly correlated to the net increase in erythrocyte magnesium content after dietary magnesium supplementation. We conclude that magnesium administration may be a useful adjuvant to the classic hypoglycemic agents in the treatment of non-insulin-dependent diabetic subjects.

Daily magnesium supplements improve glucose handling in elderly subjects.

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Am J Clin Nutr 1992 Jun;55(6):1161-7

We demonstrated similar plasma concentrations and urinary losses but lower erythrocyte magnesium concentrations (2.18 +/- 0.04 vs 1.86 +/- 0.03 mmol/L, P less than 0.01) in twelve aged (77.8 +/- 2.1 y) vs 25 young (36.1 +/- 0.4 y), nonobese subjects. Subsequently, aged subjects were enrolled in a double-blind, randomized, crossover study in which placebo (for 4 wk) and chronic magnesium administration (CMA) (4.5 g/d for 4 wk) were provided. At the end of each treatment period an intravenous glucose tolerance test (0.33 g/kg body wt) and a euglycemic glucose clamp with simultaneous [D-3H]glucose infusion and indirect calorimetry were performed. CMA vs placebo significantly increased erythrocyte magnesium concentration and improved insulin response and action. Net increase in erythrocyte magnesium significantly and positively correlated with the decrease in erythrocyte membrane microviscosity and with the net increase in both insulin secretion and action. In aged patients, correction of a low erythrocyte magnesium concentration may allow an improvement of glucose handling.

Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients.

Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'Onofrio F. Department of Geriatric Medicine and Metabolic Diseases, First Medical School, University of Naples, Italy.

Am J Clin Nutr 1993 May;57(5):650-6

Ten control (healthy) subjects and 15 non-insulin-dependent diabetics underwent an oral glucose-tolerance test and a euglycemic hyperinsulinemic glucose clamp before and after vitamin E supplementation (900 mg/d for 4 mo). In control subjects (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E reduced the area under the curve for glucose (344 +/- 21 vs 287 +/- 13 mmol.L-1 x min-1; P < 0.05) and increased total body glucose disposal (39.0 +/- 0.3 vs 47.6 +/- 0.4 mumol.kg lean body mass-1 x min-1; P < 0.05) and non-oxidative glucose metabolism (23.4 +/- 0.2 vs 30.8 +/- 0.3 mumol.kg lean body mass-1 x min-1; P < 0.05). In diabetics (placebo-treated vs vitamin E-supplemented subjects, respectively) vitamin E supplementation reduced glucose area under the curve (614 +/- 129 vs 544 +/- 98 mmol.L-1 x min-1; P < 0.03) and increased glucose disappearance (19.4 +/- 0.4 vs 26.4 +/- 0.7 mumol.kg lean body mass-1.min-1; P < 0.03), total glucose disposal (19.0 +/- 0.7 vs 28.1 +/- 0.4 mumol.kg lean body mass-1 x min-1; P < 0.02), and nonoxidative glucose metabolism (8.5 +/- 0.3 vs 13.9 +/- 0.3 mumol.kg lean body mass-1 x min-1; P < 0.02). Therefore we conclude that administration of pharmacologic doses of vitamin E is a useful tool to reduce oxidative stress and improve insulin action.

In experimental diabetes the decrease in the eye of lens carnitine levels is an early important and selective event.

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Exp Eye Res 1997 Feb;64(2):195-201

Carnitine is present in the eye tissues of the rabbit and the highest concentration is found in the lens. In streptozotocin-diabetic rats, the carnitine loss of the lens is an initial and important event. At 8 days after the induction of diabetes, the carnitine content in the rat lens was reduced by 63% compared to control. The loss of lens carnitine continued at 15 and 45 days after the induction. Total carnitine level in the serum was diminished by 15 days, and the reduction in percentage term was much lower in comparison to the loss of lens carnitine. In the rabbit after alloxan-diabetes induction, there is an extensive loss of carnitine in the lens: -85% after 4 months. The carnitine levels in the other eye tissues seem substantially unaffected. The loss of lens carnitine was present even with an inconsistent hyperglycaemia. No difference was found in serum carnitine levels between controls and alloxan-treated rabbits. The role of carnitine in lens is still unclear, but its loss may be related to the appearance of cataract. A derivative of carnitine, acetylcarnitine, might prevent the processes involved in the formation of cataracts by a pharmacological action, as has been shown for aspirin.

Effects of coenzyme Q10 treatment on antioxidant pathways in normal and streptozotocin-induced diabetic rats.

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J Biochem Mol Toxicol 2001;15(1):41-6

Coenzyme Q10 is an endogenous lipid soluble antioxidant. Because oxidant stress may exacerbate some complications of diabetes mellitus, this study investigated the effects of subacute treatment with exogenous coenzyme Q10 (10 mg/kg/day, i.p. for 14 days) on tissue antioxidant defenses in 30-day streptozotocin-induced diabetic Sprague-Dawley rats. Liver, kidney, brain, and heart were assayed for degree of lipid peroxidation, reduced and oxidized glutathione contents, and activities of catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. All tissues from diabetic animals exhibited increased oxidative stress and disturbances in antioxidant defense when compared with normal controls. Treatment with the lipophilic compound coenzyme Q10 reversed diabetic effects on hepatic glutathione peroxidase activity, on renal superoxide dismutase activity, on cardiac lipid peroxidation, and on oxidized glutathione concentration in brain. However, treatment with coenzyme Q10 also exacerbated the increase in cardiac catalase activity, which was already elevated by diabetes, further decreased hepatic glutathione reductase activity, augmented the increase in hepatic lipid peroxidation, and further increased glutathione peroxidase activity in the heart and brain of diabetic animals. Subacute dosing with coenzyme Q10

ameliorated some of the diabetes-induced changes in oxidative stress. However, exacerbation of several diabetes-related effects was also observed.

The influence of zinc supplementation on glucose homeostasis in NIDDM.

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Diabetes Res 1989 Jun;11(2):73-9

Decreased serum zinc levels and hyperzincuria occur in some non-insulin dependent diabetic subjects (NIDDM). Zinc deficiency was demonstrated in various tissues of animal models for NIDDM. Serum zinc and 24-hr urine zinc of subjects with NIDDM were compared with that of age- and sex-matched healthy volunteers. Zincuria was significantly increased in the diabetic group. Thirteen diabetic subjects with hyperzincuria and hypozincemia were supplemented with zinc sulfate 220 mg x 3/day for 7-8 weeks. At the end of the study, glucose disposal (evaluated by kg) decreased significantly from 0.562 +/- 0.03 to 0.414 +/- 0.05 (p less than 0.05) and fasting glucose and fructosamine were significantly increased from 177 +/- 10 mg/dl to 207 +/- 15 mg/dl (p less than 0.05) and from 2.7 +/- 0.2% to 3.2 +/- 0.28% (p less than 0.05), respectively. T-lymphocyte response to phytohemagglutinin was increased significantly. We conclude that zinc supplementation to NIDD patients with hypozincemia and hyperzincemia might aggravate their glucose intolerance. More accurate methods to assess zinc deficiency in NIDD patients is needed to justify the supplementation of zinc in these patients.

Relationship between acute insulin response and vitamin K intake in healthy young male volunteers.

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Diabetes Nutr Metab 1999 Feb;12(1):37-41

To evaluate the effects of vitamin K (VK) on pancreatic function, especially on acute insulin response, 25 healthy young male volunteers were given an oral load of 75 g of glucose, and their mean daily VK intake was estimated by a one-week food check list. After excluding low (<20) and high (> or =25) body mass index (BMI) subjects, the remaining 16 participants were divided into three semi-equal groups according to VK intake. Blood VK status of the low VK intake group tended to be poorer than that of the high intake group (median of 5 samples: prothrombin time; 12.5 vs 12.2s and protein-induced VK absence-factor-II; 23 vs 15 mAU/ml), but fasting plasma glucose status was not markedly different between both groups: [plasma glucose (PG); 87 vs 86 mg/dl, immunoreactive insulin (IRI); 6.7 vs 5.3 microU/ml, HbA1c; 4.8 vs 4.9%]. However, at 30 min after glucose loading, PG of the low VK intake group tended to be higher than those of the high intake group (160 vs 145 mg/dl) and IRI was lower (36.1 vs 52.3 microU/ml). Insulinogenic index (incremental

IRI/incremental PG, 0-30 min) of the low VK intake group was significantly lower than that of the high intake group (0.4 vs 0.9). These results suggested that VK may play an important role on the acute insulin response in glucose tolerance.

Vitamin C and hyperglycemia in the European Prospective Investigation into Cancer--Norfolk (EPIC-Norfolk) study: a population-based study.

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Diabetes Care 2000 Jun;23(6):726-32

OBJECTIVE: To examine the cross-sectional association between plasma vitamin C, self-reported diabetes, and HbA1c. RESEARCH DESIGN AND METHODS: Data from a population-based study of diet, cancer, and chronic disease were analyzed. A total of 2,898 men and 3,560 women 45-74 years of age who were registered with general practices in Norfolk, U.K., were recruited to the European Prospective Investigation Into Cancer-Norfolk study between 1995 and 1998. RESULTS: Mean plasma vitamin C levels were significantly higher in individuals with HbA1c levels < 7% than in those with self-reported diabetes or prevalent undiagnosed hyperglycemia (HbA1c > or = 7%). An inverse gradient of mean plasma vitamin C was found in both sexes across quintiles of HbA1c distribution < 7%. The odds ratio (95% CI) of having prevalent undiagnosed hyperglycemia per 20 micromol/l (or 1 SD) increase in plasma vitamin C was 0.70 (0.52-0.95) (adjusted for sex, age, BMI, waist-to-hip ratio, tertiary education, any use of dietary supplements, vegetarian diet, alcohol consumption, physical activity, dietary vitamin E, dietary fiber, dietary saturated fat, and smoking history). The unadjusted change in HbA1c per 20 micromol/l increase in vitamin C estimated by linear regression was -0.12% (-0.14 to -0.09) in men and -0.09% (-0.11 to -0.07) in women. After adjusting for the possible confounders, these values were -0.08% (-0.11 to -0.04) in men and -0.05% (-0.07 to -0.03) in women. CONCLUSIONS: An inverse association was found between plasma vitamin C and HbA1c. Dietary measures to increase plasma vitamin C may be an important public health strategy for reducing the prevalence of diabetes.

Postprandial hyperinsulinaemia, insulin resistance and inappropriately high phosphaturia are features of younger males with idiopathic calcium urolithiasis: attenuation by ascorbic acid supplementation of a test meal.

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Urol Res 1997;25(1):49-58

In idiopathic recurrent calcium urolithiasis (RCU) the state of insulin and carbohydrate metabolism, and relationships to minerals such as phosphate, are insufficiently understood. Therefore, in two groups of males with RCU (n = 30) and healthy controls (n = 8) the response to an oral carbohydrate- and calcium-

rich test meal was studied with respect to glucose, insulin, and C-peptide in peripheral venous blood (taken before and up to 180 min post-load), and phosphate and glucose in fasting and post-load urine. In one RCU group (n = 16) the meal was supplemented with ascorbic acid (ASC; 5 mg/kg body weight). The mean age (RCU 29, RCU + ASC 30, controls 27 years) and mean body mass index [RCU 24.4, RCU + ASC 25.0, controls 24.0 kg/m2] were similar. Insulin resistance (synonymous sensitivity of peripheral organs to insulin) was calculated from insulin serum concentration, as was also integrated insulin, C-peptide, and glucose. Untreated stone patients (RCU) developed hyperinsulinaemia between 60 and 120 min post-load, increased integrated insulin, and insulin resistance (P < or = 0.05 vs controls), whereas the rise of C-peptide and glycaemia (absolute and integrated values) was only of borderline significance. Fasting phosphaturia was low in both RCU subgroups vs controls; however, phosphaturia in untreated RCU rose in response to the meal, contrasting sharply with a decrease in controls. ASC supplementation of the meal (in the RCU + ASC subgroup) normalized insulin, failed to normalize post-load phosphaturia, but reduced post-load glucosuria and urinary pH significantly (mean pH values 5.55 vs 5.93 in untreated RCU, controls 5.50). Postprandial urinary oxalate, calcium, protein, and supersaturation products were not changed. The postprandial changes in phosphaturia and insulin sensitivity were inversely correlated (n = 38, r = -0.44, P = 0.007). It was concluded that in younger RCU males: (1) postprandial hyperinsulinaemia, the failure to reduce phosphaturia and - within limits - glucosuria, appropriately, as well as poor urine acidification are important features of the metabolism; (2) these phenomena are probably caused by insulin resistance of organs, the kidney included; and (3) the addition of a supraphysiological dose of ASC to a meal, the subsequent abolition of hyperinsulinaemia, and the restoration of normal urine acidification suggest that this antioxidant is capable of counteracting some pre-existing basic abnormality of cell metabolism in RCU.

Low plasma ascorbate levels in patients with type 2 diabetes mellitus consuming adequate dietary vitamin C.

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Diabet Med 1994 Nov;11(9):893-8

Low ascorbate concentrations in diabetes may be secondary to inadequate dietary vitamin C intake or may relate to the varied metabolic roles of the vitamin. To determine whether inadequate dietary intake is a factor we calculated daily vitamin C intakes using both a vitamin C questionnaire and a 4-day food diary in a group of 30 patients with Type 2 diabetes (mean age 68.8 +/- 6.9 yr, 17M/13F) and in 30 community controls (mean age 68.0 +/- 5.5 yr, 12M/18F)). Measures of plasma glucose, serum fructosamine, and plasma ascorbic and dehydroascorbic acid were obtained from 20 subjects in each group. There was no significant difference in daily vitamin C intake between the two groups using both methods: food diary, 61.4 +/- 28.3 (patients) vs 69.5 +/- 33.4 (controls) mg; questionnaire, 54.0 +/- 28.9 (patients) vs 65.0 +/- 30.9 (controls) mg. Vitamin C intake derived

from both methods was significantly correlated (p < 0.001). Plasma ascorbate (30.4 +/- 19.1 mumol l-1) and dehydroascorbate (27.6 +/- 6.4 mumol l-1) levels were significantly lower in patients vs in controls (68.8 +/- 36.0 and 31.8 +/- 4.8 mumol l-1, respectively), p < 0.0001 and p < 0.01. Plasma ascorbate levels were significantly correlated with vitamin C intake derived from the food diary (p < 0.01) and questionnaire (p < 0.01) methods in the diabetic group only. Low ascorbate levels in diabetes appears to be a consequence of the disease itself and not due to inadequate dietary intake of vitamin C. A short vitamin C questionnaire is a convenient and reliable estimate of vitamin C intake.(ABSTRACT TRUNCATED AT 250 WORDS)

Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate.

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Am J Clin Nutr 2000 Jul;72(1):96-105

BACKGROUND: Protein induces an increase in insulin concentrations when ingested in combination with carbohydrate. Increases in plasma insulin concentrations have been observed after the infusion of free amino acids. However, the insulinotropic properties of different amino acids or protein (hydrolysates) when co-ingested with carbohydrate have not been investigated.

OBJECTIVE: The aim of this study was to define an amino acid and protein (hydrolysate) mixture with a maximal insulinotropic effect when co-ingested with carbohydrate.

DESIGN: Eight healthy, nonobese male subjects visited our laboratory, after an overnight fast, on 10 occasions on which different beverage compositions were tested for 2 h. During those trials the subjects ingested 0.8 g*kg(-)(1)*h(-)(1) carbohydrate and 0.4 g*kg(-)(1)*h(-)(1) of an amino acid and protein (hydrolysate) mixture.

RESULTS: A strong initial increase in plasma glucose and insulin concentrations was observed in all trials, after which large differences in insulin response between drinks became apparent. After we expressed the insulin response as area under the curve during the second hour, ingestion of the drinks containing free leucine, phenylalanine, and arginine and the drinks with free leucine, phenylalanine, and wheat protein hydrolysate were followed by the largest insulin response (101% and 103% greater, respectively, than with the carbohydrate-only drink; P < 0.05).

CONCLUSIONS: Insulin responses are positively correlated with plasma leucine, phenylalanine, and tyrosine concentrations. A mixture of wheat protein

hydrolysate, free leucine, phenylalanine, and carbohydrate can be applied as a nutritional supplement to strongly elevate insulin concentrations.

Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients.

Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M. Anti-Diabetes Centre, Monfalcone Hospital, Gorizia, Italy.

J Hepatol 1997 Apr;26(4):871-9

BACKGROUND/AIMS: Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals. The aim of this study was to ascertain whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis.

METHODS: A 12-month open, controlled study was conducted in two well-matched groups of insulin-treated diabetics with alcoholic cirrhosis. One group (n=30) received 600 mg silymarin per day plus standard therapy, while the control group (n=30) received standard therapy alone. The efficacy parameters, measured regularly during the study, included fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria levels, glycosylated hemoglobin (HbA1c) and malondialdehyde levels.

RESULTS: There was a significant decrease (p<0.01) in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels already after 4 months of treatment in the silymarin group. In addition, there was a significant decrease (p<0.01) in fasting insulin levels and mean exogenous insulin requirements in the treated group, while the untreated group showed a significant increase (p<0.05) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease (p<0.01) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. Another interesting finding was the significant decrease (p<0.01) in malondialdehyde/levels observed in the treated group.

CONCLUSIONS: These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

Inhibition of aldose reductase in human erythrocytes by vitamin C.

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Diabetes Res Clin Pract 1999 Jan;43(1):1-8

Ascorbic acid, or vitamin C, has been reported to lower erythrocyte sorbitol concentrations, and present studies were performed to determine the mechanism of this effect. Incubation of erythrocytes with increasing concentrations of glucose (5-40 mM) progressively increased erythrocyte sorbitol contents, reflecting increased flux through aldose reductase. At extracellular concentrations of 90 microM, both ascorbic acid and its oxidized form, dehydroascorbate, decreased intracellular sorbitol by 25 and 45%, respectively. This inhibition was not dependent on the extracellular glucose concentration, or on erythrocyte contents of free NADPH or GSH. To test for a direct effect of ascorbate on aldose reductase, erythrocyte hemolysates were prepared and supplemented with 100 microM NADPH. Hemolysates reduced glucose to sorbitol in a dose-dependent manner that was inhibited with a Ki of 120 microM by the aldose reductase inhibitor tetramethylene glutaric acid. Above 100 microM, ascorbic acid also lowered hemolysate sorbitol generation by about 30%. Studies with ascorbic acid derivatives showed that the reducing capacity of ascorbic acid was not required for inhibition of sorbitol production from glucose in erythrocyte hemolysates. These results show that high, but physiologic, concentrations of ascorbic acid can directly inhibit erythrocyte aldose reductase, and provide a rationale for the use of oral vitamin C supplements in diabetes.

Reduced serum dehydroepiandrosterone levels in diabetic patients with hyperinsulinaemia.

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Clin Endocrinol (Oxf) 1998 Sep;49(3):377-83

OBJECTIVE: To elucidate the interaction between insulin and dehydroepi-androsterone (DHEA) concentrations, we evaluated serum DHEA and DHEA-sulphate (DHEA-S) levels in diabetic patients with hyperinsulinaemia.

PATIENTS AND DESIGN: Twenty-four subjects with non-insulin dependent diabetes mellitus, 12 hyperinsulinaemic subjects (fasting serum insulin concentrations > or = 10 mU/ml (71.8 pmol/l)) and 12 non-hyperinsulinaemic subjects, and 10 normal control subjects were studied. Serum DHEA, DHEA-S, cortisol and ACTH levels were investigated in these subjects. Moreover, their serum DHEA levels were compared during hyperinsulinaemic-euglycaemic clamp and after ACTH stimulation.

MEASUREMENTS: Serum insulin, cortisol, ACTH, DHEA and DHEA-S concentrations were evaluated by RIA. Serum glucose was determined by the glucose oxidase method.

RESULTS: Diabetic patients with hyperinsulinaemia showed significantly lower levels of serum DHEA and DHEA-S than controls. After ACTH stimulation,

these patients also showed significantly lower DHEA levels. During the hyperinsulinaemic-euglycaemic clamp, serum DHEA concentrations of diabetic patients with hyperinsulinaemia remained low and did not decline further, although those of control subjects and non-hyperinsulinaemic diabetic patients showed a significant decline of serum DHEA levels. Even after ACTH stimulation during the clamp, serum DHEA in hyperinsulinaemic patients was still significantly lower than in controls.

CONCLUSIONS: In diabetic patients with hyperinsulinaemia, baseline DHEA levels are chronically and maximally suppressed compared to control subjects and non-hyperinsulinaemic diabetic patients, and thus not decreased further by exogenous insulin infusion during hyperinsulinaemic-euglycaemic clamp.

Biotin administration improves the impaired glucose tolerance of streptozotocin-induced diabetic Wistar rats.

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J Nutr Sci Vitaminol (Tokyo) 1997 Jun;43(3):271-80

The effect of biotin administration on the glucose tolerance of streptozotocin (STZ)-induced diabetic Wistar rats was investigated. STZ-induced diabetes was induced by intraperitoneal injection of streptozotocin (45 mg/kg body weight as a single dose). The impaired glucose tolerance in response to an oral glucose load (1.8g per kg body weight) in STZ-induced diabetic rats (STZ-rat) was partially improved by intraperitoneal administration of biotin for 15 days (100 micrograms/rat/day). However, a recovery in the STZ-rat's insulin secretion was not found after biotin administration. To help clarify the mechanism underlying the improvement in glucose tolerance seen with biotin treatment, glucokinase and hexokinase activities were determined in the liver and pancreas. In STZ-rats that had received biotin (STZ-biotin rats), glucokinase activity was higher by 3.4-fold in liver and by 2.4-fold in pancreas than in the STZ-rats. The biotin level of STZ-rats was significantly lower in the liver and pancreas than that of the control rats (no STZ administration); but in STZ-biotin rats, the level in these organs recovered to the control level. These results demonstrate that injected biotin can improve glucose handling without increasing insulin secretion in STZ-rats.

Improvement of oral glucose tolerance in gestational diabetes by pyridoxine.

Bennink HJ, Schreurs WH
Br Med J 1975 Jul 5;3(5974):13-5

Fourteen pregnant women were shown by the oral glucose tolerance test to have gestational diabetes. In 13 an increased urinary xanthurenic-acid excretion after an oral load of L-tryptophan indicated a relative pyridoxine deficiency. All patients were treated with vitamin B6 (pyridoxine) 100 mg/day for 14 days by mouth, after which the pyridoxine deficiency disappeared and the oral glucose tolerance improved considerably. Only two patients then had sufficiently impaired

glucose tolerance to justify the diagnosis of gestational diabetes; Our results substantiated our hypothesis that increased xanthurenic-acid synthesis during pregnancy may cause gestational diabetes. Treatment with vitamin B6 makes the production of xanthurenic-acid normal by restoring tryptophan metabolism and improves the oral glucose tolerance in patients with gestational diabetes.

Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: the Rancho Bernardo Study.

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J Clin Endocrinol Metab 1996 Jan;81(1):59-64

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) levels were determined in morning specimens from 659 fasting postmenopausal women who were not using estrogen therapy or antidiabetic medication. All women had concurrent oral glucose tolerance tests and measurements of body mass index (BMI) and waist-hip ratio (WHR). DHEA levels were weakly and inversely associated with BMI but not with WHR or glucose tolerance status. DHEAS levels were not associated with BMI but were positively associated with WHR, diabetes, and impaired glucose tolerance. In analyses adjusted for or stratified by WHR, the DHEAS association with abnormal carbohydrate tolerance was reduced but still independent of fat distribution. Because this was a cross-sectional study, it was not possible to determine whether DHEAS levels were raised by central obesity or vice versa. At a minimum, these data strongly suggest that the positive association of DHEAS with both central obesity and abnormal glucose tolerance does not support the thesis that DHEAS protect against diabetes or obesity in older women as had been suggested by animal studies.

Differential expression of hepatic oestrogen, phenol and dehydroepiandrosterone sulphotransferases in genetically obese diabetic (ob/ob) male and female mice.

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J Endocrinol 1995 Jan;144(1):31-7

Sulphotransferases (STs) are a family of closely related enzymes playing a key role in regulation of the bioavailability and activity of important endogenous molecules such as steroid hormones. A relationship between the expression of steroid STs and the diabetic state has been demonstrated in various laboratory animal models, and steroid sulphates such as dehydroepiandrosterone sulphate are

known to have anti-diabetic properties. In order to further our understanding of the molecular basis for the association of steroid hormone sulphation and diabetes, we have examined the expression of oestrogen, phenol and dehydroepiandrosterone (DHEA) STs in mice carrying the obesity mutation (ob), which in the homozygous state (ob/ob) produces mice which are obese and diabetic. Our data show that, in male mice, ST activities towards oestrone (E1), oestriol (E3), DHEA and the xenobiotic 1-naphthol are elevated in ob/ob mice, whereas in female mice, only the oestrogen ST activities were elevated, with the DHEA and 1-naphthol ST activities reduced. Using antibodies directed against oestrogen ST, it was demonstrated that the induction of E1 and E3 ST activity in ob/ob mice correlated with the expression of an ST isoenzyme not constitutively expressed in control mouse liver.

Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men.

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Department of Medicine, University of Texas Health Science Center, San Antonio, TX 78284
Metabolism 1994 May;43(5):599-603

Although many studies indicate that increased androgenicity is associated with insulin resistance and hyperinsulinemia in both premenopausal and postmenopausal women, relatively few data are available on this relationship in men. We examined the association of sex hormone-binding globulin (SHBG), total and free testosterone, dehydroepiandrosterone sulfate (DHEA-SO4), and estradiol to glucose and insulin concentrations before and during an oral glucose tolerance test in 178 men from the San Antonio Heart Study, a population-based study of diabetes and cardiovascular disease. Total and free testosterone and DHEA-SO4 were significantly inversely associated with insulin concentrations. Free testosterone and DHEA-SO4 were also significantly inversely correlated with glucose concentrations. SHBG was weakly positively associated with glucose concentrations. Estradiol was not related to glucose or insulin concentrations. After adjustment for age, obesity, and body fat distribution, insulin concentrations remained significantly inversely correlated with free testosterone ($r = -.23$), total testosterone ($r = -.21$), and DHEA-SO4 ($r = -.21$; all $P < .01$). In conclusion, we observed that increased testosterone and DHEA-SO4 are associated with lower insulin concentrations in men. This is in striking contrast to women, where increased androgenicity is associated with insulin resistance and hyperinsulinemia.

[Dehydroepiandrosterone. Renaissance after 13 years]

Sonka J
Cas Lek Cesk 1989 Sep 8;128(37):1157-60

DHEA, a steroid precursor of androgens and estrogens has also an inhibitory effect on several enzymes, namely on 11 beta-hydroxylase, NADH oxidase and glucose 6-phosphate dehydrogenase. The latter is the rate limiting enzyme of the pentose phosphate cycle. This metabolic pathway provides the cells with extramitochondrial NADPH and pentose phosphates. NADPH is used for the synthesis of fatty acids and steroids. Together with ribose 5-phosphate, NADPH (as coenzyme of folate reductases) is required for the synthesis of nucleic acids. A deficient production of DHEA has been found to be responsible for several diseases obesity, diabetes type 2, hypertension, arteriosclerosis and hyperuricemia as well as malignant growth (low DHEA syndrome). DHEA administration favourably modified several of these metabolic disorders. These studies were started in our laboratory in 1962 and stopped in 1976 because we were short of DHEA. At that time the response to our results was rather theoretical, but the last years a new wave of interest in DHEA called for two consecutive symposia, where important findings were presented (Paris in January and Jena in April 1989). It is a damage that this new trend, started in our laboratory, could not be pursued up to now without interruption.

[Effect of androgen on the onset of diabetes in the KK mice treated with monosodium aspartate]

Higuchi N, Sasaki M, Arai T, Oki Y
Department of Veterinary Biochemistry, Nippon Veterinary and Zootechnical College, Tokyo, Japan.
Jikken Dobutsu 1989 Jan;38(1):25-9

Obese diabetes was induced by monosodium aspartate (MSA) administration in KK male mice and the diabetic KK mice were divided into two groups, younger (12-week-old) and older (35-week-old). The diabetic KK mice were castrated and administered with androgen and effect of androgen on glycosuria appearance was investigated. Androgen dependent tear proteins (Mtp-M) were detected by the method of polyacrylamide gel electrophoresis. Blood androgen level was estimated by observation of change of the pattern of Mtp-M. In the younger mice group, glycosuria disappeared temporarily after castration and then appeared naturally again. The Mtp-M declined with castration, but did not disappear in this experimental period. In the older mice group, glycosuria and Mtp-M disappeared completely and blood glucose level decreased considerably after castration. However, in the castrated older mice, the glycosuria and the Mtp-M appeared again after the administration of dehydroepiandrosterone (DHEA), and the increasing of blood glucose level was observed. These results strongly suggested that androgen had an important role in the onset of diabetes in the KK mice treated with MSA.

Therapeutic effects of dehydroepiandrosterone (DHEA) and its metabolites in obese-hyperglycemic mutant mice.

Coleman DL
Jackson Laboratory, Bar Harbor, ME 04609.
Prog Clin Biol Res 1988;265:161-75

Dehydroepiandrosterone (DHEA) fed at 0.4%, and its metabolites, 3 alpha-hydroxyetiocholanolone (alpha-ET) and 3 beta-hydroxyetiocholanolone (beta-ET), fed at 0.1%, had marked anti-hyperglycemic and anti-obesity properties in mutant mice with single gene obesity mutations (diabetes, db; obese, ob; viable yellow, Avy). The therapeutic effects differed depending on the mutation as well as the inbred background on which the mutation was maintained. These steroids prevented onset of hyperglycemia and reduced the rate of weight gain in C57BL/6J-db/db and ob/ob mice, whereas in C57BL/KsJ-db/db mice, only hyperglycemia was prevented. The viable yellow (Avy) mutant, exhibiting a more slowly developing obesity condition, responded to all steroids with a marked decrease in rate of weight gain associated with decreased plasma insulin concentrations. Steroid treatment of most mouse mutants was associated with normal or increased food intake, a feature that suggests a decrease in metabolic efficiency. In order to assess any potential energy wastage by steroid stimulation of futile cycles we looked at the rates of lipogenesis, gluconeogenesis and oxygen consumption in steroid-treated normal and mutant mice. With the possible exception of the rate of gluconeogenesis that in obesity mutants was consistently reduced to normal by treatment, no metabolic changes were of sufficient magnitude to account for the marked decrease in metabolic efficiency. All treatments potentiated the action of insulin. This potentiation may change the hormonal balance such that minor changes in the rates of many metabolic pathways may interact to produce a large decrease in metabolic efficiency.

Modulation of growth, differentiation and carcinogenesis by dehydroepiandrosterone.

Gordon GB, Shantz LM, Talalay P
Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
Adv Enzyme Regul 1987;26:355-82

Dehydroepiandrosterone (3 beta-hydroxy-5-androsten-17-one; DHEA) and its conjugates are abundant circulating steroids that originate largely from the adrenal cortex. Their levels decline profoundly with age in human beings of both sexes, as the incidence of most cancers rises. Low levels of these steroids have been associated with the presence and risk ofdevelopment of cancer. Administration of DHEA to rodents produces protection against spontaneous tumors and chemical carcinogenesis, suppresses weight gain without significantly affecting food intake,

ameliorates the severity of diabetes in genetically diabetic mice, and restrains autoimmune processes. DHEA and related steroids also depress the mitogenic effects of carcinogens, tumor promoters and plant lectins, and block viral and carcinogen-induced cell transformations. DHEA and certain congeners are also potent and quite specific inhibitors of mammalianglucose-6-phosphate dehydrogenases. We have observed that the conversion of 3T3-L1 and 3T3-F442A preadipocyte clones to the adipocyte phenotype, in response to appropriate differentiation stimuli (fetal calf serum, insulin, dexamethasone, and 1-methyl-3-isobutylxanthine), is blocked by DHEA and other steroidal inhibitors of glucose-6-phosphate dehydrogenase. The structural requirements for blocking adipocyte differentiation and for inhibiting glucose-6-phosphate dehydrogenase are closely correlated. Evidence is reviewed suggesting that the inhibition of glucose-6-phosphatedehydrogenase is central to the anticarcinogenic and differentiation-blocking actions of DHEA and related steroids. The 3T3 preadipocyte clones provide a valuable system for the analysis of the mechanisms of the effects of DHEA on growth, differentiation and carcinogenesis. (94 Refs.)

Androgenic and estrogenic metabolites in serum of mice fed dehydroepiandrosterone: relationship to antihyperglycemic effects.

Leiter EH, Beamer WG, Coleman DL, Longcope C
Metabolism 1987 Sep;36(9):863-9

The steroid prehormone, dehydroepiandrosterone (DHEA) has potentanti hyperglycemic effects when fed in the diet of genetically diabetic C57BL/KsJ-db/db mice. The purpose of this investigation was to analyze changes in sex steroid levels in serum of mice fed DHEA, and to compare the antihyperglycemic potencies of the various metabolites in order to clarify the mechanism of DHEA action. Steroid radioimmunoassays showed that dietary DHEA entered the blood in high concentrations and was actively metabolized to both androgens (testosterone, T; dihydrotestosterone, DHT) and estrogens (estrone, E1; 17 beta-estradiol, E2). This metabolism did not require intact adrenal glands or gonads. In C57BL/KsJ normal (+/+) males, conversion of DHEA to androgens was the prominent feature; in db/db males, DHEA feeding not only increased serum T and DHT, but also serum E1 and E2 levels. The db/db mice had increased amounts of adipose tissue that sequestered more intravenously injected 3H-E2; this additional body fat could account for increased aromatization of DHEA-derived estrogen precursors. Comparisons of the relative antihyperglycemic potencies of androgenic and estrogenic steroid metabolites of DHEA in db/db mice showed that the estrogens and metabolites with estrogenic properties (androstenediol) or those convertible to estrogens (DHEA sulfate) were the most potent. Although 17 beta-E2 was effective by injection or per os, DHEA was effective only when administered per os, implicating alimentary tract conversion of DHEA to more biologically active reactants. Based on the pivotal position of DHEA as a prehormone for androgens, estrogens, andetiocholanolones, an explanation of the seemingly paradoxical effects exerted by this compound in blocking autoimmune disease, hyperglycemia, obesity, and neoplasia was proposed

Effect of genetic background on the therapeutic effects of dehydroepiandrosterone (DHEA) in diabetes-obesity mutants and in aged normal mice.

Coleman DL, Schwizer RW, Leiter EH
Diabetes 1984 Jan;33(1):26-32

Dehydroepiandrosterone (DHEA) was fed at 0.1-0.4% in the diet to genetically diabetic (db/db) or obese (ob/ob) C57BL/KsJ (BL/Ks) or C57BL/6J (BL/6) mice. Treatment of BL/Ks-db/db or ob/ob mice with 0.4% DHEA prevented hyperglycemia, islet atrophy, and severe diabetes associated with this inbred background, but did not affect weight gain and food consumption. Homozygous obese (ob) or diabetes (db) mice on the BL/6 background were more sensitive to DHEA, and the mild, transient hyperglycemia associated with ob or db gene expression on the BL/6 inbred background could be prevented by 0.1% DHEA. Both body weight and food consumption were decreased in BL/6 mutants maintained on 0.1% DHEA whereas this effect was not seen in BL/Ks mutants fed up to 0.4% DHEA. Early therapy with 0.4% DHEA, initiated at 2 wk of age, prevented the developmentof most diabetes symptoms and decreased the rate of weight gain in pups of all genotypes. In addition to therapeutic effects on both obese mutants, DHEA effected significant changes in an aging study using normal BL/6 female mice. Four weeks of DHEA treatment initiated at 2 yr of age improved glucose tolerance and at the same time reduced plasma insulin to a "younger" level. This suggests that DHEA may act in insulin-resistant mutant mice and in aging normal mice to increase the sensitivity to insulin.

Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice.

Coleman DL, Leiter EH, Schwizer RW
Diabetes 1982 Sep;31(9):830-3

Dehydroepiandrosterone (DHEA), a major adrenal secretory steroid in humans, was therapeutic when fed in a concentration of 0.4% to C57BL/KsJ mice with either non-insulin-dependent or insulin-dependent diabetes. Genetically diabetic (db/db) mice of both sexes develop obesity and aglucose intolerance and hyperglycemia associated with insulin resistance by 2 mo of age, and exhibit beta-cell necrosis and islet atrophy by 4 mo. In contrast, DHEA feeding initiated between 1 and 4 mo of age, while only moderately effective in preventing obesity, did prevent the other pathogenic changes and effected a rapid remission of hyperglycemia, a preservation of beta-cell structure and function, and an increased insulin sensitivity as measured by glucose tolerance tests. DHEA feeding was also therapeutic to normal C57BL/KsJ male mice made diabetic by multiple low doses of streptozotocin (SZ). While DHEA treatments did not block either the direct cytotoxic action of SZ on beta-cells or the development of insulitis, the steroid significantly moderated the severity of the ensuing diabetes

(reduced hyperglycemia and water consumption, and increased plasma insulin and numbers of residual, granulated beta-cells.

Interaction of alpha-lipoic acid enantiomers and homologues with the enzyme components of the mammalian pyruvate dehydrogenase complex.

Loffelhardt S, Bonaventura C, Locher M, Borbe HO, Bisswanger H
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Biochem Pharmacol 1995 Aug 25;50(5):637-46

Lipoic acid (alpha-lipoic acid, thioctic acid) is applied as a therapeutic agent in various diseases accompanied by polyneuropathia such as diabetes mellitus. The stereoselectivity and specificity of lipoic acid for the pyruvate dehydrogenase complex and its component enzymes from different sources has been studied. The dihydrolipoamide dehydrogenase component from pig heart has a clear preference for R-lipoic acid, a substrate which reacts 24 times faster than the S-enantiomer. Selectivity is more at the stage of the catalytic reaction than of binding. The Michaelis constants of both enantiomers are comparable (Km = 3.7 and 5.5 mMfor R- and S-lipoic acid, respectively) and the S-enantiomer inhibits the R-lipoic acid dependent reaction with an inhibition constant similar to its Michaelis constant. When three lipoic acid homologues were tested, RS-1,2-dithiolane-3-caproic acid was one carbon atom longer than lipoic acid, while RS-bisnorlipoic acid and RS-tetranorlipoic acid were two and four carbon atoms shorter, respectively. All are poor substrates but bind to and inhibit the enzyme with an affinity similar to that of S-lipoic acid. No essential differences with respect to its reaction with lipoicacid enantiomers and homologues exist between free and complex-bound dihydrolipoamide dehydrogenase. Dihydrolipoamide dehydrogenase from human renal carcinoma has a higher Michaelis constant for R-lipoic acid (Km = 18mM) and does not accept the S-enantiomer as a substrate. Both enantiomers of lipoic acid are inhibitors of the overall reaction of the bovine pyruvate dehydrogenase complex, but stimulate the respective enzyme complexes from rat as well as from Escherichia coli. The S-enantiomer is the stronger inhibitor, the R-enantiomer the better activator. The two enantiomers have no influence on the partial reaction of the bovine pyruvate dehydrogenase component, but do inhibit this enzyme component from rat kidney. The implications of these results are discussed.

alpha-Lipoic acid as a biological antioxidant.

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Free Radic Biol Med 1995 Aug;19(2):227-50

alpha-Lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant. Lipoate, or its reduced form, dihydrolipoate, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E. In addition to its antioxidant activities, dihydrolipoate may exert prooxidant actions through reduction of iron. alpha-Lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as ischemia-reperfusion injury, diabetes (both alpha-lipoic acid and dihydrolipoic acid exhibit hydrophobic binding to proteins such as albumin, which can prevent glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-kappa B transcription factor. We review the properties of lipoate in terms of

(1) reactions with reactive oxygen species;
(2) interactions with other antioxidants;
(3) beneficial effects in oxidative stress models or clinical conditions. (153 Refs.)

[Diabetes mellitus--a free radical-associated disease. Results of adjuvant antioxidant supplementation]

Kahler W, Kuklinski B, Ruhlmann C, Plotz C
Klinik fur Innere Medizin, Klinikums Rostock-Sudstadt.
Z Gesamte Inn Med 1993 May;48(5):223-32

Our investigations carried out in patients with diabetes mellitus revealed oxidative stress loads. The study presented here was to clarify whether a therapy with antioxidants can contribute to an improvement of prognosis. 80 patients affected with a long term diabetic late syndrome were randomised and arranged to 4 groups of n = 20 each. In contrast to a control group these patients received 600 mg of alpha lipoic acid or 100 micrograms of selenium (sodium selenite) daily or 1200 IE of D-alpha-tocopherol respectively for a time of 3 months. In comparison with the control group all groups treated in an antioxidative way showed significantly diminished serum concentrations of thiobarbituric acid reactive substances and of urinary albumin excretion rates. The symptoms of distal symmetric neuropathy measured according to the thermo- and vibration sensitivity also improved in a highly significant manner. The results prove that oxidative stress plays a promoting role in developing of long term diabetic late complications and that a therapy with adjuvant antioxidants may lead to a regression of diabetic late complications.

Lipoate prevents glucose-induced protein modifications.

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Free Radic Res Commun 1992;17(3):211-7

Nonenzymatic glycation has been found to increase in a variety of proteins in diabetic patients. The present study examined a possibility of preventing glycation and subsequent structural modifications of proteins by alpha-lipoic acid (thioctic acid) as lipoate, a substance which has gained attention as a potential therapeutic agent for diabetes-induced complications. Incubation of bovine serum albumin (BSA) at 2 mg/ml with glucose (500 mM) in a sterile condition at 37 degrees C for seven days caused glycation and structural modifications of BSA observed by SDS-PAGE, near UV absorption, tryptophan and nontryptophan fluorescence, and fluorescence of an extrinsic probe, TNS (6-(p-toluidinyl) naphthalene-2-sulfonate). When BSA and glucose were incubated in the presence of lipoate (20mM), glycation and structural modifications of BSA were significantly prevented. Glycation and inactivation of lysozyme were also prevented by lipoate. These results suggest a potential for the therapeutic use of lipoic acid against diabetes-induced complications.

Neural dysfunction and metabolic imbalances in diabetic rats. Prevention by acetyl-L-carnitine.

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Diabetes 1994 Dec;43(12):1469-77

The rationale for these experiments is that administration of L-carnitine and/or short-chain acylcarnitines attenuates myocardial dysfunction

1) in hearts from diabetic animals (in which L-carnitine levels are decreased);
2) induced by ischemia-reperfusion in hearts from nondiabetic animals; and
3) in nondiabetic humans with ischemic heart disease.

The objective of these studies was to investigate whether imbalances in carnitine metabolism play a role in the pathogenesis of diabetic peripheral neuropathy. The major findings in rats with streptozotocin-induced diabetes of 4-6 weeks duration were that 24-h urinary carnitine excretion was increased approximately twofold and L-carnitine levels were decreased in plasma (46%) and sciatic nerve endoneurium (31%). These changes in carnitine levels/excretion were associated with decreased caudal nerve conduction velocity (10-15%) and sciatic nerve changes in Na(+)-K(+)-ATPase activity (decreased 50%), Mg(2+)-ATPase (decreased 65%), 1,2-diacyl-sn-glycerol (DAG) (decreased 40%), vascular

albumin permeation (increased 60%), and blood flow (increased 65%). Treatment with acetyl-L-carnitine normalized plasma and endoneurial L-carnitine levels and prevented all of these metabolic and functional changes except the increased blood flow, which was unaffected, and the reduction in DAG, which decreased another 40%. In conclusion, these observations

1) demonstrate a link between imbalances in carnitine metabolism and several metabolic and functional abnormalities associated with diabetic polyneuropathy and
2) indicate that decreased sciatic nerve endoneurial ATPase activity (ouabain-sensitive and insensitive) in this model of diabetes is associated with decreased DAG.

Serum and urine levels of levocarnitine family components in genetically diabetic rats.

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Arzneimittelforschung 1994 Aug;44(8):965-8

Serum concentration and urinary excretion of levocarnitine (L-carnitine, CAS 541-15-1) family components were evaluated in a Wistar derived strain of genetically diabetic rats BB/BB, in comparison with normal Wistar rats, and their control rats BB/WB of both sexes. BB/BB diabetic animals have lower serum concentration of total-L-carnitine (TC), L-carnitine (LC), acetyl-L-carnitine (ALC), and short chain L-carnitine esters (SCLCE) than both the strains of non-diabetic rats, as previously observed in streptozotocin diabetic rats. No or marginal variations between control and diabetic rats were detected in cumulative urinary excretion of L-carnitine family components. A strain difference was observed between Wistar and BB/WB non-diabetic rats, BB/WB showing higher serum concentration and lower cumulative urinary excretion of LC and TC than Wistar animals. Renal clearance of L-carnitine components proved to be markedly higher in BB/BB diabetic rats, as previously shown in streptozotocin rats. The reduction of serum concentration of the carnitines endogenous pool may explain this finding. The lack of an increased urinary excretion of L-carnitine components in diabetic animals despite the high increase of diuresis suggests that the saturable tubular reabsorption of L-carnitine family components also in diabetes is the primary mechanism to preserve the homeostatic equilibria of the L-carnitine family, the variation in serum concentration being attributable to the complex systemic metabolicalterations typical of diabetes. In agreement with previous investigations,male animals of all the strains showed higher serum concentration andurinary excretion of L-carnitine components as compared to females.

Acetyl-L-carnitine corrects electroretinographic deficits in experimental diabetes.

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Diabetes 1993 Aug;42(8):1115-8

Acetyl-L-carnitine reduces the latencies of electroretinogram oscillatory potentials in healthy humans. The effect of acetyl-L-carnitine (50mg.kg-1.day-1) on the increased electroretinogram latencies found in rats with STZ-induced hyperglycemia of 3-wk duration was evaluated. The aldosereductase inhibitor sorbinil, which has been shown to normalize abnormal electroretinogram tracings associated with STZ-induced diabetes, was used as a positive control. Aldose reductase inhibitors are thought to lower tissue sorbitol while increasing myo-inositol. The electroretinograms of the STZ-induced diabetic rats in this study were abnormal; treatment withacetyl-L-carnitine as well as sorbinil significantly improved electroretinogram b-wave amplitude and decreased the latencies of oscillatory potentials 2 and 3. Acetyl-L-carnitine treatment of STZ-induced diabetic rats did not affect hyperglycemia or erythrocyte polyol pathway activity as reflected by erythrocyte sorbitol levels. In contrast, sorbinil did reduce elevated erythrocyte sorbitol levels. This suggests that the impaired electroretinograms associated with STZ-induced diabetes may not be caused solely by increased polyol pathway activity.

Acetyl-L-carnitine effect on nerve conduction velocity in streptozotocin-diabetic rats.

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Arzneimittelforschung 1993 Mar;43(3):343-6

Measurement of nerve conduction velocity (NCV) is a useful and sensitive tool for evaluating diabetes related neurological dysfunctions. The method used allows to monitor the parameter at different times in the same group of rats, so that it is possible to observe simultaneously the development of the damage in time, and to evaluate the improvement related to the treatment. The repeated oral treatment with acetyl-L-carnitine (ALC, CAS 5080-50-2) 250 mg/kg caused an improvement in NCV of the diabetic rats; the effect was higher when the treatment started early with respect to the diabetes induction. The improvement in NCV was constant in time and comparable from 2 to 6 weeks of the treatment. In conclusion, oral treatment with ALC was able to normalize the impairment of NCV in streptozotocin rats, the effect being constant in time from 2 to 6 weeks of treatment and up to 8 weeks after induction when administration started in early stage of diabetes (2-3 weeks after induction); however, at this time the NCV is already significantly decreased.

Effect of acetyl-L-carnitine treatment on the levels of levocarnitine and its derivatives in streptozotocin-diabetic rats.

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Arzneimittelforschung 1993 Mar;43(3):339-42

The effect of diabetes induced by streptozotocin and that of acetyl-L-carnitine (ALC) hydrochloride (CAS 5080-50-2) treatment on the homeostasis of the levocarnitine (L-carnitine) moiety was investigated in Sprague-Dawley rats. The diabetic status was ascertained by measuring blood glucose. L-carnitine (LC), total acid soluble L-carnitine (TC) and ALC were measured in serum, tissues and urine by radioenzymatic methods. Short-chain L-carnitine esters (SCLCE) were obtained by subtracting LC from TC. Serum concentration of L-carnitine moiety was decreased in diabetic when compared to normal rats; whereas ALC oral treatment (50 and 150 mg/kg p.o. for 4 weeks) in diabetic rats increased, dose-dependently, all the components of L-carnitine moiety, SCLCE and ALC being completely restored. In the liverof diabetic rats all the analytes proved to be higher than in normal rats, mainly LC and TC. A similar trend was observed in skeletal muscle, at least with LC and TC, whereas SCLCE and ALC were not affected. The treatment with ALC increased the liver concentration of all the analytes in a dose-related way whereas in skeletal muscle only LC and TC showed an increase with the highest dose of ALC. Myocardium and kidneys showed a decrease of all the analytes in diabetes; the treatment with ALC normalized the situation in kidneys, in a dose-related way, but not in the myocardium. Urinary excretion and renal clearance of L-carnitine moiety increased in diabetes; an additional dose-related increase was observed with the ALC treatment.

Acetyl-L-carnitine prevents substance P loss in the sciatic nerve and lumbar spinal cord of diabetic animals.

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Int J Clin Pharmacol Res 1992;12(5-6):243-6

Diabetic neuropathy is a disease of peripheral nerves, characterized by axonal atrophy and degeneration that might be preceded by a marked impairment of axonal transport and by a reduced conduction velocity. Sensory nerves are particularly susceptible to diabetes. In the present report it is shown that experimental diabetes in rats causes a significant reduction of the content of the pain-related neuropeptide substance P insciatic nerve and lumbar spinal cord. Such a loss of substance P is fully prevented by acetyl-L-carnitine treatment. The neuroprotective pharmacological effect is selective and takes place without

significant changes of hyperglycaemia and without modifications of the reduced rate of body growth typical of diabetic animals.

Altered neuroexcitability in experimental diabetic neuropathy: effect of acetyl-L-carnitine.

Malone JI, Lowitt S, Corsico N, Orfalian Z
University of South Florida, Tampa.
Int J Clin Pharmacol Res 1992;12(5-6):237-41

Sciatic nerve conduction velocity (NCV) is reduced in rats made hyperglycaemic with streptozotocin (STZ). This neurophysiologicaldys function has been associated with increased nerve sorbitol and reduced nerve inositol. Treatment of STZ diabetic rats with aldose reductase inhibitors (ARIs) which reduce sorbitol and increase inositol in the nerve results in normalization of NCVs. Male Wistar rats were made diabetic with 50 mg/kg of streptozotocin given intraperitoneally. Those animals with blood glucose > 300 mg/dl two weeks later were included in this study. The STZ-diabetic rats were treated with either the ARI sorbinil (40 mg/kg per day), or acetyl-L-carnitine (ALC) (300 mg/kg per day) or sterile 0.15% aqueous NaCl for 16 weeks after 4 or 8 weeks of untreated hyperglycaemia. A control group of non-diabetic rats received no treatment during the interval. Sciatic-nerve sorbitol was elevated (1.08 +/- 0.13 nanomol/mg wet weight vs. 0.19 +/- 0.03 nm/mg wet weight) and inositol was reduced (1.21+/- 0.12 nm/mg ww vs. 2.02 +/- 0.08 nm/mg ww) in the STZ diabetic rats, which were untreated for 4 weeks. Treatment with sorbinil was associated with normalization of the tissue sorbitol (0.10 +/- 0.05 nm/mg ww), while ALC treatment also significantly reduced the nerve sorbitol but only to a level (0.34 +/- 0.08 nm/mg ww) more elevated than the normal level. The nerves of STZ animals treated with sorbinil or ALC had inositol levels no different from untreated diabetic rats. Thus, hyperglycaemic animals treated with either ALC or sorbinil had similar improvements in NCVs as the diabetic, even though the effect on nerve sorbitol was different and nerve inositol was unchanged.(ABSTRACT TRUNCATED AT 250 WORDS)

[The action of carnitine-series preparations in experimental alloxan diabetes mellitus]

Kim EK, Trevisani C, Trevisani M
Eksp Klin Farmakol 1992 Jul-Aug;55(4):35-6

The study was undertaken to examine the effects of l-carnitine and acetyl-l-carnitine in rats and mice with experimental alloxan diabetes. The findings suggest that acetyl-l-carnitine is more effective against diabetes in increasing glucose tolerance, restoring the impaired response of glucagon to glucose, showing glycogen-sparing action than is l-carnitine.

Effect of aminoguanidine on the frequency of neuroaxonal dystrophy in the superior mesenteric sympathetic autonomic ganglia of rats with streptozocin-induced diabetes.

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Diabetes 1996 Mar;45(3):284-90

Aminoguanidine, which prevents formation of advanced glycation end products and is a relatively selective potent inhibitor of the inducible (versus constitutive) isoform(s) of nitric oxide synthase, has been reported to ameliorate structural and functional abnormalities in peripheral somatic nerves in rats with streptozocin (STZ)-induced diabetes. In the present studies, the effects of aminoguanidine treatment on ultrastructural changes in the autonomic nervous system of rats with STZ-induced diabetes were examined. The frequency of neuroaxonal dystrophy, the neuropathological hallmark of sympathetic autonomic neuropathy in diabetic rats, increased 9- to 11-fold in the superior mesenteric ganglia of 7- and 10-month STZ-diabetic rats compared with that in age-matched controls. Administration of aminoguanidine continuously from the time of induction of diabetes at a dose equal to or in excess of that providing a salutary effect in the diabetic somatic peripheral nervous system did not alter the severity of diabetes as assessed by plasma glucose level, 24-hurine volume, and levels of glycated hemoglobin. Chronic aminoguanidine therapy did not diminish the frequency or affect the ultrastructural appearance of neuroaxonal dystrophy in diabetic or age-matched control rat sympathetic ganglia after 7 or 10 months of continuous administration. Our findings (under these experimental conditions) do not support a role for aminoguanidine-sensitive processes in the development of sympathetic neuroaxonal dystrophy in diabetic rats. Glycation-linked aminoguanidine-insensitive processes, however, such as the formation of early glucose adducts (Schiff bases and Amadori products) withintra cellular and/or extracellular proteins and amine-containing lipids, superoxide anion generation during subsequent autoxidation of these glucoseadducts, and non-glycative processes, remain potential pathogenetic mechanisms for diabetic autonomic neuropathy.

L-fucose reduces collagen and noncollagen protein production in cultured cerebral microvessel endothelial cells.

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J Cell Physiol 1995 Dec;165(3):658-66

L-fucose is a monosaccharide which is present in low concentrations in normal serum but is increased in diabetes, cancer, and inflammatory diseases. The contribution that abnormal L-fucose levels make to the progression of these disorders is unknown. In a previous study we showed that increased L-fucose concentration reduced proliferation and proteoglycan production by cultured cerebral microvessel endothelial cells. In the present study we show that exposing cerebral microvessel endothelial cells for 2 weeks to medium containing an increased concentration of L-fucose causes a significant decrease in collagen and to a lesser extent noncollagen protein production. The effect of L-fucose on collagen and noncollagen protein production is concentration-dependent: 1 mM L-fucose causes a significant decrease in collagen production but has no effect on noncollagen protein production; a 5 mM L-fucose concentration causes a maximum decrease in both collagen and noncollagen protein production. This defect is unrelated to the reduction in myo-inositol uptake caused by L-fucose and is not prevented by aminoguanidine. Collagen production can be improved by restoring L-fucose-conditioned cells to normal medium. Culturing cells for 2 weeks in medium containing 10 mM L-fucose resulted in a 50% decrease in collagen production, which was restored to 75% of control after cells were transferred to normal medium for 7 days. In contrast, noncollagen protein production was totally restored after 3 days in normal medium. Increasing levels of L-fucose in serum of rats also resulted in a decrease in collagen production. Collagenase digestible in corporation of L-[2,3,4,5-3H]proline into protein of the articular cartilage from rats fed a diet containing 20% L-fucose for 3 weeks was reduced by about 40%compared to rats fed a normal diet. The decrease in collagen production in L-fucose fed rats was less than the reduction that occurred in streptozotocin-induced diabetic rats. These data suggest that changes in L-fucose concentration itself may be a factor in the regulation of collagen production.

Aminoguanidine does not inhibit the initial phase of experimental diabetic retinopathy in rats.

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Diabetologia (Germany) Mar 1995, 38 (3) p269-73

We have previously shown that long-term administration of aminoguanidine, an inhibitor of advanced glycosylation product formation, reduces the extent of experimental diabetic retinopathy in the rat by 85%. In order to determine whether the residual retinopathy that developed despite aminoguanidine was attributable to advanced glycation endproduct formation, a time-course study was performed in three different groups of male Wistar rats: non-diabetic controls (NC), streptozotocin-diabetic controls (DC) and streptozotocin-diabetic rats treated with aminoguanidine HCL, 50 mg/100 ml drinking water (D-AG). Eyes

were obtained at 24, 32, 44 and 56 weeks of diabetes/treatment duration and morphologic evaluation was done on retinal digest preparations. At 56 weeks, retinal basement membrane thickness was additionally measured. After 24 weeks of diabetes, the number of acellular capillaries was significantly elevated in DC (44.6 +/- 5.7/mm2 of retinal area, NC 19.6 +/- 4.9; $p < 0.001$) and increased continuously over time (DC56 weeks 87.4 +/- 15.1; $p < 0.001$ vs DC24 weeks). In contrast, acellular capillaries in D-AG increased over the first 24 weeks and then remained constant for the rest of the study (D-AG 24 weeks 35.7 +/- 5.18; $p < 0.01$ vs NC 24 weeks and NS vs DC 24 weeks; D-AG 56 weeks 42.0 +/- 6.20; p NS vsD-AG 24 weeks). (ABSTRACT TRUNCATED AT 250 WORDS)

Neurotoxicity of advanced glycation endproducts during focal stroke and neuroprotective effects of aminoguanidine.

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Proc Natl Acad Sci U S A (United States) Apr 25 1995, 92 (9) p3744-8

Cerebral infarction (stroke) is a potentially disastrous complication of diabetes mellitus, principally because the extent of cortical loss is greater in diabetic patients than in nondiabetic patients. The etiology of this enhanced neurotoxicity is poorly understood. We hypothesized that advanced glycation endproducts (AGEs), which have previously been implicated in the development of other diabetic complications, might contribute to neurotoxicity and brain damage during ischemic stroke. Using a rat model of focal cerebral ischemia, we show that systemically administered AGE-modified bovine serum albumin (AGE-BSA) significantly increased cerebral infarct size. The neurotoxic effects of AGE-BSA administration were dose- and time-related and associated with a paradoxical increase in cerebral blood flow. Aminoguanidine, an inhibitor of AGE cross-linking, attenuated infarct volume in AGE-treated animals. We conclude that AGEs may contribute to the increased severity of stroke associated with diabetes and other conditions characterized by AGE accumulation.

Nitric oxide synthesis and the effect of aminoguanidine and NG-monomethyl-L-arginine on the onset of diabetes in the spontaneously diabetic BB rat.

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Diabetes (United States) Mar 1995, 44 (3) p360-4

Nitric oxide (NO) synthesis and the effect of aminoguanidine (AG) and NG-monomethyl-L-arginine (NMMA) (inhibitors of NO synthase) on the onset of

diabetes were studied in the spontaneously diabetic BB rat. To measure in vivo NO production, 20 male 50-day-old diabetes-prone BB (BBdp) rats and age-matched non-diabetes-prone BB (BBn) rats were individually placed in metabolism cages. The animals had free access to a casein-based semipurified diet and deionized and double-distilled water. Urine excretion was collected every other day for 70 days, and urinary excretion of nitrate was measured as an index of in vivo NO synthesis. The urinary excretion of nitrate was enhanced by 150-200% in BBdp rats 4-6 days before the onset of diabetes, compared with aged-matched BBn rats. There was no difference in urinary excretion of nitrate between BBn rats and those BBdp rats that did not develop diabetes by the age of up to 120 days. To determine a role of NO in the development of spontaneous diabetes, 40-day-old male BBdp rats (30 rats per group) received daily subcutaneous injections of NMMA (acetate salt) (5 mg/kg body wt) or equal amounts of acetate (control) or oral administration of AG (0 or 3 g/l of drinking water) for 80 days. Both NMMA and AG delayed the onset of diabetes in BBdp rats by 13-15 days without altering the rate of incidence of diabetes.

The pharmacokinetics of aminoguanidine in end-stage renal disease patients on hemodialysis.

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Am J Kidney Dis (United States) Mar 1995, 25 (3) p420-5

Aminoguanidine is an investigational agent that may slow or prevent many diabetes-related complications. Since the elimination of aminoguanidine is dependent on renal function, its pharmacokinetics was investigated in eight chronic renal failure patients maintained on hemodialysis. Each patient received 300 mg of aminoguanidine hydrochloride during both an interdialytic and an intradialytic period. During the interdialytic period, the maximum aminoguanidine concentration (Cmax) and time to reach Cmax was 4.5 micrograms/mL and 1.5 hours, respectively. The terminal elimination hallife in these patients was prolonged (37.9 hours). The renal clearance was 2.1 mL/min. Only 8.7% of the administered dose was recovered unchanged in the urine, which is markedly reduced from what is recovered in urine in subjects with normal renal function. There was a positive correlation between the renal clearance of aminoguanidine and the patients' residual renal function ($P < 0.05$). During hemodialysis, the hallife of aminoguanidine was shortened to 3.9 hours. The hemodialysis clearance of aminoguanidine was 203.6 mL/min. After cessation of hemodialysis, a significant rebound in plasma aminoguanidine concentrations (mean, 39%) was observed. Thus, the dose of aminoguanidine hydrochloride will need to be significantly reduced in patients with end-stage renal disease. Given the interdialytic and intradialytic pharmacokinetics of aminoguanidine, three times weekly dosing after each hemodialysis session is suggested.

Effect of aminoguanidine on the impaired nitric oxide-mediated neurotransmission in anococcygeus muscle from diabetic rats.

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Neuropharmacology (England) Nov 1994, 33 (11) p1315-22

The contribution of advanced glycation end-product (AGE) formation to alterations in nitrergic neurotransmission caused by 8-week streptozotocin-induced diabetes has been examined in the rat anococcygeus muscle. Relaxant responses to nitrergic nerve stimulation (0.5-5 Hz, 10-sectrain), to nitric oxide (NO; 0.1-3 microM), to the NO donor, sodium nitroprusside (SNP; 5-500 nM), and to the cell-permeable analogue of cyclic guanosine monophosphate (cGMP), 8-bromo-cGMP (15 and 30 microM), were significantly smaller in muscles from diabetic rats than from control rats.Pretreatment with aminoguanidine hemisulphate (1 milligram drinking water) to inhibit AGE formation, did not alter the relaxant responses to nitrergic nerve stimulation, NO or SNP in tissues from control rats, or responses to NO or SNP in tissues from diabetic rats, however relaxations to nitrergic nerve stimulation were further reduced in tissues from diabetic rats. In anococcygeus muscles from untreated animals, a 20-min exposure to aminoguanidine (1 mM) in vitro had no effect on relaxations to nitrergic nerve stimulation. The results suggest that diabetes impairs nitrergic transmission in the rat anococcygeus at least partly through alterations in the cGMP-relaxation pathway. The impaired neurotransmission does not appear to be related to the formation of AGEs.

Interleukin 1 beta induces diabetes and fever in normal rats by nitric oxide via induction of different nitric oxide synthases.

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Cytokine (United States) Sep 1994, 6 (5) p512-20

Substantial in vitro evidence suggests that nitric oxide may be a major mediator of interleukin 1 (IL-1) induced pancreatic beta-cell inhibition and destruction in the initial events leading to insulin-dependent diabetes mellitus. Using NG-nitro-L-arginine methyl ester, an inhibitor of both the constitutive and the cytokine inducible forms of nitric oxide synthase, andaminoguanidine, a preferential inhibitor of the inducible form of nitric oxide synthase, we investigated the impact of inhibiting nitric oxide production on food-intake, body weight and temperature, blood glucose,plasma insulin, glucagon, corticosterone and leukocyte- and differential-counts in normal rats injected once daily for 5 days with interleukin 1 beta (IL-1 beta) (0.8 microgram/rat = 4.0 micrograms/kg). Inhibition of both the constitutive and the inducible forms of nitric oxide synthase prevented IL-1 beta-

induced fever, hyperglycaemia, hypoinsulinemia, and hyperglucagonemia, and partially prevented lymphopenia and neutrophilia, but had no effect on IL-1 beta-induced anorexia and changes in plasma corticosterone. Preferential inhibition of the inducible form of nitric oxide synthase using two daily injections of 5 mg/rat of aminoguanidine prevented IL-1 beta-induced hyperglycaemia and hypoinsulinaemia, and slightly reduced the pyrogenicity of IL-1 on 3 out of 5 days. Higher doses of aminoguanidine (100 mg/rat) prevented lymphopenia and neutrophilia. We conclude that nitric oxide produced by the inducible form of nitric oxide synthase, mediates the IL-1 beta-induced inhibition of insulin release and that the effect of IL-1 beta on temperature, pancreatic alpha-cells, and leukocyte differential counts seems to be mediated by nitric oxide produced by the constitutive form of nitric oxide synthase.

The reaction of methylglyoxal with aminoguanidine under physiological conditions and prevention of methylglyoxal binding to plasma proteins.

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Biochem Pharmacol (England) Nov 16 1994, 48 (10) p1865-70

Increased formation of methylglyoxal in clinical diabetes mellitus and metabolism by the glyoxalase system has been linked to the development of clinical complications of diabetes: retinopathy, neuropathy and nephropathy. Aminoguanidine has been proposed as a prophylactic agent for preventive therapy of diabetic complications. Methylglyoxal reacted with aminoguanidine under physiological conditions to form two isomerictriazines, 3-amino-5-methyl-1,2,4-triazine and 3-amino-6-methyl-1,2,4-triazine. The mean second order rate constant for the reaction of methylglyoxal with aminoguanidine, kMG.AG = 0.39 +/- 0.06 M-1 sec-1 at pH 7.4 and 37degrees. Under these conditions, no methylglyoxal bisguanylhydrazone was detected. Aminoguanidine prevented the irreversible modification of human plasma protein by a physiological concentration of methylglyoxal (1microM); the median inhibitory concentration IC50 value of aminoguanidine was 203 +/- 16 microM (N = 28). The scavenging of methylglyoxal by aminoguanidine may contribute to the beneficial effects of aminoguanidine in the prevention of vascular pathogenesis in diabetes.

Advanced glycation end products induce glomerular sclerosis and albuminuria in normal rats.

Vlassara H, Striker LJ, Teichberg S, Fuh H, Li YM, Steffes M
Picower Institute for Medical Research, Manhasset, NY 11030.
Proc Natl Acad Sci U S A (United States) Nov 22 1994, 91 (24) p11704-8

High levels of tissue advanced glycation end products (AGEs) that result from the spontaneous modification of proteins by glucose occur in diabetes and aging. To address the potential pathogenic role of AGEs in the glomerulosclerosis of diabetes or nephrosclerosis of aging, doses of AGE-modified rat albumin (25 mg per kg per day, i.v.) sufficient to elevate circulating AGE levels to the range of diabetic serum were administered daily to healthy rats alone or in combination with the AGE inhibit oraminoguanidine. After 5 months, the AGE content of renal tissues in AGE-treated rats rose to 50% above controls ($P < 0.025$), whereas serum contained 2.8-fold greater AGE levels ($P < 0.025$). Light and electronmicroscopy of kidneys from AGE-treated rats revealed a more than 50% increase in glomerular volume compared to controls ($P < 0.001$), significant periodic acid/Schiff reagent-positive deposits, basement membrane widening, and mesangial extracellular matrix increase and indicated significant glomerulosclerosis compared to untreated ($P < 0.002$) or albumin-treated controls ($P < 0.002$). These changes were associated with significant loss of protein ($P < 0.005$) and albumin ($P < 0.002$) in the urine of AGE-treated rats compared to controls. Cotreatment with aminoguanidine markedly limited both the structural and functional defects. These in vivo data demonstrate that AGEs influence glomerular structure and function in a manner leading to glomerulosclerosis. The effects are AGE-specific, as they are ameliorated by a pharmacological AGE inhibitor, aminoguanidine.

Active and passive mechanical properties of isolated arterioles from STZ-induced diabetic rats. Effect of aminoguanidine treatment.

Hill MA, Ege EA
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Diabetes (United States) Dec 1994, 43 (12) p1450-6

Studies were performed to examine the effect of experimental diabetes (4-6 weeks duration) on both the passive elastic and active myogenic properties of isolated skeletal muscle arterioles. Studies were conducted on untreated streptozotocin (60 mg/kg)-induced diabetic rats and in similar rats treated daily with either amino-guanidine (25 mg/kg) ormethylguanidine (25 mg/kg). First-order cremaster muscle arterioles were isolated, cannulated, and pressurized in the absence of intraluminal flow.Video microscopy was used to determine relationships between arteriolar diameter and intraluminal pressure both in the active and passive (o mmol/lCa(2+)-2 mmol/l EGTA superfusated) tes. The measurements were used to calculate active myogenic responses, arteriolar distensibility, and stress-strain relationships. Under passive conditions, arterioles from untreated diabetic animals appeared to be stiffer and less distensible compared with similar arterioles from control animals. Under active conditions, i.e., in the presence of extracellular Ca2+, arterioles from the untreated diabetic group showed impaired myogenic reactivity as evidenced by a significant ($P < 0.001$) reduction in the negative slope of the pressure-diameter relationship over a physiological range of intraluminal pressures. Chronic treatment with aminoguanidine prevented the diabetes-induced changes in the active and passive properties of the isolated arterioles while

treatment with methylguanidine appeared ineffective. Vasodilator responses to topically applied acetylcholine (10(-8) to 5 x 10(-6) mol/l) were significantly impaired in diabetic animals irrespective of treatment with aminoguanidine. The data indicate that experimental diabetes is associated with a decreased passive distensibility, or stiffening, of skeletal muscle arterioles that, in addition, may contribute to impaired active myogenic responses.

Effects of aminoguanidine on insulin release from pancreatic islets.

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Endocr J (England) Jun 1994, 41 (3) p309-13

Aminoguanidine (AG) is a potential therapeutic agent for preventing the generation of advanced glycation end products in diabetes mellitus. In this study, the effect of AG on insulin secretion was investigated in in vitro rat pancreatic islets. The islets were aseptically isolated and cultured in tissue culture medium 199 for 48 h with or without AG. After the culture, batches of 10 islets were incubated in Krebs-Ringer bicarbonate buffer containing 3.3 mM or 16.7 mM glucose. Islets previously exposed to 0.18 mM AG or 0.45 mM AG showed similar insulin release to control islets at a 16.7 mM glucose concentration, but high glucose-stimulated insulin release was inhibited in the islets exposed to 1.8 mM. In the perifusion experiment, insulin release caused by 16.7 mM glucose from the islets previously exposed to 1.8 mM AG was not significantly different from that of the control islets. However, culture of the islets with higher AG concentrations, 4.55 mM and 9.1 mM, significantly inhibited glucose-stimulated insulin release (< 0.02 and 0.002, respectively). These results suggest that AG at high concentrations impairs pancreatic B-cell response to a high concentration of glucose.

TNF-alpha and IFN-gamma potentiate the deleterious effects of IL-1 beta on mouse pancreatic islets mainly via generation of nitric oxide.

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Cytokine (United States) Jul 1994, 6 (4) p399-406

Cytokines may be important mediators of beta-cell damage in early insulin-dependent diabetes mellitus. In order to further characterize the mechanism(s) of action of cytokines on insulin-producing cells, mouse pancreatic islets were exposed for 48 h to IL-1 beta, IFN-gamma or TNF-alpha, alone or in combinations. The three cytokines induced islet nitric oxide (NO) production, an effect most marked when islets were exposed to the three cytokines together. In parallel with NO production, IL-1 beta+IFN-gamma+TNF-alpha impaired islet function, as judged by decreased islet DNA and insulin content, decreased

glucose metabolism and decreased glucose-induced insulin release. Aminoguanidine, an inhibitor of NO production, prevented all the above described suppressive effects of the cytokines, with exception of depletion in islet insulin content. In parallel experiments, insulin-producing RIN cells were exposed for 6 h to the same cytokines. Both IL-1 beta and TNF-alpha, but not IFN-gamma, induced NO production and expression of the mRNA encoding for the inducible form of the enzyme NO synthase (iNOS). These effects were most pronounced when combinations of IL-1 beta+IFN-gamma or IL-1 beta+IFN-gamma+TNF-alpha were used. As a whole, the data suggest that combinations of cytokines induce higher amounts of NO generation by mouse pancreatic islets than each of the cytokines isolated. An important source of islet NO production are probably the beta-cells, as pointed by data obtained with an insulinoma cell line. Most of the deleterious effects of the cytokines of mouse islets are prevented by blocking NO production, suggesting that NO is the main mediator of cytokine-induced beta-cell damage.

Creatine reduces collagen accumulation in the kidneys of diabetic db/db mice.

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Nephron (Switzerland) 1994, 67 (2) p214-7

In the present study, we tested the hypothesis whether creatine, a metabolite of arginine metabolism, shares the pharmacological activities of arginine reducing collagen accumulation in the diabetic kidney. Ten db/db mice were given, for 3 months, a solution containing a daily dosage of creatine of 50 mg/kg body weight. Eleven db/db mice served as controls. At the end of the 3-month study period, the mean N-carboxymethyllysine concentration in the untreated group was significantly higher than in the treated group (0.163 +/- 0.18 versus 0.096 +/- 0.017 nmol/mumol hydroxyproline, $p < 0.001$). Collagen accumulation was also significantly higher in the untreated than in the treated group (2.21 +/- 0.24 versus 1.68 +/- 0.22 mumol hydroxyproline/100 mg kidney weight, $p < 0.001$). We conclude that creatine led to a significant reduction in collagen type IV accumulation resembling arginine or aminoguanidine action. We do suggest that the guanidino group common to both compounds is able to block reactive carbonyls.

L-arginine reduces heart collagen accumulation in the diabetic db/db mouse.

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Circulation (United States) Jul 1994, 90 (1) p479-83

BACKGROUND: Diabetic cardiomyopathy presents with significant collagen accumulation; decreased solubility, increased glucose-mediated abnormal cross-linking, free radical cross-linking, or glucose-induced increased transcription of collagen is incriminated. In a previous study, we reducedcollagen accumulation in the kidneys of diabetic mice by treatment with oral arginine. This observation led us to examine the effect of arginine oncardial fibrosis.

METHODS AND RESULTS: Twenty-nine db/db spontaneouslydiabetic mice were used in the experiments. Sixteen were given L-arginine(free base, in tap water, 50 mg/kg body wt per day) for 4 months. At theend of the experiment, we determined total collagen content of total ventricular tissue, acid solubility, carboxymethyllysine, O-tyrosine, glutathione, blood glucose, and fructosamine as parameters for glycemic control. Heart collagen level was significantly (P = .0001) reduced in the experimental group (mean, 0.24 +/- 0.05) compared with the control group (mean, 0.49 +/- 0.10 mumol hydroxyproline per 100 mg heart tissue). Significantly more collagen could be eluted from heart samples of the experimental group (P = .02). Carboxymethyllysine and O-tyrosine did not differ when related to heart weight. Glutathione level was significantly higher in the untreated group (P = .003). Parameters of glycemic control did not differ between the groups.

CONCLUSIONS: Our findings clearly indicate that L-arginine reduced total heart collagen and increased acid solubility of heart collagen. Both findings are compatible with the cross-linking hypothesis. The data for carboxymethyllysine, O-tyrosine, and glutathione would rule out the glycoxidation hypothesis and, therefore, free radical cross-linking. The postulated mechanism of action is most likely the blocking of reactive carbonyl functions by L-arginine in analogyto amino guanidine activity. Correlations of collagen with glycemic control, however, point to an association of glucose with collagen metabolism, a phenomenon documented in cell cultures at the transcriptional level.

Cytokines suppress human islet function irrespective of their effects on nitric oxide generation.

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J Clin Invest (United States) May 1994, 93 (5) p1968-74

Cytokines have been proposed as inducers of beta-cell damage in human insulin-dependent diabetes mellitus via the generation of nitric oxide (NO). This concept is mostly based on data obtained in rodent pancreatic islets using heterologous cytokine preparations. The present study examined whether exposure of human pancreatic islets to different cytokines induces NO and impairs beta-cell function. Islets from 30 human pancreata were exposed for 6-144 h to the following human recombinant cytokines, alone or in combination: IFN-gamma (1,000 U/ml), TNF-alpha (1,000 U/ml), IL-6 (25U/ml), and IL-1 beta (50 U/ml). After 48 h, none of

the cytokines alone increased islet nitrite production, but IFN-gamma induced a 20% decrease in glucose-induced insulin release. Combinations of cytokines, notably IL-1beta plus IFN-gamma plus TNF-alpha, induced increased expression of inducible NO synthase mRNA after 6 h and resulted in a fivefold increase in medium nitrite accumulation after 48 h. These cytokines did not impair glucose metabolism or insulin release in response to 16.7 mM glucose, but there was an 80% decrease in islet insulin content. An exposure of 144 h toIL-1 beta plus IFN-gamma plus TNF-alpha increased NO production and decreased both glucose-induced insulin release and insulin content. Inhibitors of NO generation, aminoguanidine or NG-nitro-L-arginine, blocked this cytokine-induced NO generation, but did not prevent the suppressive effect of IL-1 beta plus IFN-gamma plus TNF-alpha on insulin release andcontent. In conclusion, isolated human islets are more resistant to thesuppressive effects of cytokines and NO than isolated rodent islets. Moreover, the present study suggests that NO is not the major mediator of cytokine effects on human islets.

Amelioration of dermal lesions in streptozotocin-induced diabetic rats by aminoguanidine.

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Diabetes Res (Scotland) 1992, 20 (4) p87-95

As aminoguanidine (AG) is known to prevent non-enzymatic glycosylation in various tissues, we have histologically and biochemically evaluated AG effects on the skin in control, SZ-diabetic and AG-treated (25 mg/kgbw/day, 10w) diabetic rats. HbA1c and plasma glucose levels in diabetic andAG-treated diabetic rats were maintained about two times higher than those in control rats during the 10 weeks of the experiment. Histological findings revealed that the dermis in diabetic rats was thin and edematous, associated with swelling and degeneration of collagen fibers. Necrobiotic changes were seen in the lower dermis. These changes were greatly improved in AG-treated diabetic rats. Skin glucose contents in diabetic andAG-treated diabetic rats were about 10 times higher than those in the controls, whereas there was no difference in the sorbitol contents between three groups. Dry weight of the skin and collagen content was wellcorrelated (r = 0.9044) and collagen represented 78.0 +/- 2.3% of the dryweight. By SDS-PAGE analysis of cyanogen bromide digests it was shown that high molecular weight peptides were increased in diabetic rats, but were decreased in AG-treated diabetic rats. The mean of glycosaminoglycan (GAG) contents of diabetic skin was 54% of that in the controls (1.58 +/- 0.09vs. 2.94 +/- 0.39 micrograms/mg dry weight, $P < 0.0025$), which increased significantly in AG-treated diabetic rats (1.75 +/- 0.07 microgram/mg dryweight, $P < 0.01$ vs. diabetic).

Glycation, glycoxidation, and cross-linking of collagen by glucose. Kinetics, mechanisms, and inhibition of late stages of the Maillard reaction.

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Diabetes (United States) May 1994, 43 (5) p676-83

The Maillard or browning reaction between sugar and protein contributes to the increased chemical modification and cross-linking of long-lived tissue proteins in diabetes. To evaluate the role of glycation and oxidation in these reactions, we have studied the effects of oxidative and antioxidative conditions and various types of inhibitors on the reaction of glucose with rat tail tendon collagen in phosphate buffer at physiological pH and temperature. The chemical modifications of collagen that were measured included fructoselysine, the glycoxidation products Nepsilon-(carboxymethyl) lysine and pentosidine and fluorescence. Collagen cross-linking was evaluated by analysis of cyanogen bromide peptides using sodium dodecyl sulfate-polyacrylamide gel electrophoresis and by changes in collagen solubilization on treatment with pepsin or sodium dodecylsulfate. Although glycation was unaffected, formation of glycoxidation products and cross-linking of collagen were inhibited by antioxidative conditions. The kinetics of formation of glycoxidation products proceeded with a short lag phase and were independent of the amount of Amadori adduct on the protein, suggesting that autoxidative degradation of glucose was a major contributor to glycoxidation and cross-linking reactions. Chelators, sulfhydryl compounds, antioxidants, and aminoguanidine also inhibited formation of glycoxidation products, generation of fluorescence, and cross-linking of collagen without significant effect on the extent of glycation of the protein. We conclude that autoxidation of glucose or Amadori compounds on protein plays a major role in the formation of glycoxidation products and cross-liking of collagen by glucose in vitro and that chelators, sulfhydryl compounds, antioxidants, and aminoguanidine act as uncouplers of glycation from subsequent glycoxidation and cross-linking reactions.

Aminoguanidine inhibits the development of accelerated diabetic retinopathy in the spontaneous hypertensive rat.

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Diabetologia (Germany) Jan 1994, 37 (1) p32-5

Arterial hypertension has been identified as a major secondary risk factor for diabetic retinopathy. However, the mechanisms by which hypertension worsens retinopathy are unknown. Inhibition of advanced glycation product formation prevents the development of experimental diabetic retinopathy in normotensive diabetic rats. In this study the effect of hypertension on the rate of diabetic retinopathy development and the formation of arteriolar thrombosis was

evaluated. We also evaluated the effect of aminoguanidine, an inhibitor of advanced glycation and product formation on retinal pathology of diabetic hypertensive rats. After 26 weeks of diabetes, hypertension accelerated the development of retinopathy despite a lower mean blood glucose level than in the non-hypertensive group (diabetic spontaneous hypertensive rats (SHR) 16.00 +/- 6.83 mmol/l; diabetic normotensive Wistar Kyoto rats (WKY) 34.9 +/- 3.64 mmol/l; p <0.0001). Diabetic SHR had nearly twice as many acellular capillaries as diabetic WKY (SHR diabetic: 91.9 +/- 7.5 acellular capillaries per mm2 of retinal area vs WKY diabetic: 53.7 +/- 8.5 acellular capillaries per mm2 of retinal area), and a 3.8-fold increase in the number of arteriolar microthromboses (SHR diabetic 23,504 +/- 5523 microns2 vs SHR non-diabetic 6228 +/- 2707 microns2). Aminoguanidine treatment of SHR diabetic rats reduced the number of acellular capillaries by 50%, and completely prevented both arteriolar deposition of PAS-positive material and abnormal microthrombus formation. These data suggest that hypertension-induced deposition of glycated proteins in the retinal vasculature plays a central role in the acceleration of diabetic retinopathy by hypertension.

Aminoguanidine reduces regional albumin clearance but not urinary albumin excretion in streptozotocin-diabetic rats.

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Diabetologia (Germany) Jan 1994, 37 (1) p10-4

Advanced glycation end-product-formation is thought to play a role in the development of diabetic angiopathy. By altering the structure of different extracellular matrix components advanced glycation end-products might affect vascular and glomerular permeability. In this study we investigated the effect of treatment with an inhibitor of advanced glycation end-product-formation, aminoguanidine, on vascular permeability and the development of albuminuria in streptozotocin-induced diabetic rats. Male Wistar Rp rats were randomized into a control group, a diabetic group, and an aminoguanidine-treated diabetic group. After 8 weeks, 24-h urine collections were taken and rats were implanted with an arterial and avenous catheter. mean arterial blood pressure was determined by intra-arterial measurement. Regional albumin clearances were assessed in the eye, ileum, lung, skeletal muscle and skin using an isotope technique. Mean arterial pressure in the diabetic group was significantly lower in the control and aminoguanidine-treated groups ($p < 0.02$). Regional albumin clearances were significantly increased in all tissues of diabetic rats compared to control rats ($p < 0.05$). Aminoguanidine treatment of diabetic rats resulted in a significant decrease of regional albumin clearance in all tissues except the lung ($p < 0.05$, lung $p = 0.07$). The development of albuminuria in diabetic rats however, was not affected by aminoguanidine.

Aminoguanidine: a drug proposed for prophylaxis in diabetes inhibits catalase and generates hydrogen peroxide in vitro.

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Biochem Pharmacol (England) Oct 5 1993, 46 (7) p1139-44

Aminoguanidine (AG) has been proposed as a drug of potential benefit in prophylaxis of the complications of diabetes. We show here that AG irreversibly inhibits catalase with an efficacy similar to aminotriazole. AG also produces hydrogen peroxide, in a transition metal-catalysed process which may be partially dependent upon prior hydrolysis of AG to semicarbazide and hydrazine. These observations may be of importance in proposals for the long term administration of AG in diabetes.

Nitric oxide production in islets from nonobese diabetic mice: aminoguanidine-sensitive and -resistant stages in the immunological diabetic process.

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Proc Natl Acad Sci U S A (United States) Oct 1 1993, 90 (19) p8992-5

The role of nitric oxide (NO.) in the development of immunologically induced diabetes was examined. Transfer of spleen cells obtained from diabetic female nonobese diabetic (NOD) mice to nondiabetic irradiated males induced diabetes 11-13 days after transfer. Islets isolated from recipient male mice produced NO. in a time-dependent fashion. The production of nitrite was initially detected at day 6 after transfer, with increasing levels by days 9 and 13. Under similar conditions glucose-induced insulin secretion by isolated NOD mouse islets was irreversibly reduced by approximately 40% at days 6, 9, and 13 after transfer of spleen cells. The number of islets harvested per pancreas by the 9th and 13th day after transfer was decreased by 20-25% as compared to controls. Treatment of male NOD mice with aminoguanidine, an inhibitor of the inducible form of NO. synthase, reduced the production of NO. in islets and delayed the development of diabetes by 3-8 days. The temporary inhibition by aminoguanidine was dependent on both inhibitor concentration and number of spleen cells transferred. These results indicate that NO. is produced in NOD islets as a result of an immunological diabetogenic process and suggests a role of this compound in the immunological diabetic process.

15. Epilepsy

Preventative and curative options include:

B vitamins, taurine, glycine, alanine, calcium, vitamin D, dimethylglycine, vitamin E, magnesium, manganese, selenium, zinc, coleus forskohlii, hyssop, black cohosh, blue cohosh, lobelia, saiko-Keishi-To.

The involvement of taurine in the action mechanism of sodium valproate (VPA) in the treatment of epilepsy

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ACTA PHYSIOL.PHARMACOL. THER. LATINOAM. (Argentina), 1993, 43/1-2 (20-27)

Several lines of evidence have shown that sodium valproate (VPA) mechanism of action in the therapy of epilepsy is based on the phenomena of its interaction with neurotransmitters (GABA), receptor sites and ion channels. However, there is no conclusive evidence to show the extent of VPA interactions with other neurotransmitters in the brain. Based on this fact, taurine (an amino acid 'neurotransmitter') found distributed in the brain the visual system may probably be involved in the drug action mechanism of VPA. The application of taurine in experimental and human epilepsy started over thirty years ago and it has been known to possess some mild anticonvulsant activity in both humans and experimental animal models. This review, therefore, will attempt to draw together all the available information on the involvement of taurine in epilepsy and its possible association with the action mechanism of VPA in suppressing epileptic seizures. Structural and physiological distribution of taurine in the brain will be discussed. Its association with the phenomena of VPA action in epilepsy will be cited. Its neurotransmitter candidacy, involvement in ocular pathology, receptor sites and modulatory activity will be dealt with in relation to valproate action in the therapy of epilepsy.

Seizure related elevations of extracellular amino acids in human focalepilepsy

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Neurosci Lett (NETHERLANDS) Jun 8 1992, 140 (1) p30-2

Intracerebral microdialysis combined with electrocorticographic recordings was used in a patient subjected to epilepsy surgery. The patient developed a series of partial seizures during an 8 min period. Marked elevations of aspartate (79-fold), glycine (21-fold), glutamate (16-fold) and serine (8-fold) dialysate concentrations occurred in association with onset of the period with seizures. Recurrent seizures occurred, in spite of normalizing amino acid levels. Other amino acids analyzed (aspargine, threonine, arginine, alanine , taurine, tyrosine, phenylalanine, isoleucine and leucine) showed less pronounced changes (1-5 times the basal levels).

Effect of sustained pyridoxine treatment on seizure susceptibility and regional brain amino acid levels in genetically epilepsy-prone BALB/c mice

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EPILEPSIA (USA) , 1993, 34/1 (33-42)

Epilepsy-prone and epilepsy-resistant substrains were selectively bred from a strain of BALB/c mice; audiogenic-sensitive epilepsy-prone animals showed enhanced sensitivity to chemical convulsants. Treatment with pyridoxine (100 mg/L in drinking water) initiated at mating and continued throughout pregnancy and the life of the offspring abolished the enhanced sensitivity to chemical convulsants and reduced the severity of audiogenic seizures. Withdrawal of pyridoxine restored the enhanced seizure sensitivity. (1H) Nuclear magnetic resonance (NMR) spectroscopy of perchloric acid extracts of tissue was used to determine the concentrations of several compounds (N-acetylaspartate (NAA), GABA, glutamate, aspartate, alanine, taurine, creatine, cholines, inositol) in the hippocampus, neocortex, brainstem, and cerebellum of untreated and pyridoxine-treated 6-week-old female animals. The ratios of the concentrations of excitatory to inhibitory putative neurotransmitter amino acids tended to be higher in epilepsy-prone animals, with the most pronounced difference being a significantly elevated glutamate/GABA ratio in every brain region examined. Pyridoxine treatment abolished this imbalance in the hippocampus, brainstem, and cerebellum, but not in the neocortex. Treatment of epilepsy-resistant animals with pyridoxine using the same protocol decreased the glutamate/GABA concentration ratio in the hippocampus, brainstem, and neocortex and resulted in impaired development of the animals. The amino acid imbalance and the accompanying seizure susceptibility in these genetically epilepsy prone mice may originate from an inborn error in pyridoxine metabolism or in a pyridoxine-dependent enzyme system.

Interictal behavioral alterations and cerebrospinal fluid amino acid changes in a chronic seizure model of temporal lobe epilepsy

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EPILEPSIA (USA), 1991, 32/6 (767-777)

This study extends our previous work in which we described the presence of an interictal behavioral disturbance in a chronic animal model of temporal lobe epilepsy (TLE). In this study, we investigated the cerebrospinal fluid (CSF) neurotransmitter changes underlying the development of chronic recurrent seizures of temporal lobe origin and interictal behavioral disturbance in cats made epileptic after intrahippocampal injection of kainic acid (KA). Using high-performance liquidchromatography, we measured 22 putative neurotransmitter amino acids. After intrahippocampal KA injection, cats developed an initial acute period of intense seizure activity. Cisternal CSF amino acids, which were repeatedly sampled during the acute period through a permanent indwelling cannula, were unchanged apart from a mild elevation in CSF alanine. The high-level seizure activity gradually decreased, and cats entered a chronic epileptic period characterized by recurrent yet intermittent temporal lobe seizures. CSF GABA levels during the chronic epileptic period were significantly decreased. In contrast, CSF levels of other amino acids - alanine, tyrosine, taurine, aspartic acid, and glutamic acid - did not change significantly. Behavioral testing also showed a heightened interictal defensive reactivity during the chronic epileptic period. To the extent that CSF GABA concentration reflects brain GABA concentration, this study suggests that a decrease in brain GABA may contribute both to the epilepsy and interictal emotional lability of animals with a chronic seizure disorder of temporal lobe origin.

Protection of the brain by carnitine

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Journal of Occupational Health (Japan) , 1995, 37/2 (75-82)

Carnitine (beta-hydroxy-gamma-trimethylammonium butyrate) is widely distributed in the body including the nervous system. Its physiological function, viz. a carrier of long-chain fatty acids through the inner mitochondrial membrane, has been well established. In this review, mainly based on our experiments, we discuss the possibility that carnitine may have effects other than the 'physiological' function and that it may be a potent protector of the brain. When mice were exposed to ammonia (intraperitoneal injection of ammonium acetate), they developed seizures and concentrations of brain energy metabolites were altered; ATP and phosphocreatine decreased while ADP, AMP, pyruvate and lactate increased. The seizures and changes in brain energy metabolites were clearly suppressed when the mice were pre-treated with carnitine. Furthermore, changes in energy metabolites in the brain caused by severe ischemia (decapitation) were also suppressed by carnitine. Since D-carnitine showed

similar effects as those of L-carnitine, the effects seem due to function(s) of carnitine yet to be defined. Intrinsic substances including carnitine appear to deserve further studies for possible use in protecting the brain.

Increased plasma glutamic acid in a genetic model of epilepsy

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NEUROCHEM. RES. (USA) , 1992, 17/3 (293-296)

A significant increase in the plasma levels of glutamic acid and a significant decrease in aspartic acid and taurine in epileptic patients and their first degree relatives was reported more than a decade ago and an underlying genetic basis for these amino acid changes was suggested. The main objective of the present study was to determine the plasma levels of glutamic acid, aspartic acid and taurine in El mice which are an inbred epileptic mutant mouse strain. The results show a significant increase in plasma glutamic acid but no changes in aspartic acid or taurine in the epileptic mice as compared to controls. The data provide the first evidence of a significant increase in plasma glutamic acid in an animal model of hereditary epilepsy and substantiate the hypothesis that a genetic defect underlies the elevated plasma glutamic acid levels in association with epilepsy. The findings are also compatible with neurochemical and neurophysiological evidence implicating glutamic acid in the mechanism of seizures.

Differential changes in induced seizures after hippocampal treatment of rats with an antisense oligodeoxynucleotide to the GABA(A) receptor gamma2 subunit

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Eur J Pharmacol (NETHERLANDS) Dec 11 1997, 340 (2-3) p153-60

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the brain. Impairment of GABAergic neurotransmission may be involved in the pathogenesis of epileptic phenomena. We have previously characterized biochemical and histological changes following unilateral intrahippocampal infusion of a phosphorothioate antisense oligodeoxynucleotide to the GABA(A) receptor gamma2 subunit in rats in vivo. The aim of the present study was to investigate the behavioral changes of rats following unilateral hippocampal antisense 'knockdown' of the GABA(A) receptor gamma2 subunit. Antisense, but not mismatch control oligodeoxynucleotide treated rats had a significant weight loss (10%) during 6 d of treatment. Antisense treated rats exhibited no changes in spontaneous behavior, including anxiety?like behavior as measured in the social interaction test, compared to mismatch oligodeoxynucleotide treated rats. However, antisense treated rats developed pronounced changes in induced seizure activity. Seizures induced by subcutaneously injected pentylenetetrazol were markedly accentuated in antisense treated rats compared to treatment naive rats, whereas mismatch treated rats showed a lower seizure score than that of naive

rats. Antisense treated rats had a significantly elevated threshold for seizures induced by electrical stimulation in the maximal electroshock seizure threshold test. The results suggest that intrahippocampal infusion of antisense oligodeoxynucleotide to the GABA(A) receptor gamma2 subunit leads to specific alterations in the sensitivity to induced seizures . The results are viewed as consequences of selective down-regulation of GABA(A) receptors and diminished inhibitory neurotransmission in the hippocampus.

Disappearance of neonatal seizures and low CSF GABA levels after treatment with vitamin B6

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Epilepsy Res (NETHERLANDS) Mar 1987, 1 (2) p152-4

In an infant with neonatal seizures, CSF GABA levels were determined before and after treatment with vitamin B6. Before onset of treatment, the level of GABA in CSF was very low (13 pmol/ml). Injection of vitamin B6 blocked the seizures immediately. When GABA level in CSF was again analysed after continued treatment with vitamin B6, a value of 127 pmol/ml was determined, which is within the normal concentration range in children. The data substantiate previous findings in brain tissue from a patient with vitamin B6-dependent seizures , and strongly indicate that impairment of central GABAergic activity was the cause of the seizures .

Effects of soman-induced seizures on different extracellular amino acid levels and on glutamate uptake in rat hippocampus

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BRAIN RES. (Netherlands), 1991, 563/1-2 (234-240)

Extracellular amino acid levels in CA3 and CA1 fields of rat hippocampus, an area highly sensitive to seizures, were determined by intracranial microdialysis during seizures induced by systemic administration of soman (o-1,2,2-trimethylpropyl methylphosphonofluoridate), a potent inhibitor of acetylcholinesterase. The glutamate uptake level was determined on another series of animals in hippocampus homogenates. An early and transient increase in the extracellular glutamate level occurred in CA3 within 30 min of seizures, with correlated brief elevations of taurine, glycine and glutamine levels. The glutamate level increased early in CA1, declined and then became more sustained (after 50 min of seizures). Apparent elevations of taurine, glycine and glutamine levels in CA1 accompanied changes in glutamate concentrations. Changes of glutamate level correlated with an increase in the glutamate uptake which rapidly declined after 40 min of seizures. The role of the transient release of glutamate in CA3 and of the sustained release in CA1 in prolonged soman-induced seizures is

considered. The correlation between glutamate and other amino acid release is studied.

Topiramate increases brain GABA, homocarnosine, and pyrrolidinone in patients with epilepsy

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Neurology (NEUROLOGY) (United States) 1999, 52/3 (473-478)

Objective: To measure the effects of topiramate on brain gamma-aminobutyric acid (GABA) in patients with epilepsy. Background: Topiramate is a new antiepileptic medication with multiple putative mechanisms of action. In a recent meta-analysis of the newer antiepileptic drugs, topiramate was the most potent. Homocarnosine and pyrrolidinone are important metabolites of GABA with antiepileptic actions. Methods: in vivo measurements of GABA, homocarnosine, and pyrrolidinone were made of a 14-cmsup 3 volume in the occipital cortex using sup 1H spectroscopy with a 2.1-Tesla magnetic resonance spectrometer and an 8-cm surface coil. Twelve patients (eight women) with refractory complex partial seizures were studied while using topiramate. Nine epilepsy-free, drug-free volunteers served as control subjects. Results: Topiramate increased mean brain GABA, homocarnosine, and pyrrolidinone concentrations in all patients. In paired measurements, brain GABA increased by 0.7 malemol/g (SD 0.3, n 7, 95% CI 0.4 to 1.0, < 0.01). Homocarnosine increased by 0.5 mumol/g (SD 0.2, n 7, 95% CI 0.3 to 0.7, < 0.001). Pyrrolidinone increased by 0.21 mumol/g (SD 0.06, n 7, 95% CI 0.16 to 0.27, < 0.01). In two additional patients, GABA, homocarnosine, and pyrrolidinone increased after they were switched from vigabatrin to topiramate. Conclusions: Topiramate increased brain GABA, homocarnosine, and pyrrolidinone to levels that could contribute to its potent antiepileptic action in patients with complex partial seizures.

Intracerebral microdialysis of extracellular amino acids in the human epileptic focus

Ronne-Engstrom E.; Hillered L.; Flink R.; Spannare B.; Ungerstedt U.; Carlson H. Department of Neurosurgery, University Hospital, S-751 85 Uppsala Sweden

J. CEREB. BLOOD FLOW METAB. (USA) , 1992, 12/5 (873-876)

Extracellular levels of aspartate (ASP), glutamate (GLU), serine (SER), asparagine (ASN), glycine (GLY), threonine (THR), arginine (ARG), alanine (ALA), taurine (TAU), tyrosine (TYR), phenylalanine (PHE), isoleucine (ILEU), and leucine (LEU) were monitored by using intracerebral microdialysis in seven patients with medically intractable epilepsy, undergoing epilepsy surgery. In association with focal seizures, dramatic increases of the extracellular ASP, GLU, GLY, and SER concentrations were observed. The other amino acids analyzed, including TAU, showed small changes. The results support the hypothesis that

ASP, GLU, GLY, and possibly SER, play an important role in the mechanism of seizure activity and seizure-related brain damage in the human epileptic focus.

Excitatory and inhibitory amino acid levels in the cerebrospinal fluids of children with neurological disorders

Shen E.-Y.; Lai Y.-J.; Ho C.-S.; Lee Y.-L. Dr. E.-Y. Shen, Department of Pediatrics, Mackay Memorial Hospital, Chung-San North Road, 104, Taipei Taiwan

Acta Paediatrica Sinica (ACTA PAEDIATR. SIN.) (Taiwan) 1999, 40/2 (65-69)

Measurement of amino acid levels in the cerebrospinal fluid (CSF) of children with various neurological disorders was performed with high performance liquid chromatography (HPLC). Glutamate increased in patients with bacterial meningitis, aseptic meningitis and encephalitis. Aspartate increased in bacterial meningitis and seizure disorders. Glycine increased in both bacterial and aseptic meningitis. Taurine increased in bacterial meningitis and encephalitis. GABA, the main inhibitory amino acid, increased in encephalitis. Excitatory and inhibitory amino acids are richly distributed in brain tissue and are related to neuron activity. Changes in amino acid levels in the CSF may reflect the pathologic state and severity of brain insults, and may be useful in monitoring disease processes. Further study is necessary to determine whether CSF aminos acid levels have a role in practical clinical application.

16. Glaucoma

Preventative and curative options include:

Methylcobalamin, aminoguanidine, alpha-lipoic acid, n-acetyl-L-carnosine drops, magnesium, zinc, chromium, selenium, vitamin A, thiamine, vitamin C, bioflavonoids, grape-seed-skin extract, vitamin E, bilberry, acetyl-L-carnitine, vitamin A. coleus forskohlii.

Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons.

Akaike A, Tamura Y, Sato Y, Yokota T. Department of Neuropharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Japan.

Eur J Pharmacol 1993 Sep 7;241(1):1-6

The effects of methylcobalamin, a vitamin B12 analog, on glutamate-induced neurotoxicity were examined using cultured rat cortical neurons. Cell viability was markedly reduced by a brief exposure to glutamate followed by incubation with glutamate-free medium for 1 h. Glutamate cytotoxicity was prevented when the cultures were maintained in methylcobalamin-containing medium. Glutamate cytotoxicity was also prevented by chronic exposure to S-adenosylmethionine, which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and S-adenosylmethionine also inhibited the cytotoxicity induced by N-methyl-D-aspartate or sodium nitroprusside that releases nitric oxide. In cultures maintained in a standard medium, glutamate cytotoxicity was not affected by adding methylcobalamin to the glutamate-containing medium. In contrast, acute exposure to MK-801, a NMDA receptor antagonist, prevented glutamate cytotoxicity. These results indicate that chronic exposure to methylcobalamin protects cortical neurons against NMDA receptor-mediated glutamate cytotoxicity.

Blood levels of thiamine and ascorbic acid in chronic open-angle glaucoma.

Asregadoo ER

Ann Ophthalmol (United States) Jul 1979, 11 (7) p1095-1100

Blood levels of thiamine and ascorbic acid in chronic open-angle glaucoma are determined in this study. Dietary vitamin intake was compared with thiamine and ascorbic acid blood levels in a sample of 38 patients with glaucoma and 12 controls. These patients had a statistically significant lower thiamine blood level than controls (P less than 0.001), but no significant difference was found for ascorbic acid blood levels. Poor absorption of thiamine occurred in the glaucomatous patients in this study.

Forskolin lowers intraocular pressure by reducing aqueous inflow.

Caprioli J, Sears M, Bausher L, Gregory D, Mead A.

Invest Ophthalmol Vis Sci 1984 Mar;25(3):268-77

Forskolin is a diterpene derivative of the plant Coleus forskohlii that stimulates adenylate cyclase activity without interacting with cell surface receptors. Forskolin lowers the intraocular pressure of rabbits, monkeys, and humans. In rabbits, net aqueous humor inflow decreases, outflow facility remains unchanged, and ciliary blood flow increases. Tolerance to the intraocular pressure lowering effect did not occur in rabbits after topical doses given every 6 hr for 15 days. In vitro forskolin activates adenylate cyclase of crude particulate homogenates prepared from cultured human ciliary epithelia or from dissected ciliary epithelial processes of rabbit or human eyes. This activation is not blocked by timolol. The stimulation of adenylate cyclase by isoproterenol in vitro is potentiated in the presence of forskolin. Forskolin represents a potentially useful class of antiglaucoma agents differing in molecular mechanism of action from previously used drugs.

[Lipoic acid as a means of metabolic therapy of open-angle glaucoma].
[Article in Russian]

Filina AA, Davydova NG, Endrikhovskii SN, Shamshinova AM

Vestn Oftalmol 1995 Oct-Dec;111(4):6-8

A total of 45 patients (90 eyes) with stages I and II open-angle glaucoma (OAG) were examined, 26 of these were administered lipoic acid in a daily dose of 0.075 g for 2 months and 19 were given 0.15 g daily for 1 month. Control group consisted of 31 patients with OAG who were administered only local hypotensive therapy. Vision acuity and visual field were checked up, tonometry, tonography, and campimetry carried out, and levels of nonprotein SH-groups and activity of gamma-glutamyl transpeptidase measured in the lacrimal fluid. Improvement of the biochemical parameters, visual function, and of the coefficient of efficacy of liquid discharge was more expressed in the patients administered lipoic acid in a daily dose of 0.15 g. Color campimetry results indicate improved sensitivity of the visual analyzer under the effect of treatment. Improvement was attained in approximately 45-47.5% of examined eyes, and was more often seen in patients with stage II OAG: in 57-58% eyes. The effect of lipoic acid may be explained by its antioxidant properties and direct influence on ocular tissue metabolism.

Natural therapies for ocular disorders, part two: cataracts and glaucoma.

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Altern Med Rev 2001 Apr;6(2):141-66

Pathophysiological mechanisms of cataract formation include deficient glutathione levels contributing to a faulty antioxidant defense system within the lens of the eye. Nutrients to increase glutathione levels and activity include lipoic acid, vitamins E and C, and selenium. Cataract patients also tend to be deficient in vitamin A and the carotenes, lutein and zeaxanthin. The B vitamin riboflavin appears to play an essential role as a precursor to flavin adenine dinucleotide (FAD), a co-factor for glutathione reductase activity. Other nutrients and botanicals, which may benefit cataract patients or help prevent cataracts, include pantethine, folic acid, melatonin, and bilberry. Diabetic cataracts are caused by an elevation of polyols within the lens of the eye catalyzed by the enzyme aldose reductase. Flavonoids, particularly quercetin and its derivatives, are potent inhibitors of aldose reductase. Glaucoma is characterized by increased intraocular pressure (IOP) in some but not all cases. Some patients with glaucoma have normal IOP but poor circulation, resulting in damage to the optic nerve. Faulty glycosaminoglycan (GAG) synthesis or breakdown in the trabecular meshwork associated with aqueous outflow has also been implicated. Similar to patients with cataracts, those with glaucoma typically have compromised antioxidant defense systems as well. Nutrients that can impact GAGs such as vitamin C and glucosamine sulfate may hold promise for glaucoma treatment. Vitamin C in high doses has been found to lower IOP via its osmotic effect. Other nutrients holding some potential benefit for glaucoma include lipoic acid, vitamin B12, magnesium, and melatonin. Botanicals may offer some therapeutic potential. Ginkgo biloba increases circulation to the optic nerve; forskolin (an extract from Coleus forskohlii) has been used successfully as a topical agent to lower IOP; and intramuscular injections of Salvia miltiorrhiza have shown benefit in improving visual acuity and peripheral vision in people with glaucoma.

Protective effects of methylcobalamin, a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell culture.

Kikuchi M, Kashii S, Honda Y, Tamura Y, Kaneda K, Akaike A. Department of Ophthalmology, Graduate School of Medicine, Faculty of Pharmaceutical Sciences, Kyoto University, Japan.

Invest Ophthalmol Vis Sci 1997 Apr;38(5):848-54

PURPOSE: To examine the effects of methylcobalamin on glutamate-induced neurotoxicity in the cultured retinal neurons. METHODS: Primary cultures obtained from the fetal rat retina (gestation days 16 to 19) were used for the experiment. The neurotoxicity was assessed quantitatively using the trypan blue exclusion method. RESULTS: Glutamate neurotoxicity was prevented by chronic exposure to methylcobalamin and S-adenosylmethionine (SAM), which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and SAM also inhibited the neurotoxicity induced by sodium nitroprusside that release nitric oxide. By contrast, acute exposure to methylcobalamin did not protect retinal neurons against glutamate neurotoxicity. CONCLUSIONS: Chronic administration of methylcobalamin protects cultured retinal neurons against N-methyl-D-aspartate-receptor-mediated glutamate

neurotoxicity, probably by altering the membrane properties through SAM-mediated methylation.

[The antioxidant activity of the lacrimal fluid in patients with primary open-angle glaucoma]. [Article in Russian]

Makashova NV, Babenkova IV, Teselkin IuO

Vestn Oftalmol 1999 Sep-Oct;115(5):3-4

Antioxidant activity (AOA) of lacrimal fluid and blood plasma was studied in 10 normal subjects (20 eyes) and 35 patients with primary open-angle glaucoma (POAG) (67 eyes with glaucoma at different stages). The findings indicate that the progress of glaucoma is paralleled by a gradual decrease in the lacrimal fluid AOA, which becomes significant at the third stage of POAG. Plasma AOA also decreased significantly in the third far advanced stage. A course of total antioxidant therapy including oral aevit and vitamin complexes and intramuscular ascorbic acid normalized plasma AOA even in patients with far advanced glaucoma, while the lacrimal AOA did not normalize. Therefore, local antioxidants are preferable in glaucoma patients.

Nitric oxide mediates excitotoxic and anoxic damage in rat retinal ganglion cells cocultured with astroglia.

Morgan J, Caprioli J, Koseki Y. Cardiff Eye Unit, University Hospital of Wales.

Arch Ophthalmol 1999 Nov;117(11):1524-9

BACKGROUND: Nitric oxide has been implicated in the process of retinal ganglion cell death in glaucoma. OBJECTIVE: To investigate the role of nitric oxide in mediating retinal ganglion cell death in a culture system that models glial-neuronal interactions at the level of the optic nerve head. METHODS: Dissociated retinal ganglion cells from neonatal rats were plated on monolayers of astroglia and identified by retrograde labeling with the fluorescent marker 1.1-dioctadecyl-,3,3,3,tetramethylindocarbocyanineperchlorate. Two days after dissociation, cocultures of retinal ganglion cells and glia were treated with graded concentrations of the nitric oxide synthase inhibitor N-nitro-L-arginine (NNA), and exposed to either anoxia for 1 to 24 hours or excitatory amino acids for 6 hours. Surviving retinal ganglion cells were counted with fluorescence microscopy and expressed as a percentage of retinal ganglion cells surviving in control cultures. RESULTS: Cell survival after anoxia increased in a dose-dependent fashion with exposure to NNA. Mean +/- SD survival rate of retinal ganglion cells after 6 hours of anoxia was 57%+/-10% with NNA treatment compared with 31%+/-3% without treatment ($P<.01$). When treated with excitatory amino acids, cell survival was 31%+/-6% after administration of N-methyl D-aspartate, 500 micromol/L, and 27%+/-8% after administration of sodium glutamate, 500 micromol/L. Survival was increased in cultures with exposure to NNA, 100 micromol/L, to 53%+/-11% and 69%+/-11%, respectively ($P<.01$). CONCLUSION: In this coculture of retinal ganglion cells and astroglia,

reduction of the glial source of nitric oxide through nitric oxide synthase inhibition provided partial but significant protection against the lethal effects of anoxia and excitatory amino acids on retinal ganglion cells. CLINICAL RELEVANCE: Neuroprotective agents may play a role in patients with glaucoma who have progressive visual field loss, despite satisfactory control of intraocular pressure. Inhibition of nitric oxide synthase at the level of the optic nerve head may contribute to a clinically significant level of neuroprotection.

Ascorbic acid in the treatment of alkali burns of the eye.

Pfister RR, Paterson CA.

Ophthalmology 1980 Oct;87(10):1050-7

Severe ocular alkali burns in rabbits result in a decrease in aqueous humor ascorbate levels to one-third normal levels. If this deficiency is reversed by immediate treatment with parenteral or topical ascorbate, there is a significantly decreased incidence of subsequent corneal ulceration and perforation. The morphologic changes in these ulcerating corneas are typical of those noted in scorbutus (scurvy). It is concluded that alkali injury to the ciliary epithelial transport processes or ciliary body vasculature results in localized deficiency of ascorbic acid in the aqueous humor and cornea. The development of corneal ulceration is thought to be based on this deficiency which results in the failure of fibroblasts to produce sufficient collagen for repair. A randomized clinical trial of ascorbic acid in the treatment of human alkali burned eyes is now underway.

Optic neuropathy from thiamine deficiency in a patient with ulcerative colitis.

van Noort BA, Bos PJ, Klopping C, Wilmink JM. Department of Ophthalmology, University of Amsterdam, The Netherlands.

Doc Ophthalmol 1987 Sep-Oct;67(1-2):45-51

A 35-year-old man with ulcerative colitis who was receiving parenteral feeding with large amounts of glucose, suddenly developed severe optic neuropathy and oculomotor palsy. The visual acuity fell bilaterally to 0. Although it was stated that thiamine has been regularly supplemented in the preceding period, high doses of vitamin B1 were given. Visual acuity promptly returned to 1.0 but large visual field defects persisted. Later on it appeared that erroneously no vitamin B1 has been given before.

Hyperbaric oxygen dose of choice in the treatment of glaucoma.

Bojic L, Kovacevic H, Andric D, Romanovic D, Petri NM. Department of Ophthalmology, New Hospital, Split, Croatia.

Arh Hig Rada Toksikol 1993 Sep;44(3):239-47

The subjects in the study were 111 patients with open angle glaucoma who were submitted to treatment by hyperbaric oxygenation. Two groups were formed at random, an experimental one of 91 patients and a control group of 20 patients. The experimental group consisted of four subgroups classified according to the course of treatment they received: 30 sessions (31 patients), 20 sessions (20 patients), 15 sessions (20 patients) and 10 sessions (20 patients). For the treatment a large walk-in recompression chamber was utilized, once a day, at a pressure of 2.0 bars, for 90 minutes. Visual acuity and mean intraocular pressure values taken before and after hyperbaric oxygen treatment did not show a statistically significant difference either between the treated and control subjects, or at control examinations after three and six months. During the follow-up period, changes in the visual field area in control subjects were discrete and statistically not significant. At the same time the visual field values increased after the therapy in all the subgroups. In the 10-session course subgroup the increase was not statistically significant. In all other dubgroups, statistical significance was at the level of $P < 0.01$. Control after three months demonstrated the same level of statistical significance; control at the end of six months failed to show a statistically significant difference. The 20-session course is recommended for initial treatment. When visual field values return to 50 percent of the improved values achieved during initial treatment, it is suggested that hyperbaric oxygen treatment be repeated.

Nutrient antioxidants in oregano.

Lagouri V, Boskou D. Laboratory of Food Chemistry and Technology, Faculty of Chemistry, Aristotle University, Thessaloniki, Greece.

Int J Food Sci Nutr 1996 Nov;47(6):493-7

Oregano and its various extracts have been studied as inhibitors of autoxidation but so far the research work has focused mainly on the polar non nutrient compounds. Very little is known about the non polar fraction extracted by hexane which is also antioxidant and has been reported to suppress the mutagenicity of Trp-P-2, a dietary carcinogen. In this work four different species of oregano, Origanum vulgare subsp. hirtum, Satureja thymbra, Origanum dictamnus and Origanum onites, were extracted with hexane. The extracts were saponified and in the unsaponifiable fraction thin layer chromatography and high performance liquid chromatography were applied for the isolation, detection and determination of tocopherols. The four known homologues of tocopherol, alpha-, beta-, gamma- and delta-, were found to be present in all the samples but the concentration of the gamma-

Aqueous humour and serum zinc and copper concentrations of patients with glaucoma and cataract

Akyol N.; Deger O.; Keha E.E.; Kilic S. Dept of Ophthalmology, Faculty of Medicine, Karadeniz Tech University,61080 Trabzon Turkey

British Journal of Ophthalmology (United Kingdom) 1990, 74/11 (661-662)

Serum and aqueous humour zinc and copper concentrations of 44 patients with glaucoma and cataract were determined. Serum values were found within normal ranges. The highest mean copper concentration was seen in the glaucoma group. In addition there was a significant negative correlation between the aqueous humour levels of zinc and copper in patients with glaucoma. It was concluded that an increased copper value together with a low zinc value might be of importance in patients with glaucoma.

Vitamins B 1 and PP in treating glaucomatous patients (Russian)

Zhukovsky V.S. Kaf. Glazn. Bol., Fak. Usover. Vrachej, Med. Inst., L'vov Russia

Vestnik Oftalmologii 1974, No.3/- (19-21)

The supply of and demand for thiamine were studied in 142 glaucomatous patients. Thiamine deficiency was found in all these patients, being however more pronounced in cases of secondary and congestive glaucoma and after antiglaucomatous operations. Seasonal fluctuations in the supply were recorded. In winter and spring the thiamine dosages administered daily were 8 mg parenterally and 12 mg orally, while in summer and fall they were 6 and 10 mg, respectively. With these doses saturation of the body supervened on the 2nd to 4th day in cases of simple glaucoma and on the 4th to 6th day during glaucoma attacks and after surgery. An improvement of visual functions could then be observed.

Forskolin lowers intraocular pressure by reducing aqueous inflow

Caprioli J.; Sears M.; Bausher L.; et al. Department of Ophthalmology and Visual Science, Yale University School of Medicine, Box 3333, New Haven, CT 06510 USA

Invest. Ophthalmol. Visual Sci. (USA), 1984, 25/3 (268-276)

Forskolin is a diterpene derivative of the plant Coleus forskohlii that stimulates adenylate cyclase activity without interacting with cell surface receptors. Forskolin lowers the intraocular pressure of rabbits, monkeys, and humans. In rabbits, net aqueous humor inflow decreases, outflow facility remains unchanged, and ciliary blood flow increases. Tolerance to the intraocular pressure lowering effect did not occur in rabbits after topical doses given every 6 hr for 15 days. In vitro forskolin activates adenylate cyclase of crude particulate homogenates prepared from cultured human ciliary epithelia or from dissected ciliary epithelial processes of rabbit or human eyes. This activation is not blocked by timolol. The stimulation of adenylate cyclase by isoproterenol in vitro is potentiated in the presence of forskolin. Forskolin represents a potentially useful class of antiglaucoma agents differing in molecular mechanism of action from previously used drugs.

17. HIV and AIDS

Preventative and curative options include:

NAC, Vitamin C, Alpha-lipoic acid, Whey protein, SAMe, Glutathione, Co-Enzyme Q10, Beta carotene, Vitamin A, Vitamin E, Vitamin B12, Vitamin B6, Folic acid, TMG, Lactoferrin, Silibinin, Plant sterols, Selenium, Zinc, Magnesium, L-Glutamine, L-Carnitine, Olive leaf extract, Digestive Enzymes, Growth Hormone, Melatonin, DHEA.

Effects of glutamine-supplemented diets on immunology of the gut.

Alverdy JC. Department of Surgery, Michael Reese Hospital and Medical Center, Chicago, Illinois.

J Parenter Enteral Nutr 1990 Jul-Aug;14(4 Suppl):109S-113S

Recent research developments have identified the gastrointestinal tract as the most metabolically active organ after surgical stress. In addition to fulfilling its role as an organ of digestion and absorption, the gut must maintain immunologic function in order to protect the host from invading pathogens. Central to the function of the intestinal immune system is the expression of secretory IgA, the most abundant immunoglobulin in external secretions. The synthesis and expression of IgA in secretions appear to be sensitive to dietary alteration and may be impaired after surgical stress. Data are presented suggesting that maintenance of gut mass and barrier function to bacteria via dietary manipulation may be essential to ensure host survival during critical illness.

Markedly disturbed glutathione redox status in CD45RA+CD4+ lymphocytes in human immunodeficiency virus type 1 infection is associated with selective depletion of this lymphocyte subset.

Aukrust P, Svardal AM, Muller F, Lunden B, Nordoy I, Froland SS. Medical Department A, University of Oslo, National Hospital, Norway.

Blood 1996 Oct 1;88(7):2626-33

We investigated the percentage of CD45RA+ and CD45RO+ T cells in peripheral blood and the intracellular glutathione redox balance in these lymphocyte subsets in patients with human immunodeficiency virus type 1 (HIV-1) infection and healthy controls. In HIV-1-infected patients there was a preferential depletion of CD45RA+CD4+ cells, which was most pronounced in symptomatic patients. In CD4+ lymphocytes from HIV-1-infected patients the glutathione abnormalities were clearly most pronounced in the CD45RA+ subset with a marked increase in

level of oxidized glutathione and decreased ratio of reduced to total glutathione as the major characteristics. These abnormalities were shown in CD45RA+ CD4+ lymphocytes from both symptomatic and asymptomatic patients, whereas similar abnormalities in CD45RO+CD4+ cells were found only in symptomatic patients. The glutathione abnormalities in CD45RA+CD4+ lymphocytes were significantly correlated with low numbers of total CD4+ lymphocytes, decreased proportion of CD45RA+CD4+ lymphocytes, and raised serum levels of tumor necrosis factor-alpha. In the CD8+ lymphocytes a decrease in both proportion and absolute numbers of CD45RA+ cells was found, with markedly increased level of oxidized glutathione and decreased ratio of reduced to total glutathione in this subset. These findings suggest that glutathione redox disturbances in CD45RA+ T cells may be of pathogenic importance for the preferential depletion of this subset considered to represent naive T cells, during HIV-1 infection.

Preventive actions of a synthetic antioxidant in a novel animal model of AIDS dementia.

Bjugstad KB, Flitter WD, Garland WA, Su GC, Arendash GW. Dept. of Psychology, University of South Florida, Tampa, FL 33620, USA.

Brain Res 1998 Jun 8;795(1-2):349-57

Accumulating evidence indicates that the mechanism for causing AIDS dementia complex (ADC) involves the release of damaging inflammatory-related agents by HIV-infected microglia in the brain resulting in CNS oxidative damage. One such agent, tumor necrosis factor alpha (TNF-alpha) is consistently elevated in the brains of ADC patients compared to non-demented HIV patients. To model this aspect of ADC in rats, chronic ventricular infusions of TNF-alpha were given and found to induce several aspects of ADC, including weight loss, learning/memory impairment, enlarged lateral ventricles, and increased apoptosis. Concurrent oral treatment with the antioxidant CPI-1189 prevented all of these TNF-alpha induced effects. The results support TNF-alpha as a key toxic agent in ADC and provide the first in vivo evidence that chronic treatment with a synthetic antioxidant may protect HIV-infected patients against ADC. Our findings may also have implications in other neurological diseases where brain TNF-alpha levels are elevated and inflammation/oxidative stress is suspected to be a contributing cause, such as Alzheimer's disease and Parkinson's disease.

Plant sterols and sterolins: a review of their immune-modulating properties.

Bouic PJ, Lamprecht JH. Department of Medical Microbiology, Medical Faculty, University of Stellenbosch. Tygerberg 7505, South Africa. pjdb@gerga.sun.ac.za

Altern Med Rev 1999 Jun;4(3):170-7

Beta-sitosterol (BSS) and its glycoside (BSSG) are sterol molecules which are synthesized by plants. When humans eat plant foods phytosterols are ingested, and are found in the serum and tissues of healthy individuals, but at

concentrations orders of magnitude lower than endogenous cholesterol. Epidemiological studies have correlated a reduced risk of numerous diseases with a diet high in fruits and vegetables, and have concluded that specific molecules, including b-carotene, tocopherols, vitamin C, and flavonoids, confer some of this protective benefit. However, these epidemiologic studies have not examined the potential effect that phytosterols ingested with fruits and vegetables might have on disease risk reduction. In animals, BSS and BSSG have been shown to exhibit anti-inflammatory, anti-neoplastic, anti-pyretic, and immune-modulating activity. A proprietary BSS:BSSG mixture has demonstrated promising results in a number of studies, including in vitro studies, animal models, and human clinical trials. This phytosterol complex seems to target specific T-helper lymphocytes, the Th1 and Th2 cells, helping normalize their functioning and resulting in improved T-lymphocyte and natural killer cell activity. A dampening effect on overactive antibody responses has also been seen, as well as normalization of the DHEA:cortisol ratio. The re-establishment of these immune parameters may be of help in numerous disease processes relating to chronic immune-mediated abnormalities, including chronic viral infections, tuberculosis, rheumatoid arthritis, allergies, cancer, and auto-immune diseases.

Improvement of immune functions in HIV infection by sulfur supplementation: two randomized trials.

Breitkreutz R, Pittack N, Nebe CT, Schuster D, Brust J, Beichert M, Hack V, Daniel V, Edler L, Droge W. Deutsches Krebsforschungszentrum, Division of Immunochemistry, Heidelberg, Germany.

J Mol Med 2000;78(1):55-62

To determine the therapeutic effect of sulfur amino acid supplementation in HIV infection we randomized 40 patients with antiretroviral therapy (ART; study 1) and 29 patients without ART (study 2) to treatment for 7 months with N-acetyl-cysteine or placebo at an individually adjusted dose according to a defined scheme. The main outcome measures were the change in immunological parameters including natural killer (NK) cell and T cell functions and the viral load. Both studies showed consistently that N-acetyl-cysteine causes a marked increase in immunological functions and plasma albumin concentrations. The effect of N-acetyl-cysteine on the viral load, in contrast, was not consistent and may warrant further studies. Our findings suggest that the impairment of immunological functions in HIV+ patients results at least partly from cysteine deficiency. Because immune reconstitution is a widely accepted aim of HIV treatment, N-acetyl-cysteine treatment may be recommended for patients with and without ART. Our previous report on the massive loss of sulfur in HIV-infected subjects and the present demonstration of the immunoreconstituting effect of cysteine supplementation indicate that the HIV-induced cysteine depletion is a novel mechanism by which a virus destroys the immune defense of the host and escapes immune elimination.

Biochemistry and pharmacology of S-adenosyl-L-methionine and rationale for its use in liver disease.

Chawla RK, Bonkovsky HL, Galambos JT. Department of Medicine, Emory University School of Medicine, Atlanta, GA.

Drugs 1990;40 Suppl 3:98-110

The major biological functions of S-adenosyl-L-methionine (SAMe) include methylation of various molecules (transmethylation) and synthesis of cysteine (trans-sulphuration). A stable double salt of SAMe has been found to be effective in intrahepatic cholestasis. The mechanism of its therapeutic effect is not fully understood but presumably involves methylation of phospholipids. Methylation of plasma membrane lipids may affect membrane fluidity and viscosity, which modulate the activities of a number of membrane-associated enzymes, for example, the activity of enzymes involved in Na+/Ca++ exchange (e.g. sarcolemmal vesicles), Na+/K+ adenosine triphosphatase (ATPase) [e.g. hepatocyte plasma membranes], and Na+/H+ exchange (e.g. plasma membranes of colonic cells). Recently, patients with cirrhosis were shown to have an acquired metabolic block in the hepatic conversion of methionine to SAMe. These patients, when administered conventional elemental diets, develop abnormally low plasma concentrations of cysteine and choline, 2 nonessential nutrients present in low concentrations in most elemental diets. These low concentrations probably reflect systemic deficiencies attributable to reduced endogenous syntheses of cysteine and choline caused by limited availability of hepatic SAMe. Such cirrhotic patients are often in negative nitrogen balance and have abnormal hepatic functions, which are corrected by cysteine and choline supplements. Noncirrhotic patients on parenteral elemental diets also become deficient in cysteine and choline. Consequently, these patients may require SAMe as an essential nutrient to normalise their overall hepatic transmethylation and trans-sulphuration activities.

Changes in cortisol/DHEA ratio in HIV-infected men are related to immunological and metabolic perturbations leading to malnutrition and lipodystrophy.

Christeff N, Nunez EA, Gougeon ML. Viral Oncology Unit, CNRS URA 1930, AIDS and Retroviruses Department, Institut Pasteur, Paris, France.

Ann N Y Acad Sci 2000;917:962-70

HIV-1 infection is associated with immune deficiency and metabolic perturbations leading to malnutrition and lipodystrophy. Because immune response and metabolic perturbations (protein and lipid metabolism) are partly regulated by glucocorticoids and DHEA, we determined serum cortisol and DHEA concentrations, and the cortisol/DHEA ratio in HIV-positive men, either untreated or receiving various antiretroviral treatments (ART), including highly active antiretroviral therapy (HAART). Cortisol levels were found increased in all patients, whatever the stage of the disease and independently of the ART treatment. In contrast, serum DHEA was elevated in the asymptomatic stage, and it was below normal values in AIDS patients, either untreated or mono-ART-treated. The DHEA level was low in HAART-treated patients with lipodystrophy

(LD+) and highly increased in HAART-treated patients without lipodystrophy (LD-). Consequently, the cortisol/DHEA ratio was similar to controls in asymptomatic untreated or mono-ART-treated patients, but increased in AIDS patients. Interestingly, this ratio was increased in LD+ HAART-treated men, but normalized in LD- HAART-treated patients. Changes in the cortisol/DHEA ratio were negatively correlated with the in vivo CD4 T-cell counts, with the malnutrition markers, such as body-cell mass and fat mass, and with the increased circulating lipids (cholesterol, triglycerides, and apolipoprotein B) associated to the lipodystrophy syndrome. Our observations show that the cortisol/DHEA ratio is dramatically altered in HIV-infected men, particularly during the syndromes of malnutrition and lipodystrophy, and this ratio remains elevated whatever the antiretroviral treatment, including HAART. These findings have practical clinical implications, since manipulation of this ratio could prevent metabolic (protein and lipid) perturbations.

Effect of L-carnitine treatment in vivo on apoptosis and ceramide generation in peripheral blood lymphocytes from AIDS patients

Cifone MG; Alesse E; Di Marzio L; Ruggeri B; Zazzeroni F; Moretti S; Famularo G; Steinberg SM; Vullo E; De Simone C. Department of Experimental Medicine, University of L'Aquila, Italy.

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Lymphocyte apoptosis in HIV-infected individuals may play a role in T- cell depletion and therefore favor progression to AIDS. In this study, we examined the effects of a short-term (5-day) intravenous treatment with L- carnitine (6 g/day) on apoptosis of CD4 and CD8 cells from 10 AIDS patients. L-carnitine administration has been shown to induce a strong reduction in the percentage of both CD4 and CD8 cells undergoing apoptosis. Interestingly, the L-carnitine treatment, which did not show relevant side effects in our patients, led to a strong and significant reduction of peripheral blood mononuclear cell-associated ceramide, an intracellular messenger of apoptosis, that positively correlated with the decrease of apoptotic CD4- and CD8-positive cells. These results suggest that L-carnitine could be an effective antiapoptotic drug in the treatment of AIDS patients.

Beta-carotene in HIV infection.

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beta-carotene has been reported to have an immunostimulatory effect. Recent studies suggest that beta-carotene supplementation can increase CD4 counts in HIV-infected patients. Our double-blind, placebo-controlled clinical trial was designed to test the efficacy of beta-carotene in raising CD4 counts in HIV-infected patients. Twenty-one HIV-seropositive patients were randomized to

receive either beta-carotene, 180 mg/day or placebo for 4 weeks, and then crossed over to receive the alternative treatment for the following 4 weeks. beta-carotene resulted in a statistically significant increase in total WBC count (p = 0.01), % change in CD4 count (p = 0.02), and % change in CD4/CD8 ratios (p = 0.02) compared to placebo. The absolute CD4 count, absolute CD4/CD8 ratio, and total and B-lymphocytes all increased on carotene and fell during placebo, but these differences did not reach statistical significance. No toxicity was observed on either treatment. beta-carotene appears to have an immunostimulatory effect in HIV-infected patients. Further studies are needed to demonstrate whether beta-carotene has a role as adjunct therapy in treatment of HIV-infected patients.

Prasterone (DHEA) and mania.

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Ann Pharmacother 2000 Dec;34(12):1419-22

OBJECTIVE: To inform clinicians and investigators of the potential for severe mania in conjunction with the use of prasterone (DHEA; dehydroepiandrosterone). CASE SUMMARY: A 31-year-old Hispanic man was admitted on a 72-hour observation period from a neighboring hospital after threatening to kill himself, family members, and a friend. A loaded rifle was found under his bed. The family confirmed that he had begun using DHEA several weeks prior to his mood and behavioral changes. He denied any past violence, but had once been given an unsubstantiated diagnosis of bipolar disorder. He used alcohol episodically, and had difficulties controlling his anger while intoxicated. Although he improved with valproate, his threats of homicide led to involuntary commitment. DISCUSSION: Several studies and case reports strongly suggest that anabolic steroids can induce significant psychiatric difficulties, including mania, impaired cognition, and overt psychosis. Although the Food and Drug Administration noted in 1985 that the efficacy and safety of DHEA were never confirmed, the agent continues to be sold over the counter. Several groups have used DHEA in the treatment of AIDS, memory loss, and depression, but reported no serious adverse events; however, recent studies indicate that severe psychiatric symptoms can develop in a subset of users. Although uncertain, potential risk factors include high doses of DHEA; history of mood disorder; concurrent use of alcohol, street drugs, or antidepressants; and cytochrome P450 polymorphisms. CONCLUSIONS: The use of DHEA in those under age 35 years may be especially risky, as endogenous DHEA concentrations peak at age 20-30 years. Those using or investigating DHEA should be cognizant of the potential for severe psychiatric complications.

Impairment of circulating lactoferrin in HIV-1 infection.

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Cell Mol Biol (Noisy-le-grand) 1995 May;41(3):417-21

Levels of plasma lactoferrin are decreased in HIV-1-infected patients in relation to the progression of the disease. Plasma lactoferrin concentrations were determined using a specific and sensitive enzyme immunoassay. 97 plasma were studied (22 asymptomatic, 45 symptomatic patients compared to 30 healthy controls) and the results showed a highly significant decrease ($p < 0.001$) of the level of lactoferrin in HIV-1-infected patients (respectively 2.79 +/- 1.2 and 0.68 +/- 0.22 micrograms/ml) compared to controls (4.37 +/- 0.83 micrograms/ml). Since it is well established that plasma lactoferrin level could be influenced by the number of neutrophils, the experiments were reproduced in neutropenic patients who represent 10% of recruitment (6 among 45 symptomatic patients). The plasma from neutropenic symptomatic patients (neutrophils < or = 1,300/mm3) showed their mean lactoferrin level at 0.36 micrograms/ml still far above the normal values. In view of the different reported biological effects of lactoferrin that are of great importance in the non-specific defences, the real biological place of the lack of such a molecule could be one important component of the multifactorial nature of HIV-1 infection.

High dose L-carnitine improves immunologic and metabolic parameters in AIDS patients

De Simone C, Tzantzoglou S, Famularo G, Moretti S, Paoletti F, Vullo V, Delia S. Universita di L'Aquila, Italy.

Immunopharmacol. Immunotoxicol. (USA), 1993, 15/1 (1-12)

Several reports indicate that systemic carnitine deficiency could occur in acquired immunodeficiency disease syndrome (AIDS), and that primary and secondary carnitine deficiency leads to critical metabolic dysfunctions. L-carnitine supplementation to peripheral blood mononuclear cells (PBMCs) of AIDS patients resulted in significant enhancement of the phytohemagglutinin (PHA)-driven proliferative response. High dose L-carnitine administration (6 gr per day for two weeks) to AIDS patients treated with zidovudine also led to increased PBMCs proliferation and reduced blood levels of triglycerides. In addition, a reduction of beta2-microglobulin serum levels as well as circulating tumor necrosis factor (TNF)-alpha, mostly in patients exhibiting highly elevated levels, were found at the end of the treatment period. Our data suggest that in vivo L-carnitine could prove useful in ameliorating both the immune response and lipid metabolism in patients with AIDS, irrespective of initial serum carnitines levels. The mechanism(s) accounting for the observed results are currently not clear. Further studies are needed to confirm the hypothesis that L-carnitine affects the expression of HIV-induced cytokines.

Carnitine depletion in peripheral blood mononuclear cells from patients with AIDS: Effect of oral L-carnitine.

De Simone C, Famularo G, Tzantzoglou S, Trinchieri V, Moretti S, Sorice F. Department of Infectious Diseases, University of L'Aquila, Italy.

AIDS 1994 May;8(5):655-60

Objective: Reduced levels of serum carnitines (3-hydroxy-4-N-trimethyl-am moniobutanoate) are found in most patients treated with zidovudine. However, since serum carnitines do not strictly reflect cellular concentrations we examined whether a carnitine depletion could be found in peripheral blood mononuclear cells (PBMC) from AIDS patients with normal serum carnitine levels. In addition, we explored whether it was possible to relate the host's immunoreactivity to the content of carnitine in PBMC and whether carnitine levels can be corrected by oral supplementation of L-carnitine. Design: Immunopharmacologic study.

Methods: Twenty male patients with advanced AIDS (Centers for Disease Control and Prevention stage IVCI) and normal serum levels of carnitines were enrolled. Patients were randomly assigned to receive either L-carnitine (6 g/day) or placebo for 2 weeks. At baseline and at the end of the trial, we measured carnitines in both sera and PBMC, serum triglycerides, CD4 cell counts, and the frequency of cells entering the S and G2-M phases of cell cycle following mitogen stimulation.

Results: Concentrations of total carnitine in PBMC from AIDS patients was lower than in healthy controls. A significant trend towards the restoration of appropriate intracellular carnitine levels was found in patients treated with high-dose L-carnitine and was associated with an increased frequency of S and G2-M cells following mitogen stimulation. Furthermore, at the end of the trial we found a strong reduction in serum triglycerides in the L-carnitine group compared with baseline levels.

Conclusions: Our data indicate that carnitine deficiency occurs in PBMC from patients with advanced AIDS, despite normal serum concentrations. The increase in cellular carnitine content strongly improved lymphocyte proliferative responsiveness to mitogens. Because carnitine status is an important contributing factor to immune function in patients with advanced AIDS, we therefore believe that L-carnitine supplementation could have a role as a complementary therapy for HIV-infected individuals.

Influence of L-carnitine on CD95 cross-linking-induced apoptosis and ceramide generation in human cell lines: Correlation with its effects on purified acidic and neutral sphingomyelinases in vitro.

Di Marzio L, Alesse E, Roncaioli P, Muzi P, Moretti S, Marcellini S, Amicosante G, De Simone C, Cifone MG. Department of Experimental Medicine, University of L'Aquila, Italy.

Proc Assoc Am Physicians 1997 Mar;109(2):154-63

Recently, we examined the effects of a short-term (5-days) intmvenous L-carnitine (6 g/die) treatment on apoptosis of CD4 and CD8 cells from 10 AIDS patients. Without inducing side effects, L-carnitine administration has been shown to induce a potent reduction in the percentage of cells undergoing apoptosis, paralleled by a significant increase of CD4 and CD8 cells. Interestingly, L-carnitine treatment led to a significant reduction of peripheral blood mononuclear cell-associated ceramide (an intracellular messenger for apoptosis) that correlated

with the decrease of apoptotic CD4- and CDS-positive cells. These results suggest that L-carnitine could be an effective antiapoptotic drug for use with AIDS patients. In this article we report the results of in vitro studies performed to better characterize the effects of L-carnitine on cell apoptosis. Previously, a high expression of the Fas (CD95/APO-1)/Fas ligand system in peripheral blood mononuclear cells from HIV-positive individuals has been reported and could be responsible for the observed relevant apoptosis of both infected and uninfected cells. Thus, we investigated the in vitro effects of L-carnitine on CD95 cross-linking- induced apoptosis through an anti-CD95 mAb in Fas-sensitive cell lines (HUT78 and U937). The results strongly support the in vivo observations. Our data indicate that L-carnitine is able to inhibit CD95-induced apoptosis of these cells, most likely by preventing sphingomyelin breakdown and consequent ceramide synthesis. The effect of L-carnitine seems to be specific for acidic sphingomyelinase as shown by experiments performed in vitro and using purified neutral or acidic sphingomyelinases.

Low concentrations of acid-soluble thiol (cysteine) in the blood plasma of HIV-1-infected patients.

Eck HP, Gmunder H, Hartmann M, Petzoldt D, Daniel V, Droge W. Institut fur Immunologie und Genetik Deutsches Krebsforschungszentrum, Heidelberg.

Biol Chem Hoppe Seyler 1989 Feb;370(2):101-8

Blood plasma samples from HIV-1-infected persons contain elevated glutamate concentrations up to 6-fold the normal level and relatively low concentrations of acid-soluble thiol (i.e. decreased cysteine concentrations). The intracellular glutathione concentration in peripheral blood-mononuclear cells (PBMC) and monocytes from HIV antibody-positive persons are also significantly decreased. Therapy with azidothymidine (AZT) causes a substantial recovery of the plasma thiol levels; but glutamate levels remain significantly elevated and intracellular glutathione levels remain low. Cell culture experiments with approximately physiological amino-acid concentrations revealed that variations of the extracellular cysteine concentration have a strong influence on the intracellular glutathione level and the rate of DNA synthesis [(3H]thymidine incorporation) in T cell clones and human and murine lymphocyte preparations even in the presence of several-fold higher cystine and methionine concentrations. Cysteine cannot be replaced by a corresponding increase of the extracellular cystine or methionine concentration. These experiments suggest strongly that the low cysteine concentration in the plasma of HIV-infected persons may play a role in the pathogenetic mechanism of the acquired immunodeficiency syndrome.

Malabsorption and deficiency of vitamin B12 in HIV-infected patients with chronic diarrhea.

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Dig Dis Sci 1994 Oct;39(10):2159-62

Deficiency of vitamin B12 is commonly reported in HIV-infected patients. We measured vitamin B12 levels in 36 HIV-infected patients with chronic diarrhea (> 3 stools/day for six weeks or more). Eight patients had an identifiable cause of diarrhea. Vitamin B12 levels were low in 39%. Sixteen of these patients were selected to undergo further testing, eight patients with low levels of vitamin B12 and eight with normal B12 levels. These 16 patients had both a stage II Schilling test and measurement of multiple serum D-xylose concentrations performed after both oral and intravenous doses of D-xylose. Integrated areas under the curves (AUC) for D-xylose concentration versus time were calculated for intravenous and oral doses, and D-xylose bioavailability was determined. Stage II Schilling tests were abnormal in 11 patients, (69%). D-Xylose bioavailability correlated closely with vitamin B12 absorption ($r = 0.648$, $P < 0.01$). Comparisons of mean values for CD4 count, serum albumin, Karnovsky score, six-month weight loss, 1-hr serum D-xylose levels and MCV failed to reveal a significant difference between those with and without abnormal serum vitamin B12 levels. These data indicate that below-normal levels of vitamin B12 are highly prevalent in HIV-infected patients with chronic diarrhea. Malabsorption of vitamin B12 occurs in the setting of an enteropathic process effecting both the proximal and distal small bowel. Since no risk factors for vitamin B12 deficiency could be identified, screening for vitamin B12 deficiency in HIV-infected patients with chronic diarrhea is strongly recommended.

Dehydroepiandrosterone sulfate (DHEAS) and testosterone: relation to HIV illness stage and progression over one year.

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J Acquir Immune Defic Syndr 1999 Oct 1;22(2):146-54

This study explored associations between serum dehydroepiandrosterone sulfate (DHEAS), free and total testosterone levels, and HIV illness markers, including viral load, and the behavioral problems of fatigue and depressed mood. Subjects were 169 HIV-positive men evaluated at baseline, 6, and 12 months for levels of DHEAS, total and free testosterone, HIV RNA, CD4, HIV symptoms, opportunistic illnesses, fatigue, and depression. Men with AIDS (N = 105), compared with men with less advanced illness, had lower mean levels of DHEAS. Baseline DHEAS was positively correlated with CD4 count, HIV symptom severity, and was inversely correlated with HIV RNA. Baseline DHEAS below the laboratory reference range (96 microg/dl) was associated with history of opportunistic infections and malignancies (adjusted odds ratio [OR], 4.4; 95% confidence interval [CI], 1.9-10.4) and with incidence of these complications or death over 1 year (adjusted OR, 2.6; 95% CI, 1-7.2). Initiating protease inhibitor combination therapy was associated with an increase in DHEAS over 6 months. Free testosterone was inversely correlated with HIV RNA, but there were no other significant associations between testosterone and HIV illness markers. No hormone was related to fatigue or depression. This study confirms that low serum DHEAS is associated with HIV illness markers, including viral load, and carries

negative prognostic value. Further, protease inhibitor therapy may result in increased circulating DHEAS.

Milk thistle (Silybum marianum) for the therapy of liver disease.

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Am J Gastroenterol 1998 Feb;93(2):139-43

Silymarin, derived from the milk thistle plant, Silybum marianum, has been used for centuries as a natural remedy for diseases of the liver and biliary tract. As interest in alternative therapy has emerged in the United States, gastroenterologists have encountered increasing numbers of patients taking silymarin with little understanding of its purported properties. Silymarin and its active constituent, silybin, have been reported to work as antioxidants scavenging free radicals and inhibiting lipid peroxidation. Studies also suggest that they protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumor promoters, stabilize mast cells, chelate iron, and slow calcium metabolism. In this article we review silymarin's history, pharmacology, and properties, and the clinical trials pertaining to patients with acute and chronic liver disease.

Biochemical deficiencies of coenzyme Q10 in HIV-infection and exploratory treatment.

Folkers K, Langsjoen P, Nara Y, Muratsu K, Komorowski J, Richardson PC, Smith TH. Institute for Biomedical Research, University of Texas, Austin 78712.

Biochem Biophys Res Commun 1988 Jun 16;153(2):888-96

AIDS patients (2 groups) had a blood deficiency (p less than 0.001) of coenzyme Q10 vs. 2 control groups. AIDS patients had a greater deficiency (p less than 0.01) than ARC patients. ARC patients had a deficiency (p less than 0.05) vs. control. HIV-infected patients had a deficiency (p less than 0.05) vs. control. The deficiency of CoQ10 increased with the increased severity of the disease, i.e., from HIV positive (no symptoms) to ARC (constitutional symptoms, no opportunistic infection or tumor) to AIDS (HIV infection, opportunistic infection and/or tumor). This deficiency, a decade of data on CoQ10 on the immune system, on IgG levels, on hematological activity constituted the rationale for treatment with CoQ10 of 7 patients with AIDS or ARC. One was lost to follow-up; one expired after stopping CoQ10; 5 survived, were symptomatically improved with no opportunistic infection after 4-7 months. In spite of poor compliance of 5/7 patients, the treatment was very encouraging and at times even striking.

Coenzyme Q10 increases T4/T8 ratios of lymphocytes in ordinary subjects and relevance to patients having the AIDS related complex.

Folkers K, Hanioka T, Xia LJ, McRee JT Jr, Langsjoen P. Institute for Biomedical Research, University of Texas, Austin 78713.

Biochem Biophys Res Commun 1991 Apr 30;176(2):786-91

Coenzyme Q10 (CoQ10) is indispensable to biochemical mechanisms of bioenergetics, and it has a non-specific role as an antioxidant. CoQ10 has shown a hematological activity for the human and has shown an influence on the host defense system. The T4/T8 ratios of lymphocytes are known to be low in patients with AIDS, ARC and malignancies. Our two patients with ARC have survived four-five years without any symptoms of adenopathy or infection on continuous treatment with CoQ10. We have newly found that 14 ordinary subjects responded to CoQ10 by increases in the T4/T8 ratios and an increase in blood levels of CoQ10; both by p less than 0.001. This knowledge and survival of two ARC patients for four-five years on CoQ10 without symptoms, and new data on increasing ratios of T4/T8 lymphocytes in the human by treatment with CoQ10 constitute a rationale for new double blind clinical trials on treating patients with AIDS, ARC and diverse malignancies with CoQ10.

The activities of coenzyme Q10 and vitamin B6 for immune responses.

Folkers K, Morita M, McRee J Jr. Institute for Biomedical Research, University of Texas, Austin 78712.

Biochem Biophys Res Commun 1993 May 28;193(1):88-92

Coenzyme Q10 (CoQ10) and vitamin B6 (pyridoxine) have been administered together and separately to three groups of human subjects. The blood levels of CoQ10 increased (p ^lt; 0.001) when CoQ10 and pyridoxine were administered together and when CoQ10 was given alone. The blood levels of IgG increased when CoQ10 and pyridoxine were administered together (p ^lt; 0.01) and when CoQ10 was administered alone (p ^lt; 0.05). The blood levels of T4-lymphocytes increased when CoQ10 and pyridoxine were administered together (p ^lt; 0.01) and separately (p ^lt; 0.001). The ratio of T4/T8 lymphocytes increased when CoQ10 and pyridoxine were administered together (p ^lt; 0.001) and separately (p ^lt; 0.05). These increases in IgG and T4-lymphocytes with CoQ10 and vitamin B6 are clinically important for trials on AIDS, other infectious diseases, and on cancer.

S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism.

Friedel HA, Goa KL, Benfield P. ADIS Drug Information Services, Auckland, New Zealand.

Drugs 1989 Sep;38(3):389-416

S-Adenosyl-L-methionine (SAMe) is a naturally occurring molecule distributed to virtually all body tissues and fluids. It is of fundamental importance in a number of biochemical reactions involving enzymatic transmethylation, contributing to the synthesis, activation and/or metabolism of such compounds as hormones, neurotransmitters, nucleic acids, proteins, phospholipids and certain drugs. The administration of a stable salt of SAMe, either orally or parenterally, has been shown to restore normal hepatic function in the presence of various chronic liver diseases (including alcoholic and non-alcoholic cirrhosis, oestrogen-induced and other forms of cholestasis), to prevent or reverse hepatotoxicity due to several drugs and chemicals such as alcohol, paracetamol (acetaminophen), steroids and lead, and to have antidepressant properties. In all of these studies SAMe has been very well tolerated, a finding of great potential benefit given the well-known adverse effects of tricyclic antidepressants with which it has been compared in a few trials. Thus, with its novel mechanisms of action and good tolerability, SAMe is an interesting new therapeutic agent in several diverse disease conditions, but its relative value remains to be determined in appropriate comparisons with other treatment modalities in current use.

The effect of supplemental beta-carotene on immunologic indices in patients with AIDS: a pilot study.

Fryburg DA, Mark RJ, Griffith BP, Askenase PW, Patterson TF. Division of Endocrinology and Metabolism, Yale University School of Medicine, New Haven, Connecticut, USA.

Yale J Biol Med 1995 Jan-Apr;68(1-2):19-23

Patients with the acquired immunodeficiency syndrome (AIDS) are characterized by a decrease in the number of T helper cells, a defect that is linked to the impaired immunologic competence. Vitamin A and its dietary precursor, beta-carotene, increase absolute T helper cell counts as well as indices of T cell function in both human and animal models. To determine if short-term beta-carotene treatment affects T lymphocyte subsets in patients with AIDS, a single-blind, non-randomized clinical trial of beta-carotene was performed in seven patients with AIDS. Enrollment criteria included no evidence of: a) active opportunistic infection: b) greater than 1 kilogram change in weight in the month preceding enrollment; c) chronic diarrhea or malabsorption; and d) hepatic disease or significant anemia. Beta-carotene was given with meals in two divided doses of 60 mg/day for four weeks; this was followed by no therapy for six weeks. Samples for total white blood cell, lymphocyte and T lymphocyte subset counts were measured at baseline, at the end of four weeks of treatment and another six weeks after treatment had stopped. P24 antigen, beta-2 microglobulin and liver function tests were also measured. All subjects tolerated the treatment well without evidence of toxicity. In response to beta-carotene, total lymphocyte counts rose by 66 percent ($.05 < p < .10$), and CD4+ cells rose slightly, but insignificantly, in the entire group. In all three of the patients who had baseline CD4+ cells greater than 10/microliters, however, the mean absolute increase in CD4+ cells in response to beta-carotene was 53 +/- 10 cells/microliters ($p < .01$). Six weeks off beta-carotene treatment, the absolute CD4+ cell count returned to

pretreatment levels ($p < .01$). No change was observed in CD8+ cells. P24 antigen and beta-2 microglobulin did not change during treatment. These preliminary observations suggest that short-term treatment with beta-carotene may increase CD4+ cell counts in patients with AIDS who have greater than 10 cells/microliters.

Comparative study of the anti-HIV activities of ascorbate and thiol-containing reducing agents in chronically HIV-infected cells.

Harakeh S, Jariwalla RJ. Viral Carcinogenesis Laboratory, Linus Pauling Institute of Science and Medicine, Palo Alto, CA 94306.

Am J Clin Nutr 1991 Dec;54(6 Suppl):1231S-1235S

To elucidate the action of vitamin C on pathogenic human retroviruses, we investigated and compared the effects of noncytoxic concentrations of ascorbic acid (AA), its calcium salt (Ca-ascorbate), and two thiol-based reducing agents [glutathione (GSH) and N-acetyl-L-cysteine (NAC)] against human immunodeficiency virus (HIV)-1 replication in chronically infected T lymphocytes. Ca-ascorbate reduced extracellular HIV reverse transcriptase (RT) activity by about the same magnitude as the equivalent dose of AA. Long-term experiments showed that continuous presence of ascorbate was necessary for HIV suppression. NAC (10 mmol/L) caused less than twofold inhibition of HIV RT and conferred a synergistic effect (approximately eightfold inhibition) when tested simultaneously with AA (0.426 mmol/L). In contrast, nonesterified GSH (less than or equal to 1.838 mmol/L) had no effect on RT concentrations and did not potentiate the anti-HIV effect of AA. These results further support the potent antiviral activity of ascorbate and suggest its therapeutic value in controlling HIV infection in combination with thiols.

Glutathione deficiency is associated with impaired survival in HIV disease.

Herzenberg LA, De Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, Deresinski SC. Department of Genetics, Stanford University Medical School, CA 94305-5125, USA.

Proc Natl Acad Sci U S A 1997 Mar 4;94(5):1967-72

Glutathione (GSH), a cysteine-containing tripeptide, is essential for the viability and function of virtually all cells. In vitro studies showing that low GSH levels both promote HIV expression and impair T cell function suggested a link between GSH depletion and HIV disease progression. Clinical studies presented here directly demonstrate that low GSH levels predict poor survival in otherwise indistinguishable HIV-infected subjects. Specifically, we show that GSH deficiency in CD4 T cells from such subjects is associated with markedly decreased survival 2-3 years after baseline data collection (Kaplan-Meier and logistic regression analyses, P ^lt; 0.0001 for both analyses). This finding, supported by evidence demonstrating that oral administration of the GSH prodrug N-acetylcysteine replenishes GSH in these subjects and suggesting that N-

acetylcysteine administration can improve their survival, establishes GSH deficiency as a key determinant of survival in HIV disease. Further, it argues strongly that the unnecessary or excessive use of acetaminophen, alcohol, or other drugs known to deplete GSH should be avoided by HIV-infected individuals.

Selenium supplementation suppresses tumor necrosis factor alpha-induced human immunodeficiency virus type 1 replication in vitro.

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AIDS Res Hum Retroviruses 1997 Oct 10;13(15):1325-32

Selenium is a nutritionally essential trace element that is important for optimal function of the immune system. It is incorporated into selenoproteins as the amino acid selenocysteine and it is known to inhibit the expression of some viruses. In this study, we show that selenium supplementation for 3 days prior to exposure to tumor necrosis factor alpha (TNF-alpha) partially suppresses the induction of human immunodeficiency virus type 1 (HIV-1) replication in both chronically infected T lymphocytic and monocytic cell lines. In acute HIV-1 infection of T lymphocytes and monocytes in the absence of exogenous TNF-alpha, the suppressive effect of selenium supplementation was not observed. However, selenium supplementation did suppress the enhancing effect of TNF-alpha on HIV-1 replication in vitro in acutely infected human monocytes, but not in T lymphocytes. Selenium supplementation also increased the activities of the selenoproteins, glutathione peroxidase (GPx) and thioredoxin reductase (TR), which serve as cellular antioxidants. Taken together, these results suggest that selenium supplementation may prove beneficial as an adjuvant therapy for AIDS through reinforcement of endogenous antioxidative systems.

Decreased serum dehydroepiandrosterone is associated with an increased progression of human immunodeficiency virus infection in men with CD4 cell counts of 200-499.

Jacobson MA, Fusaro RE, Galmarini M, Lang W. University of California, San Francisco.

J Infect Dis 1991 Nov;164(5):864-8

Dehydroepiandrosterone (DHEA) and its interconvertible sulfate derivative (DHEA-S) are human androgenic steroids that have been reported to inhibit viral expression and have been associated with a decreased risk of cancer. The relationship between serum DHEA and DHEA-S levels and subsequent progression to AIDS was investigated in a sample of human immunodeficiency virus (HIV)-infected men from the San Francisco Men's Health Study followed prospectively since 1984. Among 108 men seropositive for HIV at study entry and with CD4 lymphocyte counts of 200-499 microliters 24 months later, serum DHEA levels below the lower limit of normal (less than 180 ng/dl) at this later

date were predictive of subsequent progression to AIDS (relative hazard = 2.34; 95% confidence interval = 1.18-4.63; P = .01) after controlling for hematocrit, age, and log absolute CD4 cell number in a Cox proportional hazards model. This is the first large prospective cohort in which an endocrinologic variable has been observed to independently predict progression to AIDS. These observations, in addition to recent in vitro data, suggest that DHEA might have a protective effect in HIV infection.

Immune enhancing effect of a growth hormone secretagogue.

Koo GC, Huang C, Camacho R, Trainor C, Blake JT, Sirotina-Meisher A, Schleim KD, Wu TJ, Cheng K, Nargund R, McKissick G. Departments of. Immunology Research, Laboratory Animal Resources, Basic Animal Science Research, and Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065.

J Immunol 2001 Mar 15;166(6):4195-201

Growth hormone (GH) has been known to enhance immune responses, whether directly or through the insulin like growth factor-1, induced by GH. Recently a nonpeptidyl small m.w. compound, a GH secretagogue (GHS), was found to induce the production of GH by the pituitary gland. In this study, we examined the effect of GHS in immunological functions of 5- to 6-wk-old and 16- to 24-month-old mice. In young mice, we observed a significant increase in PBLs, but T and B cell-proliferative responses were not consistently enhanced. The old mice, treated with GHS for 3 wk, did not show increases in peripheral lymphocytes, but they exhibited a statistically significant increase in thymic cellularity and differentiation. When inoculated with a transplantable lymphoma cell line, EL4, the treated old mice showed statistically significant resistance to the initiation of tumors and the subsequent metastases. Generation of CTL to EL4 cells was also enhanced in the treated mice, suggesting that GHS has a considerable immune enhancing effect, particularly in the old mice. We have also found that GHS promoted better thymic engraftment in bone marrow transplant of SCID mice. We found more cycling cells in the spleens of treated mice, suggesting that GHS may exert its immune enhancing effect by promoting cell division in lymphoid cells. These observations ascribe to GHS a novel therapy possible for aging, AIDS, and transplant individuals, whose immune functions are compromised.

Randomised, double-blind, placebo-controlled trial of ditiocarb sodium ('Imuthiol') in human immunodeficiency virus infection.

Lang JM, Touraine JL, Trepo C, Choutet P, Kirstetter M, Falkenrodt A, Herviou L, Livrozet JM, Retornaz G, Touraine F et al. Hopital Hautepierre, Strasbourg, France.

Lancet 1988 Sep 24;2(8613):702-6

83 patients with human immunodeficiency virus (HIV) infection (CDC groups II, III, or IV-A) were randomised in a crossover trial of sodium-

diethyldithiocarbamate (ditiocarb sodium, 'Imuthiol') (10 mg/kg body weight given orally once a week) against placebo. Each arm of the trial lasted 16 weeks. The disease did not progress to CDC-defined acquired immunodeficiency syndrome in the ditiocarb group but did so in 4 patients in the placebo group (3 between week 0 and 16, 1 between week 17 and 32). Ditiocarb was also associated to a significantly greater extent than placebo with relief of constitutional symptoms, improvement in clinical status (including shrinkage of enlarged spleen and lymph nodes), and improvement in immune function (as measured by CD4+ cell count and skin test reactivity). When placebo was replaced by ditiocarb, similar improvements were observed, whereas symptoms slowly reappeared and CD4+ cell levels progressively declined when ditiocarb treatment was replaced by placebo.

Neuroimmunotherapy with low-dose subcutaneous interleukin-2 plus melatonin in AIDS patients with CD4 cell number below 200/mm3: a biological phase-II study.

Lissoni P, Vigore L, Rescaldani R, Rovelli F, Brivio F, Giani L, Barni S, Tancini G, Ardizzoia A, Vigano MG. Divison of Oncological Radiotherapy, San Gerardo Hospital, Monza, Milano, Italy.

J Biol Regul Homeost Agents 1995 Oct-Dec;9(4):155-8

A phase-II pilot clinical study was performed to evaluate the effects of low-dose subcutaneous IL-2 with the pineal hormone melatonin (MLT) in AIDS patients with CD4 counts below 200/mm3. The study included 11 patients. IL-2 was given subcutaneously at 3 million IU/ day in the evening for 6 days/week for 3 weeks. MLT was given orally at 40 mg/day in the evening every day, starting 7 days prior to IL-2. The treatment was substantially well tolerated, and in particular no cardiovascular or pulmonary complication occurred. An increase in CD4 cell number greater than 30% occurred in 4/11 (36%) patients, and CD4 cell mean values observed during the study were significantly higher with respect to those found before. In addition, the treatment induced a significant increase in mean number of lymphocytes, eosinophils, T lymphocytes, NK cells, CD25- and DR-positive lymphocytes. Finally, CD4/CD8 mean ratio significantly increased during the study. This preliminary clinical study suggests that the combined neuroimmunotherapy with low-dose subcutaneous IL-2 and MLT may improve the immune status also in AIDS patients with CD4 cell counts below 200/mm3, who generally do not respond to IL-2 alone.

Serum selenium versus lymphocyte subsets and markers of disease progression and inflammatory response in human immunodeficiency virus-1 infection.

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Biol Trace Elem Res 1997 Jan;56(1):31-41

Serum selenium levels were determined cross-sectionally in 57 HIV- infected patients who were classified according to the Centers for Disease Control (CDC) 1993 classification system. Mean serum selenium levels were lower in CDC stage II (58.7 plus or minus 12.2 microg/L; $p < 0.01$; $n = 18$) and stage III (47.6 plus or minus 11.3 microg/L; $p < 0.01$; $n = 19$) HIV-infected patients, than in healthy subjects (80.6 plus or minus 9.6 microg/L; $n = 48$) and stage I patients (73.6 plus or minus 16.5 microg/L; $n = 20$). Serum selenium levels were positively correlated with CD4 count, CD4/8 ratio, hematocrit, and serum albumin ($r = 0.42$; $r = 0.39$; $r = 0.48$; and $r = 0.45$; $p < 0.01$, respectively) and inversely with serum levels of thymidine kinase ($r = - 0.49$; $p < 0.01$; $n = 49$) and beta2-microglobulin ($r = - 0.46$; $p < 0.001$; $n = 49$). In addition, serum selenium levels in 20 randomly selected AIDS-free individuals (CDC I: $n = 10$; CDC II: $n = 10$) were inversely correlated with serum concentrations of interleukin-8 (IL-8) and soluble tumor necrosis factor receptors (sTNFR) types I and II. There was no correlation with serum immunoglobulin A and total serum protein levels. The results show that the progressive deprivation of serum selenium in HIV- infection is associated with loss of CD4+-cells and with increased levels of markers of disease progression and inflammatory response.

The role of oxidative imbalance in progression to AIDS: effect of the thiol supplier N-acetylcysteine.

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AIDS Res Hum Retroviruses 1998 Nov 20;14(17):1589-96

In this study we investigate the redox profile of HIV+ patients at different stages of disease with regard to immunological parameters, i.e., the number of circulating CD4+ and CD8+ lymphocytes. For this purpose, peripheral blood mononuclear cells (PBMCs) obtained from healthy donors, HIV+ patients in the asymptomatic phase, long-term nonProgressors (LTNPs), and AIDS patients have been considered. Cells have been exposed in vitro to the prooxidizing agent menadione, which is able to induce superoxide anion formation, and the susceptibility of the cells to the induced oxidative stress was estimated. Moreover, the possibility that the susceptibility of the cells to oxidative stress might be reduced by preexposing them to the antioxidizing agent N-acetylcysteine (NAC) has also been analyzed. The results obtained can be summarized as follows: (1) treatment with the prooxidant agent is capable of inducing massive morphological alterations in PBMCs. In particular, a significant correlation was found between the decrease in number of CD4+ lymphocytes in patients at different stages of disease and the susceptibility of their PBMCs to oxidative stress; (2) preincubation with NAC was able to preserve partially the ultrastructural characteristics of PBMCs isolated from HIV+ patients. In particular, a direct relationship was found between the efficacy of NAC protection and CD4 counts; (3) evaluation of the plasma index of peroxidation and the number of circulating CD4 lymphocytes indicates the existence of a positive correlation between "systemic" oxidative imbalance and stage of the disease; and (4) cells from

LTNPs display either oxidative susceptibility or oxidative markers similar to those of healthy donor cells. Our study suggests that the redox profile of patients may be considered a predictive marker of AIDS progression and that the acute infection and the asymptomatic phase of the disease may represent a useful period in which the combined use of antiretroviral and antioxidant drugs may be beneficial.

S-adenosylmethionine and Pneumocystis carinii.

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J Biol Chem 2000 May 19;275(20):14958-63

We previously reported that S-adenosylmethionine (AdoMet), a key molecule in methylation reactions and polyamine biosynthesis, enhances axenic culture of the AIDS-associated opportunistic fungal pathogen Pneumocystis carinii. Here we report that AdoMet is absolutely required for continuous growth. Two transporters are present, one high affinity, K(m) = 4.5 microm, and one low affinity, K(m) = 333 microm. The physiologically relevant high affinity transporter has a pH optimum of 7.5 and no related natural compounds compete for uptake. Transport is 98% inhibited at 4 degrees C, 24% inhibited by 20 mm sodium azide, and 95% inhibited by the combination of 20 mm sodium azide and 1 mm salicylhydroxamic acid; thus transport is active and dependent on both a cytochrome chain and an alternative oxidase. In vitro, AdoMet is used at a rate of 1. 40 x 10(7) molecules cell(-1) min(-1). AdoMet synthetase activity was not detected by a sensitive radiolabel incorporation assay capable of detecting 0.1% of the activity in rat liver. In addition, the AdoMet plasma concentration of rats is inversely correlated with the number of P. carinii in the lungs. These findings demonstrate that P. carinii is an AdoMet auxotroph. The uptake and metabolism of this compound are rational chemotherapeutic targets.

Dehydroepiandrosterone as predictor for progression to AIDS in asymptomatic human immunodeficiency virus-infected men.

Mulder JW, Frissen PH, Krijnen P, Endert E, de Wolf F, Goudsmit J, Masterson JG, Lange JM. Department of Infectious Diseases, University of Amsterdam, The Netherlands.

J Infect Dis 1992 Mar;165(3):413-8

The steroid hormone dehydroepiandrosterone (DHEA) has been reported to protect against certain viral infections in animal models and to be a modest inhibitor of human immunodeficiency virus type 1 (HIV-1) infection in vitro. Serum DHEA levels were determined in 41 asymptomatic HIV-1-seropositive subjects, who progressed to AIDS within 5 years after entering a cohort study, in 41 HIV-1-seropositive controls, who remained asymptomatic, and in 41 HIV-1-seronegative controls. At entry, DHEA levels were higher in the seronegative

group (median, 13.3 nmol/l) than in either the seropositive nonprogressors (median, 9.2 nmol/l; P = .01) or the progressors (median, 7.2 nmol/l; P less than .001). DHEA levels in the progressors approximately 5 months before the diagnosis of AIDS were lower than the levels in the nonprogressors after the same follow-up (median, 5.6 vs. 8.8 nmol/l; P = .007). DHEA levels less than 7 nmol/l and CD4+ cell counts less than 0.5 x 10(9)/l both proved to be independent predictors for disease progression in HIV-1-infected men.

Regulation of the activity of caspases by L-carnitine and almitoylcarnitine.

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FEBS Lett 2000 Jul 28;478(1-2):19-25

L-Carnitine facilitates the transport of fatty acids into the mitochondrial matrix where they are used for energy production. Recent studies have shown that L-carnitine is capable of protecting the heart against ischemia/reperfusion injury and has beneficial effects against Alzheimer's disease and AIDS. The mechanism of action, however, is not yet understood. In the present study, we found that in Jurkat cells, L-carnitine inhibited apoptosis induced by Fas ligation. In addition, 5 mM carnitine potently inhibited the activity of recombinant caspases 3, 7 and 8, whereas its long-chain fatty acid derivative palmitoylcarnitine stimulated the activity of all the caspases. Palmitoylcarnitine reversed the inhibition mediated by carnitine. Levels of carnitine and palmitoyl-CoA decreased significantly during Fas-mediated apoptosis, while palmitoylcarnitine formation increased. These alterations may be due to inactivation of beta-oxidation or to an increase in the activity of the enzyme that converts carnitine to palmitoylcarnitine, carnitine palmitoyltransferase I (CPT I). In support of the latter possibility, fibroblasts deficient in CPT I activity were relatively resistant to staurosporine-induced apoptosis. These observations suggest that caspase activity may be regulated in part by the balance of carnitine and palmitoylcarnitine.

Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance.

Newsholme EA, Crabtree B, Ardawi MS.

Q J Exp Physiol 1985 Oct;70(4):473-89

Glutamine is utilized at a high rate (fourfold higher than that of glucose) by isolated incubated lymphocytes and produces glutamate, aspartate, lactate and ammonia. The pathway for glutamine metabolism includes the reactions catalysed by glutaminase, aspartate aminotransferase, oxoglutarate dehydrogenase, succinate dehydrogenase, fumarase, malate dehydrogenase and phosphoenolpyruvate carboxykinase. In fact little if any of the carbon of the glutamine that is used is converted to acetyl-CoA for complete oxidation. For this

reason, the oxidation of glutamine is only partial and, in an analogous manner to the terminology used to describe the partial oxidation of glucose to lactate as glycolysis, the term glutaminolysis is used to describe the process of partial glutamine oxidation. The role of glutaminolysis in lymphocytes and perhaps other rapidly dividing cells is to provide both nitrogen and carbon for precursors for synthesis of macromolecules (e.g. purines and pyrimidines for DNA and RNA) and also energy. However, the rate of glutamine utilization by lymphocytes is markedly in excess of the precursor requirements (which are at most 4%) and if glutamine was vitally important in energy production it would be expected that more would be converted to acetyl-CoA for complete oxidation via the Krebs cycle. Indeed most of the energy for lymphocytes may be obtained by the complete oxidation of fatty acids and ketone bodies. Consequently the role of the high rate of glutaminolysis in lymphocytes and other rapidly dividing cells may be identical to that of glycolysis: the high rates provide ideal conditions for the precise and sensitive control of the rate of use of the intermediates of these pathways for biosynthesis when required. High rates of glycolysis and glutaminolysis can be seen as part of a mechanism of control to permit synthesis of macromolecules when required without any need for extracellular signals to make more glucose or glutamine available for these cells. In order to maintain a high rate of glutaminolysis despite fluctuation in the plasma level of glutamine, the flux through the glutaminolytic pathway can be controlled and the key processes in the lymphocyte that may play a role in this process include glutamine transport across the cell and mitochondrial membranes, glutaminase and oxoglutarate dehydrogenase. Changes in the intracellular concentration of Ca2+ may play a role in control of one or more of these reactions.(ABSTRACT TRUNCATED AT 400 WORDS)

Short-term growth hormone administration at the time of opportunistic infections in HIV-positive patients.

Paton NI, Newton PJ, Sharpstone DR, Ross HM, Cotton J, Calder AG, Milne E, Elia M, Shah S, Engrand P, Macallan DC, Gazzard BG, Griffin GE. St. George's Hospital Medical School, London, UK.

AIDS 1999 Jul 9;13(10):1195-202

OBJECTIVES: A 12-week course of recombinant human growth hormone is an effective but expensive therapy for established HIV-related wasting. Wasting in HIV disease is often episodic, coinciding with bouts of acute opportunistic infection. We hypothesized that a short course of growth hormone, targeted at the time of opportunistic infection, might improve protein metabolism thereby reducing lean tissue loss. METHODS: HIV-infected men with acute opportunistic infections, who received standard antimicrobial treatment for their infection as well as intensive nutritional counselling and oral energy supplements, were randomized to receive growth hormone or placebo for 14 days. Principal assessments were protein metabolism (measured by 13C-leucine infusion), body composition (measured by DEXA) and safety. RESULTS: There were no significant changes in outcome parameters in the placebo group (n = 11). In the growth hormone group (n = 9), protein catabolic rate decreased by 60% in the

fasted state (P = 0.02 versus placebo), lean body mass increased by 2.2 kg (P = 0.03 versus baseline) and fat mass decreased by 0.7 kg (P = 0.002 versus baseline). There was no increase in adverse or serious adverse events in the growth hormone as compared with the placebo group. CONCLUSIONS: A two-week course of growth hormone at the time of acute opportunistic infection in HIV-infected patients improves protein metabolism and body composition during therapy and appears to be safe. This may represent a rational and economical approach to the use of growth hormone therapy.

Nutrients and HIV: part two-vitamins A and E, zinc, B-vitamins, and magnesium.

Patrick L.

Altern Med Rev 2000 Feb;5(1):39-51

There is compelling evidence that micronutrient deficiencies can profoundly affect immunity; micronutrient deficiencies are widely seen in HIV, even in asymptomatic patients. Direct relationships have been found between deficiencies of specific nutrients, such as vitamins A and B12, and a decline in CD4 counts. Deficiencies appear to influence vertical transmission (vitamin A) and may affect progression to AIDS (vitamin A, B12, zinc). Correction of deficiencies has been shown to affect symptoms and disease manifestation (AIDS dementia complex and B12; diarrhea, weight loss, and zinc), and certain micronutrients have demonstrated a direct anti-viral effect in vitro (vitamin E and zinc). The previous article in this series focused on selenium and beta carotene deficiencies in HIV/AIDS. This literature review elucidates how deficiencies of the micronutrients zinc, magnesium, vitamins A, E, and specific B vitamins relate to HIV symptomology and progression, and clearly illustrates the need for nutritional supplementation in HIV disease.

Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns.

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Proc Natl Acad Sci U S A 1998 Mar 17;95(6):3071-6

Current thinking attributes the balance between T helper 1 (Th1) and Th2 cytokine response patterns in immune responses to the nature of the antigen, the genetic composition of the host, and the cytokines involved in the early interaction between T cells and antigen-presenting cells. Here we introduce glutathione, a tripeptide that regulates intracellular redox and other aspects of cell physiology, as a key regulatory element in this process. By using three different methods to deplete glutathione from T cell receptor transgenic and conventional mice and studying in vivo and/or in vitro responses to three distinct antigens, we show that glutathione levels in antigen-presenting cells determine whether Th1 or

Th2 response patterns predominate. These findings present new insights into immune response alterations in HIV and other diseases. Further, they potentially offer an explanation for the well known differences in immune responses in "Th1" and "Th2" mouse strains.

Vitamin B-12 abnormalities in HIV-infected patients.

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Eur J Haematol 1991 Jul;47(1):60-4

A prospective study of 60 consecutively admitted patients with HIV infection was performed to document the prevalence, etiology and manifestations of low serum vitamin B-12 in such patients. Low serum B-12 levels were found in 10 patients (16.7%). In 6, vitamin B-12 absorption was impaired and hog intrinsic factor addition did not improve it. Patients with low vitamin B-12 levels showed lower hemoglobin, leukocytes, lymphocytes, CD4 lymphocytes and CD4/CD8 lymphocyte ratio than HIV patients with physiological serum vitamin B-12 levels. However, bone marrow megaloblastosis was found in only 3 low vitamin B-12 patients and the deoxyuridine suppression test was pathological in only 1 case. In 7 patients, parenteral treatment was begun with variable response despite serum vitamin B-12 correction. In conclusion, low serum vitamin B-12 is often found in HIV-infected patients and it could be related to malabsorption, but clear megaloblastic abnormalities and treatment response could not be demonstrated. A decreased concentration of the serum binders due to disturbances in the leukocytes and related immunocompetent cell may play an additional role.

Increased uptake and accumulation of Vitamin-C in human immunodeficiency virus 1-infected hematopoietic cell lines.

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J Biol Chem 1997 Feb 28;272(9):5814-20

Vitamin-C (ascorbic acid) is required for normal host defense and functions importantly in cellular redox systems. To define the interrelationship between human immunodeficiency virus (HIV) infection and Vitamin-C flux at the cellular level, we analyzed Vitamin-C uptake and its effects on virus production and cellular proliferation in HIV-infected and uninfected human lymphoid, myeloid, and mononuclear phagocyte cell lines. Chronic or acute infection of these cell lines by HIV-1 led to increased expression of glucose transporter 1, associated with increased transport and accumulation of Vitamin-C. Infected cells also showed increased transport of glucose analogs. Exposure to Vitamin-C had a complex effect on cell proliferation and viral production. Low concentrations of Vitamin-C increased or decreased cell proliferation depending on the cell line and

either had no effect or caused increased viral production. Exposure to high concentrations of Vitamin-C preferentially decreased the proliferation and survival of the HIV-infected cells and caused decreased viral production. These findings indicate that HIV infection in lymphocytic, monocytic, and myeloid cell lines leads to increased expression of glucose transporter 1 and consequent increased cellular Vitamin-C uptake. High concentrations of Vitamin-C were preferentially toxic to HIV-infected host defense cell lines in vitro.

The keys of oxidative stress in acquired immune deficiency syndrome apoptosis.

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Med Hypotheses 1998 Aug;51(2):169-73

Apoptosis is the main cause of CD4+ T-lymphocyte depletion in acquired immune deficiency syndrome (AIDS). Various agents appear to be able to trigger apoptosis in CD4+ T cells, including viral proteins (i.e. gp120, Tat), inappropriate secretion of inflammatory cytokines by activated macrophages (i.e. tumor necrosis factor alpha) and toxins produced by opportunistic micro-organisms. Since oxidative stress can also induce apoptosis, it can be hypothesized that such a mechanism could participate in CD4+ T-cell apoptosis observed in AIDS. This correlates strongly with the observation that AIDS patients present low levels of antioxidants (i.e. superoxide dismutase-Mn, vitamin E, selenium and glutathion) most likely due to inappropriate nutrition (i.e. diets poor in antioxidants), alcohol and drug consumption, and digestive problems associated with the disease. Furthermore, the coadministration of the antiviral drug zidovudine with antioxidants increases its therapeutic potential. Finally, the following additional observations support the hypothesis that oxidative stress is involved in cell apoptosis in AIDS: (1) The depletion of the anti-apoptotic/antioxidant protein Bcl-2 in human immunodeficiency virus (HIV)-infected CD4+ cells; (2) a decrease of apoptosis in HIV-infected cells treated with antioxidants and; (3) the presence of the pro-apoptotic/pro-oxidant cytokines secreted by activated macrophages in AIDS patients. Therefore, anti-apoptotic/antioxidant strategies should be considered, alongside antiviral strategies, in order to design a more efficient therapy for AIDS in the near future.

Serum vitamin B12 and transcobalamin levels in early HIV disease.

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Am J Hematol 1994 Nov;47(3):167-71

A cohort of asymptomatic human immunodeficiency virus (HIV) seropositive patients was followed over a 2 1/2-year period, to establish changes in serum vitamin B12 (B12) concentrations. Serum B12, CD4 count, and clinical progression to acquired immunodeficiency syndrome (AIDS) or AIDS-related

complex (ARC) were measured. The unsaturated B12 binding capacities of the transcobalamins were also determined at the start of the study and compared to those from a homosexual HIV seronegative control group. The geometric mean of serum B12 in 218 asymptomatic HIV seropositive patients was significantly lower than of a homosexual HIV seronegative control group (P = 0.02) and the unsaturated B12 binding capacities of transcobalamins I and II were significantly higher in the asymptomatic patients compared with the same control group (P < 0.03, P < 0.0001, respectively). Fifty-nine of the asymptomatic HIV seropositive patients were followed over a 2 1/2-year period during which most had falling serum B12 levels (64%). Twelve patients progressed clinically to ARC or AIDS, of which nine had repeat serum B12 estimation prior to progression. All nine patients had or developed falling serum B12 levels without any evidence of an HIV-related bowel disorder. All patients progressing had falling CD4 counts. Subnormal serum B12 levels are common in HIV disease and occur at an early stage. B12 levels fall in most patients with time and may help predict those patients whose disease will progress the most rapidly.

Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized, double-blind controlled trial.

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Nutrition 1999 Nov-Dec;15(11-12):860-4

Loss of body cell mass, the active functioning tissue of the body, commonly occurs in patients with human immunodeficiency virus (HIV) infection, and the extent of wasting is related to the length of survival. We evaluated the anabolic role of the amino acid L-glutamine (GLN) and antioxidants in a double-blind, placebo-controlled trial in 26 patients with > 5% weight loss since disease onset. Subjects received GLN-antioxidants (40 g/d) in divided doses or glycine (40 g/d) as the placebo for 12 wk. Throughout the study, the subjects were seen weekly by a nutritionist, and body weight, bioelectric impedance assessment, and nutritional counseling were performed. Twenty-one subjects completed the study, and the groups were well matched. The 5 patients excluded from analysis all met a priori exclusion criteria. Over 3 mo, the GLN-antioxidant group gained 2.2 kg in body weight (3.2%), whereas the control group gained 0.3 kg (0.4%, P = 0.04 for difference between groups). The GLN-antioxidant group gained 1.8 kg in body cell mass, whereas the control group gained 0.4 kg (P = 0.007). Intracellular water increased in the GLN-antioxidant group but not in the control group. In conclusion, GLN-antioxidant nutrient supplementation can increase body weight, body cell mass, and intracellular water when compared with placebo supplementation. GLN-antioxidant supplementation provides a highly cost-effective therapy for the rehabilitation of HIV+ patients with weight loss.

Impairment of intestinal glutathione synthesis in patients with inflammatory bowel disease.

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Gut 1998 Apr;42(4):485-92

BACKGROUND: Reactive oxygen species contribute to tissue injury in inflammatory bowel disease (IBD). The tripeptide glutathione (GSH) is the most important intracellular antioxidant. AIMS: To investigate constituent amino acid plasma levels and the GSH redox status in different compartments in IBD with emphasis on intestinal GSH synthesis in Crohn's disease.

METHODS: Precursor amino acid levels were analysed in plasma and intestinal mucosa. Reduced (rGSH) and oxidised glutathione (GSSG) were determined enzymatically in peripheral blood mononuclear cells (PBMC), red blood cells (RBC), muscle, and in non-inflamed and inflamed ileum mucosa. Mucosal enzyme activity of gamma-glutamylcysteine synthetase (gamma GCS) and gamma-glutamyl transferase (gamma GT) was analysed. Blood of healthy subjects and normal mucosa from a bowel segment resected for tumor growth were used as controls.

RESULTS: Abnormally low plasma cysteine and cystine levels were associated with inflammation in IBD (p ^lt; 10(-4)). Decreased rGSH levels were demonstrated in non-inflamed mucosa (p ^lt; 0.01) and inflamed mucosa (p = 10(-6)) in patients with IBD, while GSSG increased with inflammation (p = 0.007) compared with controls. Enzyme activity of gamma GCS was reduced in non-inflamed mucosa (p ^lt; 0.01) and, along with gamma GT, in inflamed mucosa (p ^lt; 10(-4)). The GSH content was unchanged in PBMC, RBC, and muscle.

CONCLUSIONS: Decreased activity of key enzymes involved in GSH synthesis accompanied by a decreased availability of cyst(e)ine for GSH synthesis contribute to mucosal GSH deficiency in IBD. As the impaired mucosal antioxidative capacity may further promote oxidative damage, GSH deficiency might be a target for therapeutic intervention in IBD.

Micronutrient profiles in HIV-1-infected heterosexual adults.

Skurnick JH, Bogden JD, Baker H, Kemp FW, Sheffet A, Quattrone G, Louria DB. Department of Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School, Newark, New Jersey 07103-2714, USA.

J Acquir Immune Defic Syndr Hum Retrovirol 1996 May 1;12(1):75-83

There is compelling evidence that micronutrients can profoundly affect immunity. We surveyed vitamin supplement use and circulating concentrations of 22 nutrients and glutathione in 64 HIV-1 seropositive men and women and 33 seronegative controls participating in a study of heterosexual HIV-1 transmission. We assayed antioxidants (vitamins A, C, and E; total carotenes), vitamins B6 and B12, folate, thiamin, niacin, biotin, riboflavin, pantothenic acid, free and total choline and carnitine, biopterin, inositol, copper, zinc, selenium, and magnesium,

HIV-infected patients had lower mean circulating concentrations of magnesium ($p < 0.0001$), total carotenes ($p = 0.009$), total choline ($p = 0.002$), and glutathione ($p = 0.045$), and higher concentrations of niacin ($p < 0.0001$) than controls. Fifty-nine percent of HIV+ patients had low concentrations of magnesium, compared with 9% of controls ($p < 0.0001$). These abnormal concentrations were unrelated to stage of disease. Participants who took vitamin supplements had consistently fewer low concentrations of antioxidants, across HIV infection status and disease stage strata ($p = 0.0006$). Nevertheless, 29% of the HIV+ patients taking supplemental vitamins had subnormal levels of one or more antioxidants. The frequent occurrence of abnormal micronutrient nutriture, as found in these HIV+ subjects, may contribute to disease pathogenesis. The low magnesium concentrations may be particularly relevant to HIV-related symptoms of fatigue, lethargy, and impaired mentation.

Lactoferrin. Antiviral activity of lactoferrin.

Swart PJ, Kuipers EM, Smit C, Van Der Strate BW, Harmsen MC, Meijer DK. Department of Pharmacology, University of Groningen, The Netherlands.

Adv Exp Med Biol 1998;443:205-13

A series of native and chemically derivatized lactoferrins (Lfs) purified from milk and colostrum were assayed in vitro for their anti-HIV and anti-HCMV-cytopathic effects in MT4 cells and fibroblasts respectively. All Lfs from bovine and human milk or colostrum were able to completely block HCMV replication as well as inhibited HIV-1 induced cytopathic effects. Through acylation of the amino function of the lysine residues in Lf, using anhydrides of succinic acid or cis-aconitic acid, negatively charged Lf derivatives were obtained that all showed a strong antiviral activity against the HIV-1 in vitro. Acylated-Lf exhibited a 4-fold stronger antiviral effect on HIV-1 than the parent compound but the activity on HCMV was abolished. Peptide scanning studies indicated that the native Lf as well as acylated Lf strongly bind to the V3 domain of the HIV envelope protein gp120, with Kd values in the same concentration range as the in vitro IC50. Therefore, shielding of this domain, resulting in inhibition of the virus-cell fusion and entry of the virus in MT4 cells is the likely mechanism underlying the anti-HIV activity. In contrast, addition of positive charges to Lf through amination of the proteins resulted in an increased anti-HCMV activity and a loss of anti-HIV activity, with anti-HCMV IC50 values in the low micromolar concentration range. The N-terminal portion of LF appeared essential to this anti-HCMV effect. The specific distribution of positively and negatively charged domains in the molecule appears to be important in both the anti-HIV and anti-HCMV effects.

Association between serum vitamin A and E levels and HIV-1 disease progression.

Tang AM, Graham NM, Semba RD, Saah AJ. Department of Epidemiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

AIDS 1997 Apr;11(5):613-20

OBJECTIVE: To examine the associations between serum vitamin A and E levels and risk of progression to three key outcomes in HIV-1 infection: first AIDS diagnosis, CD4+ cell decline to < 200 cells x 10(6)/l, and mortality.

DESIGN: Non-concurrent prospective study.

METHODS: Serum levels of vitamins A and E were measured at the enrollment visit of 311 HIV-seroprevalent homo-/bisexual men participating in the Baltimore/ Washington DC site of the Multicenter AIDS Cohort Study. Cox proportional hazards models were used to estimate the relative hazard of progression to each outcome over the subsequent 9 years, adjusting for several independent covariates.

RESULTS: Men in the highest quartile of serum vitamin E levels (> or = 23.5 mumol/l) showed a 34% decrease in risk of progression to AIDS compared with those in the lowest quartile [relative hazard (RH), 0.66; 95% confidence interval (CI), 0.41-1.06)]. This effect was statistically significant when comparing the highest quartile of serum vitamin E to the remainder of the cohort (RH, 0.67; 95% CI, 0.45-0.98). Associations between serum vitamin A levels and risk of progression to AIDS were less clear, but vitamin A levels were uniformly in the normal to high range (median = 2.44 mumol/l). Similar trends were observed for each vitamin with mortality as the outcome, but neither vitamin was associated with CD4+ cell decline to ^lt; 200 cells x 10(6)/l. Men who reported current use of multivitamin or single vitamin E supplements had significantly higher serum tocopherol levels than those who were not taking supplements (P = 0.0001). Serum retinol levels were unrelated to intake of multivitamin or single vitamin A supplements.

CONCLUSIONS: These data suggest that high serum levels of vitamin E may be associated with slower HIV-1 disease progression, but no relationship was observed between retinol levels and disease progression in this vitamin A-replete population.

Reactive oxygen species and proinflammatory cytokine signaling in endothelial cells: effect of selenium supplementation.

Tolando R, Jovanovic A, Brigelius-Flohe R, Ursini F, Maiorino M. Dipartimento di Chimica Biologica, Padova, Italy.

Free Radic Biol Med 2000 Mar 15;28(6):979-86

The release of superoxide (O(2)(*-)) and hydrogen peroxide (H(2)O(2)), induced by tumor necrosis factor-alpha (TNF-alpha) or interleukin-1beta (IL-1beta), has been studied in the endothelial cell line ECV 304 in the presence and absence of selenium (Se) supplementation. Both cytokines elicit the production of both species. Selenium supplementation, which increases Se-enzyme activity, decreases the amount of H(2)O(2) but not O(2)(*-) detectable in the extracellular medium. Inhibition of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by diphenyliodonium (DPI) or phenylarsine oxide (PAO),

largely prevents O(2)(*-) production, whereas H(2)O(2) remains above the amount accounted for by disproportion of residual O(2)(*-). Thus, a fraction of H(2)O(2) found in the medium, derives from an intracellular pool, which is under control of selenium-dependent peroxidases. This is further supported by the observation that in Se-supplemented cells, the rate of intracellular glutathione (GSH) depletion induced by cytokine treatment is faster and more extensive. Because Se supplementation decreases cytokine-induced NF-kappaB activity, whereas added H(2)O(2) is inactive and catalase does not affect the activation induced by TNF-alpha, it is concluded that only intracellularly generated H(2)O(2) has a role in transcription factor activation by both TNF-alpha and IL-1beta.

Effects of oral S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease.

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Scand J Gastroenterol 1989 May;24(4):407-15

S-Adenosyl-L-methionine (SAMe) is a physiologic precursor of thiols and sulfurated compounds, which are known to be decreased in patients with liver disease. The effect of its administration on the hepatic glutathione content of liver patients was investigated. Four groups of subjects were selected: a) 9 patients with alcoholic liver disease treated with SAMe (1.2 g/day orally for 6 months); b) 7 patients with non-alcoholic liver disease treated as above; c) 8 placebo-treated patients with alcoholic liver disease; and d) 15 normal subjects as a control group. Total and oxidized glutathione were assayed by high-performance liquid chromatography of liver biopsy specimens before and after the treatment period. In all patients pre-treatment hepatic glutathione was significantly decreased as compared with controls. SAMe therapy resulted in a significant increase of hepatic glutathione levels both in patients with alcoholic and in those with non-alcoholic liver diseases as compared with placebo-treated patients. SAMe may therefore exert an important role in reversing hepatic glutathione depletion in patients with liver disease.

Zinc serum level in human immunodeficiency virus-infected patients in relation to immunological status.

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Biol Trace Elem Res 2000 Feb;73(2):139-49

In human immunodeficiency virus (HIV) infection, serum level of zinc, an important micronutrient for immune function, is frequently diminished. The aim of this study was to determine the zinc status in relation to immunological parameters and disease stage in 79 HIV-1 seropositive patients. The median serum level of zinc was within normal limits (12.5 micromol/L) but in 23% of

patients, zinc deficiency was seen. Decreased serum zinc was associated with a low CD4 cell count, high viral load, and increased neopterin and IgA levels. According to current treatment recommendations, the majority of patients received antiretroviral triple therapy. Zinc levels in treated and untreated patients were comparable. Referring to disease stage (CDC classification, 1993), the mean zinc level was highest in stage C and lowest in stage A. In conclusion, even under antiretroviral triple therapy, zinc deficiency is still of great importance in HIV infection, and zinc substitution in zinc deficient individuals should be taken into account to optimize therapeutical success.

Simultaneous detection of ubiquinol and ubiquinone in human plasma as a marker of oxidative stress.

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Anal Biochem 1997 Jul 15;250(1):66-73

A method is described for the simultaneous detection of ubiquinol-10 and ubiquinone-10 in human plasma. In this procedure, heparinized human plasma was mixed with 5 vol of methanol and 10 vol of hexane. After vigorous shaking and centrifugation, an aliquot of the hexane phase (5 microl) was injected immediately and directly onto a reversed-phase HPLC to minimize the oxidation of ubiquinol to ubiquinone. A post-separation, on-line reduction column converts ubiquinone to ubiquinol which is quantified by electrochemical detection. The detection limit of plasma ubiquinol-10 and ubiquinone-10 is about 4 nM with excellent reproducibilities. Tocopherols, lycopene, and beta-carotene are also detectable in this method. In addition, free cholesterol, and cholesteryl esters can be quantified by their absorption at 210 nm. Using this method we have determined the ratio of ubiquinol to ubiquinone is about 95/5 in human plasma from healthy donors. We suggest that this method will be useful since the ratio of ubiquinol to ubiquinone has been suggested as a good marker of oxidative stress.

Inhibition of 3'azido-3'deoxythymidine-resistant HIV-1 infection by dehydroepiandrosterone in vitro.

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Biochem Biophys Res Commun 1994 Jun 30;201(3):1424-32

Human immunodeficiency virus type 1 (HIV-1) isolated from patients with acquired immunodeficiency syndrome (AIDS) shows resistance to 3'azido-3'deoxythymidine (AZT) after one or two years of treatment. AZT also has significant toxic side effects, further limiting its use in the therapy of HIV-1-infected individuals. Dehydroepiandrosterone (DHEA) has been shown to have a broad spectrum of biological functions, to be bioavailable orally and to be relatively nontoxic. Epidemiological studies provide evidence that reduced serum levels of DHEA are related to the progression of AIDS in HIV-1 infection. DHEA

has also been shown to inhibit HIV-1 replication in vitro and block HIV-1 reactivation from chronically infected cell lines. However, there have been no reports on the ability of DHEA to inhibit the replication of AZT-resistant strains of HIV-1. We investigated whether DHEA treatment could inhibit replication of AZT-resistant strains of HIV-1. Addition of DHEA to MT-2 cell cultures infected with either AZT-sensitive or AZT-resistant isolates of HIV-1 resulted in dose-dependent inhibition of HIV-1-induced cytopathic effect and suppression of HIV-1 replication as measured by accumulation of reverse transcriptase activity. At a concentration as low as 50 microM, DHEA reduced AZT-resistant HIV-1 replication over 50 percent as measured by cytopathic effect and accumulation of reverse transcriptase activity. This study provides evidence that DHEA can inhibit the replication of AZT-resistant as well as wild-type HIV-1. Since the main targets for DHEA are metabolic and cellular signaling pathways leading to HIV-1 replication-activation, DHEA should be effective against multidrug-resistant strains of HIV-1. Combined with recently discovered immunoregulatory properties, the finding that DHEA is able to inhibit replication of both wild-type and AZT-resistant HIV-1 suggests that in vivo DHEA may have a much broader spectrum of action than originally anticipated.

Vitamin E supplementation normalizes immune dysfunction in murine AIDS induced by LP-BM5 retrovirus infection

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Nutrition Research (USA), 1996, 16/10 (1709-1720)

It is known that murine AIDS, induced by i.p. injection of LP-BM5 retrovirus, is functionally similar to human AIDS. In this study, we tried to examine the effect of vitamin E (dl-alpha-tocopheryl acetate) supplementation on the decrease of cellular immune functions following the development of murine AIDS. Female C57BL/6 mice, 4 weeks old, were infected with LP-BM5 retrovirus and then fed control (50 IU/kg diet) or high vitamin E (500 or 2500 IU/kg diet) diets for 10 weeks. The spleen weight and number of splenocytes were largely increased following the development of murine AIDS. On the contrary, vitamin E supplementation suppressed the enlargement of spleen and the increased number of splenocytes following retrovirus infection. The decrease of NK activity shown in mice infected with LP-BM5 retrovirus was also partly improved by high vitamin E diet. Proliferation of splenic T lymphocytes, showing the marked decrease following murine AIDS, was significantly restored by higher vitamin E (2500 IU/kg diet) diet compared to control group, which was still lower in comparison with that of uninfected control group. Furthermore, vitamin E supplementation increased production of interferon-gamma (IFN-gamma) and suppressed production of tumor necrosis factor-alpha (TNF-alpha) from splenocytes. In addition, high vitamin E diet also decreased the increased ratio of CD4 and CD8 single positive T cells following the development of murine AIDS, which was almost equal to the levels of uninfected control and high vitamin E groups. These results suggest that vitamin E supplementation normalizes the decrease of immune functions following the development of murine AIDS.

Serum selenium, plasma glutathione (GSH) and erythrocyte glutathione peroxidase GSH-Px)-levels in asymptomatic versus symptomatic human immunodeficiency virus-1 (HIV-1)-infection

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Eur J Clin Nutr 1997 Apr;51(4):266-72

Objectives: Antioxidant defense status was investigated in HIV-infected patients by measuring serum selenium, erythrocyte glutathione peroxidase (GSH-Px) activity, plasma thiol (-SH) and glutathione (GSH) concentrations along with the assessment of the clinical stage and surrogate markers of HIV-disease.

Design, setting and subjects: Serum selenium levels were determined cross-sectionally in 104 sequentially selected HIV-infected patients (83 outpatients and 21 patients with ongoing AIDS defining events). The patients were classified into three stages of the disease, I, II and III according to the 1993 Centers For Disease Control (CDC) classification system for HIV-infection. GSH-Px activities, plasma SH and plasma GSH concentrations were determined in a subset of 24 patients at stage I and 12 patients at stage III with an active AIDS-defining disease.

Results: Mean serum selenium levels were lower in CDC stage II (68.7 plus or minus 20.9 microg/l; $P < 0.01$; $n = 34$) and stage III (51.4 plus or minus 14.7 microg/l; P (0.01; $n = 37$) HIV-infected patients than in healthy subjects (89.2 plus or minus 20.9 microg/l; $n = 72$) and stage I patients (82.3 plus or minus 20.5; microg/l; $n = 33$). Serum selenium levels were positively correlated with CD4-count ($r = 0.42$; $P < 0.001$; $n = 104$) and inversely with levels of soluble tumor necrosis factor receptors type II ($r= -0.58$; $P < 0.01$; $n = 35$), neopterin ($r = -0.5$; $P < 0.001$; $n = 80$) and beta2-microglobulin ($r = -0.4$; $P < 0.001$; $n = 94$). Hepatitis C virus (HCV) and HIV-coinfected patients at CDC stages I and II showed markedly lower selenium concentrations compared to HIV-infected patients without concomitant HCV-infection. Serum selenium and GSH-Px activity in hospitalized AIDS patients was significantly lower as compared to asymptomatic patients and healthy subjects, whereas plasma SH and GSH concentrations were lower in both, asymptomatic -and AIDS-patients, than in the controls.

Conclusion: The results show that stages I-III of HIV-disease are characterized by significant impairments of antioxidative defenses provided by selenium, GSH-Px, SH-groups and GSH.

Intracellular glutathione as a possible direct blocker of HIV type 1 reverse transcription

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AIDS Res Hum Retroviruses 1996 Nov 20;12(17):1635-8

In AIDS patients, chronic inflammation and elevated levels of cytokines seem to be associated with reduced levels of glutathione (GSH). GSH has been proposed to inhibit the activation of NF-kappaB, which results in the inhibition of HIV-1 replication. Here, we show the evidence that GSH and N- acetylcysteine, but not L-cysteine or dithiothreitol, could inhibit the reverse transcriptase (RT) process of HIV-1. Such inhibition was not observed with the RT of murine leukemia virus.

Markedly disturbed glutathione redox status in CD45RA+CD4+ lymphocytes in human immunodeficiency virus type 1 infection is associated with selective depletion of this lymphocyte subset

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Blood 1996 Oct 1;88(7):2626-33

We investigated the percentage of CD45RA+ and CD45RO+ T cells in peripheral blood and the intracellular glutathione radox balance in these lymphocyte subsets in patients with human immunodeficiency virus type 1 (HIV- 1) infection and healthy controls. In HIV-l-infected patients there was a preferential depletion of CD45RA+CD4+ cells, which was most pronounced in symptomatic patients. In CD4+ lymphocytes from HIV-l-infected patients the glutathione abnormalities were clearly most pronounced in the CD45RA+ subset with a marked increase in level of oxidized glutathione and decreased ratio of reduced to total glutathione as the major characteristics. These abnormalities were shown in CD45RA+ CD4+ lymphocytes from both symptomatic and asymptomatic patients, whereas similar abnormalities in CD45RO+CD4+ cells were found only in symptomatic patients. The glutathione abnormalities in CD45RA+CD4+ lymphocytes were significantly correlated with low numbers of total CD4+ lymphocytes, decreased proportion of CD45RA+CD4+ lymphocytes, and raised serum levels of tumor necrosis factor-alpha. In the CD8+ lymphocytes a decrease in both proportion and absolute numbers of CD45RA+ cells was found, with markedly increased level of oxidized glutathione and decreased ratio of reduced to total glutathione in this subset. These findings suggest that glutathione redox disturbances in CD45RA+ T cells may be of pathogenic importance for the preferential depletion of this subset considered to represent naive T cells, during HIV-1 infection.

Micronutrient profiles in HIV-1-infected heterosexual adults

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J Acquir Immune Defic Syndr Hum Retrovirol 1996 May 1;12(1):75-83

There is compelling evidence that micronutrients can profoundly affect immunity. We surveyed vitamin supplement use and circulating concentrations of 22 nutrients and glutathione in 64 HIV-1 seropositive men and women and 33 seronegative controls participating in a study of heterosexual HIV-1 transmission. We assayed antioxidants (vitamins A, C, and E; total carotenes), vitamins B6 and B12, folate, thiamin, niacin, biotin, riboflavin, pantothenic acid, free and total choline and carnitine, biopterin, inositol, copper, zinc, selenium, and magnesium, HIV-infected patients had lower mean circulating concentrations of magnesium ($p < 0.0001$), total carotenes ($p = 0.009$), total choline ($p = 0.002$), and glutathione ($p = 0.045$), and higher concentrations of niacin ($p < 0.0001$) than controls. Fifty-nine percent of HIV+ patients had low concentrations of magnesium, compared with 9% of controls ($p < 0.0001$). These abnormal concentrations were unrelated to stage of disease. Participants who took vitamin supplements had consistently fewer low concentrations of antioxidants, across HIV infection status and disease stage strata ($p = 0.0006$). Nevertheless, 29% of the HIV+ patients taking supplemental vitamins had subnormal levels of one or more antioxidants. The frequent occurrence of abnormal micronutrient nutriture, as found in these HIV+ subjects, may contribute to disease pathogenesis. The low magnesium concentrations may be particularly relevant to HIV-related symptoms of fatigue, lethargy, and impaired mentation.

Serum selenium versus lymphocyte subsets and markers of disease progression and inflammatory response in human immunodeficiency virus-1 infection

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Biol Trace Elem Res 1997 Jan;56(1):31-41

Serum selenium levels were determined cross-sectionally in 57 HIV- infected patients who were classified according to the Centers for Disease Control (CDC) 1993 classification system. Mean serum selenium levels were lower in CDC stage II (58.7 plus or minus 12.2 microg/L; $p < 0.01$; $n = 18$) and stage III (47.6 plus or minus 11.3 microg/L; $p < 0.01$; $n = 19$) HIV-infected patients, than in healthy subjects (80.6 plus or minus 9.6 microg/L; $n = 48$) and stage I patients (73.6 plus or minus 16.5 microg/L; $n = 20$). Serum selenium levels were positively correlated with CD4 count, CD4/8 ratio, hematocrit, and serum albumin ($r = 0.42$; $r = 0.39$; $r = 0.48$; and $r = 0.45$; $p < 0.01$, respectively) and inversely with serum levels of thymidine kinase ($r = - 0.49$; $p < 0.01$; $n = 49$) and beta2-microglobulin ($r = - 0.46$; $p < 0.001$; $n = 49$). In addition, serum selenium levels in 20 randomly selected AIDS-free individuals (CDC I: $n = 10$; CDC II: $n = 10$) were inversely correlated with serum concentrations of interleukin-8 (IL-8) and soluble tumor necrosis factor receptors (sTNFR) types I and II. There was no correlation with serum immunoglobulin A and total serum protein levels. The results show that the

progressive deprivation of serum selenium in HIV- infection is associated with loss of CD4+-cells and with increased levels of markers of disease progression and inflammatory response.

Influence of L-carnitine on CD95 cross-linking-induced apoptosis and ceramide generation in human cell lines: Correlation with its effects on purified acidic and neutral sphingomyelinases in vitro

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Proc Assoc Am Physicians 1997 Mar;109(2):154-63

Recently, we examined the effects of a short-term (5-days) intmvenous L-carnitine (6 g/die) treatment on apoptosis of CD4 and CD8 cells from 10 AIDS patients. Without inducing side effects, L-carnitine administration has been shown to induce a potent reduction in the percentage of cells undergoing apoptosis, paralleled by a significant increase of CD4 and CD8 cells. Interestingly, L-carnitine treatment led to a significant reduction of peripheral blood mononuclear cell-associated ceramide (an intracellular messenger for apoptosis) that correlated with the decrease of apoptotic CD4- and CDS-positive cells. These results suggest that L-carnitine could be an effective antiapoptotic drug for use with AIDS patients. In this article we report the results of in vitro studies performed to better characterize the effects of L-carnitine on cell apoptosis. Previously, a high expression of the Fas (CD95/APO-1)/Fas ligand system in peripheral blood mononuclear cells from HIV-positive individuals has been reported and could be responsible for the observed relevant apoptosis of both infected and uninfected cells. Thus, we investigated the in vitro effects of L-carnitine on CD95 cross-linking- induced apoptosis through an anti-CD95 mAb in Fas-sensitive cell lines (HUT78 and U937). The results strongly support the in vivo observations. Our data indicate that L-carnitine is able to inhibit CD95-induced apoptosis of these cells, most likely by preventing sphingomyelin breakdown and consequent ceramide synthesis. The effect of L-carnitine seems to be specific for acidic sphingomyelinase as shown by experiments performed in vitro and using purified neutral or acidic sphingomyelinases.

Effect of L-carnitine treatment in vivo on apoptosis and ceramide generation in peripheral blood lymphocytes from AIDS patients

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Proc Assoc Am Physicians 1997 Mar;109(2):146-53

Lymphocyte apoptosis in HIV-infected individuals may play a role in T- cell depletion and therefore favor progression to AIDS. In this study, we examined the effects of a short-term (5-day) intravenous treatment with L- carnitine (6 g/day) on apoptosis of CD4 and CD8 cells from 10 AIDS patients. L-carnitine administration has been shown to induce a strong reduction in the percentage of both CD4 and CD8 cells undergoing apoptosis. Interestingly, the L-carnitine treatment, which did not show relevant side effects in our patients, led to a strong and significant reduction of peripheral blood mononuclear cell-associated ceramide, an intracellular messenger of apoptosis, that positively correlated with the decrease of apoptotic CD4- and CD8-positive cells. These results suggest that L-carnitine could be an effective antiapoptotic drug in the treatment of AIDS patients.

Increased uptake and accumulation of Vitamin-C in human immunodeficiency virus 1-infected hematopoietic cell lines

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J Biol Chem 1997 Feb 28;272(9):5814-20

Vitamin-C (ascorbic acid) is required for normal host defense and functions importantly in cellular redox systems. To define the interrelationship between human immunodeficiency virus (HIV) infection and Vitamin-C flux at the cellular level, we analyzed Vitamin-C uptake and its effects on virus production and cellular proliferation in HIV-infected and uninfected human lymphoid, myeloid, and mononuclear phagocyte cell lines. Chronic or acute infection of these cell lines by HIV-1 led to increased expression of glucose transporter 1, associated with increased transport and accumulation of Vitamin-C. Infected cells also showed increased transport of glucose analogs. Exposure to Vitamin-C had a complex effect on cell proliferation and viral production. Low concentrations of Vitamin-C increased or decreased cell proliferation depending on the cell line and either had no effect or caused increased viral production. Exposure to high concentrations of Vitamin-C preferentially decreased the proliferation and survival of the HIV-infected cells and caused decreased viral production. These findings indicate that HIV infection in lymphocytic, monocytic, and myeloid cell lines leads to increased expression of glucose transporter 1 and consequent increased cellular Vitamin-C uptake. High concentrations of Vitamin-C were preferentially toxic to HIV-infected host defense cell lines in vitro.

Antioxidant-micronutrients and HIV infection

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Int J Std AIDS 1996 Nov-Dec;7(7):485-9

We measured plasma levels of all the antioxidant-micronutrients in subjects with HIV infection and controls. Plasma levels of all the carotenoids, including lutein, cryptoxanthin, lycopene, alpha-carotene and beta-carotene as well as vitamins A, C and E and cholesterol were assayed in 35 subjects with HIV infection and 38 controls. We found a significant depletion of all the carotenoids ($P < 0.001$) and Vitamin-C ($P < 0.01$) and cholesterol ($P < 0.001$) but not vitamins A or E in HIV-infected subjects. Further analysis of the HIV-infected subjects revealed that plasma levels of 4 of the groups of carotenoids and cholesterol were correlated with CD4 count but that beta-carotene and vitamins A, C and E were not. These results are reviewed in the light of the published literature and we conclude that these abnormalities of antioxidant-micronutrients are likely to reflect a metabolic phenomenon associated with HIV infection. However, an additional contribution to these deficiencies from malabsorption later in HIV disease cannot be ruled out.

Relationship between high incidence of adverse dapsone reactions and slow acetylate phenotype or low plasma/lymphocyte glutathione level

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Chin Med J (Engl) 1996 Dec;109(12):933-6

Objective. To investigate the relationship between high incidence of adverse dapsone reactions in acquired immunodeficiency syndrome (AIDS) patients and slow acetylate phenotype or low plasma/lymphocyte glutathione level of these patients.

Methods. Twenty-one cases of advanced AIDS patients (CD4 < 200/microl) were involved in this study, all Europeans except one black, were acetylate phenotyped via analysis of caffeine metabolites, named 5-Acetylamino-6-formylamino-3-methyluracil, 1-Methylxant hine and 5-Acetylamino-6-amino-3-methyluracil, in human urine collected 2 hours after a cup of caffeine-spiked coffee and their plasma/lymphocyte glutathione concentrations were determined, by high performance liquid chromatographic method.

Results. Of the 21 AIDS patients, 15 are slow acetylators, accounting for 74.8%. One of 6 rapid acetylators has adverse dapsone reactions, acounting for 17%, compared with 46% for slow acetylators (7/15). The concentrations of glutathione in plasma/lymphocyte (6.97 plus or minus 0.95 micromol and 28.75 plus or minus 2.78 nmol/mg protein) in AIDS patients with adverse dapsone reactions are significantly lower than those (10.90 plus or minus 1.45 micromol and 32.15 plus or minus 2.21 nmol/mg protein) of AIDS patients without adverse dapsone

reactions, and also than those (11.85 plus or minus 1.83 micromol and 33.76 plus or minus 2.32 nmol/mg protein) of health controls.

Conclusions: Slow acetylators, which lead to accumulation of toxic dapsone metabolites and those subjects who are lower in glutathione level in plasma/lymphotye because of certain kinds of diseases as advanced AIDS are risk population of adverse dapsone reactions. Routinely determining human acetylate phenotype status might be helpful in adjusting and modifying dapsone dosage regimen.

Selenium and HIV in Pediatrics

J. Nutr. Immunol. (USA), 1994, 3/1 (41-49)

An important role for selenium in immune processes has been described, with selenium appearing to affect non-specific immune indices, humoral immunity, cell-mediated immunity and cytotoxicity. Whereas low plasma selenium levels have been correlated with decreased natural killer (NK) cell activity, as well as proliferative response of lymphocytes to mitogens in vitro, supplementation with selenium has been associated with enhanced lymphocyte response to phytohemagglutinin (PHA) and pokeweed (PWM) and with enhanced NK activity when administered in physiological ranges, but not at pharmacological doses. The investigation of selenium status in HIV-1 infection is of particular interest, in light of studies documenting low plasma selenium levels and decreased glutathionine peroxidase activity in adult patients with AIDS. Moreover, alterations in selenium levels have been associated with immune dysregulation in early HIV-1 infection. As examination of pediatric nutritional status in HIV-1 disease has been restricted in scope, this study was designed to characterize selenium status and examine its relationship to immune function, in HIV-1 infected children.

N-Acetylcysteine enhances T cell functions and T cell growth in culture

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Int Immunol 1993 Jan;5(1):97-101

N-Acetylcysteine (NAC) is highly nontoxic for peripheral blood T cells and immunostimulatory enhancing T cell functions such as mitogenesis, interleukin-2 (IL-2) production, and growth in culture. NAC has been proposed for the treatment of AIDS based on its inhibition of human immunodeficiency virus (HIV) replication in cultured cells. Therefore its effect on normal T cells from 10 young donors and one elderly donor has been investigated as a prelude to clinical consideration. T cell function was evaluated in the presence and absence of accessory cells. With concanavalin A and anti-CD3 activation, NAC enhanced mitogenesis by similar2- to 2.5-fold at 5-10 mM. Mitogenesis of purified T cells

with anti-CD2 was not affected by NAC; in the presence of accessory cells, NAC enhanced mitogenesis by similar2-fold at 1-10 mM. Importantly, NAC levels above 10 mM completely inhibited activation of peripheral blood mononuclear cells by anti-CD2. IL-2 secreted by T cells was also enhanced by NAC, similar1.5-fold, but IL-2 secreted by cells from old donors was enhanced by 3-fold. In cultures of peripheral blood T cells, NAC (10 mM) stimulated growth by at least 4- to 6-fold after two passages. These results show that NAC, nontoxic even at 20 mM, is an effective enhancer of T cell function and a remarkable enhancer of growth. Results from other laboratories show that NAC, which increases glutathione levels, suppresses HIV replication presumably via suppression of the activation of transcriptional factor NF-kappa B. For normal T cells, however, this mechanism does not appear applicable because IL-2 production, regulated by several factors including NF-kappa B, is enhanced by NAC. Rather, glutathione may enhance the activity of other transcriptional factors modulating IL-2 expression. NAC did exhibit one inhibitory characteristic, however, towards T cell adhesion. Slow cluster formation, induced by PMA, was moderately inhibited (0-30%) by 5-10 mM NAC in cells from most donors studied.

Cysteine and glutathione deficiency in HIV-infected patients. The basis for treatment with N-acetyl-cysteine

AIDS-Forschung (Germany), 1992, 7/4 (197-199)

Clinical studies and complementary laboratory investigations suggest that the deterioration of the immune system in HIV-infected patients may be the consequence of a virus-induced cysteine deficiency. HIV-infected persons at all stages of the disease have, on the average, decreased plasma cystine and cysteine and decreased intracellular glutathione levels. Cysteine levels also decrease in rhesus macaques within 1 to 2 weeks after infection with SIV(mac). HIV-infected persons and SIV-infected macaques also have, on the average, markedly increased plasma glutamate levels, which aggravate the cysteine deficiency by inhibiting the membrane transport of cystine. Even moderately increased extracellular glutamate levels as they are found in HIV-infected persons cause a profound decrease of intracellular cyst(e)ine levels. A correlation between individual T4+ cell counts (but not T8+ cell counts) and individual cystine and glutamate levels has been found not only in HIV-infected persons but also in healthy individuals, indicating that the linkage between cysteine supply and immune system is demonstrable even in the absence of the virus. There is suggestive evidence that the HIV-induced cysteine deficiency is not only responsible for the 'cellular dysfunction' but also for the abnormal activation which is exemplified by the lymphadenopathy syndrome and abnormal antibody production. HIV-infected persons were found to have abnormally high TNFalpha, IL-2 receptor alpha-chain and beta2-microglobulin levels. All the corresponding genes are associated with kappaB-like enhancer sequences. And the activation of the transcription factor NFkappaB is negatively regulated by cysteine or cysteine derivatives. We have, therefore, suggested that N-acetyl-cysteine (NAC) may be considered for the

replenishment of cysteine and glutathione levels in HIV-infected persons, since NAC is a well-established and safe drug with well-documented pharmacokinetics.

N-acetylcysteine (NAC) enhances interleukin-2 but suppresses interleukin-4 secretion from normal and HIV+ CD4+ T-cells.

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Cell Mol Biol (Noisy-le-grand) 1995;41 Suppl 1:S35-40

We find that purified CD4+ T cells from 30 HIV+ individuals have a suppressed Interleukin-4 (IL-4) production compared to normal controls regardless of activator (anti-CD3 or Con A) or co-activator [phorbol ester (PMA or anti-CD28)], generally by 2-4 fold. In every case, the cells producing IL-4 respond more strongly to anti-CD28 co-activation than to PMA, ie, 1150 pg/ml compared to 2070 pg/ml for controls and 398 pg/ml compared to 1250 pg/ml for HIV+ cells, respectively. In contrast, anti-CD3 with PMA gives a more vigorous IL-2 response than with anti-CD28, ie, 37.3 ng/ml compared to 12.3 ng/ml for controls and 28.5 ng/ml versus 15.1 ng/ml for HIV+ cells, respectively. These data are not compatible with the TH1/TH2 switch hypothesis since IL-4 production is decreased, not increased for CD4+ HIV+ T-cells and while IL-2 production is decreased with PMA, it is not decreased significantly with anti-CD28. Interestingly, 5 mM N-acetylcysteine (NAC) acts as an immunoenhancer; mitogenesis was enhanced 2 fold or more in general for control and HIV+ CD4+ T-cells and IL-2 production was enhanced 2-3 fold for anti-CD3 (with PMA or anti-CD28) for both controls and HIV+ CD4+ cells. However, NAC suppressed IL-4 production induced by anti-CD3 and anti-CD28 in both control and HIV+ CD4+ T cells. In the other cases, it produced in general no significant change.

N-acetylcysteine enhances antibody-dependent cellular cytotoxicity in neutrophils and mononuclear cells from healthy adults and human immunodeficiency virus-infected patients.

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J Infect Dis (United States) Dec 1995, 172 (6) p1492-502

Patients with AIDS have decreased levels of the intracellular antioxidant, glutathione, in their circulating lymphocytes and plasma. N-acetylcysteine (NAC) increases intracellular stores of glutathione and has direct antioxidant properties. In this study, the effects of glutathione and NAC on the cytotoxicity of neutrophils and mononuclear cells were tested using cells from healthy controls and human immunodeficiency virus (HIV)-infected patients. NAC (1 and 5 mM) enhanced the antibody-dependent cellular cytotoxicity (ADCC) of neutrophils from healthy adult controls and HIV-infected adults and children. The antineoplastic drug, 1,3 bis(2-chloroethyl)-1-nitrosourea (BCNU), which depletes

intracellular glutathione, inhibited the ADCC of neutrophils; the addition of NAC partially reversed this inhibition. Similar effects of BCNU and NAC were seen when the cytotoxicity of mononuclear cells was tested using CEM tumor cells bearing the HIV gp120 antigen as targets. Thus, NAC enhances various forms of cytotoxicity and may be beneficial to AIDS patients whose defects in leukocyte cytotoxicity may be due to glutathione depletion.

Glutathione precursor and antioxidant activities of N-acetylcysteine and oxothiazolidine carboxylate compared in in vitro studies of HIV replication.

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AIDS Res Hum Retroviruses (United States) Aug 1994, 10 (8) p961-7

N-Acetyl-L-cysteine (NAC) and L-2-oxothiazolidine 4-carboxylate (OTC) are pro-GSH drugs that been proposed for AIDS therapy. In this article we compare the antiviral activities of these compounds in various in vitro HIV infection models. Although both compounds blocked cytokine induction of HIV in acute and chronic infection models, and in HIV-LTR reporter cell systems, NAC was far more effective than OTC, even at suboptimal doses. To test whether this difference is due to GSH conversion efficacies of these compounds, we measured GSH restoration by NAC or OTC in GSH-depleted peripheral blood mononuclear cells (PBMCs), using flow cytometry. In isolated PBMCs, NAC fully replenishes depleted intracellular GSH whereas OTC only minimally replenishes GSH. This ability to replenish GSH in vitro and its ability to scavenge free radicals directly explain why NAC has more potent antiviral activities in vitro.

Role for oxygen radicals in self-sustained HIV-1 replication in monocyte-derived macrophages: enhanced HIV-1 replication by N-acetyl-L-cysteine.

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J Leukoc Biol (United States) Dec 1994, 56 (6) p702-7

N-acetyl-L-cysteine (NAC) has been proposed as a therapeutic agent for AIDS patients because it reduces human immunodeficiency virus type 1 (HIV-1) replication in stimulated T cells. However, NAC and glutathione enhanced acute HIV-1 replication in monocyte-derived macrophages. Buthionine sulfoximine did not affect NAC-mediated enhanced HIV-1 replication, indicating that the NAC-mediated effects are glutathione-independent. Superoxide dismutase and the hydroxyl radical scavengers dimethylthiourea and thiourea, but not urea, inhibited acute HIV-1 replication in macrophages. NAC reduced ferricytochrome c and increased dose-dependently Fe(III)-citrate and Fe(III)-EDTA-catalyzed hydroxyl

radical formation in a system using glucose and glucose oxidase. Dimethylthiourea and thiourea, but not urea and superoxide dismutase, dose-dependently inhibited NAC-mediated enhancement of HIV-1 replication. These data suggest that oxygen radicals play an important role in self-sustained HIV-1 replication in macrophages and that oxygen radical scavengers other than NAC should be considered as therapeutic agents for AIDS patients.

Effects of glutathione precursors on human immunodeficiency virus replication.

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Chem Biol Interact (Ireland) Jun 1994, 91 (2-3) p217-24

Asymptomatic human immunodeficiency virus (HIV)-seropositive individuals have reduced glutathione (GSH) levels. This has led to the suggestion that elevated intracellular thiols levels may inhibit HIV replication and progression of the disease. We confirmed that N-acetyl-L-cysteine (NAC), a cysteine prodrug which maintains intracellular GSH levels during oxidative stress, inhibits in the chronically infected U1 cells, the stimulation of HIV replication induced by phorbol 12-myristate 13-acetate (PMA), interleukin-6 (IL-6) or granulocyte-macrophage colony stimulating factor (GM-CSF). However, we found no significant inhibition of PMA-mediated long terminal repeat (LTR)-directed beta-galactosidase expression in transiently transfected Jurkat T-cells. We have compared NAC effects with the effects of other GSH precursors on HIV expression. Treatment of the U1 cell line by L-2-oxo-4-thiazolidine carboxylic acid (OTC), which is converted to cysteine by 5-oxoprolinase, or by homocysteine (HC), a natural cysteine precursor, reduced the PMA-induced HIV expression, but surprisingly, markedly stimulated the expression mediated by IL-6 and GM-CSF. Several experiments to investigate the effect of OTC on LTR transactivation were carried out, but beta-galactosidase activity was never modified in a significant fashion in PMA-induced Jurkat T-cells after OTC treatment. Furthermore, HC stimulated the PMA-mediated HIV-LTR transactivation in Jurkat T-cells. GSH assays showed that treatment of U937 and Jurkat T-cells with NAC and OTC moderately increased the GSH level, while HC led to a significantly higher increase of the thiol level. In conclusion, it appeared that an increase of the GSH intracellular level did not lead solely to an inhibition of HIV replication but could also lead to an activation of viral expression. This seemed the case when HIV replication was stimulated by compounds which act mainly at a post-transcriptional level.

Effect of glutathione depletion and oral N-acetyl-cysteine treatment on CD4+ and CD8+ cells.

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FASEB J (United States) Apr 1 1994, 8 (6) p448-51

HIV-infected individuals and SIV-infected rhesus macaques have, on the average, decreased plasma cysteine and cystine concentrations and decreased intracellular glutathione levels. We show that the cysteine supply and the intracellular glutathione levels have a strong influence on the T cell system. A study of healthy human subjects revealed that persons with intracellular glutathione levels of 20-30 nmol/mg protein had significantly higher numbers of CD4+ T cells than persons with either lower or higher glutathione levels. Persons who moved during a 4-week observation period from the optimal to the suboptimal range (10-20 nmol/mg) experienced, on the average, a 30% decrease in CD4+ T cell numbers. This decrease was prevented by treatment with N-acetyl-cysteine (NAC). NAC caused this relative increase of CD4+ T cell numbers in spite of decreasing glutathione levels and not by increasing the glutathione level. Our studies suggest that the immune system may be exquisitely sensitive not only against a cysteine and glutathione deficiency but also against an excess of cysteine.

Comparative study of the anti-HIV activities of ascorbate and thiol-containing reducing agents in chronically HIV-infected cells.

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Am J Clin Nutr (United States) Dec 1991, 54 (6 Suppl) p1231S-1235S

To elucidate the action of Vitamin-C on pathogenic human retroviruses, we investigated and compared the effects of noncytoxic concentrations of ascorbic acid (AA), its calcium salt (Ca-ascorbate), and two thiol-based reducing agents [glutathione (GSH) and N-acetyl-L-cysteine (NAC)] against human immunodeficiency virus (HIV)-1 replication in chronically infected T lymphocytes. Ca-ascorbate reduced extracellular HIV reverse transcriptase (RT) activity by about the same magnitude as the equivalent dose of AA. Long-term experiments showed that continuous presence of ascorbate was necessary for HIV suppression. NAC (10 mmol/L) caused less than twofold inhibition of HIV RT and conferred a synergistic effect (approximately eightfold inhibition) when tested simultaneously with AA (0.426 mmol/L). In contrast, nonesterified GSH (less than or equal to 1.838 mmol/L) had no effect on RT concentrations and did not potentiate the anti-HIV effect of AA. These results further support the potent antiviral activity of ascorbate and suggest its therapeutic value in controlling HIV infection in combination with thiols.

Antioxidant status and lipid peroxidation in patients infected with HIV

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Chem.-Biol. Interact. (Ireland), 1994, 91/2-3 (165-180)

Deficiency in antioxidant micronutrients have been observed in patients with AIDS. These observations concerning only some isolated nutrients demonstrate a defect in zinc, selenium, and glutathione. An increase in free radical production and lipid peroxidation has been also found in these patients, and takes a great importance with recent papers presenting an immunodeficiency and more important an increase in HIV-1 replication secondary to free radicals overproduction. We have assessed different studies, trying to obtain a global view of the antioxidant status of these patients. In adults we observe a progressive decrease for zinc, selenium, and vitamin E with the severity of disease, except that selenium remains normal at stage II. However, the main dramatic decrease concerns carotenoids whose level at stage II is only half the normal value. To understand if these decreases in antioxidant and increases in oxidative stress occur secondary to the aggravation of the disease or, conversely, are responsible for it, we undertook a longitudinal survey of asymptotic patients. The preliminary results of this evaluation are presented. Paradoxically, lipid peroxidation is higher at stage II than at stage IV. This may be consecutive to a more intense overproduction of oxygen free radicals by more viable polymorphonuclear (PMN) at the asymptomatic stage. The free radicals production and lipid peroxidation seem secondary to a direct induction by the virus of PMN stimulation and cytokines secretion. N-Acetyl cystein or ascorbate have been demonstrated in cell culture to be capable of blocking the expression of HIV-1 after oxidative stress and N-acetyl cysteine inhibits in vitro TNF-induced apoptosis of infected cells. In regard to all these experimental data, few serious and large trials of antioxidants have been conducted in HIV-infected patients, although some preliminary studies using zinc or selenium have been performed. In our opinion it is now time to evaluate in humans the beneficial effect of antioxidants. The more promising candidates for presenting synergistic effects when associated with N-acetyl cysteine seem to be beta-carotene, selenium and zinc.

N-acetylcysteine inhibits latent HIV expression in chronically infected cells

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AIDS Res. Hum. Retroviruses (USA), 1991, 7/6 (563-567)

The progression of the human immunodeficiency virus (HIV) infection from its early latent (asymptomatic) stage to active, late-stage acquired immunodeficiency syndrome (AIDS) apparently begins with the production of inflammatory

cytokines that stimulate the expression and replication of the latent virus. We have shown that N-acetylcysteine, a cysteine precursor that is converted intracellularly into glutathione, blocks cytokine-stimulated HIV replication in an acutely infected T-cell line and in acutely infected peripheral blood mononuclear cells from normal individuals. In this report, we show that N-acetylcysteine also inhibits stimulated HIV expression in chronically infected monocyte and T-cell lines which are used as models for latent infection in AIDS. Furthermore, we show that N-acetylcysteine blocks viral production in monocyte cell lines more effectively than it blocks viral production in T cells. Since monocytes are a major reservoir for HIV in infected individuals, these results suggest that N-acetylcysteine may slow the change from latency to the later stages of AIDS in HIV-infected individuals.

Selenium mediated inhibition of transcription factor NF-kappaB and HIV-1 LTR promoter activity

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Arch Toxicol 1996;70(5):277-83

The eukaryotic transcription factor NF-kappaB is involved in the inducible expression of various inflammatory genes as well as in HIV-1 replication. Activation of NF-kappaB is induced by prooxidants and several stimuli eliciting oxidative stress, such as cytokines, lipopolysaccharide, UV irradiation and other mediators. Various antioxidants inhibit NF-kappaB activation in response to these stimuli. In this study, we have investigated the effects of selenium, an integral component of glutathione peroxidase (GPX), on NF-kappaB activation. In selenium-deprived Jurkat and ESb-LT lymphocytes, supplementation of selenium led to a substantial increase of GPX activity. Analysis of DNA binding revealed that NF-kappaB activation in response to TNF was significantly inhibited under these conditions. Likewise, reporter gene assays using luciferase constructs driven by the HIV-1 long terminal repeat showed a dose-dependent inhibition of NF-kappaB controlled gene expression by selenium. The effects of selenium were specific for NF-kappaB, since the activity of the transcription factor AP-1 was not suppressed. These data suggest that selenium supplementation may be used to modulate the expression of NF-kappaB target genes and HIV-1.

Release of nitric oxide from astroglial cells: A key mechanism in neuroimmune disorders

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Advances in Neuroimmunology (United Kingdom), 1995, 5/4 (421-430)

Astrocytes are glial cells able to release nitric oxidc (NO) under basal conditions as well as following different neurochemical stimuli including cytokines, endotoxins and soluble antigens, thereby participating in neuroimmune responses. In particular, the inducible isoform of NO synthase seems to be activated during co-incubation of this cell type with cytokines as well as in the presence of the HIV coating gp120 glycoprotein, an effect which is associated with an enhancement of prostanoid release. This seems also to occur via activation of cyclooxygenase by NO. Thus, the L-arginine-NO pathway fouud in astrocytes may represent a novel approach in the treatment of neuroimmune disorders such as multiple sclerosis, Alzheimer's disease and AIDS.

Carnitine depletion in peripheral blood mononuclear cells from patients with AIDS: Effect of oral L-carnitine

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AIDS 1994 May;8(5):655-60

Objective: Reduced levels of serum carnitines (3-hydroxy-4-N-trimethyl-am moniobutanoate) are found in most patients treated with zidovudine. However, since serum carnitines do not strictly reflect cellular concentrations we examined whether a carnitine depletion could be found in peripheral blood mononuclear cells (PBMC) from AIDS patients with normal serum carnitine levels. In addition, we explored whether it was possible to relate the host's immunoreactivity to the content of carnitine in PBMC and whether carnitine levels can be corrected by oral supplementation of L-carnitine. Design: Immunopharmacologic study.

Methods: Twenty male patients with advanced AIDS (Centers for Disease Control and Prevention stage IVCI) and normal serum levels of carnitines were enrolled. Patients were randomly assigned to receive either L-carnitine (6 g/day) or placebo for 2 weeks. At baseline and at the end of the trial, we measured carnitines in both sera and PBMC, serum triglycerides, CD4 cell counts, and the frequency of cells entering the S and G2-M phases of cell cycle following mitogen stimulation.

Results: Concentrations of total carnitine in PBMC from AIDS patients was lower than in healthy controls. A significant trend towards the restoration of appropriate intracellular carnitine levels was found in patients treated with high-dose L-carnitine and was associated with an increased frequency of S and G2-M cells following mitogen stimulation. Furthermore, at the end of the trial we found a strong reduction in serum triglycerides in the L-carnitine group compared with baseline levels.

Conclusions: Our data indicate that carnitine deficiency occurs in PBMC from patients with advanced AIDS, despite normal serum concentrations. The increase in cellular carnitine content strongly improved lymphocyte proliferative responsiveness to mitogens. Because carnitine status is an important contributing factor to immune function in patients with advanced AIDS, we therefore believe

that L-carnitine supplementation could have a role as a complementary therapy for HIV-infected individuals.

High dose L-carnitine improves immunologic and metabolic parameters in AIDS patients

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Immunopharmacol. Immunotoxicol. (USA), 1993, 15/1 (1-12)

Several reports indicate that systemic carnitine deficiency could occur in acquired immunodeficiency disease syndrome (AIDS), and that primary and secondary carnitine deficiency leads to critical metabolic dysfunctions. L-carnitine supplementation to peripheral blood mononuclear cells (PBMCs) of AIDS patients resulted in significant enhancement of the phytohemagglutinin (PHA)-driven proliferative response. High dose L-carnitine administration (6 gr per day for two weeks) to AIDS patients treated with zidovudine also led to increased PBMCs proliferation and reduced blood levels of triglycerides. In addition, a reduction of beta2-microglobulin serum levels as well as circulating tumor necrosis factor (TNF)-alpha, mostly in patients exhibiting highly elevated levels, were found at the end of the treatment period. Our data suggest that in vivo L-carnitine could prove useful in ameliorating both the immune response and lipid metabolism in patients with AIDS, irrespective of initial serum carnitines levels. The mechanism(s) accounting for the observed results are currently not clear. Further studies are needed to confirm the hypothesis that L-carnitine affects the expression of HIV-induced cytokines.

Vitamin B-12 abnormalities in HIV-infected patients

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Eur. J. Haematol. (Denmark), 1991, 47/1 (60-64)

A prospective study of 60 consecutively admitted patients with HIV infection was performed to document the prevalence, etiology and manifestations of low serum vitamin B-12 in such patients. Low serum B-12 levels were found in 10 patients (16.7%). In 6, vitamin B-12 absorption was impaired and hog intrinsic factor addition did not improve it. Patients with low vitamin B-12 levels showed lower hemoglobin, leukocytes, lymphocytes, CD4 lymphocytes and CD4/CD8 lymphocyte ratio than HIV patients with physiological serum vitamin B-12 levels. However, bone marrow megaloblastosis was found in only 3 low vitamin B-12 patients and the deoxyuridine suppression test was pathological in only 1 case. In 7 patients, parenteral treatment was begun with variable response despite serum vitamin B-12 correction. In conclusion, low serum vitamin B-12 is often found in HIV-infected patients and it could be related to malabsorption, but clear

megaloblastic abnormalities and treatment response could not be demonstrated. A decreased concentration of the serum binders due to disturbances in the leukocytes and related immunocompetent cell may play an additional role.

The activities of coenzyme Q10 and vitamin B6 for immune responses

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Biochem Biophys Res Commun 1993 May 28;193(1):88-92

Coenzyme Q10 (CoQ10) and vitamin B6 (pyridoxine) have been administered together and separately to three groups of human subjects. The blood levels of CoQ10 increased ($p<0.001$) when CoQ10 and pyridoxine were administered together and when CoQ10 was given alone. The blood levels of IgG increased when CoQ10 and pyridoxine were administered together ($p<0.01$) and when CoQ10 was administered alone ($p<0.05$). The blood levels of T4- lymphocytes increased when CoQ10 and pyridoxine were administered together ($p<0.01$) and separately ($p<0.001$). The ratio of T4/T8 lymphocytes increased when CoQ10 and pyridoxine were administered together ($p<0.001$) and separately ($p<0.05$). These increases in IgG and T4-lymphocytes with CoQ10 and vitamin B6 are clinically important for trials on AIDS, other infectious diseases, and on cancer.

Coenzyme Q10 increases T4/T8 ratios of lymphocytes in ordinary subjects and relevance to patients having the AIDS related complex

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Biochem Biophys Res Commun 1991 Apr 30;176(2):786-91

Coenzyme Q10 (CoQ10) is indispensable to biochemical mechanisms of bioenergetics, and it has a non-specific role as an antioxidant. CoQ10 has shown a hematological activity for the human and has shown an influence on the host defense system. The T4/T8 ratios of lymphocytes are known to be low in patients with AIDS, ARC and malignancies. Our two patients with ARC have survived four-five years without any symptoms of adenopathy or infection on continuous treatment with CoQ10. We have newly found that 14 ordinary subjects responded to CoQ10 by increases in the T4/T8 ratios and an increase in blood levels of CoQ10; both by $p < 0.001$. This knowledge and survival of two ARC patients for four-five years on CoQ10 without symptoms, and new data on increasing ratios of T4/T8 lymphocytes in the human by treatment with CoQ10 constitute a rationale for new double blind clinical trials on treating patients with AIDS, ARC and diverse malignancies with CoQ10.

Biochemical deficiencies of coenzyme Q10 in HIV-infection and exploratory treatment

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Biochem Biophys Res Commun 1988 Jun 16;153(2):888-96

AIDS patients (2 groups) had a blood deficiency ($p<0.001$) of coenzyme Q10 vs. 2 control groups. AIDS patients had a greater deficiency ($p<0.01$) than ARC patients. ARC patients had a deficiency ($p<0.05$) vs. control. HIV-infected patients had a deficiency ($p<0.05$) vs. control. The deficiency of CoQ10 increased with the increased severity of the disease, i.e., from HIV positive (no symptoms) to ARC (constitutional symptoms, no opportunistic infection or tumor) to AIDS (HIV infection, opportunistic infection and/or tumor). This deficiency, a decade of data on CoQ10 on the immune system, on IgG levels, on hematological activity ocnstituted the rationale for treatment with CoQ10 of 7 patients with AIDS or ARC. One was lost to follow-up; one expired after stopping CoQ10; 5 survived, were symptomatically improved with no opportunistic infection after 4-7 months. In spite of poor compliance of 5/7 patients, the treatment was very encouraging and at times even striking.

Inhibition of 3'azido-3'deoxythymidine-resistant HIV-1 infection by dehydroepiandrosterone in vitro

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Biochem Biophys Res Commun 1994 Jun 30;201(3):1424-32

Human immunodeficiency virus type 1 (HIV-1) isolated from patients with acquired immunodeficiency syndrome (AIDS) shows resistance to 3'azido-3' deoxythymidine (AZT) after one or two years of treatment. AZT also has significant toxic side effects, further limiting its use in the therapy of HIV-1-infected individuals. Dehydroepiandrosterone (DHEA) has been shown to have a broad spectrum of biological functions, to be bioavailable orally and to be relatively nontoxic. Epidemiological studies provide evidence that reduced serum levels of DHEA are related to the progression of AIDS in HIV-1 infection. DHEA has also been shown to inhibit HIV-1 replication in vitro and block HIV-1 reactivation from chronically infected cell lines. However, there have been no reports on the ability of DHEA to inhibit the replication of AZT-resistant strains of HIV-1. We investigated whether DHEA treatment could inhibit replication of AZT-resistant strains of HIV-1. Addition of DHEA to MT-2 cell cultures infected with either AZT-sensitive or AZT-resistant isolates of HIV-1 resulted in dose-dependent inhibition of HIV-1-induced cytopathic effect and suppression of HIV-1 replication as measured by accumulation of reverse transcriptase activity. At a concentration as low as 50 microM, DHEA reduced AZT-resistant HIV-1

replication over 50 percent as measured by cytopathic effect and accumulation of reverse transcriptase activity. This study provides evidence that DHEA can inhibit the replication of AZT-resistant as well as wild-type HIV-1. Since the main targets for DHEA are metabolic and cellular signaling pathways leading to HIV-1 replication- activation, DHEA should be effective against multidrug-resistant strains of HIV-1. Combined with recently discovered immunoregulatory properties, the finding that DHEA is able to inhibit replication of both wild-type and AZT- resistant HIV-1 suggests that in vivo DHEA may have a much broader spectrum of action than originally anticipated.

Inhibition of HIV-1 latency reactivation by dehydroepiandrosterone (DHEA) and an analog of DHEA

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AIDS Res Hum Retroviruses 1993 Aug;9(8):747-54

The initial infection with human immunodeficiency virus type 1 (HIV-1) in most individuals usually results in the establishment of a latent or chronic infection before eventual progression toward acquired immunodeficiency syndrome. HIV-1 can also establish a latent or persistent infection in some T cell lines that show minimal constitutive virus expression. However, activation of the T cell lines leading to enhanced HIV-1 replication can be induced by antigens, mitogens, and cytokines (tumor necrosis factor alpha (TNF- alpha), interleukin 1, and interleukin-2). Various gene products from other viruses (HTLV-1, HSV, EBV, CMV, HBV, and HHV-6) can also enhance HIV-1 long terminal repeat (LTR)-driven reporter gene activity. On the basis of these observations, it has been proposed that reactivation of latent HIV-1 harbored in chronically infected T lymphocytes, monocytes, or macrophages plays an important role in the pathogenesis of AIDS. So far, there are no drugs or therapy available that can provide protection against HIV-1 latency reactivation. ACH-2, derived from a human T cell line (CEM), is chronically infected with HIV-1, with low levels of constitutive virus expression. ACH-2 can be converted to productive infection by stimulation of the cells with 12- O-tetradecanoylphorbol-13-acetate (TPA), mitogen or cytokines (TNF-alpha), or infection with HSV. Therefore the ACH-2 cell line is a good candidate for studying the effects of drugs on HIV-1 activation. Previously, we have reported that DHEA and synthetic analogs of DHEA can be modest inhibitors of HIV-1 IIIB replication in phytohemagglutinin-stimulated peripheral blood lymphocyte cultures. Here we report that DHEA and a synthetic analog of DHEA, 8354, can also reduce HIV-1 latency reactivation in the ACH-2 cell line. The inhibitory effect is not due to cytotoxicity of these drugs. Treatment with DHEA or 8354 resulted in downregulation of HIV-1 latency reactivation in a TPA- or TNF-alpha-stimulated ACH-2 cell line as measured by syncytium formation and accumulation of reverse transcriptase activity. The mechanisms of inhibition are not clear, but evidence suggests that reduction of NF-kappaB activation plays a role.

Dehydroepiandrosterone as predictor for progression to AIDS in asymptomatic human immunodeficiency virus-infected men

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J Infect Dis 1992 Mar;165(3):413-8

The steroid hormone dehydroepiandrosterone (DHEA) has been reported to protect against certain viral infections in animal models and to be a modest inhibitor of human immunodeficiency virus type 1 (HIV-1) infection in vitro. Serum DHEA levels were determined in 41 asymptomatic HIV-1-seropositive subjects, who progressed to AIDS within 5 years after entering a cohort study, in 41 HIV-1-seropositive controls, who remained asymptomatic, and in 41 HIV-1-seronegative controls. At entry, DHEA levels were higher in the seronegative group (median, 13.3 nmol/l) than in either the seropositive nonprogressors (median, 9.2 nmol/l; P = .01) or the progressors (median, 7.2 nmol/l; P < .001). DHEA levels in the progressors similar5 months before the diagnosis of AIDS were lower than the levels in the nonprogressors after the same follow-up (median, 5.6 vs. 8.8 nmol/l; P = .007). DHEA levels <7 nmol/l and CD4+ cell counts <0.5 x 109/l both proved to be independent predictors for disease progression in HIV-1-infected men.

Decreased serum dehydroepiandrosterone is associated with an increased progression of human immunodeficiency virus infection in men with CD4 cell counts of 200-499

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J Infect Dis 1991 Nov;164(5):864-8

Dehydroepiandrosterone (DHEA) and its interconvertible sulfate derivative (DHEA-S) are human androgenic steroids that have been reported to inhibit viral expression and have been associated with a decreased risk of cancer. The relationship between serum DHEA and DHEA-S levels and subsequent progression to AIDS was investigated in a sample of human immunodeficiency virus (HIV)-infected men from the San Francisco Men's Health Study followed prospectively since 1984. Among 108 men seropositive for HIV at study entry and with CD4 lymphocyte counts of 200-499 microl 24 months later, serum DHEA levels below the lower limit of normal (<180 ng/dl) at this later date were predictive of subsequent progression to AIDS (relative hazard = 2.34; 95% confidence interval = 1.18-4.63; P = .01) after controlling for hematocrit, age, and log absolute CD4 cell number in a Cox proportional hazards model. This is the first large prospective cohort in which an endocrinologic variable has been observed to independently predict progression to AIDS. These observations, in

addition to recent in vitro data, suggest that DHEA might have a protective effect in HIV infection.

18. Hypertension

Preventative and curative options include:

Garlic, coenzyme Q10, magnesium, calcium, potassium, fish oil, vitamin C, arginine.

Dietary factors in the pathogenesis and treatment of hypertension

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Annals of Medicine (United Kingdom), 1998, 30/2 (143-150)

Data accumulated from epidemiological observations, intervention trials and studies on experimental animals provide a growing body of evidence of the influence of various dietary components on blood pressure. Dietary sodium, usually taken in the form of sodium chloride (common salt), is positively associated with blood pressure, and in many hypertensive patients reduction in sodium intake lowers blood pressure. On the other hand, in certain patients potassium, calcium and magnesium may be protective electrolytes against hypertension. Dietary fats, especially n-3polyunsaturated fatty acids, may also influence blood pressure, whereas the possible role of other macronutrients, such as proteins and carbohydrates, or vitamins in the regulation of blood pressure is less well understood. Occasional ingestion of coffee transiently increases blood pressure, but the effects of habitual coffee consumption are controversial. Excessive use of alcohol on a regular basis has been associated with elevated blood pressure. It has also been shown in case reports that large amounts of liquorice lead to the development of hypertension. Thus, with appropriate dietary modifications, it is possible to prevent the development of high blood pressure and to treat hypertensive patients with fewer drugs and with lower doses. In some patients antihypertensive medication may not be at all necessary.

Role of adequate dietary calcium intake in the prevention and management of salt- sensitive hypertension

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American Journal of Clinical Nutrition (USA), 1997, 65/2 Suppl. (712S-716S)

During the past decade, a credible body of evidence has emerged supporting the concept that maintaining an adequate dietary mineral intake, specifically of calcium, magnesium, and potassium, protects against high blood pressure in humans. Observational and interventional studies in humans and extensive use of laboratory models showed that a significant portion of blood pressure variability

in response to sodium chloride can be linked to the adequacy of the mineral content of the diet. This review summarizes the observational data from several large databases showing that when adults meet or exceed the recommended dietary allowances of calcium, potassium, and magnesium, the simultaneous ingestion of a diet high in sodium chloride is not associated with elevated arterial pressure. In fact, a higher sodium chloride intake in these adults is most likely associated with the lowest blood pressure in the society. This interaction between adequacy of mineral intake and protection against salt sensitivity in humans provides an important opportunity for further improving blood pressure control in our society. Educating individuals to maintain, on a daily basis, adequate intakes of calcium, potassium, and magnesium rather than limit their sodium chloride is a viable health recommendation that individuals can implement to reduce their risk of sodium chloride-induced hypertension.

Onion extract in treatment of hypertension and hyperlipidemia: A preliminary communication

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Crude onion extract was given in an open trial to 34 persons who suffered from moderate hypertension (systolic <185 mm Hg, diastolic <110 mm Hg) or hypercholesterolemia (245 to >300 mg/dl), or both. In 13 of 20 trials, there was a clear blood pressure reduction. In 9 of 18 trials cholesterol concentrations decreased by 7 to 33%. These effects occurred in the absence of weight loss. These results are encouraging and suggest controlled studies with larger numbers of participants.

Role of elements in pathophysiology of hypertension and antihypertensive drug development.

Arora RB; Roy S; Khan SU
Acta Pharmacol Toxicol (Copenh) (Denmark) 1986, 59 Suppl 7 p344-7

Cadmium and Zinc levels were determined in 100 patients of Essential hypertension by Atomic Absorption Spectrophotometer. It was shown that themean levels of Serum cadmium were 43.34% +/- 6.5% higher and zinc were 28.42% +/- 5.4% lower in hypertensive when compared with normotensive controls. A statistically significant relationship between the height of diastolic blood pressure and Serum cadmium levels was observed. Ajmaloon a preparation from Rauvolfia serpentina with corrective herbs lowered the blood pressure effectively and significantly P less than 0.001. The side effects were minimal. It also tends to decrease the elevated serum cadmium levels in hypertensive

individuals. A plea for development of Catecholamine depleting agents as drug for hypertension is advanced.

Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension.

Fujita T; Ando K; Noda H; Ito Y; Sato Y
Circulation (United States) Mar 1987, 75 (3) p525-32

Recent studies showed that taurine, a sulphonic amino acid, could decrease blood pressure and increase sympathoadrenal tone in DoCA-salt-treated hypertensive rats. To determine whether taurine exerts its antihypertensive action in man in a similar fashion, we studied the effect of oral administration of taurine (6 g for 7 days) on blood pressure and plasma catecholamines in 19 young patients with borderline hypertension in a double-blind, placebo-controlled fashion. Systolic blood pressure in the 10 patients who were treated with taurine decreased by 9.0 +/- 2.9 mm Hg (mean +/- SE; p less than .05 by paired t test), compared with a 2.7 +/- 2.3 mm Hg decrease (NS) in the nine patients treated with placebo and diastolic blood pressure in the taurine -treated patients decreased by 4.1 +/- 1.7 mm Hg (p less than .05) compared with 1.2 +/- 3.0 mm Hg (NS) in the placebo-treated subjects. In the patients receiving taurine plasma epinephrine (E) decreased significantly, with a negligible decrease in plasma norepinephrine (NE). The effect of taurine on plasma catecholamines and the response of plasma E after the stimulation with glucagon was also studied in 12 borderline hypertensive and nine age-matched normotensive subjects. Basal plasma E was significantly higher in borderline hypertensive than in normal subjects, but basal plasma NE did not differ in the two groups.(ABSTRACT TRUNCATED AT 250 WORDS)

Zinc, cadmium, and hypertension in parturient women

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Am J Obstet Gynecol (United States) Aug 1989, 161 (2) p437-40

Zinc deficiency and cadmium toxicity have both been implicated in hypertension during pregnancy. The goals of this study were twofold: first, to assess the different zinc indices (plasma, red blood cell zinc, heat-labile alkaline phosphatase, and placental zinc) in normotensive and hypertensive parturients to determine whether they are altered in the different types of hypertension that occur during pregnancy; second, to assess whole-blood cadmium and placental cadmium with regard to hypertension and zinc status. Patients were diagnosed as having chronic hypertension or preeclamptic toxemia and were then further divided into groups on the basis of smoking status. Each patient was matched with

a normal control subject based on age, parity, and smoking status. Forty-three hypertensive patients and their matched control subjects were studied. No differences were found in the various zinc indices between chronic hypertensive parturients and normal control subjects. However, in parturients with preeclamptic toxemia, the plasma zinc level was 19% lower than in control subjects (p less than 0.02); these patients had the lowest plasma zinc level of the three groups. Placental zinc was also 12% lower in patients with preeclamptic toxemia than in control subjects (p less than 0.04). Whole-blood cadmium and placental cadmium levels did not differ between control subjects or hypertensive patients. However, a significant positive correlation was found between whole-blood cadmium and plasma zinc levels in preeclamptic toxemia (r = 0.53; p less than 0.05). The results support a marginal zinc deficiency in parturients with preeclamptic toxemia but not in those with chronic hypertension. The role of cadmium in the cause of preeclamptic toxemia remains unclear.

A prospective study of nutritional factors and hypertension among US women.

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Circulation (United States) Nov 1989, 80 (5) p1320-7, 0009-7322

The relation of various nutritional factors with hypertension was examined prospectively among 58,218 predominantly white US female registered nurses, aged 34-59 years. In 1980, all women completed an independently validated dietary questionnaire. During 4 years of follow-up, 3,275 women reported a diagnosis of hypertension; the validity of the self-report was shown in a subsample. Age, relative weight, and alcohol consumption were the strongest predictors for the development of hypertension. Dietary calcium and magnesium had independent and significant inverse associations with hypertension. For women with a calcium intake of at least 800 mg/day, the relative risk of hypertension was 0.78 (95% confidence interval, 0.69-0.88) when compared with an intake of less than 400 mg/day. The relative risk for magnesium intake of 300 mg/day or more compared with an intake of less than 200 mg/day was 0.77 (95% confidence interval, 0.67-0.88). For women with high intakes of both calcium and magnesium compared with those having low intakes of both, the relative risk of hypertension was 0.65 (95% confidence interval, 0.53-0.80). No independent associations with hypertension were observed for intakes of potassium, fiber, and saturated and polyunsaturated fatty acids. These prospective findings add to the growing evidence to support the need for randomized trials to determine whether there is a protective role of dietary calcium and magnesium in the regulation of blood pressure.

Hypertension prophylaxis with omega-3 fatty acids in heart transplant recipients.

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J Am Coll Cardiol (United States) May 1997, 29 (6) p1324-31

OBJECTIVES: This study sought to determine whether omega-3 fatty acids act as hypertension prophylaxis in heart transplant recipients and have an impact on vascular reactivity.

BACKGROUND: Cyclosporine-induced hypertension is probably related to endothelial dysfunction. Suggested vasodilatory mechanisms of omega-3 fatty acids may therefore be particularly beneficial in heart transplant recipients.

METHODS: Heart transplant recipients were randomized to receive either 4 g of omega-3 fatty acids (treatment group, n = 14) daily or corn oil (placebo group, n = 14) from the fourth postoperative day. Twenty-four hour blood pressure monitoring was performed at day 12 and 1,2,3 and 6 months postoperatively. Microvascular endothelium-dependent vasodilation, evaluated by skin laser Doppler perfusion measurements of postocclusive reactive hyperemia, was determined preoperatively and at the end of the study.

RESULTS: With comparable characteristics at the time of randomization, blood levels of cyclosporine did not at any point differ between the groups. After 6 months, systolic blood pressure decreased 2 +/- 4 mm Hg (mean +/- SEM) in the treatment group and increased 17 +/- 4 mm Hg in the placebo group ($p < 0.01$), whereas diastolic blood pressure increased 10 +/- 3 and 21 +/- 2 mm Hg ($p < 0.01$), respectively. The decrease in systolic blood pressure was inversely proportional to increases in concentrations of serum eicosapentaenoic and docosahexaenoic acid ($p = 0.01$). After 6 months, five patients in the treatment group and nine in the placebo group needed additional antihypertensive treatment. Although the endothelial-dependent phase of the reactive hyperemic response remained unchanged in the treatment group, it decreased significantly in the placebo group.

CONCLUSIONS: Postoperative daily administration of 4 g of omega-3 fatty acids in heart transplant recipients is effective as hypertension prophylaxis, depending on increases in serum eicosapentaenoic and docosahexaenoic acids. Preservation of microvascular endothelial function, demonstrated by a more pronounced response to forearm skin ischemia in the treatment group, may contribute to the hypotensive role of omega-3 fatty acids.

Phytotherapy of hypertension and diabetes in oriental Morocco.

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Oujda, Morocco.
J Ethnopharmacol (Ireland) Sep 1997, 58 (1) p45-54

In order to select the main medicinal plants used in folk medicine to treat arterial hypertension and/or diabetes, a survey was undertaken in different areas of oriental Morocco. The patients (370 women and 256 men) were divided into three groups: diabetics (61%), hypertensives (23%) and hypertensive diabetic persons (16%). On average, 67.51% of patients regularly use medicinal plants. This proportion is perceptibly the same in all groups and does not depend on sex, age and socio-cultural level. This result shows that phytotherapy is widely adopted in northeastern Morocco. For diabetes, 41 plants were cited, of which the most used were Trigonella foenum-graecum L. (Leguminosae), Globularia alypum L. (Globulariaceae), Artemisia herba -alba Asso. (Compositae), Citrullus colocynthis (L.) Schrad. (Cucurbitaceae) and Tetraclinis articulata Benth. (Cupressaceae). In the hypertension's therapy 18 vegetal species were reported, of which the most used were Allium sativum L. (Liliaceae), Olea europea L. (Oleaceae), Arbutus unedo L. (Ericaceae), Urtica dioica L. (Urticaceae) and Petroselinum crispum A.W. Hill (Apiaceae). Among the 18 species used for hypertension, 14 were also employed for diabetes. Moreover, these two diseases were associated in 41% of hypertensives. These findings suggest that hypertension observed in this region would be in a large part related to diabetes.

Treatment of essential hypertension with coenzyme Q10.

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Mol Aspects Med (England) 1994, 15 Suppl pS265-72

A total of 109 patients with symptomatic essential hypertension presenting to a private cardiology practice were observed after the addition of CoQ10 (average dose, 225 mg/day by mouth) to their existing antihypertensive drug regimen. In 80 per cent of patients, the diagnosis of essential hypertension was established for a year or more prior to starting CoQ10 (average 9.2 years). Only one patient was dropped from analysis due to noncompliance. The dosage of CoQ10 was not fixed and was adjusted according to clinical response and blood CoQ10 levels. Our aim was to attain blood levels greater than 2.0 micrograms/ml (average 3.02 micrograms/ml on CoQ10). Patients were followed closely with frequent clinic visits to record blood pressure and clinical status and make necessary adjustments in drug therapy. Echocardiograms were obtained at baseline in 88% of patients and both at baseline and during treatment in 39% of patients. A definite and gradual improvement in functional status was observed with the concomitant need to gradually decrease antihypertensive drug therapy within the first one to six months. Thereafter, clinical status and cardiovascular drug requirements stabilized with a significantly improved systolic and diastolic blood pressure. Overall New York Heart Association (NYHA) functional class improved from a mean of 2.40 to 1.36 ($P < 0.001$) and 51% of patients came completely off of between one and three antihypertensive drugs at an average of 4.4 months after starting CoQ10.

Only 3% of patients required the addition of one antihypertensive drug. In the 9.4% of patients with echocardiograms both before and during treatment, we observed a highly significant improvement in left ventricular wall thickness and diastolic function.

Coenzyme Q10 in essential hypertension.

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Mol Aspects Med (England) 1994, 15 Suppl ps257-63

This study was undertaken to clarify the mechanism of the antihypertensive effect of coenzyme Q10 (CoQ10). Twenty-six patients with essential arterial hypertension were treated with oral CoQ10, 50 mg twice daily for 10 weeks. Plasma CoQ10, serum total and high-density lipoprotein (HDL) cholesterol, and blood pressure were determined in all patients before and at the end of the 10-week period. At the end of the treatment, systolic blood pressure (SBP) decreased from 164.5 +/- 3.1 to 146.7 +/- 4.1 mmHg and diastolic blood pressure (DBP) decreased from 98.1 +/- 1.7 to 86.1 +/- 1.3 mmHg ($P < 0.001$). Plasma CoQ10 values increased from 0.64 +/- 0.1 microgram/ml to 1.61 +/- 0.3 micrograms/ml ($P < 0.02$). Serum total cholesterol decreased from 222.9 +/- 13 mg/dl to 213.3 +/- 12 mg/dl ($P < 0.005$) and serum HDL cholesterol increased from 41.1 +/- 1.5 mg/dl to 43.1 +/- 1.5 mg/dl ($P < 0.01$). In a first group of 10 patients serum sodium and potassium, plasma clinostatic and orthostatic renin activity, urinary aldosterone, 24-hour sodium and potassium were determined before and at the end of the 10-week period. In five of these patients peripheral resistances were evaluated with radionuclide angiocardiography. Total peripheral resistances were 2,283 +/- 88 dyne.s.cm-5 before treatment and 1,627 +/- 158 dyn.s.cm-5 after treatment ($P < 0.02$). Plasma renin activity, serum and urinary sodium and potassium, and urinary aldosterone did not change. In a second group of 11 patients, plasma endothelin, electrocardiogram, two-dimensional echocardiogram and 24-hour automatic blood pressure monitoring were determined.

Usefulness of coenzyme Q10 in clinical cardiology: a long-term study.

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Mol Aspects Med (England) 1994, 15 Suppl ps165-75

Over an eight year period (1985-1993), we treated 424 patients with various forms of cardiovascular disease by adding coenzyme Q10 (CoQ10) to their medical regimens. Doses of CoQ10 ranged from 75 to 600 mg/day by mouth (average 242 mg). Treatment was primarily guided by the patient's clinical

response. In many instances, CoQ10 levels were employed with the aim of producing a whole blood level greater than or equal to 2.10 micrograms/ml (average 2.92 micrograms/ml, n = 297). Patients were followed for an average of 17.8 months, with a total accumulation of 632 patient years. Eleven patients were omitted from this study: 10 due to non-compliance and one who experienced nausea. Eighteen deaths occurred during the study period with 10 attributable to cardiac causes. Patients were divided into six diagnostic categories: ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), primary diastolic dysfunction (PDD), hypertension (HTN), mitral valve prolapse (MVP) and valvular heart disease (VHD). For the entire group and for each diagnostic category, we evaluated clinical response according to the New York Heart Association (NYHA) functional scale, and found significant improvement. Of 424 patients, 58 per cent improved by one NYHA class, 28% by two classes and 1.2% by three classes. A statistically significant improvement in myocardial function was documented using the following echocardiographic parameters: left ventricular wall thickness, mitral valve inflow slope and fractional shortening. Before treatment with CoQ10, most patients were taking from one to five cardiac medications. During this study, overall medication requirements dropped considerably: 43% stopped between one and three drugs. Only 6% of the patients required the addition of one drug. No apparent side effects from CoQ10 treatment were noted other than a single case of transient nausea. In conclusion, CoQ10 is a safe and effective adjunctive treatment for a broad range of cardiovascular diseases, producing gratifying clinical responses while easing the medical and financial burden of multidrug therapy.

Influence of coenzyme Q-10 on the hypotensive effects of enalapril and nitrendipine in spontaneously hypertensive rats.

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Pol J Pharmacol (Poland) Sep-Oct 1994, 46 (5) p457-61

Administration of coenzyme Q-10 (10 mg/kg) once a day for 4 weeks decreased the arterial blood pressure in SHR's. Enalapril and nitrendipine administered in a single dose caused significant decrease of blood pressure. Application of enalapril and nitrendipine to rats chronically pretreated with coenzyme Q-10 revealed, that the maximal hypotensive effect was not greater, but it lasted much (ca. 2-times) longer. Independently of mechanism of this interaction it may be suggested that the chronic administration of coenzyme Q-10 would create the possibility of significant decrease of the frequency of some antihypertensive drug administration.

Isolated diastolic dysfunction of the myocardium and its response to CoQ10 treatment.

Langsjoen PH; Langsjoen PH; Folkers K
Clin Investig (Germany) 1993, 71 (8 Suppl) pS140-4

Symptoms of fatigue and activity impairment, atypical precordial pain, and cardiac arrhythmia frequently precede by years the development of congestive heart failure. Of 115 patients with these symptoms, 60 were diagnosed as having hypertensive cardiovascular disease, 27 mitral valve prolapse syndrome, and 28 chronic fatigue syndrome. These symptoms are common with diastolic dysfunction, and diastolic function is energy dependent. All patients had blood pressure, clinical status, coenzyme Q10 (CoQ10) blood levels and echocardiographic measurement of diastolic function, systolic function, and myocardial thickness recorded before and after CoQ10 replacement. At control, 63 patients were functional class III and 54 class II; all showed diastolic dysfunction; the mean CoQ10 blood level was 0.855 micrograms/ml; 65%, 15%, and 7% showed significant myocardial hypertrophy, and 87%, 30%, and 11% had elevated blood pressure readings in hypertensive disease, mitral valve prolapse and chronic fatigue syndrome respectively. Except for higher blood pressure levels and more myocardial thickening in the hypertensive patients, there was little difference between the three groups. CoQ10 administration resulted in improvement in all; reduction in high blood pressure in 80%, and improvement in diastolic function in all patients with follow-up echocardiograms to date; a reduction in myocardial thickness in 53% of hypertensives and 36% of the combined prolapse and fatigue syndrome groups; and a reduced fractional shortening in those high at control and an increase in those initially low.

Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats.

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Department of Cardiovascular, Hokkaido University, Japan.
Biochem Med Metab Biol (United States) Apr 1991, 45 (2) p216-26

To test the hypothesis that structural abnormalities exist in the kidney membrane of spontaneously hypertensive rats, we examined the effect of long-term administration of coenzyme Q10 on membrane lipid alterations in the kidney of stroke-prone spontaneously hypertensive rats (SHRSP). As compared with normotensive Wistar-Kyoto rats, renal membrane phospholipids, especially phosphatidylcholine and phosphatidylethanolamine, decreased and renal phospholipase A2 activity was enhanced with age in untreated SHRSP. Treatment with coenzyme Q10 attenuated the elevation of blood pressure, the membranous phospholipid degradation, and the enhanced phospholipase A2 activity. These results suggest that one factor contributing to the progress of hypertension is a structural membrane abnormality that alters the physical and functional properties of the cell membrane, and coenzyme Q10 might protect the renal membrane from damage due to hypertension in SHRSP.

Co-enzyme Q10: a new drug for cardiovascular disease.

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J Clin Pharmacol (United States) Jul 1990, 30 (7) p596-608

Co-enzyme Q10 (ubiquinone) is a naturally occurring substance which has properties potentially beneficial for preventing cellular damage during myocardial ischemia and reperfusion. It plays a role in oxidative phosphorylation and has membrane stabilizing activity. The substance has been used in oral form to treat various cardiovascular disorders including angina pectoris, hypertension, and congestive heart failure. Its clinical importance is now being established in clinical trails worldwide.

Coenzyme Q10: a new drug for myocardial ischemia?

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Med Clin North Am (United States) Jan 1988, 72 (1) p243-58

A biochemical rationale for using CoQ in treating certain cardiovascular diseases has been established. CoQ subserves an endogenous function as an essential cofactor in several metabolic pathways, particularly oxidative respiration. As an exogenous source in supraphysiologic doses, CoQ may have pharmacologic effects that are beneficial to tissues rendered ischemic and then reperfused. Its mechanism of action appears to be that of a free radical scavenger and/or direct membrane stabilizer. Initial clinical studies performed abroad and in the United States indicate that CoQ may be effective in treating certain patients with ischemic heart disease, congestive heart failure, toxin-induced cardiotoxicity, and possibly hypertension. The most intriguing property of CoQ is its potential to protect and preserve ischemic myocardium during surgery. Currently, CoQ is still considered an experimental agent and only further studies will determine whether it will be useful therapy for human cardiovascular disease states.

Bioenergetics in clinical medicine. XVI. Reduction of hypertension in patients by therapy with coenzyme Q10.

Folkers K; Drzewoski J; Richardson PC; Ellis J; Shizukuishi S; Baker L
Res Commun Chem Pathol Pharmacol (United States) Jan 1981, 31 (1) p129-40

Six untreated hypertensive patients and ten on therapy, but having elevated blood pressures, were treated with coenzyme Q10(CoQ10); 14/16 patients showed reductions (p less than 0.05-less than 0.001) in systolic pressures; 11/16 showed reductions (p less than 0.05-less than 0.001) in diastolic pressure; 9/10 showed reductions of elevated pressures to a normal range. By impedance cardiography and electrocardiography, there were no changes in cardiac outputs, stroke volumes and Heather Indices except for a few patients with changes of doubtful biological significance. 3/16 patients had exceptionally low basal specific activities of the succinate dehydrogenase-coenzyme Q10 reductase in blood which increased to a normal range on treatment. A greater deficiency of CoQ10 in the vascular system than in blood is likely. We consider that (1) the mechanism of reduction of elevated blood pressures by CoQ10 is based upon normalization or autoregulation of peripheral resistance rather than cardiac regulation, and (2) that the therapeutic activity of CoQ10 is not pharmacodynamic, but results from a translational increase in levels of CoQ10-enzymes in vascular tissue during ca. 4-12 weeks.

Bioenergetics in clinical medicine. VIII. Adminstration of coenzyme Q10 to patients with essential hypertension.

Yamagami T; Shibata N; Folkers K
Res Commun Chem Pathol Pharmacol (United States) Aug 1976, 14 (4) p721-7

Coenzyme Q10 has been administered to five patients having essential hypertension and deficiencies of activity of succinate dehydrogenase-co-enzyme Q10 reductase in leucocyte preparations ranging from 20-40%. For a 74-year old male, the systolic pressure was reduced (p less than 0.001), the diastolic pressure was reduced (p less than 0.05), the specific activity of the coenzyme Q10-enzyme was increased (p less than 0.001), and the deficiency of coenzyme Q10 activity was negated (p less than 0.01). Four patients receiving CoQ10 for 3-5 months showed reductions (p less than 0.05 to p less than 0.001) of diastolic pressure, and 3 of these 4 showed reductions (p less than 0.05 to p less than 0.01) of diastolic pressure. Initial deficiencies of enzyme activity were reduced (p less than 0.01 to 0.05) in two patients. Three other patients did not show the high level of deficiency on treatment as initially observed. These effects of CoQ10 on the reduction of systolic and diastolic blood pressures, increase in CoQ10-enzyme activity, and reduction of CoQ10-deficiency are presumably due to improved bioenergetics through correction of a deficiency of coenzyme Q10.

Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used anti-hypertensive drugs.

Kishi H; Kishi T; Folkers K
Res Commun Chem Pathol Pharmacol (United States) Nov 1975, 12 (3) p533-40

Background data revealed that some American and Japanese patients with essential hypertension, including many who were not being treated with any anti-hypertensive drug, had a deficiency of coenzyme Q10. Eight clinically used anti-hypertensive drugs have now been tested for inhibition of two mitochondrial coenzyme Q10-enzymes of heart tissue, succinoxidase and NADH-oxidase. Diazoxide and propranolol significantly inhibited the CoQ10-succinoxidase and CoQ10-NADH-oxidase, respectively. Metoprolol did not inhibit succinoxidase, and was one-fourth as active as propranolol for inhibition of NADH-oxidase. Hydrochlorothiazide, hydralazine, ans clonidine also inhibited CoQ10-NADH-oxidase. Reserpine did not inhibit either CoQ10-enzyme, and methyldopa was a very eak inhibitor of succinoxidase. The internationally recognized clinical side-effects of propranolol may be due, in part, to inhibition of CoQ10-enzymes which are indispensable in the bioenergetics of cardiac function. A pre-existing deficiency of coenzyme Q10 in the myocardium of hypertensive patients could be augmented by subsequent treatment with propranolol, possibly to the "life-threatening" state described by others.

Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension.

Yamagami T; Shibata N; Folkers K
Res Commun Chem Pathol Pharmacol (United States) Jun 1975, 11 (2) p273-88

The specific activities (S.A.) of the succinate dehydrogenase-coenzyme Q10 (CoQ10) reductase of a control group of 65 Japanese adults and 59 patients having essential hypertension were determined. The mean S.A. of the hypertensive group was significantly lower (p less than 0.001) and the mean % deficiency of enzyme activity was significantly higher (p less than 0.001) than the values for the control group. These data on Japanese in Osaka agree with data on Americans in Dallas. Some patients showed no CoQ10-deficiency, and others showed definite deficiencies. Emphasizing the CoQ10-enzyme for patient selection, CoQ10 was administered to hypertensive patients. Four individuals showed significant but partial reductions of blood pressure. Monitoring the CoQ10-enzyme before, during, and after administration of CoQ10 indicated responses. The maintenance of high blood pressure could be primarily due to contraction of the arterial wall. Contraction or relaxation of an arterial wall is dependent upon bioenergetics, which also provide the energy for biosynthesis of angiotensin II, renin, aldosterone, and the energy for sodium and potassium transport. A clinical benefit from administration of CoQ10 to patients with essential hypertension could be based upon correcting a deficiency in bioenergetics, and point to possible combination treatments with a form of CoQ and anti-hypertensive drugs.

[Garlic (Allium sativum)--a potent medicinal plant]

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Fortschr Med (Germany) Jul 20 1995, 113 (20-21) p311-5

A good deal of evidence suggests beneficial effects of the regular dietary intake of garlic on mild hypertension and hyperlipidemia. Garlic seems to have anti-microbial and immunostimulating properties, enhance fibrinolytic activity, and exert favorable effects on platelet aggregation and adhesion. Standardised preparations guarantee exact dosing and minimize the problem of the strong odour of raw garlic. Thus, a traditional folk remedy has established its usefulness for many patients with less severe forms of cardiovascular disease as a medical drug with very few side effects. The available evidence gives rise to the hope that the list of indications may even be considerably extended in the future. (43 Refs.)

A meta-analysis of the effect of garlic on blood pressure.

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J Hypertens (England) Apr 1994, 12 (4) p463-8

OBJECTIVE: To undertake a systematic review, including meta-analysis, of published and unpublished randomized controlled trials of garlic preparations to determine the effect of garlic on blood pressure relative to placebo and other antihypertensive agents.

DATA IDENTIFICATION: Studies were identified by a search of Medline and the Alternative Medicine electronic databases, from references listed in primary and review articles, and through direct contact with garlic manufacturers.

STUDY SELECTION: Only randomized controlled trials of garlic preparations that were at least 4 weeks in duration were deemed eligible for inclusion in the review.

DATA EXTRACTION: Data were extracted from the published reports by the two authors independently, with disagreements resolved by discussion.

RESULTS: Eight trials were identified (all using the same dried garlic powder preparation (Kwai) with data from 415 subjects included in the analyses. Only three of the trials were specifically conducted in hypertensive subjects, and many had other methodological shortcomings. Of the seven trials that compared the effect of garlic with that of placebo, three showed a significant reduction in systolic blood pressure (SBP) and four in diastolic blood pressure (DBP). The overall pooled mean difference in the absolute change (from baseline to final measurement) of SBP was greater in the subjects who were treated with garlic then in those treated with placebo. For DBP the corresponding reduction in the garlic-treated subjects was slightly smaller.

CONCLUSIONS: The results suggest that this garlic powder preparation may be of some clinical use in subjects with mild hypertension. However, there is still insufficient evidence to recommend it is a routine clinical therapy for the treatment of hypertensive subjects. More-rigorously designed and analysed trials are needed.

Patient preferences for novel therapy: an N-of-1 trial of garlic in the treatment for hypertension.

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Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan 48202.
J Gen Intern Med (United States) Nov 1993, 8 (11) p619-21

The authors used the N-of-1 clinical trial methodology to obtain insights about a patient's preference for garlic for the management of his hypertension. The 61-year-old man received garlic, 500 mg by mouth three times a day (3 weeks), or identical placebo (3 weeks) in three treatment pairs. While the patient was taking garlic the mean systolic blood pressure decreased by 2 mm Hg (95% confidence interval 0.4 to 4.7, $p < 0.05$), and the diastolic blood pressure decreased by 2.4 mm Hg (95% confidence interval 0.4 to 4, $p < 0.025$). The treatment effect of garlic was small, but the patient believed continuing garlic for the management of his hypertension was justified.

Can garlic lower blood pressure? A pilot study.

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Pharmacotherapy (United States) Jul-Aug 1993, 13 (4) p406-7

A popular garlic preparation containing 1.3% allicin at a large dose (2400 mg) was evaluated in this open-label study in nine patients with rather severe hypertension (diastolic blood pressure > or = 115 mm Hg). Sitting blood pressure fell 7/16 (+/- 3/2 SD) mm Hg at peak effect approximately 5 hours after the dose, with a significant decrease in diastolic blood pressure ($p < 0.05$) from 5-14 hours after the dose. No significant side effects were reported. Our results indicate that this garlic preparation can reduce blood pressure. Further controlled studies are needed, particularly with more conventional doses (e.g., < or = 900 mg/day), in patients with mild to moderate hypertension and under placebo-controlled, double-blind conditions.

Hypertension and hyperlipidaemia: garlic helps in mild cases.

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Incorporated Society, Nittendorf, West Germany.
Br J Clin Pract Symp Suppl (England) Aug 1990, 69 p3-6

Forty-seven non-hospitalised patients with mild hypertension took part in a randomised, placebo-controlled, double-blind trial conducted by 11 general practitioners. The patients who were admitted had diastolic blood pressures between 95 and 104 mmHg after a two-week acclimatization phase. The patients then took either a preparation of garlic powder (Kwai) or a placebo of identical appearance for 12 weeks. Blood pressure and plasma lipids were monitored during treatment after four, eight and 12 weeks. Significant differences between the placebo and the drug group were found during the course of therapy. For example, the supine diastolic blood pressure in the group having garlic treatment fell from 102 to 91 mmHg after eight weeks (p less than 0.05) and to 89 mmHg after 12 weeks (p less than 0.01). The serum cholesterol and triglycerides were also significantly reduced after eight and 12 weeks of treatment. In the placebo group, on the other hand, no significant changes occurred.

Renal response to L-arginine in salt-sensitive patients with essential hypertension.

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First Department of Internal Medicine, Hiroshima University School of Medicine, Japan.
Hypertension (United States) Mar 1996, 27 (3 Pt 2) p643-8

This study examined whether disturbances in nitric oxide formation contribute to renal dysfunction in salt-sensitive essential hypertensive patients. We evaluated the effects of intravenous administration of L-arginine (500 mg/kg given over 30 minutes) on systemic and renal hemodynamics in 23 patients with mild essential hypertension during 1 week of a low NaCl diet (50 mmol/d) followed by 1 week of a high NaCl diet (340 mmol/d). Patients were classified as salt sensitive (n=10) or salt resistant (n=13) based on salt-induced changes in their blood pressures. Salt loading increased renal vascular resistance but not renal plasma flow in salt-sensitive patients. The L-arginine-induced renovascular relaxation was significantly reduced by a high NaCl diet (renal vascular resistance: low NaCl -12.4 +/- 2.3% versus high NaCl -7.1 +/- 1.8%, P < .001) in salt-sensitive patients, whereas it was unchanged in salt-resistant patients. The increase in plasma cGMP in response to L-arginine was also reduced by a high NaCl diet in the salt-sensitive patients (low NaCl 49 +/- 7% versus high NaCl 36 +/- 8%, P < .05) but not in the salt-resistant patients (low NaCl 51 +/- 6% versus high NaCl 58 +/- 6%). These findings suggest that NaCl loading in salt-sensitive patients with mild essential hypertension reduces the ability of L-arginine to produce nitric oxide in the endothelium of the renal vasculature.

L-arginine restores dilator responses of the basilar artery to acetylcholine during chronic hypertension.

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Department of Internal Medicine, Cardiovascular Center, University of Iowa College of Medicine, Iowa City 52242, USA.
Hypertension (United States) Apr 1996, 27 (4) p893-6

The objective of this study was to test the hypothesis that administration of L-arginine, a substrate for nitric oxide synthase, restores acetylcholine-induced dilatation of the basilar artery in chronically hypertensive rats. Basilar artery diameter was measured through a cranial window in anesthesized stroke-prone spontaneously hypertensive rats (SHRSP) and normotensive Wistar-Kyoto rats (WKY) aged 6 to 7 months (adult) and 12 months (older adult). Under control conditions, baseline basilar artery diameter was smaller in SHRSP (adult, 239 +/- 30 micron; older adult, 198 +/- 13 micron) (mean +/- SE) than in WKY (adult, 261 +/- 10 micron; older adult, 259 +/- 7 micron) (P <.05 versus SHRSP). Topical application of acetylcholine (10(-5) mol/L) produced dilatation of the basilar artery in WKY, which was impaired in both adult and older SHRSP (P <.05). Topical L-arginine (10(-3) mol/L for 30 minutes) did not affect responses to acetylcholine in adult SHRSP but enhanced vasodilatation in response to acetylcholine (10(-5) mol/L) in older SHRSP without affecting responses to sodium nitroprusside. In contrast, D-arginine did not affect acetylcholine-induced vasodilatation in older SHRSP. These results suggest that impaired dilatation of the basilar artery in response to acetylcholine in older SHRSP is restored toward normal by L-arginine, a substrate for nitric oxide synthase.

Vitamin-C deficiency and low linolenate intake associated with elevated blood pressure: the Kuopio Ischaemic Heart Disease Risk Factor Study.

Salonen JT; Salonen R; Ihanainen M; Parviainen M; Seppanen R; Seppanen K; Rauramaa R
Department of Community Health, University of Kuopio, Finland.
J Hypertens Suppl (England) Dec 1987, 5 (5) pS521-4

We investigated the association of dietary fatty acids and plasma antioxidative vitamins with blood pressure in 722 eastern Finnish men aged 54 years, examined in the Kuopio Ischaemic Heart Disease Risk Factor Study in 1984-1986, who had no known hypertension nor any cerebrovascular disease. Allowing for the major anthropometric, dietary, medical and psychological determinants of blood pressure in a multivariate regression analysis, plasma ascorbic acid concentration had a moderate, independent inverse association (P less than 0.0001) and the estimated dietary intake of linolenic acid an inverse (P = 0.026) independent association with mean resting blood pressure. The marked elevation of blood

pressure at the lowest levels of plasma Vitamin-C concentration supports the hypothesis of the role of antioxidants in the aetiology of hypertension.

Regulation of blood pressure by nitroxidergic nerve.

Toda N
Department of Pharmacology, Shiga University of Medical Sciences, Ohtsu, Japan.
J Diabetes Complications (United States) Oct-Dec 1995, 9 (4) p200-2

We discovered vasodilator innervation first in canine cerebral arteries, in which nitric oxide (NO) acts as a neurotransmitter; thus, the nerve is called nitroxidergic. Then, reciprocal innervation of noradrenergic and nitroxidergic nerves in canine peripheral arteries was determined; adrenergic nerve-mediated vasoconstriction is predominant over vasodilatation mediated by NO derived from the nerve. In anesthetized dogs, hypertension induced by NO synthase inhibitors is suppressed by hexamethonium. It is hypothesized that impairment of nitroxidergic nerve function by NO synthase inhibition is mainly involved in the genesis of hypertension.

Contrasting effect of antihypertensive treatment on the renal response to L-arginine.

Mimran A; Ribstein J; DuCailar G
Department of Medicine, Centre Hospitalier Universitaire, Montpellier, France.
Hypertension (United States) Dec 1995, 26 (6 Pt 1) p937-41

We assessed the renal hemodynamic response to L-arginine infusion (30 g within 60 minutes) in normotensive subjects, patients with never-treated essential hypertension, and hypertensive patients controlled by long-term (more than 2 years) treatment with or without an angiotensin-converting enzyme inhibitor. The renal vasodilator response to L-arginine observed in normotensive subjects (15 +/- 4% increase in effective renal plasma flow) was abolished in untreated hypertensive patients and restored only in the group treated by angiotensin-converting enzyme inhibition. In the whole population a positive correlation between the change in effective renal plasma flow and the change in urinary cGMP was obtained. It is suggested that abnormalities of the renal nitric oxide pathway not corrected by increased availability of L-arginine and reversible only on long-term treatment by angiotensin-converting enzyme inhibition may underlie the abnormal renal resistance observed in essential hypertension.

Prospective study of nutritional factors, blood pressure, and hypertension among US women.

Ascherio A; Hennekens C; Willett WC; Sacks F; Rosner B; Manson J; Witteman J; Stampfer MJ
Department of Nutrition, Harvard School of Public Health, Boston, Mass 02115, USA.
Hypertension (United States) May 1996, 27 (5) p1065-72

We examined prospectively the relation of nutritional factors with hypertension and blood pressure levels among 41,541 predominantly white US female nurses, aged 38 to 63 years, who completed a detailed semiquantitative food frequency questionnaire in 1984 and were without diagnosed hypertension, cancer, or cardiovascular disease. During 4 years of follow-up, from 1984 to 1988, 2,526 women reported a diagnosis of hypertension. Age, relative weight, and alcohol consumption were the strongest predictors for the development of hypertension. Dietary calcium, magnesium, potassium, and fiber were not significantly associated with risk of hypertension, after adjusting for age, body mass index, alcohol, and energy intake. Among women who did not report hypertension during the follow-up period, calcium, magnesium, potassium, and fiber were each significantly inversely associated with self-reported systolic and diastolic pressures, after adjusting for age, body mass index, alcohol consumption, and energy intake. When the four nutrients were added simultaneously to the regression model, only fiber and magnesium intakes retained significant inverse associations with systolic and diastolic pressures. In analyses of food groups, intakes of fruit and vegetables were inversely associated with systolic and diastolic pressures, and intakes of cereals and meat were directly associated with systolic pressure. These results support hypotheses that age, body weight, and alcohol consumption are strong determinants of risk of hypertension in middle-aged women. They are compatible with the possibilities that magnesium and fiber as well as a diet richer in fruits and vegetables may reduce blood pressure levels.

[Interrelationship between dietary intake of minerals and prevalence of hypertension]

Davydenko NV; Smirnova IP; Kvasha EA; Gorbas' IM; Koblianskaia AV
Vopr Pitan (Russia) 1995, (6) p17-9

1556 of men living in Kiev aged 20-59 years were examined to evaluate interrelationship between the dietary intakes of Ca, Mg, P, Fe, Cu, Zn and level of arterial blood pressure (AP). Dietary intake was studied by 24-h recall methodology. Systolic AP > 160 mm Hg and/or diastolic AP > 90 mm Hg were referred as arterial hypertension (AH). It was shown that high dietary intakes of Ca or Zn were related with the higher rate of AH. At low level of dietary intake of Mg, Cu or P the prevalence of AH was seen in 1.8-2 times more often than at high level of intake of these micronutrients. Mean systolic AP had trend to increasing and diastolic AP was significant higher at low level of dietary intake of P. Correction of dietary intake of microelements should be used in preventive measures of AH.

Potassium depletion and salt-sensitive hypertension in Dahl rats: effect on calcium, magnesium, and phosphate excretions.

Wu X; Ackermann U; Sonnenberg H
Department of Physiology, University of Toronto, Ontario, Canada.
Clin Exp Hypertens 1995 Aug;17(6):989-1008

Weanling male inbred Dahl rats (Jr salt-sensitive (S) and salt-resistant (R) strains) were placed on high (4%, HK) and low (0.2%, LK) potassium diets for 4 weeks. Both diets contained 8% sodium chloride, 2.5% calcium, 0.8% magnesium, and 2.0% phosphorous. Balance studies were carried out during the final week on the diets. Mean arterial blood pressure was determined, and dietary intake and urinary output of water, sodium, chloride, potassium, calcium, magnesium, and phosphate were monitored daily during this period. The data show that blood pressures of S rats were significantly higher than those of R rats on both HK and LK diets; however, reduced dietary potassium was associated with increased blood pressure in both strains. Urinary excretions of calcium and magnesium were higher, and urinary phosphate excretion was lower, in S compared to R rats. Decreased potassium intake was associated with increased excretion of calcium, magnesium and phosphate in both strains. The changes in calcium and magnesium excretion were significantly correlated to blood pressure across strains and diets. We conclude that the effects of a high salt diet on increasing blood pressure can be potentiated by lack of potassium, even in previously salt-resistant rats. Increased blood pressure is associated with increased divalent cation excretion. It is not yet known whether this is a cause-and-effect relationship.

Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review).

Seelig MS
Department of Nutrition, School of Public Health, University of North Carolina, Chapel Hill.
J Am Coll Nutr (United States) Oct 1994, 13 (5) p429-46

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA), A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA

metabolism and the endothelium), that are vasoconstrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical (i.e. exertion, heat, cold, trauma--accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress.

Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study.

Joffres MR; Reed DM; Yano K
Am J Clin Nutr (United States) Feb 1987, 45 (2) p469-75

Associations between blood pressure and intakes of 61 dietary variables assessed by 24-h recall method were investigated in 615 men of Japanese ancestry living in Hawaii who had no history of cardiovascular disease or treated hypertension. Magnesium, calcium, phosphorus, potassium, fiber, vegetable protein, starch, Vitamin-C, and vitamin D intakes were significant variables that showed inverse associations with blood pressure in univariate and a multivariate analyses. Magnesium had the strongest association with blood pressure, which supports recent interest in its relation to blood pressure. Nevertheless, it was not possible to separate the effect of magnesium from that of other variables because of the problem of high intercorrelation among many nutrients. While recommendations based upon cross-sectional studies must be viewed cautiously, these results suggest that foods such as vegetables, fruits, whole grains, and low-fat dairy items are major sources of nutrients that may be protective against hypertension.

[Role of electrolytes in the development and maintenance of hypertension]

Fujita T; Ando K
Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.
Nippon Naibunpi Gakkai Zasshi (Japan) May 20 1994, 70 (4) p423-30

Sodium (Na) intake is one of the important environmental factors influencing the development and maintenance of high blood pressure (BP). Patients with essential hypertension can be divided into two groups: "salt-sensitive" and "non-salt-sensitive", according to BP response to salt loading, suggesting the heterogeneity of salt sensitivity of BP. Salt-sensitive patients had greater increases in BP by salt loading, associated with greater Na retention. Although the precise mechanism for impaired renal Na handling in salt-sensitive patients is still unknown, the

sympathetic nervous system in the kidney may play an important role in the decreased renal function of Na excretion and the increased salt sensitivity. Moreover, there are several pieces of evidence indicating that increased renal sympathetic nerve activity is intimately related to the abnormal central noradrenergic systems. In addition, the renin-angiotensin system, insulin, and so on, may modulate salt sensitivity of BP. Some ions influence the hypertensinogenic effect of Na: Chloride ion facilitates it, while potassium, calcium and magnesium antagonize it. Moreover, obesity and a stressful environment increase salt sensitivity of BP.

Effect of dietary magnesium supplementation on intralymphocytic free calcium and magnesium in stroke-prone spontaneously hypertensive rats.

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Department of Pathology, Shimane Medical University, Izumo, Japan.
Clin Exp Hypertens (United States) May 1994, 16 (3) p317-26

The effects of dietary magnesium (Mg) supplementation on intralymphocytic free Ca2+ ([Ca2+]i) and Mg2+ ([Mg2+]i) were examined in the stroke-prone spontaneously hypertensive rats (SHRSP) at the age of 10 weeks. After 40 day Mg supplementation (0.8% Mg in the diet), systolic blood pressure (SBP) was significantly lower in Mg supplemented group (Mg group) than the control group (0.2% Mg). [Ca2+]i was significantly lower and [Mg2+]i was significantly higher in Mg group than in the control group. Further, [Ca2+]i was positively and [Mg2+]i was negatively correlated with SBP. These results suggest that dietary Mg supplementation modifies [Ca2+]i and [Mg2+]i, and modulates the development of hypertension.

Vasorelaxant properties of n-3 polyunsaturated fatty acids in aortas from spontaneously hypertensive and normotensive rats.

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J Cardiovasc Risk (England) Jun 1994, 1 (1) p75-80

BACKGROUND: Dietary consumption of fish, rich in n-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), has been shown to reduce blood pressure in both animal studies and clinical trials. Although the antihypertensive mechanisms are not known, the blood-pressure-lowering effect of n-3 polyunsaturated fatty acids may be partially attributed to their vasorelaxant properties.

METHODS: Aortic rings with and without endothelium, from Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR), 16-17 weeks old, were

suspended in tissue baths and isometric tension was measured. Concentration-response curves were generated for DHA and EPA (1-100 mu mol/l) in norepinephrine-contracted rings. Blood pressure was measured using the tail-cuff method and aortic media thickness was determined.

RESULTS: Blood pressure was significantly increased in SHR (n=10; 194 +/- 4.4 mmHg) compared with WKY (n=10; 124 +/- 1.2 mmHg, P < or = 0.0001). DHA (1-100 mu mol/l) relaxed aortic rings f rom WKY (-3.3 +/- 0.7 to -13 +/- 2.3%, P < or = 0.001) and from SHR (-6.5 +/- 1.8 to -22.9 +/- 4%, P < or = 0.01) in a concentration-dependent manner. EPA (1-100 mu mol/l) evoked greater relaxation in SHR (-10.1 +/- 2.0 to -33 +/- 3.9%, P < 0.01) than in WKY (-2.9 +/- 1.1 to -18.3 +/- 2.1%, P < 0.01) aortic rings. The relaxant effect of DHA in both WKY and SHR and of EPA in WKY were not dependent on an intact endothelium. However, EPA (1-10 mu mol/l) induced greater responses in intact SHR rings (-10.1 +/- 2.0 to -14.5 +/- 3.1%) than in de-endothelialized SHR rings (0 to -2.1 +/- 1.7%, P = 0.001).

CONCLUSION: The direct relaxant effects of n-3 fatty acids as seen in WKY and SHR may contribute, in part, toward the blood-pressure-lowering effect of dietary fish and fish-oil supplementation.

Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia.

D'Almeida A; Carter JP; Anatol A; Prost C
Nutrition Program, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA.
Women Health (United States) 1992, 19 (2-3) p117-31

In a placebo controlled, partially double-blinded, clinical trial, a combination of evening primrose oil and fish oil was compared to Magnesium Oxide, and to a Placebo in preventing Pre-Eclampsia of Pregnancy. All were given as nutritional supplements for six months to a group of primiparous and multiparous pregnant women. Some of these women had personal or family histories of hypertension (21%). Only those patients who received prenatal care at the Central Maternity Hospital for Luanda were included in the study. Compared to the Placebo group (29%), the group receiving the mixture of evening primrose oil and fish oil containing Gamma-linolenic acid (GLA), Eicosapentaenoic acid (EPA), and Docosahexaenoic acid (DHA) had a significantly lower incidence of edema (13%, p = 0.004). The group receiving Magnesium Oxide had statistically significant fewer subjects who developed hypertension of pregnancy. There were 3 cases of eclampsia, all in the Placebo group.

Bulgarian traditional medicine: a source of ideas for phytopharmacological investigations.

Petkov V
J Ethnopharmacol (Switzerland) Feb 1986, 15 (2) p121-32

Some data about the use of medicinal plants in Bulgarian traditional medicine in the Middle Ages and in modern times are presented and the results of 40-year-long experimental-pharmacological investigations on many medicinal plants used in Bulgarian traditional medicine are reviewed. In-depth discussion is presented on the investigations of garlic (Allium sativum L.), a plant widely used by Bulgarian people for treating different diseases. Data from studies on a large number of plants used for treatment of hypertension, infectious diseases and as diuretic and spasmolytic remedies are summarized.

Garlic as a natural agent for the treatment of hypertension: a preliminary report.

Foushee DB; Ruffin J; Banerjee U
Cytobios (England) 1982, 34 (135-36) p145-52

The major objective of this study was to re-evaluate the effects of garlic on blood pressure with respect to its ability to provoke a decrease in blood pressure and to determine the length of time that this decrease would require. Spontaneously hypertensive rats were given three doses of garlic extract (0.1 ml/kg, 0.25 ml/kg, and 0.5 ml/kg) by oral injection. The blood pressures of these ether-anaesthetized rats were measured immediately before the extract was given, and then 0.5, 2, 4, 6, and 24 h after the extract was given. A blood pressure measurement was also taken at 48 h after extract administration for the 0.5 ml/kg dose. The Gilson Duograph System was used to measure blood pressure by the tail-cuff method. There was a marked decrease in the systolic blood pressure of all of the rats after three doses and the decrease occurred within 30 min in each case. Even though the average decreases for the 0.1 ml/kg and the 0.25 ml/kg doses were calculated as 51,25 mm Hg and 56.25 mm Hg, respectively, these doses were not sufficient to sustain the blood pressure in a normal range for more than 1 or 2 h. The 0.5 ml/kg dose, showing an average decrease of 65.7 mm Hg, was sufficient to provoke a decrease to a normal level and to sustain this decrease for up to 24 h. The results indicate that garlic is effective as a natural agent for the treatment of hypertension.

Antioxidant therapy in the aging process.

Deucher GP
Clinica Guilherme Paulo Deucher, Sao Paulo, Brazil.
EXS (Switzerland) 1992, 62 p428-37

A total of 1,265 patients with age-related diseases such as diabetes, arthritis, vascular disease and hypertension as well as 1,100 persons in diminished health without apparent disease, were treated with the metal chelator EDTA and antioxidants such as vitamin C, E, beta-carotene, selenium, zinc and chromium. Good results were observed in the majority of patients. This is encouraging for the initiation of controlled clinical trials.

Antioxidants show an anti-hypertensive effect in diabetic and hypertensive subjects.

Ceriello A; Giugliano D; Quatraro A; Lefebvre PJ
Cattedra di Diabetologia e Dietoterapia I Facolta di Medicina, Universita di Napoli, Italia.
Clin Sci (Colch) (England) Dec 1991, 81 (6) p739-42

1. In this study an acute anti-hypertensive effect of three anti-oxidant agents (Vitamin-C, thiopronine and glutathione) in hypertensive subjects and in both hypertensive and non-hypertensive diabetic patients is reported.

2. The antioxidants had no effect on blood pressure in healthy normal subjects at a dose of 6 mmol, but thiopronine and glutathione produced a significant hypotensive effect at a dose of 12 mmol.

3. These data suggest that antioxidants might have a dilatatory effect and that an imbalance of the nitric oxide-free radical interaction might facilitate the development of hypertension in humans.

[Relation between Vitamin-C consumption and risk of ischemic heart disease]

Davydenko NV, Kolchinskii VI
Vopr Pitan 1983 Nov-Dec;(6):17-9

Interrelation was studied between Vitamin-C consumption and the prevalence of coronary heart disease and some risk factors in a non-organized male population in Kiev. A reverse relationship was established between Vitamin-C consumption, the prevalence of coronary heart disease and some risk factors, such as arterial hypertension, hyperlipoproteinemia and overweight.

Blood pressure and nutrient intake in the United States.

McCarron DA; Morris CD; Henry HJ; Stanton JL
Science (United States) Jun 29 1984, 224 (4656) p1392-8

A data base of the National Center for Health Statistics, Health and Nutrition Examination Survey I (HANES I), was used to perform a computer-assisted, comprehensive analysis of the relation of 17 nutrients to the blood pressure profile of adult Americans. Subjects were 10,372 individuals, 18 to 74 years of age, who denied a history of hypertension and intentional modification of their diet. Significant decreases in the consumption of calcium, potassium, vitamin A, and Vitamin-C were identified as the nutritional factors that distinguished hypertensive from normotensive subjects. Lower calcium intake was the most consistent factor in hypertensive individuals. Across the population, higher intakes of calcium, potassium, and sodium were associated with lower mean systolic blood pressure and lower absolute risk of hypertension. Increments of dietary calcium were also negatively correlated with body mass. Even though these correlations cannot be accepted as proof of causation, they have implications for future studies of the association of nutritional factors and dietary patterns with hypertension in America.

Summary of the NATO advanced research workshop on dietary omega 3 and omega 6 fatty acids: biological effects and nutritional essentiality.

Simopoulos AP
Division of Nutritional Sciences, International Life Sciences Institute Research Foundation
J Nutr (United States) Apr 1989, 119 (4) p521-8

A number of human studies presented at the workshop indicate that the premature infant at birth is biochemically deficient in docosahexaenoic acid (DHA) in both the brain and liver phospholipids, and that DHA is essential for normal visual acuity. The amount of DHA necessary to maintain normal amounts of the liver and brain phospholipids postnatally is 11 mg/kg daily. Elderly patients on long-term gastric tube feedings and others on long-term intravenous fluids and on total parenteral nutrition are particularly prone to deficiencies of alpha-linolenic acid, eicosapentaenoic acid (EPA) and DHA. The amounts estimated to prevent deficiencies in the elderly are 800-1100 mg/d of alpha-linolenic acid and 300-400 mg/d of EPA and DHA combined. Preliminary data indicate that children with malnutrition and mucoviscidosis, women with toxemia, and elderly people have decreased amounts of DHA in plasma phospholipids. The omega 3 fatty acids lower triglycerides and, at high levels, lower cholesterol. The anti-aggregatory, anti-thrombotic and anti-inflammatory properties of omega 3 fatty acids have been confirmed, and a dose-response curve is emerging. Despite the increase in bleeding time, no clinical evidence of bleeding has been noted by the investigators in any of the studies. Clinical trials are necessary in order to precisely define the dose and mechanisms involved in defining the essentiality of omega 3 fatty acids in growth and development and their beneficial effects in coronary heart disease, hypertension, inflammation, arthritis, psoriasis, other autoimmune disorders, and cancer. (56 Refs.) Summary of the NATO advanced research workshop on dietary omega 3 and omega 6 fatty acids: biological effects and nutritional essentiality.

Association of macronutrients and energy intake with hypertension.

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J Am Coll Nutr (United States) Feb 1996, 15 (1) p21-35

Hypertension, a major public health problem, becomes more prevalent during aging. Epidemiological studies suggest that environmental factors such as nutrition may play a major role in blood pressure (BP) regulation. It is generally accepted that obesity and sodium/alcohol consumption are important factors, and many believe that calcium, magnesium and potassium consumption are regulatory as well. Less emphasis has been placed on whether macronutrients influence blood pressure significantly. This review focused on the ability of excess calories and consumption of carbohydrates, fats, and proteins to regulate blood pressure. (207 Refs.)

Relations between magnesium, calcium, and plasma renin activity in black and white hypertensive patients

Touyz RM; Panz V; Milne FJ
Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa.
Miner Electrolyte Metab (Switzerland) 1995, 21 (6) p417-22

The heterogeneous status of magnesium and calcium metabolism in the hypertensive population may be related to the plasma renin activity (PRA). This study investigates the relationships between serum and erythrocyte magnesium (Mg^{2+}) and calcium (Ca^{2+}) concentrations and PRA in black and white essential hypertensive patients. Thirty-nine normotensive (20 black, 19 white) and 47 hypertensive (25 black, 22 white) subjects were studied. The PRA was measured by radioimmunoassay, Mg^{2+} and Ca^{2+} by atomic absorption spectroscopy, and serum ionized Ca^{2+} by a specific electrode. PRA and ionized Ca^{2+} were significantly lower in the black hypertensive as compared with the white hypertensive group (1.99 +/- 0.33 vs. 5.96 +/- 1.02 ng/ml/h for PRA; 1.28 +/- 0.07 vs. 1.42 +/- 0.01 mmol/l for ionized Ca^{2+}: black hypertensives vs. white hypertensives $p < 0.05$). Ionized Ca^{2+} was significantly increased ($p < 0.05$) in the white hypertensive patients as compared with the normotensive controls (1.42 +/- 0.01 vs. 1.29 +/- 0.04 mmol/l). In the black hypertensive group, serum and erythrocyte Mg^{2+} were significantly ($p < 0.05$) decreased as compared with the other groups. The erythrocyte Ca^{2+} concentration was significantly elevated in both black and white hypertensive patients. In the group as a whole, serum Mg^{2+} and PRA were negatively correlated and ionized Ca^{2+} and PRA and ionized Ca^{2+} and erythrocyte Ca^{2+} positively correlated. However, in the subgroups, these correlations were only significant in the white group: $r = -0.67$ and $p < 0.05$ serum

Mg2+ vs. PRA; r = 0.64, and p < 0.05 ionized Ca2+ vs. PRA; r = 0.82 and p < 0.01 ionized [Ca2+]i vs. erythrocyte Ca2+. These data suggest a relationship between PRA, Mg2+, and Ca2+ which may be more important in white than in black hypertensive patients.

Effect of renal perfusion pressure on excretion of calcium, magnesium, and phosphate in the rat.

Wu X; Sonnenberg H
Department of Physiology, University of Toronto, Ontario, Canada.
Clin Exp Hypertens (United States) Nov 1995, 17 (8) p1269-85

Abnormalities in renal handling of calcium, magnesium, or phosphate have been implicated in the development and/or maintenance of human hypertension. We have shown recently that renal excretion of these ions is correlated to blood pressure in Dahl salt-sensitive as well as salt-resistant rats. The present study was designed to determine whether renal perfusion pressure per se could affect excretion of these ions. Urinary excretion of calcium, magnesium, and phosphate was studied in anaesthetized Sprague-Dawley rats under basal conditions and during an intravenous infusion of angiotensin II (ANG II), vasopressin (AVP) or phenylephrine (PE). A cuff, placed around the aorta between the two renal arteries, allowed maintenance of normal perfusion pressure in the left kidney, while that in the right kidney was allowed to rise. Infusion of pressor agents raised mean arterial blood pressure to comparable levels (means +/- SE): ANG II (n = 7), before = 102 +/- 4, during = 133 +/- 3 mmHg, AVP (n = 8), before = 110 +/- 7, during = 136 +/- 5 mmHg, PE (n = 6), before = 111 +/- 6, during = 141 +/- 6 mmHg. Although there was no difference in excretion of calcium, magnesium and phosphate between the two kidneys under basal conditions, infusion of ANG II or PE induced hypercalciuria, hypermagnesiuria and hyperphosphaturia in the right kidney which was exposed to the increased arterial pressure. Such effects did not appear in the pressure-controlled left kidney. Infusion of AVP was associated with reduced excretion of calcium and magnesium, and increased excretion of phosphate, in the normotensive kidney. The response to the similarly increased renal perfusion pressure in this group was also reduced for calcium and magnesium, and enhanced for phosphate. The results indicate

(1) renal excretion of calcium, magnesium and phosphate is renal perfusion pressure-dependent; the higher the renal perfusion pressure, the greater the excretion of these ions.

(2) Independently of perfusion pressure, AVP can inhibit phosphate reabsorption and stimulate divalent cation reabsorption.

Dietary L-arginine attenuates blood pressure in mineralocorticoid-salt hypertensive rats.

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Laboratoire de Physiologie, U.F.R. Medecine et Pharmacie, Besancon, France.
Clin Exp Hypertens (United States) Oct 1995, 17 (7) p1009-24

The present study was designed to investigate the influence of dietary L-arginine supplementation on blood pressure and on ex vivo vascular reactivity in mineralocorticoid-salt (DOCA-salt) hypertensive rats. Systolic blood pressure and heart rate were determined throughout the experimental period in unanaesthetized rats. Plasma and urine electrolyte levels were measured. Vasoconstrictor response to noradrenaline and vasodilator responses to acetylcholine and sodium nitroprusside were evaluated in the isolated perfused mesenteric vascular bed. DOCA-salt hypertensive rats were divided into 2 groups: a control group and a treated group receiving 0.8% L-arginine supplementation in drinking water. Dietary L-arginine supplementation attenuated systolic blood pressure in conscious DOCA-salt hypertensive rats, but did not modify heart rate. Plasma calcium and sodium concentrations and urinary magnesium excretion were decreased by L-arginine supplementation. Noradrenaline-induced vasoconstriction decreased and acetylcholine-induced vasodilatation increased, whereas sodium nitroprusside-induced vasodilatation was not modified, in the L-arginine-supplemented rats. It is concluded that dietary L-arginine supplementation in the diet lowers systolic blood pressure in DOCA-salt hypertensive rats, probably through vascular action.

Concentration of free intracellular magnesium in the myocardium of spontaneously hypertensive rats treated chronically with calcium antagonist or angiotensin converting enzyme inhibitor

Carlier P; Smelten N; Ciancabilla F; Rorive G
Service hospitalier Frederic-Joliot, Commissariat a l'energie atomique, Orsay.
Arch Mal Coeur Vaiss (France) Aug 1994, 87 (8) p1041-5

In this study, we determined a) whether chronic antihypertensive treatment could alter myocardial free intracellular magnesium concentrations, b) whether changes in magnesium concentration would correlate with resistance to anoxia of hypertensive rat hearts. Six-month old male spontaneously hypertensive (HT) rats (n = 11) were compared to rats from the same strain treated with a calcium channel antagonist, nitrendipine (60 mg/kg/j; n = 11) or with a converting-enzyme inhibitor, perindopril (2 mg/kg/j; n = 9) during three months. The hearts were perfused in retrograde isovolumic mode and submitted to a standardized anoxia-recovery protocol. Aortic perfusion pressure and left ventricular pressure were constantly monitored. P-31 NMR spectra were simultaneously recorded and allowed to quantify the changes in myocardial inorganic phosphate, phosphocreatine and ATP. The pH was derived from the chemical shifts of inorganic phosphate and phosphocreatine, and the free intracellular magnesium concentration from the alpha-beta chemical shifts of ATP. Both treatments lowered systolic blood pressure and reversed left ventricular hypertrophy, perindopril being slightly more efficient at the dose administered. Intracellular magnesium concentration, calculated from the P-31 NMR spectra, was 277 +/- 17 microM in the untreated hypertensive group, 311 +/- 15 microM in the

nitrendipine group and 401 +/- 17 microM in the perindopril group ($p < 0.001$ versus untreated and nitrendipine). There was a significant correlation between intracellular magnesium concentration and left ventricular developed pressure at the early stage of post-anoxic recovery ($r = 0.61$; $p < 0.01$). P-31 NMR spectroscopy demonstrates an increase in myocardial free intracellular magnesium concentration following chronic administration of an angiotensin-converting enzyme inhibitor, perindopril, spontaneously hypertensive rats.(ABSTRACT TRUNCATED AT 250 WORDS)

Nonpharmacologic treatment of hypertension.

Kaplan NM
University of Texas Southwestern Medical Center at Dallas.
Curr Opin Nephrol Hypertens (United States) Oct 1992, 1 (1) p85-90

A variety of lifestyle modifications will lower both the blood pressure and various other cardiovascular risk factors that are frequently present in patients with hypertension. Numerous recent studies document the overall efficacy of some (weight reduction, sodium restriction, physical activity, moderation of alcohol) and the relative lack of effect of others (stress management and calcium, magnesium, and fish oil supplements). In particular, the Trials of Hypertension Prevention, Phase I (a control trial funded by the National Heart, Lung, and Blood Institute) provides important new data on the ability of these various modalities to prevent the development of hypertension, an equally or even more important goal than the reduction of already-established disease. (32 Refs.)

Micronutrient effects on blood pressure regulation.

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Nutr Rev (United States) Nov 1994, 52 (11) p367-75

Five micronutrients have been shown to directly influence blood pressure: sodium, calcium, potassium, magnesium, and chloride. The data presented here are based on accumulated findings from epidemiologic, laboratory, and clinical investigations, many of which focused primarily on a single nutrient. However, as also discussed here, nutrients are not consumed in isolation, and their physiologic interactions and combined effects on blood pressure are the subjects of much of the current research in the area of diet and hypertension. (71 Refs.)

Role of magnesium and calcium in alcohol-induced hypertension and strokes as probed by in vivo television microscopy, digital image microscopy, optical

spectroscopy, 31P-NMR, spectroscopy and a unique magnesium ion-selective electrode.

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Alcohol Clin Exp Res (United States) Oct 1994, 18 (5) p1057-68

It is not known why alcohol ingestion poses a risk for development of hypertension, stroke and sudden death. Of all drugs, which result in body depletion of magnesium (Mg), alcohol is now known to be the most notorious cause of Mg-wasting. Recent data obtained through the use of biophysical (and noninvasive) technology suggest that alcohol may induce hypertension, stroke, and sudden death via its effects on intracellular free Mg2+ ([Mg2+]i), which in turn alter cellular and subcellular bioenergetics and promote calcium ion (Ca2+) overload. Evidence is reviewed that demonstrates that the dietary intake of Mg modulates the hypertensive actions of alcohol. Experiments with intact rats indicates that chronic ethanol ingestion results in both structural and hemodynamic alterations in the microcirculation, which, in themselves, could account for increased vascular resistance. Chronic ethanol increases the reactivity of intact microvessels to vasoconstrictors and results in decreased reactivity to vasodilators. Chronic ethanol ingestion clearly results in vascular smooth muscle cells that exhibit a progressive increase in exchangeable and cellular Ca2+ concomitant with a progressive reduction in Mg content. Use of 31P-NMR spectroscopy coupled with optical-backscatter reflectance spectroscopy revealed that acute ethanol administration to rats results in dose-dependent deficits in phosphocreatine (PCr), the [PCr]/[ATP] ratio, intracellular pH (pHi), oxyhemoglobin, and the mitochondrial level of oxidized cytochrome oxidase aa3 concomitant with a rise in brain-blood volume and inorganic phosphate. Temporal studies performed in vivo, on the intact brain, indicate that [Mg2+]i is depleted before any of the bioenergetic changes. Pretreatment of animals with Mg2+ prevents ethanol from inducing stroke and prevents all of the adverse bioenergetic changes from taking place. Use of quantitative digital imaging microscopy, and mag-fura-2, on single-cultured canine cerebral vascular smooth muscle, human endothelial, and rat astrocyte cells reveals that alcohol induces rapid concentration-dependent depletion of [Mg2+]i. These cellular deficits in [Mg2+]i seem to precipitate cellular and subcellular disturbances in cytoplasmic and mitochondrial bioenergetic pathways leading to Ca2+ overload and ischemia. A role for ethanol-induced alterations in [Mg2+]i should also be considered in the well-known behavioral actions of alcohol. (90 Refs.)

Dietary management of blood pressure.

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J Assoc Acad Minor Phys (United States) 1994, 5 (4) p147-51

Hypertension is a major cause of morbidity and mortality in the United States, particularly in the African-American population. Although there have been indications since the beginning of this century that blood pressure might be influenced by dietary factors, this has been generally ignored, and the mainstay of hypertension treatment has been the use of pharmacologic antihypertensives. Attention is now being focused, however, on dietary management of hypertension because of the high cost of drug therapy, the adverse reactions associated with some antihypertensives, and the fact that hypertensives treated only by pharmacologic means remain at risk for target-organ damage. The literature is replete with evidence that vegetarian and low-sodium dietary patterns are associated with lower blood pressure levels. This implies that if many people could adopt vegetarian and low-salt dietary habits, the prevalence of hypertension would be significantly reduced. However, most people find "unsalted" vegetarian diets tasteless and unacceptable. We therefore need to identify the macro- and micronutrients (other than sodium) that directly influence blood pressure. Several studies indicate that dietary patterns rich in fiber, calcium, potassium, and magnesium are favorable for blood pressure control. This review highlights some of these findings and emphasizes the need for large clinical trials to test blood-pressure-reducing dietary patterns by incorporating the aforementioned macro- and micronutrients into socioculturally acceptable and palatable menus, especially in the African-American population. (77 Refs.)

Impact of increasing calcium in the diet on nutrient consumption, plasma lipids, and lipoproteins in humans

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Am J Clin Nutr (United States) Apr 1994, 59 (4) p900-7

This study examined the feasibility of increasing food-derived calcium to 1500 mg/d and the impact of this change on plasma lipids and nutrient consumption in hypertensive (n = 130) and normotensive (n = 196) participants. Three interventions were applied in a randomized, parallel, placebo-controlled fashion: 1) counseling to increase dietary calcium through food consumption to 1500 mg/d (n = 106), 2) a 1000-mg/d calcium supplement (n = 109), or 3) placebo (n = 111). Plasma lipids were measured before and after 12 wk of intervention whereas nutrient intake was monitored throughout the study. At baseline, hypertensive patients reported lower intakes of carbohydrates, calcium, magnesium, phosphorus, potassium, iron, vitamin D, thiamin, and riboflavin (all $P < 0.05$). They also had lower HDL ($P = 0.014$) and higher LDL ($P < 0.05$) compared with normotensive subjects. During intervention, calcium, magnesium, phosphorus, potassium, thiamin, riboflavin, and vitamins C and D increased ($P < 0.01$) in the group receiving food calcium but not in the placebo or supplement groups. No changes occurred in plasma lipids or lipoproteins after 12 wk of intervention.

Augmentation of the renal tubular dopaminergic activity by oral calcium supplementation in patients with essential hypertension.

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Am J Hypertens (United States) Nov 1993, 6 (11 Pt 1) p933-7

We studied the effect of oral calcium supplementation on renal tubular dopaminergic activity in patients with mild to moderate essential hypertension. Fifteen patients aged 45 to 68 years (nine men and six women, mean age 59 +/- 7 [SD]) participated in the study. We orally administered calcium (1.0 g per day for 1 week) during hospitalization. The change in 24-h blood pressure (BP), measured by ambulatory BP monitoring, and excretions of electrolytes and catecholamines were investigated before and after 1 week of oral calcium supplementation. The mean values of 24-h systolic and diastolic BP showed no significant changes by calcium loading. Daily urinary excretion of free dopamine, sodium clearance (CNa), fractional excretion of sodium (FENa), and urinary volume were significantly increased by oral calcium supplementation. Urinary excretions of epinephrine and norepinephrine and creatinine clearance showed no significant changes by oral calcium treatment. CNa and FENa showed significant correlations with urinary excretion of free dopamine. These results suggest that oral calcium supplementation induces natriuresis partly through augmentation of renal tubular dopaminergic activity.

The pathogenesis of eclampsia: the 'magnesium ischaemia' hypothesis.

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Med Hypotheses (England) Apr 1993, 40 (4) p250-6

'Magnesium ischaemia' is a term used to denote the functional impairment of the ATP-dependent sodium/potassium and calcium pumps in the cell membranes and within the cell itself. The production of ATP and the functioning of these pumps is magnesium-dependent and is critically sensitive to acidosis. Zinc and iron deficiencies may secondarily impair these pumps and thus contribute to 'magnesium ischaemia' (as does acidosis). This term is two-dimensional at its simplest; it refers to a functional magnesium deficiency, whether actual or induced. It is argued that chronic acidosis is the most common inducing factor. This simple hypothesis can begin to unify diverse pathophysiologies: some spontaneous abortions, aspects of Type II and gestational diabetes and the curious observation that heroin addicts become diabetic. It can also unify clinical thinking about pregnancy-induced hypertension, pre-eclampsia/eclampsia and acute fatty liver of pregnancy, as well as the coagulopathy of pregnancy. It makes important predictions about perinatal morbidity and suggests that early supplementation might prevent much pregnancy-induced disease.

Can guava fruit intake decrease blood pressure and blood lipids?

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J Hum Hypertens (England) Feb 1993, 7 (1) p33-8

A randomized, single-blind, controlled trial was conducted to examine the effects of guava fruit intake on BPs and blood lipids in patients with essential hypertension. Of 145 hypertensives that entered the trial, 72 patients were assigned to take a soluble fibre and a potassium-rich diet containing 0.5-1.0 kg of guava daily (group A) and 73 patients to their usual diet (group B), while salt, fat, cholesterol, caffeine and alcohol intake were similar in both groups. Mean age, mean body weight and male sex, were similar, and so were risk factors, mean BPs, mean serum sodium, potassium, calcium, magnesium, triglycerides, cholesterol and HDL-cholesterol in both groups. Dietary adherence to guava intake was checked by a questionnaire. After four weeks of follow-up on an increased consumption of dietary potassium and low sodium/potassium ratio, group A patients were associated with 7.5/8.5 mmHg net decrease in mean systolic and diastolic pressures compared with group B. Increased intake of soluble dietary fibre (47.8 +/- 11.5 vs. 9.5 +/- 0.85 g/day) was associated with a significant decrease in serum total cholesterol (7.9%), triglycerides (7.0%) and an insignificant increase in HDL-cholesterol (4.6%) with a mild increase in the ratio of total cholesterol/HDL-cholesterol in group A patients compared with group B. It is possible that an increased consumption of guava fruit can cause a substantial reduction in BPs and blood lipids with a lack of decrease in HDL-cholesterol due to its higher potassium and soluble fibre content, respectively.

Preventive nutrition: disease-specific dietary interventions for older adults.

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Geriatrics (United States) Nov 1992, 47 (11) p39-40, 45-9

Disease prevention through dietary management is a cost-effective approach to promoting healthy aging. Fats, cholesterol, soluble fiber, and the trace elements copper and chromium affect the morbidity and mortality of CHD. Decreasing sodium and increasing potassium intake improves control of hypertension. Calcium and magnesium may also have a role in controlling hypertension. The antioxidant vitamins A and beta-carotene, Vitamin-C, vitamin E, and the trace mineral selenium may protect against types of cancer. A decrease in simple carbohydrates and an increase in soluble dietary fiber may normalize moderately elevated blood glucose levels. Deficiencies of zinc or iron diminish immune function. Adequate levels of calcium and vitamin D can help prevent senile osteoporosis in both older men and women. (27 Refs.)

Intracellular Mg2+, Ca2+, Na2+ and K+ in platelets and erythrocytes of essential hypertension patients: relation to blood pressure.

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Clin Exp Hypertens [A] (United States) 1992, 14 (6) p1189-209

Alterations in intracellular cation metabolism have been implicated in the pathophysiology of essential hypertension. Total magnesium, calcium, sodium and potassium levels were studied in serum erythrocytes and platelets, from 154 subjects (76 hypertensive and 78 normotensives; 104 blacks and 50 whites). In the combined black and white hypertensive group, platelet sodium and calcium and erythrocyte calcium were elevated and serum potassium, serum magnesium and platelet magnesium decreased. In the black hypertensive patients, platelet sodium and calcium and erythrocyte calcium were increased, whereas serum magnesium, serum potassium, platelet magnesium and erythrocyte magnesium were decreased. In the white hypertensive group, platelet sodium and erythrocyte calcium were raised and platelet magnesium was decreased. In the black hypertensive patients, serum and platelet magnesium and serum calcium were negatively and erythrocyte and platelet calcium positively correlated with mean arterial pressure. In the white hypertensive patients platelet sodium was directly related to mean arterial pressure. These results suggest that intracellular sodium and calcium overload and magnesium depletion may be important in the pathophysiology of hypertension. Magnesium disturbances are more consistent and widespread in black hypertensive patients than in white hypertensive patients.

A prospective study of nutritional factors and hypertension among US men

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Circulation (United States) Nov 1992, 86 (5) p1475-84

BACKGROUND. An effect of diet in determining blood pressure is suggested by epidemiological studies, but the role of specific nutrients is still unsettled.

METHODS AND RESULTS. The relation of various nutritional factors with hypertension was examined prospectively among 30,681 predominantly white US male health professionals, 40-75 years old, without diagnosed hypertension. During 4 years of follow-up, 1,248 men reported a diagnosis of hypertension. Age, relative weight, and alcohol consumption were the strongest predictors for the development of hypertension. Dietary fiber, potassium, and magnesium were each significantly associated with lower risk of hypertension when considered individually and after adjustment for age, relative weight, alcohol consumption,

and energy intake. When these nutrients were considered simultaneously, only dietary fiber had an independent inverse association with hypertension. For men with a fiber intake of < 12 g/day, the relative risk of hypertension was 1.57 (95% confidence interval, 1.20-2.05) compared with an intake of > 24 g/day. Calcium was significantly associated with lower risk of hypertension only in lean men. Dietary fiber, potassium, and magnesium were also inversely related to baseline systolic and diastolic blood pressure and to change in blood pressure during the follow-up among men who did not develop hypertension. Calcium was inversely associated with baseline blood pressure but not with change in blood pressure. No significant associations with hypertension were observed for sodium, total fat, or saturated, transunsaturated, and polyunsaturated fatty acids. Fruit fiber but not vegetable or cereal fiber was inversely associated with incidence of hypertension.

CONCLUSIONS. These results support hypotheses that an increased intake of fiber and magnesium may contribute to the prevention of hypertension.

Minerals and blood pressure.

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Ann Med (Finland) Aug 1991, 23 (3) p299-305

The mineral elements sodium, potassium, calcium and magnesium play a central role in the normal regulation of blood pressure. In particular, these mineral elements have important interrelationships in the control of arterial resistance. These elements, especially sodium and potassium, also regulate the fluid balance of the body and, hence, influence the cardiac output. Evidence shows that the present levels of intake of mineral elements are not optimum for maintaining normal blood pressure but predispose to the development of arterial hypertension. Research results suggest that without sodium chloride (common salt) and other sodium compounds being added to the diet arterial hypertension would be virtually non existent. Moreover, blood pressure would not rise with age. In communities with a high consumption of added sodium, a high intake of potassium and, possibly, magnesium seem to protect against the development of arterial hypertension and the rise of blood pressure with age. A marked reduction of sodium intake is effective in treating even severe hypertension. A moderate restriction of sodium intake or an increase in potassium intake exert remarkable antihypertensive effects, at least in some hypertensive patients. Magnesium and possibly also calcium supplements may be effective in reducing blood pressure in some hypertensives. In hypertensive patients treated with drugs sodium restriction and potassium and magnesium supplementation enhance the therapeutic effect, reduce the number and dosage, and lessen the adverse effects of prescribed antihypertensive drugs. Hence, a fall in sodium consumption and increases in potassium and magnesium consumption are useful in preventing and treating arterial hypertension. (62 Refs.)

Nutrition and blood pressure among elderly men and women (Dutch Nutrition Surveillance System).

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J Am Coll Nutr (United States) Apr 1991, 10 (2) p149-55

Associations between blood pressure and nutrition-related variables (body mass index, dietary intake, and 24-hr excretion of sodium, potassium, magnesium, and calcium in the urine) were investigated in men (n = 138) and women (n = 117) 65-79 years old not using drugs known to affect blood pressure and not on a diet. Among men, body mass index was positively and creatinine clearance was inversely associated with systolic blood pressure, whereas body mass index and urinary sodium:potassium ratio were positively associated with diastolic blood pressure. Among women, both age and urinary calcium:creatinine ratio were positively associated with systolic as well as diastolic blood pressure. Coffee consumption was positively correlated with blood pressure and urinary calcium:creatinine ratio among the women. From the results it appears that, besides "normal" weight, increased potassium intake and urinary excretion may exert a protective effect among elderly men against hypertension when sodium exposure is relatively high. The positive association between urinary calcium:creatinine ratio and blood pressure among the women may be partly due to coffee consumption.

The effect of Ca and Mg supplementation and the role of the opioidergic system on the development of DOCA-salt hypertension.

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Am J Hypertens (United States) Jan 1991, 4 (1 Pt 1) p72-5

The effect of calcium and magnesium supplementation and the role of opioidergic system was examined in deoxycorticosterone acetate (DOCA)-salt hypertensive rats. The rats were divided into four groups receiving standard laboratory rat diet (control group; n = 9); a calcium-rich diet with 2% CaCl2 added (Ca-group; n = 12); a magnesium-rich diet with 0.5% MgO added (Mg-group; n = 11); and a calcium and magnesium-rich diet with 2% CaCl2 and 0.5% MgO added (Ca/Mg-group; n = 11); each diet contained 7% NaCl. After four weeks on these diets, the rats were decapitated and blood was obtained for the measurement of plasma electrolytes, intraerythrocyte sodium, potassium and magnesium content (RBC-Na, -K, in mEq/L cells and RBC-Mg, in mg/dL cells) and plasma beta-endorphin concentration (beta-END, in pg/mL). In the control group, systolic blood pressure and RBC-Na were obviously higher than in the other groups. Plasma beta-

endorphin concentration was 45.1 +/- 13.4 in the control group, 70.7 +/- 17.4 in the Ca-group (P less than .05 v control group), 58.0 +/- 20.1 in the Mg-group and 83.8 +/- 24.8 in the Ca/Mg-group (P less than .01 v control group). The blood pressure correlated significantly with both RBC-Na (r = 0.416, P less than .01) and beta-END (r = 0.436, P less than .005). A negative correlation was also observed between RBC-Na and beta-END (r = 0.437, P less than .005).(ABSTRACT TRUNCATED AT 250 WORDS)

Attenuated vasodilator responses to Mg2+ in young patients with borderline hypertension.

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Circulation (United States) Aug 1990, 82 (2) p384-93

Limb vascular responses to magnesium (Mg2+) and potassium (K+) ions were studied in 19 young patients with borderline hypertension (BHT) and compared with those of 22 age-matched normotensive subjects (NT) by measuring the forearm blood flow response to intra-arterial infusion of magnesium sulfate and potassium chloride using venous occlusion plethysmography. Percent decrements of forearm vascular resistance with Mg2+ infusions were significantly less in BHT subjects than in NT (-37.2 +/- 4.2% versus -53.0 +/- 2.0%, p less than 0.05, during the infusion of 0.1 meq Mg2+/min, and -52.2 +/- 4.3% versus -65.6 +/- 1.5%, p less than 0.05, during the infusion of 0.2 meq Mg2+/min). Moreover, the relation of the magnitude of Mg2+ response to initial vascular resistance in six of 10 BHT subjects lies above the 95% confidence interval for predicted values calculated for response points in 11 NT subjects, suggesting attenuated vasodilator responses of Mg2+ in a significant proportion of BHT subjects. In contrast, the response points to K+ in eight of nine BHT subjects fall within the 95% confidence interval, suggesting normal vasodilator responses to K+ in the majority of BHT subjects. Furthermore, the effect of small increments in local serum calcium concentrations on Mg2(+)- and K(+)-induced vasodilation was studied in normal volunteers. Isosmolar CaCl2 solution infused into the same brachial artery at a rate of 0.09 meq/min severely blunted the vasodilating actions of Mg2+ (-30.1 +/- 6.5% versus -65.8 +/- 3.2%, p less than 0.01, during the infusion of 0.2 meq Mg2+/min) but did not affect those of K+ (-63.1 +/- 3.1% versus -55.9 +/- 3.8%, NS, during the infusion of 0.154 meq K+/min). It appears that Mg2(+)-induced vasodilation should be due to the antagonistic action of Mg2+ to calcium, but K(+)-induced vasodilation might not be directly related to calcium movement. Thus, these attenuated responses to Mg2+ but normal responses to K+ in BHT subjects may indicate an underlying defect in vascular Mg2+ metabolism, which ultimately may be related to the alterations in calcium handling by plasma membranes rather than to the abnormalities of membrane Na(+)-K+ pump activity.

Dietary modulators of blood pressure in hypertension

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Eur J Clin Nutr (England) Apr 1990, 44 (4) p319-27

To study the role of diet, 197 patients of essential hypertension were randomized to either experimental diet (group A, 97 cases) or normal diet (group B, 100 cases) with diuretics given to both the groups. The age varied between 25 and 65 years and 154 were males. The study diet included a significantly higher content of potassium (K), magnesium (Mg), calcium (Ca), polyunsaturated fat, and complex carbohydrates compared to the normal diet. At entry to the study, age, sex, risk factors, mean blood pressures, mean serum Mg, K, Ca, and Na, and drug therapy were comparable in both groups. After 1 year of follow-up, there were significantly fewer patients with resistant hypertension in group A (5) than in group B (17). Mean systolic (148.22 +/- 10.1 mm Hg) and diastolic (90.2 +/- 4.84 mm Hg) pressures in group A were lowered compared to mean systolic (160 +/- 12.0 mm Hg) and diastolic (103.3 +/- 5.8 mm Hg) pressures in group B and initial mean systolic (152.2 +/- 12.8 mm Hg) and diastolic (99.8 +/- 7.2 mm Hg) pressures. Mean serum magnesium (1.86 +/- 9.22 mEq/l) and potassium (4.86 +/- 0.39 mEq/l) levels in group A were significantly higher compared to mean levels of 1.56 +/- 0.11 and 4.0 +/- 0.29 mEq/l, respectively, in group B. However compared to initial levels, K and Mg showed no significant changes in groups A and B. There was a significantly lower incidence of complications in group A (58) compared to group B (100). It is possible that a diet low in Na/K ratio and rich in complex carbohydrates, polyunsaturates, K and Mg may cause a significant reduction in blood pressure and its complications.

Daily intake of macro and trace elements in the diet. 4. Sodium, potassium, calcium, and magnesium

Cocchioni M; Pellegrini MG; Grappasonni I; Vitali C; Marsili G
Ann Ig (Italy) Sep-Oct 1989, 1 (5) p923-42

To complete the picture of the daily dietary intake of minerals, sodium, potassium, calcium and magnesium have now been considered. The study has been carried out in the Italian Marches Region after carefully evaluating the food consumption habits of the population. The foodstuffs comprising the 70 diets examined were collected in institutional canteens and private homes immediately prior to meals. The food was sampled ready for consumption as it had thus undergone the various preparation and cooking procedures, during which considerable changes in mineral content occur. In comparison with the various food consumption standards, the amount of sodium found appears excessively high (4.8 g/d) whereas that of magnesium is insufficient (0.24 g/d). A high sodium intake, and more recently a high Na/K ratio, have been associated with

hypertension. Also a lack of magnesium and a high Ca/Mg ratio have repeatedly been associated with hypertension risk. The data to emerge from our study: a high sodium intake, an insufficiency of magnesium, and thus high Na/K and Ca/Mg ratios, would appear likely to enhance cardiovascular disease risk. Even though not all Authors agree on the existence of such correlations, a more correct diet as regards mineral intake is undoubtedly something to encourage.

Fish oils modulate blood pressure and vascular contractility in the rat and vascular contractility in the primate

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Blood Press (Norway) May 1995, 4 (3) p177-86

The effect of dietary fish oils on development of hypertension and vascular response in vitro were studied in rats and a primate. Dietary fish oils (MaxEPA and an n-3 ethyl ester concentrate of higher EPA and DHA content) were administered to spontaneously hypertensive (SHR), stroke-prone spontaneously hypertensive (SHR-SP) and a backcross of SHR and Wistar Kyoto (SHR/WKY) rats from 4-16 weeks of age. Blood pressure was monitored during the feeding period and vascular responses measured in the aorta and mesenteric vascular bed in vitro. Depending on the strain of rat used and the composition of the fish oil the attenuation in blood pressure was 10-26 mmHg. Fish oils attenuated the response mediated by sympathetic nerve stimulation or intralumenal norepinephrine in the perfused mesenteric vascular bed preparation from the SHR. This attenuation was more pronounced for fish oils enriched with eicosapentaenoic acid and docosahexaenoic acid and was more prominent in the SHR and SHR/WKY backcross than it was in the SHR-SP. Prostanoid synthesis or nitric oxide modulation of alpha-adrenoceptor responses were shown not to be involved in the attenuation of vascular responses produced by fish oil. The maximum contraction of aortic ring preparations in response to norepinephrine (NE) was significantly smaller in SHR than WKY rats fed olive oil and for SHR rats maintained on fish oils the contraction was close to WKY olive oil values. Evidence was obtained also for a modulation of vasoconstrictor responses by dietary fish oils in the perfused mesenteric bed of the marmoset monkey.

Effects of fish oil, nifedipine and their combination on blood pressure and lipids in primary hypertension.

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J Hum Hypertens (England) Feb 1993, 7 (1) p25-32

In a double-blind, crossover, placebo-controlled study the effects of four weeks' treatment with 4.55 g/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on BP and serum lipids were assessed in 18 males with hypertension (WHO stage I-II). At the end of the double-blind phase, eight patients on placebo (olive oil) and ten patients on fish oil treatment were given nifedipine 20 mg twice daily added to their regimens for four weeks. Four weeks' fish oil treatment slightly reduced BP values; however, compared with placebo no changes were found. VLDL-cholesterol and triglycerides were significantly reduced by 24%, whereas total and LDL-cholesterol remained unchanged. Placebo did not change BP and lipid values. When nifedipine was added to fish oil/placebo, BP in the two groups was reduced to almost the same extent. When nifedipine was added to fish oil, total cholesterol was significantly reduced by 12% in comparison with baseline value and LDL-cholesterol was reduced by 15%, albeit insignificantly. Placebo plus nifedipine was lipid neutral. A significant correlation was found between the nifedipine-induced changes in supine mean arterial pressure and total, LDL- and VLDL-cholesterol, respectively, in those patients with and without fish oil treatment. In conclusion, the combined administration of fish oil and nifedipine possesses favourable antihypertensive and metabolic properties in hypertensive males with elevated lipid levels.

Garlic (Allium sativum)--a potent medicinal plant

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Fortschr Med (Germany) Jul 20 1995, 113 (20-21) p311-5

A good deal of evidence suggests beneficial effects of the regular dietary intake of garlic on mild hypertension and hyperlipidemia. Garlic seems to have anti-microbial and immunostimulating properties, enhance fibrinolytic activity, and exert favorable effects on platelet aggregation and adhesion. Standardised preparations guarantee exact dosing and minimize the problem of the strong odour of raw garlic. Thus, a traditional folk remedy has established its usefulness for many patients with less severe forms of cardiovascular disease as a medical drug with very few side effects. The available evidence gives rise to the hope that the list of indications may even be considerably extended in the future. (43 Refs.)

Garlic (Allium sativum) and onion (Allium cepa): a review of their relationship to cardiovascular disease

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Prev Med (United States) Sep 1987, 16 (5) p670-85

Garlic and onion have been used for millenia in the traditional medical practice of many cultures to treat cardiovascular and other disorders. Both Allium species, their extracts, and the chemical constituents of these plants have been investigated

for possible effects on cardiovascular disease risk factors--both definite (hyperlipidemia, hypertension and hyperglycemia) and suspected (platelet aggregation and blood fibrinolytic activity). Action of these Allium species on blood coagulability is more clearly defined than their effect on the other risk factors. While many of the studies have serious methodological shortcomings, there is some evidence to suggest that use of certain formulations of garlic and/or onion is accompanied by favorable effects on risk factors in normal subjects and in patients with atherosclerotic disease. The possibility of toxicity resulting from acute and chronic ingestion of large amounts of these plants or their extracts is unresolved. Accordingly, further clinical and epidemiological studies are required before the role of these plants in the prevention and control of cardiovascular disorders is understood and can be realized. Additional research in this area is recommended. (116 Refs.)

Plants and hypotensive, antiatheromatous and coronarodilatating action.

Petkov V
Am J Chin Med (United States) Autumn 1979, 7 (3) p197-236

However great the success in the therapy of hypertension, atherosclerosis and ischemic heart disease has been gained today by recent efficient drugs, the definite healing of patients is not yet attained. The late discovery of reserpine, such an efficient drug of plant origin against hypertension, convinced so far reluctant scientists to consider the chemical compounds of the plant world. With respect to this traditional medical knowledge, it seems necessary to define more accurately the specificity of these healings-sometimes recommended unspecifically for a whole branch of medicine. This experimental verification should not use inconsiderately the present-day classification of diseases; there should be an awareness that conventional experimental methods in pharmacology are often unsuitable for revealing the real biological activity of one or another medicinal plant. The interest in the millennial empirical field of health care is acknowledged by the World Health Organization which promotes research and development of traditional medicine, along with investigations into its psychosocial and ethnographic aspects. These studies cover a number of plants growing in Bulgaria that have a healing effect in hypertension, atherosclerosis and ischemic heart disease according to the data of traditional medicine. Using screening methods, extracts and chemically pure substances were investigated; extraction was done with solvents such as water, ether, chloroform, dichloretan, ethanol, methanol, and acetone. Most of the experiments were carried out on anesthetized cats, rabbits and dogs. The substances tested were applied mainly intravenously, and in some experiments orally. Chronic experiments were also carried out on wakeful dogs with induced hypertension, on animals fed on an atherogenic diet, and on animals with induced arrhythmia and coronary spasm. Data are presented of clinical examination of some plants or of active substances isolated from them. Major results of these studies are presented for the following plants: Garlic, Geranium; Hellebore; Mistletoe; Olive; Valerian; Hawthorn; Pseucedanum arenarium; Periwinkle; Fumitory. For another 50 plants growing in

Bulgaria and in other countries the author presents his and other investigators' experimental and clinical data about hypotensive, antiatheromatous and coronarodilatating action.

Muscle fibre types, ubiquinone content and exercise capacity in hypertension and effort angina.

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Department of Clinical Physiology, Karolinska Institute, Stockholm, Sweden.
Ann Med (Finland) Aug 1991, 23 (3) p339-44

The composition of skeletal muscle fibre expressed as a percentage of slow twitch (ST), type I or "red" and fast twitch (FT), type II or "white" were determined in patients with hypertension (HT) or with severe ischaemic heart disease (IHD) and compared to age matched controls. Similarly, exercise capacity expressed as the cycle intensity eliciting a blood lactate concentration corresponding to 2.0 mmol x 1-1 were compared with healthy controls. Both patient groups had a higher percentage of FT fibres with relatively lower exercise capacities than their controls. The exercise capacities were reduced even when the relationship of decreased capacity with the percentage of increased FT was considered. There was an increase IHD but not in HT in patients with fibre subgroup FTc, which most probably reflected fibre trauma. Both patient groups were low in the skeletal muscle mitochondrial electron carrier and unspecific antioxidant ubiquinone, coenzyme Q10 or CoQ10. Patients with IHD but not HT showed, however, a faster fall in the ratio CoQ10 over ST% the higher the percentage value of ST. The ratio reflects the antioxidant activity related to CoQ10 in the fibre hosting most of the oxidative metabolism. A low ratio indicates a risk of metabolic lesion and cell trauma. This could explain fibre plasticity and offer an alternative cause to heredity in elucidating in deviating muscle fibre composition in patients with HT and IHD.

Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report)--antiarrhythmic action of coenzyme Q10 in diabetics.

Fujioka T; Sakamoto Y; Mimura G
Tohoku J Exp Med (Japan) Dec 1983, 141 Suppl p453-63

An investigation was undertaken to evaluate the antiarrhythmic effect of CoQ10 on VPBs using the Holter ECG, in 27 patients with no clinical findings of organic cardiopathies. As a result, the effect of CoQ10 on VPBs was considered beneficial in 6 (22%) of 27 cases, consisting of 1 patient with hypertension and 5 patients with DM. Even in the remaining 2 patients with DM, the frequency of VPBs was reduced by 50% or more during treatment with CoQ10. The mean reduction of VPBs frequency in the 5 responders plus these 2 patients with DM was 85.7%.

These findings suggest that CoQ10 exhibits an effective antiarrhythmic action not merely on organic heart disease but also on VPBs supervening on DM.

Prospects for nutritional control of hypertension

McCarty MF
Med Hypotheses (England) Mar 1981, 7 (3) p271-83

Sodium restriction is not the only nutritional measure likely to prove valuable in the treatment and prevention of hypertension. The hypotensive effects of central adrenergic stimulation can be promoted by supplementary tyrosine, insulin potentiation (as with GTF), and (possibly) high-dose pyridoxine. Insulin potentiators (GTF) and prostaglandin precursors (essential fatty acids) should have direct relaxant effects on vascular muscle. A high potassium, low sodium diet, coenzyme Q, and prevention of cadmium toxicity (as with dietary selenium) may act to offset renally-mediated pressor influences. Functional combinations of these measures might prove to be substantially effective, in which case they would offer considerable advantages over potentially toxic drug therapies.

Bioenergetics in clinical medicine XV. Inhibition of coenzyme Q10-enzymes by clinically used adrenergic blockers of beta-receptors.

Kishi T; Watanabe T; Folkers K
Res Commun Chem Pathol Pharmacol (United States) May 1977, 17 (1) p157-64

Adrenergic blockers for beta-receptors were studied for inhibition of mitochrondrial CoQ10-enzymes. These enzymes are indispensable for the bioenegetics of the myocardium. Propranolol is frequently used to treat hypertension; in some patients, it depresses myocardial function as an adverse reaction. This side effect may be related to the inhibition by propranolol of CoQ10-enzymes of the myocardium. Timolol showed negligible inhibition of the CoQ10-enzyme, NADH-oxidase. Metoprolol was less inhibitory than propranolol. Five alprenolols showed inhibition which approached that of propranolol. The 1-isomer of alprenolol showed weak inhibition of another CoQ10-enzyme, succinoxidase, but the other beta-blockers were essentially non-inhibitory to this enzyme. The drug of choice is timolol, based on negligible inhibition of these bioenergetic enzymes of the heart, which correlates with its pharmacologically low cardiac depressant effects.

Antioxidant status in controlled and uncontrolled hypertension and its relationship to endothelial damage.

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Hypertension Clinic, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK.
J Hum Hypertens (England) Nov 1994, 8 (11) p843-9

Hypertension is associated with an increased risk of atherosclerosis. Free radical oxidative damage has been implicated in the atherogenic process. We measured levels of the antioxidants uric acid, thiols, vitamins C, A and E as well as the total antioxidant capacity in 21 normotensive controls, 22 patients whose hypertension was controlled on drugs and 30 patients with uncontrolled hypertension. Mean BPs in the groups were 125/76, 132/80 and 181/98 mmHg, respectively. When compared with controls, both hypertensive groups had significantly lower serum ascorbic acid (54 +/- 5 vs. 37 +/- 6 vs. 38 +/- 5 mumol/l, $P < 0.05$) and albumin-corrected thiol levels (9.91 +/- 0.18 vs. 8.69 +/- 0.20 vs. 8.92 +/- 0.19 mumol/g, $P < 0.05$). The levels of the other antioxidants did not differ significantly between the groups. Levels of von Willebrand factor, a marker of endothelial damage, were correlated with SBP but not with antioxidant status. We conclude that hypertensive subjects have lower levels of the antioxidants vitamin C and thiols and this may reflect greater oxidative consumption. The implications for atherogenesis and endothelial function and integrity in hypertension are discussed.

The role of antioxidants in the prevention of cardiovascular diseases

Ginter E
Ustav preventivnej a klinickej mediciny v Bratislave, Slovakia.
Bratisl Lek Listy (Slovakia) May 1994, 95 (5) p199-211

The potential role of natural antioxidants (vitamin C--ascorbic acid, vitamin E--tocopherols, carotenoids and selenium) in the prevention of cardiovascular diseases is reviewed. It is probable that free oxygen radicals and oxidatively modified particles of low-density lipoproteins (LDL) participate in the development of atherosclerotic lesions. A great number of experimental, cross-sectional, retrospective and prospective epidemiological studies found a substantial increase of the risk of ischemic heart disease and stroke in individuals and populations with low intake of antioxidants from diet. Extremely high cardiovascular mortality in Slovakia and other postcommunist countries could be only partially explained by "classical" risk factors (hypertension, hypercholesterolemia and smoking). In the communist European countries there was a high consumption of spirits, cigarettes and salt, polluted environment and low consumption of the chief source of antioxidants--fruits. In these countries emphasis should be given to the prevention of antioxidant deficiencies by the increase of fruit and vegetable consumption, and to the decrease in salt, spirit, cigarettes and saturated fat consumption. (30 Refs.)

A double-blind, placebo-controlled parallel trial of Vitamin-C treatment in elderly patients with hypertension.

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Gerontology (Switzerland) 1994, 40 (5) p268-72

We have investigated the effect on blood pressure of treatment with vitamin C (an antioxidant and free radical scavenger) in patients with both systolic and essential hypertension. Following a 2-week run-in phase, two age- and sex-matched groups of untreated hypertensive subjects were randomised in a double-blind study to receive 6 weeks' oral treatment with either vitamin C, 250 mg twice daily (n = 22; 8M/14F, mean age 73.7 +/- 4.9 years) or placebo, one capsule twice daily (n = 26; 10M/16F, mean age 73.8 +/- 5.3 years). Blood pressure was measured in the sitting position using a random zero sphygmomanometer on three occasions during the run-in phase, and again at 2, 4 and 6 weeks after commencing treatment. Venous blood samples for measurement of plasma ascorbic acid (AA) and lipid peroxides (LP) were measured in all subjects at baseline and at 4 and 6 weeks after the start of vitamin C or placebo treatment. During the study period, significant falls in both systolic (vitamin C group, mean change -10.3 (95% CI 0.7-20.0) mm Hg, p = 0.05) and diastolic (vitamin C group, mean change -5.9 (95% CI 0.2-11.5) mm Hg, p = 0.03; placebo group, mean change -4.7 (95% CI 0.3-9.1) mm Hg, p = 0.05) blood pressure occurred. However, no statistical difference between the effects of either treatment on blood pressure was observed. At baseline, AA concentrations were lower in the vitamin C-treated group compared with the placebo group (44.6 +/- 2.4 vs. 57.7 +/- 4.2 mumol/l, p < 0.05).(ABSTRACT TRUNCATED AT 250 WORDS)

Essential antioxidants in cardiovascular diseases--lessons for Europe

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Ther Umsch (Switzerland) Jul 1994, 51 (7) p475-82

Complementary epidemiological studies consistently reveal a substantially increased risk of cardiovascular disease (CVD) at suboptimal plasma levels of essential antioxidants in comparison with optimum ranges of vitamin C (> 50 mumol/l), of lipid-standardized vitamin E (> 30 mumol/l or a tocopherol/cholesterol ratio > 5.2 mumol/mmol), beta-carotene (> 0.4 mumol/l). The poor level of any single essential antioxidant can increase the risk, and the combination of suboptimal levels has additive or even overmultiplicative effects on the risk for CVD. Suboptimal antioxidant levels are stronger predictors of the severalfold regional differences of CVD in Europe than classical risk factor such as hypercholesterolemia, hypertension, etc. Scotsmen and Fins tend to suboptimal levels of essential antioxidants, whereas German-speaking regions may mostly reveal a fair vitamin E status, but at least one out of four subjects can reveal suboptimal levels of vitamin C and carotene, particularly in smokers. This deficit can be avoided by 'prudent diets' rich in fruits and vegetables as practiced by Frenchmen, Italians and Spaniards. The simultaneous correction of all suboptimal antioxidant levels appears to be a promising new means for CVD prevention,

particularly in the northern parts of Europe. In the USA the risk of CVD could substantially be reduced without dietary modifications by voluntary daily supplements as follows: vitamin C > 140 mg, vitamin E > 100 IU (100 mg d,l- or 74 mg d-alpha-tocopherylacetate), and in current smokers by gamma-carotene > 8.6 mg. Hence, these antioxidants may be crucial constituents of diets rich in fruits and vegetables, which are by consensus associated with a lower risk of premature death from CVD (and cancer as well).(ABSTRACT TRUNCATED AT 250 WORDS)

Antioxidant vitamin intake and coronary mortality in a longitudinal population study.

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Am J Epidemiol (United States) Jun 15 1994, 139 (12) p1180-9

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, Vitamin-C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of Vitamin-C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection.

Can anti-oxidants prevent ischaemic heart disease?

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J Clin Pharm Ther (England) Apr 1993, 18 (2) p85-95

Ischaemic heart disease remains a major cause of mortality in developed countries. A number of important risk factors for the development of coronary

atherosclerosis have been identified including hypertension, hypercholesterolaemia, insulin resistance and smoking. However, these factors can only partly explain variations in the incidence of ischaemic heart disease either between populations or within populations over time. In addition, population interventions based upon these factors have had little impact in the primary prevention of heart disease. Recent evidence suggests that one of the important mechanisms predisposing to the development of atherosclerosis is oxidation of the cholesterol-rich low-density lipoprotein particle. This modification accelerates its uptake into macrophages, thereby leading to the formation of the cholesterol-laden 'foam cell'. In vitro, low-density lipoprotein oxidation can be prevented by naturally occurring anti-oxidants such as Vitamin-C, vitamin E and beta-carotene. This article explores the evidence that these dietary anti-oxidants may influence the rate of progression of coronary atherosclerosis in vivo and discusses the need for formal clinical trials of anti-oxidant therapy. (90 Refs.)

Anthropometry, lipid- and vitamin status of 215 health-conscious Thai elderly.

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Int J Vitam Nutr Res (Switzerland) 1991, 61 (3) p215-23

A survey was carried out on 59 males and 146 females aged 60 years and above from a special clinic for the elderly in Bangkok. All of these subjects had no major complaints of ill health and, judging by their appearance, they seemed to be apparently healthy. 6.8% of the males and 11% of the females were found to be over-nourished. Less than 15% of all the individuals under investigation were suffering from hypertension, hyperglycaemia and hyperuricaemia. 35% of the males but only 13% of the females were anemic. The lipid status of the females was generally worse with statistically higher median values for total cholesterol, LDL-cholesterol and triglycerides than the males. There was no significant difference in the variation of HDL-cholesterol between the sexes. High Vitamin-C, B2 and B6 deficiency rates were observed in both the males and the females.

Calcium intake: covariates and confounders

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Am J Clin Nutr (United States) Mar 1991, 53 (3) p741-4

One common nutrient postulated to be protective against osteoporosis, hypertension, and colon cancer is dietary calcium. We report here nutrient patterns by calcium intake in older adult residents of a geographically defined community in Southern California. The analysis included all 426 men and 531 women aged 50-79 y with complete 24-h diet data. Nutrient-density-adjusted calcium intake was divided into tertiles: low intake (less than 284 mg/1000 kcal), mid intake (284-440 mg/1000 kcal), and high intake (greater than 440 mg/1000 kcal). The distribution of the reported 24-h nutrient density of protein, fat, fiber, caffeine, trace minerals, vitamin D, and Vitamin-C was examined in relation to the calcium-intake tertiles. In both men and women, the adjusted intakes of protein, saturated fatty acids, vitamin D, magnesium, and phosphorus were significantly higher in the high-calcium-intake group than in the low- and mid-calcium-intake groups. In both men and women, alcohol intake was significantly lower in the high-calcium-intake group. Studies postulating a protective role for calcium will need to consider the multicolinearity in the Western diet.

Nitric oxide and the regulation of blood pressure in the hypertension-prone and hypertension-resistant Sabra rat.

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Hypertension (United States) Sep 1996, 28 (3) p367-71

We examined the role of nitric oxide (NO) in the inherited resistance or susceptibility to hypertension in the Sabra hypertension-prone (SBH) and hypertension-resistant (SBN) rat. Basal mean arterial blood pressure was significantly greater in SBH than in SBN rats. Phenylephrine elevated blood pressure to a similar extent in both substrains, whereas the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) had a greater pressor effect in SBN rats. The vasoconstrictor potency of phenylephrine was significantly higher in endothelium-intact aortic rings from the SBH rat, whereas the vasoconstrictor potency of L-NMMA was higher in those from the SBN substrain. Acetylcholine-induced endothelium-dependent relaxation was greater in aortic rings from SBN rats. The vasodilator potency of glyceryl trinitrate was significantly higher in aortic rings from SBH rats and was enhanced after endothelium removal. Both the activity of calcium-dependent NO synthase from aortic endothelial cells and the basal concentration of nitrite/nitrate in plasma were significantly greater in SBN than in SBH rats. In normotensive Wistar rats, basal mean arterial blood pressure, the pressor effect of L-NMMA, endothelial NO synthase activity, and plasma nitrite/ nitrate concentrations were all between the values in SBH and SBN rats. These results indicate that a decrease in NO generation plays a role in the susceptibility of SBH rats to hypertension. Furthermore, the resistance to hypertension in the SBN strain may be related to increased NO generation.

Serum calcium, magnesium, copper and zinc and risk of cardiovascular death.

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Eur J Clin Nutr (England) Jul 1996, 50 (7) p431-7

OBJECTIVE: To study the association of serum calcium, magnesium, copper and zinc concentrations with cardiovascular mortality.

DESIGN: A nested case-control study within a prospective population study.

SUBJECTS AND METHODS: 230 men dying from cardiovascular diseases and 298 controls matched for age, place of residence, smoking and follow-up time. Mean follow-up time was 10 years. Serum calcium, magnesium, copper and zinc concentrations were determined from samples kept frozen at -20 degrees C.

RESULTS: High serum copper and low serum zinc concentrations were significantly associated with an increased mortality from all cardiovascular diseases and from coronary heart disease in particular. The relative risk of coronary heart disease mortality between the highest and lowest tertiles of serum copper and zinc were 2.86 (P = 0.03) and 0.69 (P = 0.04), respectively. Adjustment for social class, serum cholesterol, body mass index, hypertension and known heart disease at baseline examination did not materially alter the results. No significant differences were observed in concentrations of serum calcium and magnesium between cases and controls.

CONCLUSIONS: High serum copper and low serum zinc are associated with increased cardiovascular mortality whereas no association was found with serum calcium and magnesium and mortality risk.

Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia

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Atherosclerosis (Ireland), 1997, 129/1 (119-126)

Ubiquinol-10, the reduced form of ubiquinone-10 (coenzyme Q10), is a potent lipophilic antioxidant present in nearly all human tissues. The exceptional oxidative lability of ubiquinol-10 implies that it may represent a sensitive index of oxidative stress. The present study was undertaken to assess the hypothesis that the level of ubiquinol-10 in human plasma can discriminate between healthy subjects and patients who are expected to be subjected to an increased oxidative

stress in vivo. Using a newly developed method, we measured plasma ubiquinol-10 in 38 hyperlipidaemic patients with and without further complications, such as coronary heart disease, hypertension, or liver disease, and in 30 healthy subjects. The oxidizability of plasma samples obtained from hyperlipidaemic patients was found to be increased in comparison with control subjects, suggesting that the patients were subjected to a higher oxidative stress in vivo than the controls. Plasma ubiquinol-10, expressed as a percentage of total ubiquinol-10 + ubiquinone-10 or normalized to plasma lipids, was lower in the patients than in controls (P = 0.001 and 0.008, respectively). The proportion of ubiquinol-10 decreased in the order young controls > aged controls > hyperlipidaemic patients without complications > hyperlipidaemic patients with complications (P = 0.003). A negative correlation was found between the proportion of ubiquinol-10 and plasma triglycerides. The hyperlipidaemic patients with hypertension had a lower proportion of ubiquinol-10 than subjects without. When the study population was divided into smokers and non-smokers, plasma ubiquinol-10 was found to be reduced amongst smokers, independently of whether it was expressed as a percentage of total ubiquinol-10 + ubiquinone-10 (P = 0.006) or normalized to plasma lipids (P = 0.009). These data suggest that the level of ubiquinol-10 in human plasma may represent a sensitive index of oxidative stress in vivo especially indicative of early oxidative damage. Measuring plasma ubiquinol-10 can be proposed as a practical approach to assess oxidative stress in humans.

Role of exogenous L-arginine in hepatic ischemia-reperfusion injury

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Journal of Surgical Research (USA), 1997, 69/2 (429-434)

Plasma L-arginine is usually deficient immediately after hepatic reperfusion in orthotopic liver transplantation, which may also contribute to the occurrence of either hepatic ischemia-reperfusion injury or pulmonary hypertension. In this study, exogenous L-arginine was thus experimentally used to reverse the deficient status of the L-arginine/NO pathway. An in vivo model of 1 hr hepatic ischemia and reperfusion was thus tested in both rats (Experiment A) and pigs (Experiment B). In Experiment A, 10 mg/kg of L- arginine (group 1, n = 7), D-arginine (group 2, n = 7), or saline (group 3, n = 7) was administered through the portal vein. The hepatic tissue blood flow, at 20 min after reperfusion, improved in group 1 (70.7 plus or minus 7.0% of the preclamp levels) compared to groups 2 and 3. The serum glutamate oxaloacetate transaminase levels at 24 hr after reperfusion were also lower in group 1 (320 plus or minus 22.2 IU/L) than in either group 2 or group 3. The intrahepatic NO levels showed a temporal burst (>15,000 pA current) after reperfusion only in group 1. In Experiment B, 10 mg/kg of L-arginine (group 4, n 5), D-arginine (group 5, n= 5), or 10 ml of saline (group 6, n= 5) was administered through the portal vein. In group 4, the MPAP (mean pulmonary arterial pressure)/MAP (mean arterial pressure) was lower than that

observed in groups 5 and 6. In conclusion, exogenous L-arginine administered from the portal vein was thus found to be effective in mitigating both portal hypertension and reperfusion injury by producing an increased amount of NO immediately after reperfusion.

Effects of taurine and guanidinoethane sulfonate on toxicity of the pyrrolizidine alkaloid monocrotaline

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Biochemical Pharmacology (USA), 1996, 51/3 (321-329)

Monocrotaline (MONO), a pyrrolizidine alkaloid, causes pulmonary ial hypertension and right ventricular hypertrophy due to hepatic metabolism to the alkylating pyrrole dehydromonocrotaline. Taurine, a sulfonic amino acid, is hepato- and cardioprotective in a variety of conditions. We have examined the effects of taurine and its amidino analog, guanidinoethane sulfonate (GES), in rats injected i.p. with MONO (65 mg/kg). Taurine and GES were given as 1% solutions in drinking water beginning 14 days before administration of MONO and continuing for 14 days thereafter, when the rats were killed. The MONO group had right ventricular hypertrophy and pulmonary hyperplasia. Compared with control, no significant changes in the right ventricle/left ventricle weight ratio, or the right ventricle/body weight ratio occurred in rats also given taurine or GES. Lung weights in these two groups were higher than in the control group, but below that of the MONO-alone group. The lethality of MONO over 14 days was decreased by taurine (LD50 for MONO alone 80 mg/kg; for MONO + taurine 121 mg/kg). Rats given only MONO had lower hepatic concentrations of GSH and cysteine (Cys), and higher activities of microsomal GSH transferase and gamma-glutamyl transpeptidase. In rats also receiving taurine, hepatic GSH levels and GSH transferase activity were no different from control. gamma-Glutamylcysteine (Glu-Cys) synthetase and gamma-glutamyl transpeptidase activities were elevated. In MONO-injected rats given GES, hepatic GSH levels were higher and Cys levels were lower than in either the MONO alone or MONO + taurine groups. gamma-Glu-Cys synthetase activity was depressed. Microsomal GSH transferase, GSH peroxidase and gamma-glutamyl transpeptidase activities were elevated. Livers of MONO-injected animals showed higher levels of serine (reversed by both taurine and GES) and glycine (Gly; reversed by GES) and lower levels of glutamine. Compared with control rats, the following changes occurred in serum amino acids: MONO alone: increased aspartate, taurine and lysine; taurine-supplemented: increased taurine, methionine (Met) and lysine, and decreased Gly; GES-supplemented: decreased asparagine, serine, Gly, arginine, taurine, and valine. Compared with the MONO-alone group, the taurine-supplemented group had higher glutamate (Glu), Met and alanine, and the GES-supplemented group higher alanine and lower serine, Gly, arginine and valine. We conclude that taurine protects against MONO-induced lethality and right ventricular hypertrophy. GES also protects against right ventricular hypertrophy.

However, these agents act by different mechanisms, taurine preventing many of the biochemical changes induced by MONO, with GES inducing additional changes.

The Inuit diet. Fatty acids and antioxidants, their role in ischemic heart disease, and exposure to organochlorines and heavy metals. An international study.

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Arctic Med Res (Finland) 1996, 55 Suppl 1 p20-4

Traditional food is culturally, economically and nutritionally important for the Greenlandic Inuit people. In the 1970s the preventive effect of marine fat on cardiovascular disease, thrombosis and atherosclerosis was described. The low incidence of ischemic heart disease among Greenlanders has been related to the high intake of marine food. Since 1990 routine autopsies have taken place in two towns in Greenland, Nuuk and Ilulissat. The autopsies represent 26% of the total number of deaths in these two towns. Samples have been collected from 104 autopsies. International cooperative studies have analysed specimens in relation to ischemic heart disease as a benefit related to diet, as well as the level of heavy metals and organochlorine in organs as a risk related to diet. High amounts of mono-unsaturated and Omega-3 poly-unsaturated fatty acid were found in adipose tissue. Liver analyses of selenium have confirmed the expected high intake among Greenlanders. Reduced atherosclerotic lesions were found in the coronary arteries. Blood pressure levels calculated from renovascholopathia of hypertension indicate prevailing levels similar to those in industrialized countries. Some factors in Greenland may be protecting the coronary arteries, thereby of setting the expected effect of hypertension. The level of methyl mercury in organs is generally high. PCB concentrations found in organs of Greenlanders are higher than among other populations. Health and risk effects of the traditional foods need further investigation.

Renal denervation prevents intraglomerular platelet aggregation and glomerular injury induced by chronic inhibition of nitric oxide synthesis.

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Nephron (Switzerland) 1996, 73 (1) p34-40

Nitric oxide (NO) inhibits platelet adhesion and aggregation in vitro. In vivo, chronic inhibition of NO synthesis induces nephrosclerosis and hypertension.

Although the pathophysiological mechanism of this glomerular injury has not been clarified, sympathetic nerve activation, a potent procoagulant stimulus elicited by NO inhibition, may play a role. To investigate the role of renal sympathetic nerves in the development of renal injury induced by NG-nitro-L-arginine methyl ester (L-NAME), a specific NO synthesis inhibitor, we examined renal histological changes in four groups of Sprague-Dawley rats: (1) sham operated, vehicle treated; (2) sham operated, L-NAME treated; (3) denervated, vehicle treated, and (4) denervated, L-NAME treated. Following renal denervation or sham operation, L-NAME was administered orally for 4 weeks. Chronic NO inhibition induced platelet aggregation and erythrocyte stasis in the glomerular capillary lumen accompanied by electron-microscopic glomerular injury. Renal denervation abrogated platelet aggregation and glomerular injury in L-NAME-treated animals. Thus, chronic NO synthesis inhibition induced intraglomerular platelet aggregation and glomerular injury, which was attenuated by renal nerve denervation. These results suggest that intrinsic NO may have an antithrombotic effect in the glomeruli and may play a protective role in the progression of glomerular injury possibly mediated by renal sympathetic nerves.

Central depressor action of nitric oxide is deficient in genetic hypertension.

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Am J Hypertens (United States) Mar 1996, 9 (3) p237-41

Inhibition of NO synthase (NOS) in the central nervous system (CNS) causes a pressor response. This observation indicates that NO is normally produced at CNS site(s) where it has a tonic blood pressure lowering effect. The current study tests the hypothesis that a deficient NOS activity in the CNS may contribute to the pressure elevation in genetically hypertensive rats. NO administered intracerebroventricularly (ICV) caused a greater fall in mean arterial pressure (MAP; femoral artery) in hypertensive (SHRSP) than in normotensive (WKY) rats, -66.1 +/- 3.4 mm Hg v -23.7 +/- 3.9 mm Hg, respectively. Yet when endogenous NO was increased by stimulating NOS with ICV calcium, the depressor response was less in SHRSP than in WKY, 13.7 +/- 1.1 mm Hg v 26.7 +/- 1.9 mm Hg. Likewise, when NOS was blocked with N omega- nitro-L-arginine methyl ester (L-NAME), the resultant pressor response was less in SHRSP than in WKY, 13.8 +/- 1.1 mm Hg v 22.2 +/- 1.1 mm Hg. Blockade of the action of cGMP, a mediator of the action of NO, caused a pressor response of 6.0 +/- 2.8 mm Hg and 22.6 +/- 8.7 mm Hg ($P < .01$) in the hypertensive and normotensive rats, respectively. Electrolytic ablation of the anteroventral third cerebral ventricle (AV3V) did not alter blood pressure responses to NO or to agents that alter NOS activity. We conclude that a deficit in NOS activity in some other central cardiovascular regulatory area may contribute to the elevated arterial pressure of these genetically hypertensive rats.

Effect of salt intake and inhibitor dose on arterial hypertension and renal injury induced by chronic nitric oxide blockade.

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Hypertension (United States) May 1996, 27 (5) p1165-72

Long-term nitric oxide blockade by N omega -nitro-L-arginine methyl ester (L-NAME) leads to severe and progressive hypertension. The role of salt intake in this model is unclear. To verify whether salt dependence in this model is related to the extent of nitric oxide inhibition, we gave adult male Munich-Wistar rats a low salt, standard salt, or high salt diet and oral L-NAME treatment at either 3 or 25 mg/kg per day. At 10 to 15 days of treatment, the slope of the pressure-natriuresis line was decreased in rats receiving low-dose L-NAME compared with untreated controls. In rats treated with the higher dose, the line was shifted to the right but remained parallel to that obtained in untreated controls. Renal vascular resistance was moderately increased in rats receiving low-dose L-NAME, whereas high-dose L-NAME induced a marked vasoconstriction that was aggravated by salt overload. Low-dose L-NAME treatment induced hypertension only when associated with sodium overload. In rats receiving high-dose L-NAME, hypertension was aggravated by sodium excess but was not ameliorated by sodium restriction. Long-term (6 weeks) L-NAME treatment was associated with progressive hypertension, which was aggravated by salt overload, and with the development of albuminuria, focal glomerular collapse, glomerulosclerosis, and renal interstitial expansion. These abnormalities were worsened by salt overload and largely prevented by salt restriction. In the model of chronic nitric oxide blockade, salt dependence is a function of the inhibitor dose, and renal injury varies directly with the level of salt intake.

Role of nitric oxide in the maintenance of resting cerebral blood flow during chronic hypertension.

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Life Sci (England) 1996, 58 (15) p1231-8

The influence of nitric oxide (NO) on basal vascular tone varies with different hypertensive models or vascular beds. The goal of the present study was to examine the role of NO in the maintenance of resting cerebral blood flow (CBF)

during chronic hypertension. In 9-10 months old Wistar-Kyoto (WKY) rats (n=47) and spontaneously hypertensive rats (SHR;n=47) anesthetized with pentobarbital sodium (60 mg/kg i.p.), regional CBF of the right parietal cortex was monitored by laser-Doppler flowmetry. Reductions in CBF in response to intravenous infusion of the NO synthase inhibitor N(omega)-nitro-L-arginine methyl ester (L-NAME; 1, 3, 10, and 30 mg/kg) were similar between WKY rats (17 +/- 6 approximately 43 +/- 6%; means +/- SE) and SHR (15 +/- 6 approximately 48 +/- 6%) while arterial blood pressure was maintained on the baseline level by controlled hemorrhage. Effects of L-NAME (3 mg/kg i.v.) on arterial blood pressure and CBF were almost completely inhibited by L-arginine (300 mg/kg i.v.), but not by D-arginine (300 mg/kg i.v.). In addition, intravenous infusion of L-arginine (300 mg/kg) alone did not affect resting CBF in both WKY rats and SHR. Thus, these findings suggest that 1) NO plays an important role in the maintenance of resting CBF in both normotensive and chronically hypertensive rats and 2) the contribution of NO to the maintenance of resting CBF is not altered during chronic hypertension.

Endothelial function in deoxycorticosterone-NaCl hypertension: effect of calcium supplementation.

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Circulation (United States) Mar 1 1996, 93 (5) p1000-8

BACKGROUND: Dietary calcium intake has been suggested to correlate inversely with blood pressure in humans and experimental animals. However, the effects of calcium supplementation on hypertensive disturbances of the endothelium have not been well characterized.

METHODS AND RESULTS: Wistar-Kyoto rats made hypertensive by deoxycorticosterone (DOC)-NaCl treatment, but a concurrent increase in chow calcium content from 1.1% to 2.5% markedly attenuated the rise in blood pressure. The function of isolated mesenteric arterial rings in vitro was investigated at the close of the 10-week study. In norepinephrine-precontracted rings, the relaxations to acetylcholine (ACh) and ADP, as well as to nitroprusside, 3-morpholinosydnonimine, and isoproterenol were attenuated in hypertensive rats on 1.1% calcium supplementation. In the presence of NG-nitro-L-arginine methyl ester (L-NAME), the relaxations to ACh in hypertensive animals on normal calcium were practically absent, whereas in normotensive rats and calcium-supplemented hypertensive rats, distinct relaxations to higher concentrations of ACh were still present. These responses were reduced by 30% to 50% with apamin, a blocker of Ca2+-activated K+ channels, and were further inhibited by blockade of ATP-dependent K+ channels with glyburide. Interestingly, relaxations elicited by ACh and ADP during precontraction with 60 mmol/L KCl (preventing endothelium-dependent hyperpolarization) were not impaired in hypertensive animals. The contractile sensitivity of endothelium-intact arterial rings to 5-hydroxytryptamine and norepinephrine was higher in hypertensive rats

on either normal or high-calcium diet, whereas the increase in contractile sensitivity caused by L-NAME corresponded in all groups.

CONCLUSION: High-calcium diet markedly opposed experimental DOC-NaCl hypertension, an effect associated with improved arterial relaxation, while abnormalities of vascular contractile properties remained unaffected. In particular, the hyperpolarization-related component of endothelium-dependent arterial relaxation, mediated via opening of arterial K+ channels, could be augmented by calcium supplementation in DOC-NaCl hypertension.

Vitamin-C status and blood pressure.

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J Hypertens (England) Apr 1996, 14 (4) p503-8

OBJECTIVE: To examine the cross-sectional relationship between blood pressure and plasma Vitamin-C.

DESIGN: A cross-sectional analysis.

SETTING: A population-based study. SUBJECTS: The subjects were 835 men and 1025 women aged 45-75 years registered with general practices in Norfolk.

INTERVENTIONS: Completion of health and lifestyle questionnaire and attendance for a health check.

MAIN OUTCOME MEASURES: Diastolic blood pressure (DBP), systolic blood pressure (SBP) and plasma Vitamin-C level.

RESULTS: The mean SBP was 135.8 +/- 18.5 mmHg (mean +/- SD) and the mean DBP was 82.5 +/- 11.3 mmHg. The mean plasma vitamin C level was 52.6 +/- 19.7 mumol/l. The plasma Vitamin-C level was negatively correlated both with SBP and with DBP. These correlations persisted after adjustment for age, sex and body mass index. Adjusting for other confounders including cigarette smoking, physical activity and alcohol intake did not alter the observed association. Exclusion of subjects taking vitamin supplements and those with known hypertension did not affect the results. The differences in SBP and in DBP for a 50 mumol/l difference in Vitamin-C, estimated using linear regression, were -3.6 and -2.6 mmHg, respectively.

CONCLUSIONS: The plasma Vitamin-C level may be a marker of other factors; nevertheless, these results are consistent with other published work indicating that a high intake of Vitamin-C from food confers protection against raised blood pressure and strokes.

[Evaluation of selected parameters of zinc metabolism in patients with primary hypertension]

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Pol Arch Med Wewn (Poland) Mar 1996, 95 (3) p198-204

The aim of the study was to investigate the role of zinc (Zn) in essential hypertension (EH).

PATIENTS AND METHODS: Material of the study consisted of 31 patients (12 female, 19 male) with mild and moderate EH and 20 healthy persons (NT) (7 female, 13 male). Erythrocyte (ZnE) and serum (ZnS) zinc as well as 24 hour urinary zinc excretion (ZuU) were assessed in both groups. Zn parameters were measured by atomic absorption spectrophotomery.

RESULTS: ZnS was lower and ZnE was higher in EH ($p < 0.001$) than in normotensives. ZnU did not differ between EH and NT. ZnE and ZnS negatively correlated with age in NT but not in EH, ZnU negatively correlated with age only in EH. BP positively correlated with ZnS in EH but not in NT. In both groups negative correlations were found between BP and ZnU.

CONCLUSIONS: 1. Zinc probably plays a role in pathogenesis of essential hypertension.

L-arginine prevents corticotropin-induced increases in blood pressure in the rat.

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Hypertension (United States) Feb 1996, 27 (2) p184-9

In this study we examined whether L-arginine treatment could prevent corticotropin (ACTH)-induced increases in blood pressure in the Sprague-Dawley rat. Sixty rats were randomly divided into six groups (n = 10): sham injection, ACTH injection (0.5 mg/kg per day in divided doses), L-arginine (0.6%) in food plus sham injection, L-arginine plus ACTH treatment, D-arginine (0.6%) in food plus sham injection, and D-arginine plus ACTH. Systolic pressure, water intake, urine volume, body weight, plasma and urinary electrolytes, and serum corticosterone concentrations were measured. ACTH increased systolic pressure (from 127 +/- 2 to 165 +/- 6 mm Hg, $P < .001$), water intake, and urine volume and decreased body weight body weight. L-Arginine reduced ACTH-induced blood pressure rises (130 +/- 3 mm Hg, $P < .001$) but had no effect on blood pressure in sham-treated rats. D-Arginine did not affect blood pressure in sham-treated rats, and systolic pressure in D-arginine+ACTH-treated rats was similar to

that of ACTH-treated rats. L-Arginine decreased serum corticosterone concentrations in sham-treated rats (424 +/- 42 versus 238 +/- 25 ng/mL, P < .01), but D-arginine had no effect. However, both drugs decreased serum corticosterone concentrations in ACTH-treated rats (1071 +/- 117 versus 739 +/- 95 and 695 +/- 72 ng/mL for L- and D-arginine, respectively; both P < .05). As L-arginine but not D-arginine prevented ACTH-induced increases in blood pressure in Sprague-Dawley rats and both L- and D-arginine reduced serum corticosterone concentrations in ACTH-treated rats, the effects of L-arginine in preventing ACTH-induced hypertension were not simply a consequence of decreased corticosterone secretion.

Improvement of cardiac output and liver blood flow and reduction of pulmonary vascular resistance by intravenous infusion of L-arginine during the early reperfusion period in pig liver transplantation.

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Transplantation (United States) May 15 1997, 63 (9) p1225-33

BACKGROUND: The release of liver arginase after orthotopic liver transplantation (OLT) causes a deficiency of L-arginine and nitrite in the plasma. This deficiency is possibly related to pulmonary hypertension and reduced hepatic blood flow, which are commonly observed in the immediate reperfusion period. The aim of this study was to evaluate the impact of L-arginine supplementation on metabolic and hemodynamic parameters during liver reperfusion after OLT in pigs.

METHODS: Thirteen pig OLTs (control group, n=6; arginine group, n=7) were performed by a standard technique. Cold ischemic time was 20 hr. L-Arginine was infused at a dosage of 500 mg/kg body weight into the donor pigs (30 min before liver explantation) and also into the recipients (over a period of 3 hr from the beginning of the reperfusion period). At the end of the experimental study, the pigs were killed with an overdose of potassium.

RESULTS: In the control group, liver revascularization increased plasma arginase concentrations (+615%) and reduced plasma levels of L-arginine (-87%), nitrite (-82%), and nitrate (-53%). Infusion of L-arginine increased plasma levels of L-arginine from 94+/-21 micromol/L to 1674+/-252 micromol/L (P<0.001), L-ornithine from 46+/-8 micromol/L to 2215+/-465 micromol/L (P<0.001), and L-citrulline from 58+/-8 micromol/L to 116+/-34 micromol/L (P<0.001), but had no effect on plasma levels of nitrite and nitrate. Administration of L-arginine in the donor pigs did not produce any systemic or organ-specific hemodynamic alterations. Infusion of L-arginine into the recipient pigs improved cardiac performance (increase in heart rate [+61%, P=0.017] and cardiac index [+53%, P=0.005], reduction in pulmonary capillary wedge pressure [-54%, P=0.014]). Moreover L-arginine infusion increased oxygen consumption (+65%, P=0.003),

reduced pulmonary vascular resistance index (P=0.001), stimulated portal venous blood flow (P=0.014), and elevated body temperature during the reperfusion period (P=0.007).

CONCLUSIONS: From these data, we conclude that the infusion of L-arginine during OLT improves the hemodynamic performance of the heart, lung, and liver.

Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium

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Am J Hypertens (United States) Mar 1997, 10 (3) p346-55

Magnesium is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular magnesium concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In fact, in vitro and in vivo studies have demonstrated that insulin may modulate the shift of magnesium from extracellular to intracellular space. Intracellular magnesium concentration has also been shown to be effective on modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation-contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli, by stimulating Ca2+-dependent K+ channels. A poor intracellular magnesium concentration, as found in non-insulin-dependent diabetes mellitus (NIDDM) and in hypertensive (HP) patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance in non-insulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily magnesium administration, restoring a more appropriate intracellular magnesium concentration, contributes to improve insulin-mediated glucose uptake. Similarly, in HP patients magnesium administration may be useful in decreasing arterial blood pressure and improving insulin-mediated glucose uptake. The benefits deriving from daily magnesium supplementation in NIDDM and HP patients are further supported by epidemiological studies showing that high daily magnesium intake to be predictive of a lower incidence of NIDDM and HP. In conclusion, a growing body of studies suggest that intracellular magnesium may play a key role on modulating insulin-mediated glucose uptake and vascular tone. We further suggest that a reduced intracellular magnesium concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension. (74 Refs.)

Prevention of preeclampsia with calcium supplementation and its relation with the L-arginine:nitric oxide pathway.

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Braz J Med Biol Res (Brazil) Jun 1996, 29 (6) p731-41

Pregnancy-induced hypertension (PIH) remains a common cause of maternal and fetal morbidity and mortality. During the past 7 years, some progress has been made in the prevention of PIH. Specifically, clinical studies have shown that supplementation with calcium can significantly reduce the frequency of PIH, especially in populations with a low calcium intake. We have suggested that, in such a population, calcium supplementation is a safe and effective measure for reducing the incidence of PIH. Calcium supplementation reduces the risk of PIH by maintaining the serum ionized calcium level which is crucial for the production of endothelial nitric oxide, the increased generation of which maintains the vasodilatation that is characteristic of normal pregnancy. In PIH there is an impaired nitric oxide synthesis and cyclic GMP production. (99 Refs.)

19. Influenza Virus (Flu)

Preventative and curative options include:

Echinacea , sambucol, DHEA, multi nutrients, garlic, lactoferrin , alpha-lipoic acid, green tea, vitamin C, whey protein, curcumin, melatonin.

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines.

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Eur Cytokine Netw 2001 Apr-Jun;12(2):290-6

Sambucus nigra L. products - Sambucol - are based on a standardized black elderberry extract. They are natural remedies with antiviral properties, especially against different strains of influenza virus. Sambucol was shown to be effective in vitro against 10 strains of influenza virus. In a double-blind, placebo-controlled, randomized study, Sambucol reduced the duration of flu symptoms to 3-4 days. Convalescent phase serum showed a higher antibody level to influenza virus in the Sambucol group, than in the control group. The present study aimed to assess the effect of Sambucol products on the healthy immune system - namely, its effect on cytokine production. The production of inflammatory cytokines was tested using blood - derived monocytes from 12 healthy human donors. Adherent monocytes were separated from PBL and incubated with different Sambucol preparations i.e., Sambucol Elderberry Extract, Sambucol Black Elderberry Syrup, Sambucol Immune System and Sambucol for Kids. Production of inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, IL-8) was significantly increased, mostly by the Sambucol Black Elderberry Extract (2-45 fold), as compared to LPS, a known monocyte activator (3.6-10.7 fold). The most striking increase was noted in TNF-alpha production (44.9 fold). We conclude from this study that, in addition to its antiviral properties, Sambucol Elderberry Extract and its formulations activate the healthy immune system by increasing inflammatory cytokine production. Sambucol might therefore be beneficial to the immune system activation and in the inflammatory process in healthy individuals or in patients with various diseases. Sambucol could also have an immunoprotective or immunostimulatory effect when administered to cancer or AIDS patients, in conjunction with chemotherapeutic or other treatments. In view of the increasing popularity of botanical supplements, such studies and investigations in vitro, in vivo and in clinical trials need to be developed.

Prospects of the clinical utilization of melatonin.

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Biol Signals Recept (Switzerland) Jul-Aug 1998, 7 (4) p195-219

This review summarizes the present knowledge on melatonin in several areas on physiology and discusses various prospects of its clinical utilization. Ever increasing evidence indicates that melatonin has an immuno-hematopoietic role. In animal studies, melatonin provided protection against gram-negative septic shock, prevented stress-induced immunodepression, and restored immune function after a hemorrhagic shock. In human studies, melatonin amplified the antitumoral activity of interleukin-2. Melatonin has been proven as a powerful cytostatic drug in vitro as well as in vivo. In the human clinical field, melatonin appears to be a promising agent either as a diagnostic or prognostic marker of neoplastic diseases or as a compound used either alone or in combination with the standard cancer treatment. Utilization of melatonin for treatment of rhythm disorders, such as those manifested in jet lag, shift work or blindness, is one of the oldest and the most successful clinical application of this chemical. Low doses of melatonin applied in controlled-release preparation were very effective in improving the sleep latency, increasing the sleep efficiency and rising sleep quality scores in elderly, melatonin-deficient insomniacs. In the cardiovascular system, melatonin seems to regulate the tone of cerebral arteries; melatonin receptors in vascular beds appear to participate in the regulation of body temperature. Heat loss may be the principal mechanism in the initiation of sleepiness caused by melatonin. The role of melatonin in the development of migraine headaches is at present uncertain but more research could result in new ways of treatment. Melatonin is the major messenger of light-dependent periodicity, implicated in the seasonal reproduction of animals and pubertal development in humans. Multiple receptor sites detected in brain and gonadal tissues of birds and mammals of both sexes indicate that melatonin exerts a direct effect on the vertebrate reproductive organs. In a clinical study, melatonin has been used successfully as an effective female contraceptive with little side effects. Melatonin is one of the most powerful scavengers of free radicals. Because it easily penetrates the blood-brain barrier, this antioxidant may, in the future, be used for the treatment of Alzheimer's and Parkinson's diseases, stroke, nitric oxide, neurotoxicity and hyperbaric oxygen exposure. In the digestive tract, melatonin reduced the incidence and severity of gastric ulcers and prevented severe symptoms of colitis, such as mucosal lesions and diarrhea.

Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects.

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Lancet. 1992 Nov 7;340(8828):1124-7

Ageing is associated with impaired immune responses and increased infection-related morbidity. This study assessed the effect of physiological amounts of

vitamins and trace elements on immunocompetence and occurrence of infection-related illness. 96 independently living, healthy elderly individuals were randomly assigned to receive nutrient supplementation or placebo. Nutrient status and immunological variables were assessed at baseline and at 12 months, and the frequency of illness due to infection was ascertained. Subjects in the supplement group had higher numbers of certain T-cell subsets and natural killer cells, enhanced proliferation response to mitogen, increased interleukin-2 production, and higher antibody response and natural killer cell activity. These subjects were less likely than those in the placebo group to have illness due to infections (mean [SD] 23 [5] vs 48 [7] days per year, $p = 0.002$). Supplementation with a modest physiological amount of micronutrients improves immunity and decreases the risk of infection in old age.

Natural killer cells from aging mice treated with extracts from Echinacea purpurea are quantitatively and functionally rejuvenated.

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Exp Gerontol 2000 Aug;35(5):627-39

A growing body of anecdotal evidence in young and adult humans suggests that certain phytochemicals have the capacity to ameliorate tumors and reduce infections, especially those mediated by virus, in vivo. These indications prompted us, therefore, to investigate the potentially immuno-stimulating effect of one such phytocompound, Echinacea purpurea, on natural killer (NK) cells since these cells are active in spontaneous, non-specific immunity against neoplasms and virus-mediated infections. We elected to study aging mice, since, at this stage of life, like humans, the above-mentioned afflictions increase in frequency. We had previously found that neither the cytokine, interleukin-2, nor the pharmacological agent, indomethacin, both potent stimulators of NK cell numbers/function in younger adult mice, was effective in stimulating NK cells in elderly mice. The present study was designed to assess the numbers/production of NK cells in the spleen and bone marrow of aging, normal mice, after in vivo dietary administration of E. purpurea (14 days), or, after injection of thyroxin, a stimulant of NK cell function (10 days). Immunoperoxidase labeling techniques, coupled with hematologic tetrachrome staining were used to identify NK cells in both the spleen (primary site of NK cell function) and the bone marrow (site of NK cell generation). Double immunofluorscence staining,employing propidium iodide, was used to assess NK cell lytic function. Our results revealed that E. purpurea, but not thyroxin, had the capacity to increase NK cell numbers, in aging mice, reflecting increased new NK cell production in their bone marrow generation site, leading to an increase in the absolute numbers of NK cells in the spleen, their primary destiny. The E. purpurea-mediated increase in NK cell numbers was indeed paralleled by an increase in their anti-tumor, lytic functional capacity. Collectively, the data indicate that E. purpurea, at least, and possibly other plant compounds, appear to contain phytochemicals capable of stimulating de novo production of NK cells, as well as augmenting their cytolytic function, in animals of advanced age.

Therapeutic potential of glutathione.

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Wien Klin Wochenschr 2000 Jul 28;112(14):610-6

Reactive oxygen species, formed in various biochemical reactions, are normally scavenged by antioxidants. Glutathione in its reduced form (GSH) is the most powerful intracellular antioxidant, and the ratio of reduced to oxidised glutathione (GSH:GSSG) serves as a representative marker of the antioxidative capacity of the cell. Several clinical conditions are associated with reduced GSH levels which as a consequence can result in a lowered cellular redox potential. GSH and the redox potential of the cell are components of the cell signaling system influencing the translocation of the transcription factor NF kappa B which regulates the synthesis of cytokines and adhesion molecules. Therefore, one possibility to protect cells from damage caused by reactive oxygen species is to restore the intracellular glutathione levels. Cellular GSH concentration can be influenced by exogenous administration of GSH (as intravenous infusion or as aerosol), of glutathione esters or of GSH precursors such as glutamine or cysteine (in form of N-acetyl-L-cysteine, alpha-lipoic acid). The modulation of GSH metabolism might present a useful adjuvant therapy in many pathologies such as intoxication, diabetes, uremia, sepsis, inflammatory lung processes, coronary disease, cancer and immunodeficiency states.

Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial.

Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. Scientific and Technical Institute for Foods and Nutrition, Conservatiore National des Arts et Mettiers, Paris, France.

Arch Intern Med. 1999 Apr 12;159(7):748-54

BACKGROUND: Antioxidant supplementation is thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables.

OBJECTIVE: To determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people.

METHODS: This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo within a 2 x 2 factorial design for 2 years.

MAIN OUTCOME MEASURES: Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality.

RESULTS: Correction of specific nutrient deficiencies was observed after 6 months of supplementation and was maintained for the first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or associated with vitamins, whereas the vitamin group had significantly lower antibody titers ($P<.05$). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements ($P = .06$). Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the 2 years did not show any differences between the 4 groups.

CONCLUSIONS: Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.

Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial.

Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget AL, Arnaud J, Preziosi P, Hercberg S. Institut Scientifique et Technique de la Nutrition et de l'Alimentation, Paris, France.

Ann Nutr Metab. 1997;41(2):98-107

To determine the impact of a trace element and vitamin supplementation on infectious morbidity, a double-blind controlled trial was performed on 81 elderly subjects in a geriatric center during a 2-year period. Subjects were randomly assigned to one of four treatment groups, and received daily: placebo; trace elements/zinc 20 mg; selenium 100 micrograms); vitamins (vitamin C 120 mg; beta-carotene 6 mg; alpha-tocopherol 15 mg); or a combination of trace elements and vitamins at equal doses. (1) Before supplementation, low serum values in vitamin C, folate, zinc and selenium were observed in more than two thirds of the patients. (2) After 6 months of supplementation, a significant increase in vitamin and trace element serum levels was obtained in the corresponding treatment groups: a plateau was then observed for the whole study. (3) Subjects who received trace elements (zinc and selenium) alone or associated with vitamins had significantly less infectious events during the 2 years of supplementation. These results indicate that supplementation with low doses of vitamins and trace elements is able to rapidly correct corresponding deficiencies in the institutionalized elderly. Moreover, zinc and selenium reduced infectious events.

The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections.

Gorton HC, Jarvis K.

J Manipulative Physiol Ther 1999 Oct;22(8):530-3

BACKGROUND: An ever increasing demand to evaluate the effect of dietary supplements on specific health conditions by use of a "significant scientific" standard has prompted the publication of this study.

OBJECTIVE: To study the effect of mega dose Vitamin C in preventing and relieving cold and flu symptoms in a test group compared with a control group.

DESIGN: Prospective, controlled study of students in a technical training facility.

SUBJECTS: A total of 463 students ranging in age from 18 to 32 years made up the control group. A total of 252 students ranging in age from 18 to 30 years made up the experimental or test group.

METHOD: Investigators tracked the number of reports of cold and flu symptoms among the 1991 test population of the facility compared with the reports of like symptoms among the 1990 control population. Those in the control population reporting symptoms were treated with pain relievers and decongestants, whereas those in the test population reporting symptoms were treated with hourly doses of 1000 mg of Vitamin C for the first 6 hours and then 3 times daily thereafter. Those not reporting symptoms in the test group were also administered 1000-mg doses 3 times daily.

RESULTS: Overall, reported flu and cold symptoms in the test group decreased 85% compared with the control group after the administration of megadose Vitamin C.

CONCLUSION: Vitamin C in megadoses administered before or after the appearance of cold and flu symptoms relieved and prevented the symptoms in the test population compared with the control group.

Antimicrobial properties of Allium sativum (garlic).

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Appl Microbiol Biotechnol 2001 Oct;57(3):282-6

Although garlic has been used for its medicinal properties for thousands of years, investigations into its mode of action are relatively recent. Garlic has a wide spectrum of actions; not only is it antibacterial, antiviral, antifungal and antiprotozoal, but it also has beneficial effects on the cardiovascular and immune systems. Resurgence in the use of natural herbal alternatives has brought the use of medicinal plants to the forefront of pharmacological investigations, and many new drugs are being discovered. This review aims to address the historical use of garlic and its sulfur chemistry, and to provide a basis for further research into its antimicrobial properties.

Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing interleukin-12 production in macrophages.

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Br J Pharmacol 1999 Sep;128(2):380-4

1 Interleukin-12 (IL-12) plays a central role in the immune system by driving the immune response towards T helper 1 (Th1) type responses which are characterized by high IFN-gamma and low IL-4 production. In this study we investigated the effects of curcumin, a natural product of plants obtained from Curcuma longa (turmeric), on IL-12 production by mouse splenic macrophages and the subsequent ability of these cells to regulate cytokine production by CD4+ T cells. 2 Pretreatment with curcumin significantly inhibited IL-12 production by macrophages stimulated with either lipopolysaccharide (LPS) or head-killed Listeria monocytogenes (HKL). 3 Curcumin-pretreated macrophages reduced their ability to induce IFN-gamma and increased the ability to induce IL-4 in Ag-primed CD4+ T cells. Addition of recombinant IL-12 to cultures of curcumin-pretreated macrophages and CD4+ T cells restored IFN-gamma production in CD4+ T cells. 4 The in vivo administration of curcumin resulted in the inhibition of IL-12 production by macrophages stimulated in vitro with either LPS or HKL, leading to the inhibition of Th1 cytokine profile (decreased IFN-gamma and increased IL-4 production) in CD4+ T cells. 5 These findings suggest that curcumin may inhibit Th1 cytokine profile in CD4+ T cells by suppressing IL-12 production in macrophages, and points to a possible therapeutic use of curcumin in the Th1-mediated immune diseases.

Melatonin administration and pituitary hormone secretion.

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Clin Endocrinol (Oxf) 1998 Jan;48(1):31-7

OBJECTIVE: The relationship between the pineal gland and pituitary function remains controversial, while the role of melatonin in the adaptation of the organism to the light-dark cycle of the environment is becoming increasingly recognized. The aim of this study was to investigate the effect of a manipulation of the melatonin rhythm on pituitary hormone secretion in man.

DESIGN: Double-blind controlled clinical study.

SUBJECTS: Ten adult healthy male volunteers, aged 21-33 years, were studied on two occasions: once after the administration of melatonin 5 mg orally for 4 days at 1700 hours and once after the administration of placebo, at similar times. On the day of each study the subjects undertook their normal duties but refrained from taking heavy exercise, from smoking and drinking alcohol.

MEASUREMENTS: Serum cortisol, growth hormone, prolactin and plasma vasopressin, oxytocin, melatonin, sodium, potassium, osmolality and packed cell volume were measured over the following 24 hours.

RESULTS: The cortisol peak was advanced and prolactin release increased after melatonin administration, while growth hormone was not affected. Vasopressin and oxytocin levels were found to increase during the night in the control study, but the period of the nocturnal increase in vasopressin concentrations was reduced after the administration of melatonin and the nocturnal increase of oxytocin was absent.

CONCLUSION: Altering the melatonin rhythm may affect neuroendocrine function, influencing the nocturnal pattern of neurohypophysial hormone secretion, augmenting prolactin release and advancing the peak of cortisol release.

Immunomodulatory effects of aged garlic extract.

Kyo E, Uda N, Kasuga S, Itakura Y. Healthcare Research Institute, Wakunaga Pharmaceutical Company, Ltd., Koda-cho, Takata-gun, Hiroshima 739-1195, Japan.

J Nutr 2001 Mar;131(3s):1075S-9S

Using various kinds of models, we examined the effects of aged garlic extract (AGE) on immune functions. In the immunoglobulin (Ig)E-mediated allergic mouse model, AGE significantly decreased the antigen-specific ear swelling induced by picryl chloride ointment to the ear and intravenous administration of antitrinitrophenyl antibody. In the transplanted carcinoma cell model, AGE significantly inhibited the growth of Sarcoma-180 (allogenic) and LL/2 lung carcinoma (syngenic) cells transplanted into mice. Concomitantly, increases in natural killer (NK) and killer activities of spleen cells were observed in Sarcoma-180--bearing mice administered AGE. In the psychological stress model, AGE significantly prevented the decrease in spleen weight and restored the reduction of anti-SRBC hemolytic plaque-forming cells caused by the electrical stress. These studies strongly suggest that AGE could be a promising candidate as an immune modifier, which maintains the homeostasis of immune functions; further studies are warranted to determine when it is most beneficial.

Endocrine and immune effects of melatonin therapy in metastatic cancer patients.

Lissoni P, Barni S, Crispino S, Tancini G, Fraschini F. Divisione di Radioterapia Oncologica, Ospedale San Gerardo, Milano, Italy.

Eur J Cancer Clin Oncol 1989 May;25(5):789-95

Melatonin, the most important indole hormone produced by the pineal gland, appears to inhibit tumor growth; moreover, altered melatonin secretion has been reported in cancer patients. Despite these data, the possible use of melatonin in

human neoplasms remains to be established. The aim of this clinical trial was to evaluate the therapeutic, immunological and endocrine effects of melatonin in patients with metastatic solid tumor, who did not respond to standard therapies. The study was carried out on 14 cancer patients (colon, six; lung, three; pancreas, two; liver, two; stomach, one). Melatonin was given intramuscularly at a daily dose of 20 mg at 3.00 p.m., followed by a maintenance period in an oral dose of 10 mg daily in patients who had a remission, stable disease or an improvement in PS. Before and after the first 2 months of therapy, GH, somatomedin-C, beta-endorphin, melatonin blood levels and lymphocyte subpopulations were evaluated. A partial response was achieved in one case with cancer of the pancreas, with a duration of 18+ months; moreover, six patients had stable disease, while the other eight progressed. An evident improvement in PS was obtained in 8/14 patients. In patients who did not progress, T4/T8 mean ratio was significantly higher after than before melatonin therapy, while it decreased in patients who progressed. On the contrary, hormonal levels were not affected by melatonin administration. This study would suggest that melatonin may be of value in untreatable metastatic cancer patients, particularly in improving their PS and quality of life; moreover, based on its effects on the immune system, melatonin could be tested in association with other antitumor treatments.

A randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastases due to solid neoplasms.

Lissoni P, Barni S, Ardizzoia A, Tancini G, Conti A, Maestroni G. Division of Radiotherapy, San Gerardo Hospital, Milan, Italy.

Cancer 1994 Feb 1;73(3):699-701

BACKGROUND. Unresectable brain metastases remain an untreatable disease. Because of its antitumor cytostatic action and its anticonvulsant effect, the pineal hormone melatonin could constitute a new effective agent in the treatment of brain metastases. The current study was performed to evaluate the effect of melatonin on the survival time in patients with brain metastases due to solid neoplasms.

METHODS. The study included 50 patients, who were randomized to be treated with supportive care alone (steroids plus anticonvulsant agents) or with supportive care plus melatonin (20 mg/day at 8:00 p.m. orally).

RESULTS. The survival at 1 year, free-from-brain-progression period, and mean survival time were significantly higher in patients treated with melatonin than in those who received the supportive care alone. Conversely, steroid-induced metabolic and infective complications were significantly more frequent in patients treated with supportive care alone than in those concomitantly treated with melatonin.

CONCLUSIONS. The pineal hormone melatonin may be able to improve the survival time and the quality of life in patients with brain metastases due to solid tumors.

Pineal-opioid system interactions in the control of immunoinflammatory responses.

Lissoni P, Barni S, Tancini G, Fossati V, Frigerio F. Division of Radiation Oncology, San Gerardo Hospital, Monza, Milan, Italy.

Ann N Y Acad Sci 1994 Nov 25;741:191-6

Several studies have demonstrated involvement of the pineal gland in the regulation of neuropeptide secretion and activity. In particular, the existence of links between the pineal gland and the brain opioid system has been documented. Both opioid peptides and melatonin (MLT), the most investigated pineal hormone, play an important role in neuromodulation of the immunity. Moreover, the immune effects of MLT are mediated by endogenous opioid peptides, which may be produced by both the endocrine system and the immune cells. In addition, the immune dysfunctions that characterize some human diseases, such as cancer, depend not only on the immune system per se, but also at least in part, on altered secretion of immunomodulating neurohormones, including MLT and opioid peptides. Therefore, the exogenous administration of neurohormones could potentially improve the immune status in humans. The present study evaluates the effects of MLT on changes in the number of T lymphocytes, natural killer cells, and eosinophils induced by exogenous administration of interleukin-2 (IL-2). Macrophage activity was also evaluated by determining serum levels of its specific marker, neopterin. The study was performed in 90 patients with advanced solid neoplasms, who received IL-2 at a dose of 3 million IU/day subcutaneously for 6 days a week for 4 weeks plus MLT at a daily dose of 40 mg. Both drugs were given in the evening. The results were compared to those in 40 cancer patients treated with IL-2 alone. The mean increase in T lymphocytes, natural killer cells, and eosinophils was significantly higher in patients treated with IL-2 plus MLT than in those who received IL-2 alone.(ABSTRACT TRUNCATED AT 250 WORDS)

A randomized study of immunotherapy with low-dose subcutaneous interleukin-2 plus melatonin vs. chemotherapy with cisplatin and etoposide as first-line therapy for advanced non-small cell lung cancer.

Lissoni P, Meregalli S, Fossati V, Paolorossi F, Barni S, Tancini G, Frigerio F. Divisione di Radioterapia Oncologica, Ospedale San Gerardo, Monza, Milano, Italia.

Tumori 1994 Dec 31;80(6):464-7

AIMS AND BACKGROUND: The therapeutic role of chemotherapy in advanced non-small cell lung cancer (NSCLC) is controversial because of its potentially detrimental action on host anticancer defenses. On the contrary, IL-2 would seem to prolong survival time by improving the immune status, even though it is generally less effective in determining tumor regression in NSCLC. Our previous studies have suggested the possibility of increasing tumor sensitivity to IL-2 by concomitant administration of immunomodulating neurohormones, such as the

pineal hormone melatonin (MLT). On this basis, a study was carried out to evaluate the efficacy of immunotherapy with low-dose IL-2 plus MLT versus chemotherapy in advanced NSCLC.

METHODS: The study included 60 patients with locally advanced or metastatic NSCLC, who were randomized to receive immunotherapy or chemotherapy. The immunotherapy consisted of IL-2 (3 million IU/day subcutaneously for 6 days/week for 4 weeks) and MLT (40 mg/day orally every day, starting 7 days before IL-2); in nonprogressing patients, a second cycle was repeated after a 21-day rest period, then they underwent a maintenance period consisting of one week of therapy every month until progression. Chemotherapy consisted of cisplatin (20 mg/m2) and etoposide (100 mg/m2)/day intravenously for 3 days; cycles of chemotherapy were repeated every 21 days until progression.

RESULTS: No complete response was obtained. A partial response was achieved in 7/29 patients treated with chemotherapy and in 6/31 patients receiving chemotherapy. The difference was not significant. In contrast, the mean progression-free period and the percentage survival at 1 year was significantly higher in patients treated with immunotherapy than in those treated with chemotherapy. Toxicity was substantially lower in patients receiving immunotherapy than in those given chemotherapy.

CONCLUSIONS: This randomized study showed that immunotherapy with low-dose IL-2 plus MLT is a better tolerated and more effective therapy in terms of survival time than chemotherapy containing cisplatin in patients affected by advanced NSCLC.

Immune effects of preoperative immunotherapy with high-dose subcutaneous interleukin-2 versus neuroimmunotherapy with low-dose interleukin-2 plus the neurohormone melatonin in gastrointestinal tract tumor patients.

Lissoni P; Brivio F; Brivio O; Fumagalli L; Gramazio F; Rossi M

J Biol Regul Homeost Agents (Italy) Jan-Mar 1995, 9 (1) p31-3

Surgery-induced immunosuppression could influence tumor/host interactions in surgically treated cancer patients. Previous studies have shown that high-dose IL-2 preoperative therapy may neutralize surgery-induced lymphocytopenia. Moreover, experimental studies have demonstrated that the immunomodulating neurohormone melatonin (MLT) may amplify IL-2 activity and reduce its dose required to activate the immune system. On this basis, we have compared the immune effects of presurgical therapy with high-dose IL-2 with respect to those obtained with preoperative neuroimmunotherapy consisting of low-dose IL-2 plus MLT. The study included 30 patients with gastrointestinal tract tumors, who were randomized to undergo surgery alone, or surgery plus a preoperative biotherapy with high-dose IL-2 (18 million IU/day subcutaneously for 3 days) or low-dose IL-2 (6 million IU/day subcutaneously for 5 days) plus MLT (40 mg/day orally). Patients underwent surgery within 36 hours from IL-2 interruption. Both IL-2 plus

MLT were able to prevent surgery-induced lymphocytopenia. However, mean number of lymphocytes, T lymphocytes and T helper lymphocytes observed on day 1 of postoperative period was significantly higher in patients treated with IL-2 plus MLT than in those receiving IL-2 alone. Moreover, toxicity was less in patients treated with IL-2 and MLT. This biological study shows that both immunotherapy with high-dose IL-2 or neuroimmunotherapy with low-dose IL-2 plus MLT preoperatively are tolerated biotherapies, capable of neutralizing surgeryinduced lymphocytopnia in cancer patients. Moreover, the study would suggest that the neuroimmunotherapy may induce a more rapid effect on postoperative immune changes with respect to IL-2 alone.

The immunoneuroendocrine role of melatonin.

Maestroni GJ.

J Pineal Res (DENMARK) Jan 1993, 14 (1) p1-10

A tight, physiological link between the pineal gland and the immune system is emerging from a series of experimental studies. This link might reflect the evolutionary connection between self-recognition and reproduction. Pinealectomy or other experimental methods which inhibit melatonin synthesis and secretion induce a state of immunodepression which is counteracted by melatonin. In general, melatonin seems to have an immunoenhancing effect that is particularly apparent in immunodepressive states. The negative effect of acute stress or immunosuppressive pharmacological treatments on various immune parameters are counteracted by melatonin. It seems important to note that one of the main targets of melatonin is the thymus, i.e., the central organ of the immune system. The clinical use of melatonin as an immunotherapeutic agent seems promising in primary and secondary immunodeficiencies as well as in cancer immunotherapy. The immunoenhancing action of melatonin seems to be mediated by T-helper cell-derived opioid peptides as well as by lymphokines and, perhaps, by pituitary hormones. Melatonin-induced-immuno-opioids (MIIO) and lymphokines imply the presence of specific binding sites or melatonin receptors on cells of the immune system. On the other hand, lymphokines such as gamma-interferon and interleukin-2 as well as thymic hormones can modulate the synthesis of melatonin in the pineal gland. The pineal gland might thus be viewed as the crux of a sophisticated immunoneuroendocrine network which functions as an unconscious, diffuse sensory organ.

Inhibition of human immunodeficiency virus type-1 integrase by curcumin.

Mazumder A, Raghavan K, Weinstein J, Kohn KW, Pommier Y. Laboratory of Molecular Pharmacology, National Cancer Institute, Bethesda, MD 20892-4255, USA.

Biochem Pharmacol 1995 Apr 18;49(8):1165-70

Curcumin (diferuloylmethane) is the yellow pigment in turmeric (Curcuma longa L.) that is widely used as a spice, food coloring (curry) and preservative.

Curcumin exhibits a variety of pharmacological effects including antitumor, anti-inflammatory, and anti-infectious activities and is currently in clinical trials for AIDS patients. The effects of curcumin have been determined on purified human immunodeficiency virus type 1 (HIV-1) integrase. Curcumin has an inhibitory concentration50 (IC50) for strand transfer of 40 microM. Inhibition of an integrase deletion mutant containing only amino acids 50-212 suggests that curcumin interacts with the integrase catalytic core. Two structural analogs, methyl cinnamate and chlorogenic acid, were inactive. Energy minimization studies suggest that the anti-integrase activity of curcumin could be due to an intramolecular stacking of two phenyl rings that brings the hydroxyl groups into close proximity. The present data suggest that HIV-1 integrase inhibition may contribute to the antiviral activity of curcumin. These observations suggest new strategies for antiviral drug development that could be based upon curcumin as a lead compound for the development of inhibitors of HIV-1 integrase.

Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients.

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Eur J Clin Invest 2001 Feb;31(2):171-8

HIV infection is characterized by an enhanced oxidant burden and a systemic deficiency of the tripeptide glutathione (GSH), a major antioxidant. The semi-essential amino acid cysteine is the main source of the free sulfhydryl group of GSH and limits its synthesis. Therefore, different strategies to supplement cysteine supply have been suggested to increase glutathione levels in HIV-infected individuals. The aim of this study was to evaluate the effect of oral supplementation with two different cysteine-rich whey protein formulas on plasma GSH levels and parameters of oxidative stress and immune status in HIV-infected patients. In a prospective double blind clinical trial, 30 patients (25 male, 5 female; mean age (+/- SD) 42 +/- 9.8 years) with stable HIV infection (221 +/- 102 CD4 + lymphocytes L-1) were randomized to a supplemental diet with a daily dose of 45 g whey proteins of either Protectamin (Fresenius Kabi, Bad Hamburg, Germany) or Immunocal (Immunotec, Vandreuil, Canada) for two weeks. Plasma concentrations of total, reduced and oxidized GSH, superoxide anion (O2-) release by blood mononuclear cells, plasma levels of TNF-alpha and interleukins 2 and 12 were quantified with standard methods at baseline and after therapy. Pre-therapy, plasma GSH levels (Protectamin: 1.92 +/- 0.6 microM; Immunocal: 1.98 +/- 0.9 microM) were less than normal (2.64 +/- 0.7 microM, P = 0.03). Following two weeks of oral supplementation with whey proteins, plasma GSH levels increased in the Protectamin group by 44 +/- 56% (2.79 +/- 1.2 microM, P = 0.004) while the difference in the Immunocal group did not reach significance (+ 24.5 +/- 59%, 2.51 +/- 1.48 microM, P = 0.43). Spontaneous O2-release by blood mononuclear cells was stable (20.1 +/- 14.2 vs. 22.6 +/- 16.1 nmol h-1 10-6 cells, P = 0.52) whereas PMA-induced O2- release decreased in the Protectamin group (53.7 +/- 19 vs. 39.8 +/- 18 nmol h-1 10-6 cells, P = 0.04). Plasma concentrations of TNF-alpha and interleukins 2 and 12 (P > 0.08, all

comparisons) as well as routine clinical parameters remained unchanged. Therapy was well tolerated. In glutathione-deficient patients with advanced HIV-infection, short-term oral supplementation with whey proteins increases plasma glutathione levels. A long-term clinical trial is clearly warranted to see if this "biochemical efficacy" of whey proteins translates into a more favourable course of the disease.

Virological and immunological effects of antioxidant treatment in patients with HIV infection.

Muller F, Svardal AM, Nordoy I, Berge RK, Aukrust P, Froland SS. University of Oslo, The National Hospital, Rikshospitalet, Oslo, Norway.

Eur J Clin Invest 2000 Oct;30(10):905-14

BACKGROUND: Intracellular oxidative stress in CD4+ lymphocytes due to disturbed glutathione homeostasis may lead to impaired lymphocyte functions and enhanced HIV replication in patients with HIV infection, especially in those with advanced immunodeficiency. The aim of the present study was to assess whether short-term, high-dose antioxidant treatment might have effects on immunological and virological parameters in patients with HIV infection.

MATERIALS AND METHODS: In this pilot study, we examined virological and immunological effects of antioxidant combination treatment for 6 days with high doses of N-acetylcysteine (NAC) and vitamin C in 8 patients with HIV infection. The following were assayed before, during and after antioxidant treatment: HIV RNA plasma levels; numbers of CD4+, CD8+, and CD14+ leukocytes in blood; plasma thiols; intracellular glutathione redox status in CD4+ lymphocytes and CD14+ monocytes; lymphocyte proliferation; lymphocyte apoptosis and plasma levels of tumour necrosis factor (TNF)alpha; soluble TNF receptors and neopterin in plasma.

RESULTS: No significant changes in HIV RNA plasma levels or CD4+ lymphocyte counts in blood were noted during antioxidant treatment in the patient group. However, in the 5 patients with the most advanced immunodeficiency (CD4+ lymphocyte counts < 200 x 106 L(-1)), a significant rise in CD4+ lymphocyte count, a reduction in HIV RNA plasma level of 0.8 log, an enhanced lymphocyte proliferation and an increased level of intracellular glutathione in CD4+ lymphocytes were found. No change in lymphocyte apoptosis was noted.

CONCLUSIONS: Short-term, high-dose combination treatment with NAC and vitamin C in patients with HIV infection and advanced immunodeficiency lead to immunological and virological effects that might be of therapeutic value.

Use of echinacea in medicine.

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Biochem Pharmacol 2000 Jul 15;60(2):155-8

Echinacea, also known as the purple coneflower, is an herbal medicine that has been used for centuries, customarily as a treatment for the common cold, coughs, bronchitis, upper respiratory infections, and some inflammatory conditions. Research on echinacea, including clinical trials, is limited and argely in German. More information is needed before a definitive statement about the efficacy of echinacea can be made. Future work needs to clearly identify the species of echinacea and distinguish between the efficacy of the different plant parts (roots versus upper plant parts). Although many of the active compounds of echinacea have been identified, the mechanism of action is not known, nor is the bioavailability, relative potency, or synergistic effects of the active compounds known. Interpretation of existing literature suggests that echinacea should be used as a treatment for illness, not as a means for prevention of illness. The consensus of the studies reviewed in his article is that echinacea is indeed effective in reducing the duration and severity of symptoms, but that this effect is noted only with certain preparations of echinacea. Studies show that the plant and its active components affect the phagocytic immune system, but not the specifically acquired immune system.

Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (Sambucus nigra L.) during an outbreak of influenza B Panama.

Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. Department of Virology, Hebrew University-Hadassah Medical School, Jerusalem, Israel.

J Altern Complement Med 1995 Winter;1(4):361-9

A standardized elderberry extract, Sambucol (SAM), reduced hemagglutination and inhibited replication of human influenza viruses type A/Shangdong 9/93 (H3N2), A/Beijing 32/92 (H3N2), A/Texas 36/91 (H1N1), A/Singapore 6/86 (H1N1), type B/Panama 45/90, B/Yamagata 16/88, B/Ann Arbor 1/86, and of animal strains from Northern European swine and turkeys, A/Sw/Ger 2/81, A/Tur/Ger 3/91, and A/Sw/Ger 8533/91 in Madin-Darby canine kidney cells. A placebo-controlled, double blind study was carried out on a group of individuals living in an agricultural community (kibbutz) during an outbreak of influenza B/Panama in 1993. Fever, feeling of improvement, and complete cure were recorded during 6 days. Sera obtained in the acute and convalescent phases were tested for the presence of antibodies to influenza A, B, respiratory syncytial, and adenoviruses. Convalescent phase serologies showed higher mean and mean geometric hemagglutination inhibition (HI) titers to influenza B in the group treated with SAM than in the control group. A significant improvement of the symptoms, including fever, was seen in 93.3% of the cases in the SAM-treated group within 2 days, whereas in the control group 91.7% of the patients showed an improvement within 6 days ($p < 0.001$). A complete cure was achieved within 2 to 3 days in nearly 90% of the SAM-treated group and within at least 6 days in the placebo group ($p < 0.001$). No satisfactory medication to cure influenza type A and B is available. Considering the efficacy of the extract in vitro on all strains of influenza virus tested, the clinical results, its low cost, and absence of side-

effects, this preparation could offer a possibility for safe treatment for influenza A and B.

Protective effect of tea on immune function in mice.

Zhu M, Gong Y, Yang Z. Institute of Radiation Medicine, Academy of Military Medical Sciences, Beijing.

Zhonghua Yu Fang Yi Xue Za Zhi 1998 Sep;32(5):270-4

OBJECTIVE: To study the mechanism of preventive effect of tea on cancer by immune regulation.

METHODS: A tumor model was induced in mice using carcinogen, 4-methyl-nitrosoamino-1-(3-pyridyl)-1-butanone (NNK), to examine their changes in immune function and the effects of green tea, mixed tea and polyphenol on protection from tumor.

RESULTS: During the four weeks of observation after injection of NNK into mice, their immunological indicators, such as cytophagocytosis of macrophage in the abdominal cavity, chemiluminescence of peripheral leukocyte, delayed allergic reaction, count of antibody-forming spleen cells and activity of spleen nature killer cells, etc. increased or decreased to various extent, as compared with those in normal controls. It was found that whether green tea, mixed tea or polyphenol all showed significant protection from adverse changes in immune functions.

CONCLUSION: Tea and its components had significant protection from early adverse changes in immune function in tumorgenesis induced by NNK.

Lactoferrin immunomodulation of DTH response in mice.

Zimecki M, Hunter RL Jr, Kruzel ML. Department of Pathology and Laboratory Medicine-Program in Molecular Pathology, University of Texas-Houston Medical School, UTHHSC, 77030, USA.

Int Immunopharmacol 2002 Mar;2(4):475-86

Improved nontoxic adjuvants, especially adjuvants capable of inducing cell-mediated immunity (CMI), are needed for research in immunology and for development of human and veterinary vaccines. Bovine Lactoferrin, an effector molecule shown to directly participate in host defense, was assessed at various concentrations as an adjuvant component for induction of DTH responses to sheep red blood cells (SRBC). Subcutaneous immunization with Lactoferrin enhanced delayed type hypersensitivity (DTH) in CBA mice in a dose-dependent fashion; DTH responses were most significantly increased when sensitization was accomplished using Lactoferrin at 50 microg/dose and 250 microg/dose. Furthermore, Lactoferrin admixed with suboptimal dose of SRBC enhanced DTH responses by over 17-fold. Peritoneal cells collected from mice intraperitoneally

injected with a 100 microg/dose of Lactoferrin demonstrated modest, but significant, production of TNF-alpha, IL-12 and MIP-1alpha when cultured in vitro, compared to saline-injected controls. J774A. Murine macrophages stimulated with Lactoferrin resulted in increased TNF-alpha protein production, and upregulated IL-12 and IL-15 mRNA. Levels of message for chemokines MIP-1alpha and MIP-2 were also increased in a dose-dependent way. Taken together, these results indicate that Lactoferrin as an adjuvant may stimulate macrophages to generate a local environment likely to push immune responses towards development and maintenance of CMI.

20. Migraine

Preventative and curative options include:

Feverfew extract, magnesium, riboflavin, co-enzyme Q10, B-complex vitamins, glucosamine, ginkgo, picamilon, butterbur root, melatonin.

Visual evoked potentials and serum magnesium levels in juvenile migraine patients.

Aloisi P; Marrelli A; Porto C; Tozzi E; Cerone G Servizio di Neurofisiopatologia, University of L'Aquila, Italy.

Headache (United States) Jun 1997, 37 (6) p383-5

Changes in visual evoked potentials and decreased intracellular magnesium levels have been separately described in patients affected by migraine both during the attacks and in the interictal periods. An inverse correlation between increased P100 amplitude and lowered serum magnesium levels was found in children suffering from migraine with and without aura in a headache-free period. A 20-day treatment with oral magnesium pidolate seemed to normalize the magnesium balance in 90% of patients. After treatment, the reduced P100 amplitude confirmed the inverse correlation with the serum magnesium level. These data seem to suggest the hypothesis that higher visual evoked potential amplitude and low brain magnesium level can both be an expression of neuronal hyperexcitability of the visual pathways related to a lowered threshold for migraine attacks.

Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

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Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine

symptoms described by our patients might support a controlled trial of melatonin in migraine.

An extract of Petasites hybridus is effective in the prophylaxis of migraine.

Grossman W, Schmidramsl H. Department of Neurology, Municipal Hospital, Munchen-Harlaching, Germany.

Altern Med Rev 2001 Jun;6(3):303-10

OBJECTIVE: Migraine is still an unsolved problem. This clinical trial investigates the efficacy and tolerance of Petasites hybridus in the prophylaxis of migraine.

METHODS: A randomized, group-parallel, placebo-controlled, double-blind clinical study was carried out with a special CO2 extract from the rhizome of Petasites hybridus. Following a four-week run-in phase, 60 patients received either the special Petasites hybridus extract Petadolex or placebo at a dosage of two capsules (each capsule contains 25 mg) twice daily over 12 weeks. Outcome variables included the frequency, intensity and duration of migraine attacks as well as any accompanying symptoms.

RESULTS: The frequency of migraine attacks decreased by a maximum of 60 percent compared to the baseline. This reduction in migraine attacks with Petadolex was significant ($p < 0.05$) compared to placebo. No adverse events were reported. Petasites was exceptionally well tolerated.

CONCLUSIONS: The results suggest that migraine patients can benefit from prophylactic treatment with this special extract. The combination of high efficacy and excellent tolerance emphasizes the particular value that Petasites hybridus has for the prophylactic treatment of migraine.

The results of pycamilon therapy in patients with hemicrania.

O A Kolosova, V I Osipova, T V Luniova, All-Union Center of Vegetative Pathology of the Ministry of Health of USSR, First Medical Institute, 11, Rossolimo St., Moscow 119021, USSR

Efficiency of pycamilon in patients with hemicrania was studied. Indications for pycamilon application in response to the clinical form of hemicrania and to the course of disease were defined more exactly. It was been established that pycamilon has a pronounced effect on painful hemicrania access both decreasing its intensity and mitigating or absolute ceasing of accompanying symptoms. Pycamilon is most effective for simple forms of hemicrania with preferential left sided topoalgia in patients without pronounced depressive hypochondria.

Role of magnesium in the pathogenesis and treatment of migraines.

Mauskop A, Altura BM NY Headache Center, New York, NY 10021, USA.

Clin Neurosci 1998;5(1):24-7

The importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. However, the precise role of various effects of low magnesium levels in the development of migraines remains to be discovered. Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, NMDA receptors, and a variety of other migraine related receptors and neurotransmitters. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium. Infusion of magnesium results in a rapid and sustained relief of an acute migraine in such patients. Two double-blind studies suggest that chronic oral magnesium supplementation may also reduce the frequency of migraine headaches. Because of an excellent safety profile and low cost and despite the lack of definitive studies, we feel that a trial of oral magnesium supplementation can be recommended to a majority of migraine sufferers. Refractory patients can sometimes benefit from intravenous infusions of magnesium sulfate.

[The new cerebrovascular preparation pikamilon]

Mirzoian RS; Gan'shina TS

Farmakol Toksikol (USSR) Jan Feb 1989, 52 (1) p23 6,

Picamilon, a sodium salt of N nicotinoyl gamma aminobutyric acid, was shown to induce a significant increase of cerebral blood flow in conscious cats. Picamilon was found to inhibit neurogenic spasms of cerebral vessels that was followed by suppression of tonic activity and reflectory discharges in sympathetic nerves. Picamilon led to restoration of the initial condition of cerebral hemodynamics disturbed by a previous administration of serotonin.

Randomised double-blind placebo-controlled trial of feverfew in migraine prevention.

Murphy JJ, Heptinstall S, Mitchell JR. Department of Medicine, University Hospital, Nottingham.

Lancet 1988 Jul 23;2(8604):189-92

The use of feverfew (Tanacetum parthenium) for migraine prophylaxis was assessed in a randomised, double-blind, placebo-controlled crossover study. After a one-month single-blind placebo run-in, 72 volunteers were randomly allocated to receive either one capsule of dried feverfew leaves a day or matching placebo for four months and then transferred to the other treatment limb for a further four months. Frequency and severity of attacks were determined from diary cards which were issued every two months; efficacy of each treatment was also assessed by visual analogue scores. 60 patients completed the study and full information was available in 59. Treatment with feverfew was associated with a reduction in the mean number and severity of attacks in each two-month period,

and in the degree of vomiting; duration of individual attacks was unaltered. Visual analogue scores also indicated a significant improvement with feverfew. There were no serious side-effects.

Feverfew (Tanacetum parthenium) as a prophylactic treatment for migraine: A double-blind placebo-controlled study

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Phytotherapy Research (United Kingdom) 1997, 11/7 (508-511)

To assess the effectiveness of feverfew as a prophylactic therapy for migraine, a double-blind placebo controlled cross-over trial was conducted for a period of 4 months. Fifty seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups were treated with feverfew in the preliminary phase (phase 1), which lasted 2 months, in the second and third phases, which continued for an additional 2 months, a double-blind placebo controlled cross-over study was conducted. The results showed that feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover, a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the feverfew -treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms, in contrast, shifting the placebo group to feverfew therapy resulted in a reduction of the pain intensity as well as in the severity of the linked symptoms.

Open label trial of coenzyme Q10 as a migraine preventive.

Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, Silberstein SD. Jefferson Headache Center/Thomas Jefferson University, Philadelphia, Pennsylvania, USA. RozenT@ccf.org

Cephalalgia. 2002 Mar;22(2):137-41

The objective was to assess the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches. Thirty-two patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with coenzyme Q10 at a dose of 150 mg per day. Thirty-one of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response ($P < 0.0001$). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response ($P < 0.001$). There were no side-effects noted with coenzyme Q10. From this open label investigation

coenzyme Q10 appears to be a good migraine preventive. Placebo-controlled trials are now necessary to determine the true efficacy of coenzyme Q10 in migraine prevention.

Glucosamine for migraine prophylaxis?

Russell AL, McCarty MF. Brampton Pain Clinic, Bramalea, Ontario, Canada.

Med Hypotheses 2000 Sep;55(3):195-8

Following a fortuitous observation that migraine headaches ceased in a patient receiving glucosamine therapy for osteoarthritis, a further ten patients with migraine or migraine-like vascular headaches, refractory to established preventive or abortive therapies, have been treated with daily oral glucosamine. After a lag of 4-6 weeks, a substantial reduction in headache frequency and/or intensity has been noted; in some cases, the benefit appears to be dose-dependent. Since glucosamine can be a rate-limiting precursor for mucopolysaccharide synthesis, it is germane to note previous reports that heparin and pentosan polysulfate may have migraine-preventive activity. There is reason to suspect that mast cells are central mediators of the neurogenic inflammation associated with migraine and cluster headaches. The heparin produced by mast cells may function to provide feedback down-regulation of mast cell activation, and exerts a range of other anti-inflammatory effects. We postulate that supplemental glucosamine can boost mast cell heparin synthesis - perhaps correcting a functional heparin deficiency - thereby preventing or ameliorating the neurogenic inflammation that mediates pain in vascular headache. Whether or not this idea has validity, a controlled study of glucosamine for migraine prophylaxis appears to be warranted.

Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.

Sandor PS, Afra J, Ambrosini A, Schoenen J. Neurology Department, CHR Citadelle, University of Liege, Belgium.

Headache 2000 Jan;40(1):30-5

OBJECTIVE: To investigate the influence of different pharmacological treatments on the intensity dependence of auditory evoked cortical potentials in migraineurs.

BACKGROUND: Between attacks, patients with migraine show abnormalities in cortical information processing and decreased brain mitochondrial energy reserve. Both are most probably relevant for migraine pathogenesis, and they could be differentially modified by prophylactic drug therapy. Design.-The intensity dependence of the auditory evoked cortical potentials is, on average, increased in migraine. We have studied this intensity dependence in 26 patients before and after a 4-month period of prophylaxis with beta-blockers (n = 11, all migraine without aura; metoprolol or bisoprolol) or riboflavin (n = 15, migraine without

aura: 13, migraine with aura: 2). Recordings were performed at least 3 days before or after an attack.

RESULTS: After the treatment with beta-blockers, the intensity dependence of the auditory evoked cortical potentials was significantly decreased (before: 1.66+/-1.02 microV/10 dB; after: 0.79+/-1.06 microV/10 dB, P=.02). The decrease in intensity dependence was correlated significantly with clinical improvement (r = .69, P = .02). There was no change in intensity dependence after riboflavin treatment (before: 1.80+/-0.81 microV/10 dB; after: 1.56+/-0.83 microV/10 dB, P = .39), although the majority of patients showed improvement.

CONCLUSIONS: These results confirm that beta-blockers and riboflavin act on two distinct pathophysiological mechanisms. Combining both treatments might enhance their efficacy without increasing central nervous system side effects.

High-dose riboflavin as a prophylactic treatment of migraine: Results of an open pilot study

Schoenen J.; Lenaerts M.; Bastings E. University Department of Neurology, CHR de la Citadelle, Bd du 12 de Ligne 1, 4000 Liege Belgium

Cephalalgia (Norway), 1994, 14/5 (328-329)

If the brain of migraineurs is characterized between attacks by a reduction of mitochondrial phosphorylation potential, riboflavin, which has the potential of increasing mitochondrial energy efficiency, might have prophylactic effects in migraine. In this preliminary open pilot study, 49 patients suffering from migraine (45 without aura, 4 with aura) were treated with 400 mg of riboflavin as a single oral dose for at least 3 months. Twenty-three patients received in addition 75 mg of aspirin. Mean global improvement after therapy was 68.2% and there was no difference between the two groups of patients. With the exception of one patient in the riboflavin plus aspirin group who withdrew because of gastric intolerance, no drug-related side effects were reported. High-dose riboflavin could thus be an effective, low-cost prophylactic treatment of migraine devoid of short-term side effects. A placebo-controlled trial of its efficacy seems worthwhile.

Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content.

Barsby RW; Salan U; Knight DW; Hoult JR Pharmacology Group, King's College London, U.K.

Planta Med (Germany) Feb 1993, 59 (1) p20-5

Preparations of fresh or dried feverfew (Chrysanthemum parthenium) are widely consumed in the U.K. as a remedy for arthritis and migraine, but the pharmacological basis for this has not been established. We have, therefore, compared the properties of extracts of fresh plants with those of dried powdered

leaves available commercially from health food shops. The two extracts differed radically in their content of alpha-methylbutyrolactones and in their pharmacological profile when tested in vitro on the rabbit aortic ring and rat anococcygeus preparations. Extracts of fresh leaves caused does- and time-dependent inhibition of the contractile responses of aortic rings to all receptor-acting agonists so far tested; the effects were irreversible and may represent a toxic modification of post-receptor contractile function in the smooth muscle. The presence of potentially -SH reactive parthenolide and other sesquiterpene alphamethylenebutyrolactones in these extracts, and the close parallelism of the actions of pure parthenolide, suggest that the inhibitory effects are due to these compounds. In contrast, chloroform extracts of dried powdered leaves were not inhibitory but themselves elicited potent and sustained contractions of aortic smooth muscle that were not antagonised by ketanserin (5-HT2 receptor antagonist). These extracts did not contain parthenolide or butyrolactones according to a chemical-HPLC assay, We conclude that there are marked differences in the pharmacological potency and profiles between preparations from fresh and dried feverfew and that this may relate to their lactone content. As the effects of the lactones are potentially toxic, it will be necessary to compare the clinical profiles and side effects of preparations obtained from the two sources.

Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components.

Sumner H; Salan U; Knight DW; Hoult JR Pharmacology Group, King's College London, U.K.

Biochem Pharmacol (England) Jun 9 1992, 43 (11) p2313-20

Leaves or infusions of feverfew, Tanacetum parthenium, have long been used as a folk remedy for fever, arthritis and migraine, and derived products are widely available in U.K. health food shops. Previous reports have suggested interactions with arachidonate metabolism. Crude chloroform extracts of fresh feverfew leaves (rich in sesquiterpene lactones) and of commercially available powdered leaves (lactone-free) produced dose-dependent inhibition of the generation of thromboxane B2 (TXB2) and leukotriene B4 (LTB4) by ionophore- and chemoattractant-stimulated rat peritoneal leukocytes and human polymorphonuclear leukocytes. Approximate IC50 values were in the range 5-50 micrograms/mL, and inhibition of TXB2 and LTB4 occurred in parallel. Isolated lactones (parthenolide, epoxyartemorin) treated with cysteine (to neutralize reactive alpha-methylene butyrolactone functions of the sesquiterpenes). Inhibition of eicosanoid generation appeared to be irreversible but not time-dependent. We conclude that feverfew contains a complex mixture of sesquiterpene lactone and non-sesquiterpene lactone inhibitors of eicosanoid synthesis of high potency, and that these biochemical actions may be relevant to the claimed therapeutic actions of the herb.

Efficacy of feverfew as prophylactic treatment of migraine.

Johnson ES; Kadam NP; Hylands DM; Hylands PJ

Br Med J (Clin Res Ed) (England) Aug 31 1985, 291 (6495) p569-73

Seventeen patients who ate fresh leaves of feverfew daily as prophylaxis against migraine participated in a double blind placebo controlled trial of the herb: eight patients received capsules containing freeze dried feverfew powder and nine placebo. Those who received placebo had a significant increase in the frequency and severity of headache, nausea, and vomiting with the emergence of untoward effects during the early months of treatment. The group given capsules of feverfew showed no change in the frequency or severity of symptoms of migraine. This provides evidence that feverfew taken prophylactically prevents attacks of migraine, and confirmatory studies are now indicated, preferably with a formulation controlled for sesquiterpene lactone content, in migraine sufferers who have never treated themselves with this herb.

Herbal therapy for migraine: An unconventional approach

Diamond S. Inpatient Headache Unit at Louis A. Weiss Memorial Hospital, Chicago, IL United States

Postgraduate Medicine (United States) 1987, 82/1 (197-198)

A pilot study was conducted at the City of London Migraine Clinic to establish whether feverfew 's efficacy could be shown through orthodox clinical evaluation and also to demonstrate any adverse effects on cellular and chemical elements of the blood. Because of possible ethical objections, only patients who had previously consumed feverfew leaves were included in the study.

Platelet ionized magnesium, cyclic AMP, and cyclic GMP levels in migraine and tension-type headache.

Mishima K; Takeshima T; Shimomura T; Okada H; Kitano A; Takahashi K; Nakashima K Division of Neurology, Tottori University Faculty of Medicine, Yonago, Japan.

Headache (United States) Oct 1997, 37 (9) p561-4

Decreased serum and intracellular levels of magnesium have been reported in patients with migraine . It has been suggested that magnesium may play an important role in the attacks and pathogenesis of headaches. We measured ionized magnesium, cyclic AMP (adenosine monophosphate), and cyclic GMP (guanosine monophosphate) in platelets of patients with migraine, in patients with tension-type headache, and in healthy controls. The platelet level of ionized magnesium from patients with tension-type headache was significantly lower than the levels from the other two groups. The platelet level of cyclic AMP from patients with migraine was higher than those from the other groups. We found no significant differences in the platelet cyclic GMP levels among the three groups. It is suggested that reduced platelet ionized magnesium in patients with tension-type headache is related to abnormal platelet function, and that increased platelet

cyclic AMP in patients with migraine is related to alteration of neurotransmitters in the platelet.

Omega- 3: Essential for good health

Pelton R.

American Druggist (United States) 1997, 214/7 (52-53)

Supplements of omega -3 fatty acids may be needed to maintain a careful balance with omega-6 and regulate the production of prostaglandins and their effects.

Magnesium taurate and fish oil for prevention of migraine.

McCarty MF Nutrition 21, San Diego, CA 92109, USA.

Med Hypotheses (England) Dec 1996, 47 (6) p461-6

Although the pathogenesis of migraine is still poorly understood, various clinical investigations, as well as consideration of the characteristic activities of the wide range of drugs known to reduce migraine incidence, suggest that such phenomena as neuronal hyperexcitation, cortical spreading depression, vasospasm, platelet activation and sympathetic hyperactivity often play a part in this syndrome. Increased tissue levels of taurine, as well as increased extracellular magnesium, could be expected to dampen neuronal hyperexcitation, counteract vasospasm, increase tolerance to focal hypoxia and stabilize platelets; taurine may also lessen sympathetic outflow. Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine. Fish oil, owing to its platelet-stabilizing and antivasospastic actions, may also be useful in this regard, as suggested by a few clinical reports. Although many drugs have value for migraine prophylaxis, the two nutritional measures suggested here may have particular merit owing to the versatility of their actions, their safety and lack of side-effects and their long-term favorable impact on vascular health. (94 Refs.)

Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study.

Peikert A; Wilimzig C; Kohne-Volland R Department of Neurology and Clinical Neurophysiology, Munich-Harlaching Clinic, Germany.

Cephalalgia (Norway) Jun 1996, 16 (4) p257-63

In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18-65 years with migraine according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of 4 weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9-12 the attack frequency was reduced by 41.6% in the magnesium group and by

15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis.

Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients.

Mazzotta G; Sarchielli P; Alberti A; Gallai V Interuniversity (Perugia-Rome-Sassari-Bari) Centre for the Study of Headache and Neurotransmitter Disorders of the CNS, Italy.

Headache (United States) Jun 1996, 36 (6) p357-61

Headache has often been described in the hyperexcitability syndrome which recognizes an alteration of calcium and magnesium status in its etiopathogenesis. Moreover, in migraine patients magnesium has been shown to play an important role as a regulator of neuronal excitability and, therefore hypothetically, of headache. The present research involves a neurophysiological evaluation and magnesium status assessment of a group of headache patients. Nineteen patients (15 women and 4 men) with episodic tension-type headache and 30 patients (27 women and 3 men) with migraine without aura were examined. An ischemic test was carried out on the right arm with electromyographic (EMG) recording of motor unit potential activity during the interictal period. The determination of extracellular (serum and saliva) and intracellular (red and mononuclear blood cells) magnesium was also performed. The EMG test was positive in 25 of 30 migraine patients and in 2 of 19 tension-type headache patients. Between the two patient groups, there were no significant variations in the concentration of extracellular and white blood cell magnesium, while the red blood cell concentration of this mineral in the group of migraineurs was significantly reduced with respect to that in the group of tension-type headache patients ($P < 0.05$). The positive EMG test was significantly associated with a low concentration of red blood cell magnesium ($P < 0.0001$). These results confirm previous findings by demonstrating different etiopathogenic mechanisms as the basis of migraine and tension-type headache. Migraine seems to be related to an altered magnesium status, which manifests itself by a neuromuscular hyperexcitability and a reduced concentration in red blood cells.

Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses

Brun J.; Claustrat B.; Saddier P.; Chazot G.

Cephalalgia (Norway), 1995, 15/2 (136-139)

Nocturnal melatonin excretion was studied throughout a complete menstrual cycle in 10 women with migraine without aura attacks associated with menses and 9 women controls. Urine melatonin was determined by radioimmunoassay. The mean nocturnal melatonin excretion throughout the cycle was significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group. Results are discussed in view of the role of the pineal gland in the organization of biological rhythms and homeostasis in relation to environmental conditions.

Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine

Murialdo G.; Fonzi S.; Costelli P.; Solinas G.P.; Parodi C.; Marabini S.; Fanciullacci M.; Polleri A. Endocrinological/Metabol. Sci. Dept., Viale Benedetto XV, 6, I-16132 Genoa Italy

Cephalalgia 1994 Jun;14(3):205-9

Nocturnal urinary melatonin excretion was significantly decreased throughout an ovarian cycle in 12 migraine without aura patients compared to 8 healthy controls. Normal increases in urinary melatonin excretion during the luteal phase was less pronounced in the migraine patients. Melatonin excretion was further decreased during headache. The data indicate impaired pineal function in migraine.

Nocturnal plasma melatonin levels in migraine: A preliminary report

Claustrat B, Loisy C, Brun J, Beorchia S, Arnaud JL, Chazot G

Headache (United States) Apr 1989, 29 (4) p242-5

We determined by radioimmunoassay plasma melatonin levels on blood samples drawn at 11 p.m. in migraine patients and control subjects. Ninety-three cephalalgic outpatients (75 females, 18 males) were compared to a control group (24 females, 22 males) matched according to age. Patients were divided into subgroups presenting common migraine (n = 38); ophthalmic migraine (n = 12); and tension headache associated with ophthalmic or common migraine (n = 24), and associated depressive status (n = 19). Statistical analysis revealed a decrease in plasma melatonin levels for the entire migraine population, compared to the control one, and a heterogeneity in both controls and patients; this heterogeneity was found mainly in the depressive and tension headache subgroups. When the migraine population - from which the depressive patients were excluded - was divided into male and female subgroups, a decrease in plasma melatonin levels was observed only for the female subgroups. Results are discussed with reference to the role of the pineal gland in the synchronization of the organism with the environmental conditions.

The influence of the pineal gland on migraine and cluster headaches and effects of treatment with picoTesla magnetic fields.

Sandyk R

Int J Neurosci (England) Nov-Dec 1992, 67 (1-4) p145-71

For over half a century the generally accepted views on the pathogenesis of migraine were based on the theories of Harold Wolff implicating changes in cerebral vascular tone in the development of migraine. Recent studies, which are based on Leao's concept of spreading depression, favor primary neuronal injury with secondary involvement of the cerebral circulation. In contrast to migraine, the pathogenesis of cluster headache (CH) remains entirely elusive. Both migraine and CH are cyclical disorders which are characterised by spontaneous exacerbations and remissions, seasonal variability of symptoms, and a relationship to a variety of environmental trigger factors. CH in particular has a strong circadian and seasonal regularity. It is now well established that the pineal gland is an adaptive organ which maintains and regulates cerebral homeostasis by "fine tuning" biological rhythms through the mediation of melatonin. Since migraine and CH reflect abnormal adaptive responses to environmental influences resulting in heightened neurovascular reactivity, I propose that the pineal gland is a critical mediator in their pathogenesis. This novel hypothesis provides a framework for future research and development of new therapeutic modalities for these chronic headache syndromes. The successful treatment of a patient with an acute migraine attack with external magnetic fields, which acutely inhibit melatonin secretion in animals and humans, attests to the importance of the pineal gland in the pathogenesis of migraine headache. (242 Refs.)

Is migraine due to a deficiency of pineal melatonin?

Toglia JU

Ital J Neurol Sci (Italy) Jun 1986, 7 (3) p319-23

Recent clinical observations favor the theory that migraine is caused by a primary injury of cerebral neurons with secondary involvement of intracranial and extracranial blood vessels. The primary injury is attributed to disruption of cerebral neurotransmitters and particularly the neuroadrenergic and serotonergic systems. These theories have not explained the importance of environmental factors, which so frequently trigger migraine. The author suggests that the pineal gland, which is outside the CNS unprotected by blood brain barrier and sensitive to external stimuli, could act as the intermediate causative factor of migraine, via a derangement of melatonin. (47 Refs.)

FEVERFEW (Tanacetum pathenium):

Feverfew appears to work in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel dilating substances from platelets (serotonin and histamine), inhibiting the production of inflammatory substances (leukotrienes, serine proteases, etc.), and re-establishing proper blood vessel tone. Commercial sources providing assurance of botanical identity and minimum

required level of parthenolides are needed (Awang DVC. Feverfew. Car Pharm J 122:266-70, 1989).

In vitro Study: Feverfew was found to contain a factor that inhibits prostaglandin synthesis, but differs from salicylates by not inhibiting cyclo-oxygenase by prostaglandin (PG) synthase. "The ability of feverfew to inhibit PG production may account for its effectiveness as a herbal remedy in conditions responding to acetylsalicylate and like-acting drugs" (Collier HOJ, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. Letter. lancet October 25, 1980).

The dosage of feverfew used in one double-blind study was one capsule containing 25 mg of the freeze-dried pulverized leaves twice daily; in another double-blind study it was one capsule containing 82 mg of dried powdered leaves once daily. While these low dosages may be effective in preventing an attack, a higher dose (I to 2 grams) may be necessary during an acute attack.

Note: The efficacy of feverfew is dependent upon adequate levels of parthenolide, the active ingredient. (The preparations used in successful clinical trials have a parthenolide content of 0.4-0.66%.)

Animal Ex vivo Study: Extracts of fresh feverfew caused a dose- and time dependent, irreversible inhibition of the contractile response of rabbit aortic rings to all receptor-acting agonists tested. The presence of potentially SH reacting parthenolide and other sesquiterpene alpha-methylenebutyrolactones in, these extracts, and the close parallelism of pure parthenolide, suggest that the inhibitory effects are due to these compounds. Extracts of the dry leaves were not inhibitory and actually caused potent and sustained contractions of aortic smooth muscle; these extracts were found to be devoid or parthenolide or butyrolactones (Barsby RWJ, Salan U, Knight BW, Hoult JRS. Feverfew and vascular smooth muscle: Extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. Planta Medica 59:20-5, 1993).

Chemical Analysis: The parthenolide content of over 35 different commercial preparations of feverfew was determined by bioassay, 2 HPLC methods, and NMR. The results indicate a wide variation in the amts. of parthenolide in commercial preparations. The majority of products contained no parthenolide or only traces (Heptinstall S et al. Parthenolide content and bioactivity of feverfew (Tanacetum parthenium (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. J Pharm Pharmaco1 44:391-5, 1992).

WARNING: No long-term toxicity studies have been conducted. While feverfew is extremely well-tolerated and no serious side effects have ever been reported, chewing the leaves can result in small ulcerations in the mouth and swelling of the lips and tongue in about 10% of users (Awang DVC. Feverfew. Can Pharml 122:266-70, 1989).

Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

Claustrat B.; Brun J.; Geoffriau M.; Zaidan R.; Mallo C.; Chazot G.
B. Claustrat, Serv. Radiopharmacie/Radioanalyse, Hopital Neurologique, 59 Boulevard Pinel, 69003 Lyon France
Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine symptoms described by our patients might support a controlled trial of melatonin in migraine.

Magnesium taurate and fish oil for prevention of migraine.

McCarty MF
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basis of migraine and tension-type headache. Migraine seems to be related to an altered magnesium status, which manifests itself by a neuromuscular hyperexcitability and a reduced concentration in red blood cells.

Herbal products begin to attract the attention of brand-name drug companies.

Cottrell K
Can Med Assoc J (Canada) Jul 15 1996, 155 (2) p216-9

Many Canadians are interested in alternative medicine, and burgeoning public interest in herbal remedies has not gone unnoticed by Canada's drug companies. McNeil Consumer Products recently began selling a migraine prophylaxis made from the plant feverfew. Physicians who would like to see herbal medications subjected to outcome studies and quality-control standards, with evidence of risks and benefits being made available to consumers, welcome the interest the companies are showing. Meanwhile, physicians and pharmacists are trying to respond to consumer demand by increasing their own knowledge about herbal medications.

Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses

Brun J.; Claustrat B.; Saddier P.; Chazot G.
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Endocrinological/Metabol. Sci. Dept., Viale Benedetto XV, 6, I-16132 Genoa

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Melatonin in humans physiological and clinical studies.

Wetterberg L
J Neural Transm Suppl (Austria) 1978, (13) p289-310

Studies are reported of the variation of melatonin in serum, plasma urine and cerebrospinal fluid in normal subjects and in patients with various diseases. The diurnal variation of plasma and urine melatonin found in healthy controls on a regular dark-sleep pattern persisted when the subjects slept in light. The effect of sleep deprivation and of rapid light exposure at night is reported. There was a correlation between melatonin in morning urine and plasma at 2 a.m. Four hours of extended darkness in the morning as well as a 9-hour shift of sleep and activity cycles following travel affected the melatonin rhythm. The night increase in plasma melatonin preceeded both the cortisol and prolactin rise. A single oral dose of 4.3 X 10(5) nmol of melatonin given to a 44-year-old healthy male gave a peak plasma value of 624 nmol/l after 30 min. Plasma melatonin was not affected by electroconvulsive therapy, TRH-injection, L-Dopa or bromoergocryptine orally. Patients with alcoholism, migraine, postoperative pinealoma, panhypopituitarism, hereditary dystonia and schizophrenics on propranolol exhibited a decreased amplitude of their diurnal rhythm of melatonin. Two patients with pituitary tumors had occasional high levels of plasma melatonin. The change in melatonin secretion in human is apparently controlled by a mechanism which is at least party influenced by environmental lighting conditions, drugs and different disease states. (27 refs.)

FEVERFEW (Tanacetum pathenium):

Feverfew appears to work in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel dilating substances from platelets (serotonin and histamine), inhibiting the production of inflammatory substances (leukotrienes, serine proteases, etc.), and re-establishing proper blood vessel tone. Commercial sources providing assurance of botanical identity and minimum required level of parthenolides are needed (Awang DVC. Feverfew. Car Pharm J 122:266-70, 1989).

In vitro Study: Feverfew was found to contain a factor that inhibits prostaglandin synthesis, but differs from salicylates by not inhibiting cyclo-oxygenase by prostaglandin (PG) synthase. "The ability of feverfew to inhibit PG production may account for its effectiveness as a herbal remedy in conditions responding to acetylsalicylate and like-acting drugs" (Collier HOJ, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. Letter. lancet October 25, 1980).

The dosage of feverfew used in one double-blind study was one capsule containing 25 mg of the freeze-dried pulverized leaves twice daily; in another double-blind study it was one capsule containing 82 mg of dried powdered leaves once daily. While these low dosages may be effective in preventing an attack, a higher dose (I to 2 grams) may be necessary during an acute attack.

Note: The efficacy of feverfew is dependent upon adequate levels of parthenolide, the active ingredient. (The preparations used in successful clinical trials have a parthenolide content of 0.4-0.66%.)

Animal Ex vivo Study: Extracts of fresh feverfew caused a dose- and time dependent, irreversible inhibition of the contractile response of rabbit aortic rings to all receptor-acting agonists tested. The presence of potentially SH reacting parthenolide and other sesquiterpene alpha-methylenebutyrolactones in, these extracts, and the close parallelism of pure parthenolide, suggest that the inhibitory effects are due to these compounds. Extracts of the dry leaves were not inhibitory and actually caused potent and sustained contractions of aortic smooth muscle; these extracts were found to be devoid or parthenolide or butyrolactones (Barsby RWJ, Salan U, Knight BW, Hoult JRS. Feverfew and vascular smooth muscle: Extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. Planta Medica 59:20-5, 1993).

Chemical Analysis: The parthenolide content of over 35 different commercial preparations of feverfew was determined by bioassay, 2 HPLC methods, and NMR. The results indicate a wide variation in the amts. of parthenolide in commercial preparations. The majority of products contained no parthenolide or only traces (Heptinstall S et al. Parthenolide content and bioactivity of feverfew (Tanacetum parthenium (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. J Pharm Pharmaco1 44:391-5, 1992).

WARNING: No long-term toxicity studies have been conducted. While feverfew is extremely well-tolerated and no serious side effects have ever been reported, chewing the leaves can result in small ulcerations in the mouth and swelling of the lips and tongue in about 10% of users (Awang DVC. Feverfew. Can Pharml 122:266-70, 1989).

21. Multiple Sclerosis

Multi nutrient, fish oil, acetyl-L- carnitine, alpha-lipoic acid, coenzyme Q10, vitamin B12, soy lecithin.

Folate, vitamin B12, and neuropsychiatric disorders.

Bottiglieri T Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas, USA.

Nutr Rev (United States) Dec 1996, 54 (12) p382-90

Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.

1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

Cantorna M.T.; Hayes C.E.; DeLuca H.F. Department of Biochemistry, 420 Henry Mall, University of Wisconsin, Madison, WI 53706 USA

Proceedings of the National Academy of Sciences of the United States of America (USA), 1996, 93/15 (7861-7864)

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease multiple sclerosis (MS). Induced by immunizing B10.PL mice with myelin basic protein (MBP). EAE was completely prevented by the administration of 1,25-dihydroxy vitamin D3 (1,25- (OH)2D3). 1,25-(OH)2D3 could also prevent the progression of EAE when administered at the appearance of the first disability symptoms. Withdrawal of 1,25-(OH)2D3 resulted in a resumption of the progression of EAE. Thus, the block by 1,25-(OH)2D3 is reversible. A deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, 1,25-(OH)2D3 or its analogs are potentially important for treatment of MS

Exogenous lipids in myelination and myelination.

Di Biase A; Salvati S Dept. of Metabolism and Pathological Biochemistry, Istituto Superiore di Sanita, Rome, Italy.

Kao Hsiung I Hsueh Ko Hsueh Tsa Chih (Taiwan) Jan 1997 , 13 (1) p19-29

Myelinogenesis is a scheduled process that depends on both the intrinsic properties of the cell and extracellular signals. In rat brain, myelin development is an essentially postnatal event and environmental interferences could affect myelin synthesis. Nutrition plays an important role, since severe postnatal malnutrition and essential fatty acid (EFA) deficiency cause hypomyelination. Even though the dietary effects are more pronounced in the postnatal period, dietary lipids can affects myelin development also in the postweaning period. Rats fed with diets rich in polyunsaturated n3 fatty acids showed a decrease of the relative amount of myelin basic protein (MBP) and a CNPase activity indicating a delay in myelin deposition and/or an instability of its structure. Our recent studies have shown that dietary fatty acids can be positively involved in the control of central nervous system (CNS) myelinogenesis. Offspring of rats fed diets containing odd chain fatty acid during pregnancy and lactation show an early development of behavioral reflexes linked to myelination compared to controls fed a diet containing margarine. Subsequent studies have shown that the expression of myelin proteins is higher in test than in control animals, but the mechanism of the action of fatty acids is still unknown. Also human brain myelinogenesis can be affected by environmental factors. EFA deficiency has been well studied for the important role of C22:6 (a C18:3 metabolite) in the vision system development. The observation that dietary fatty acids can affect membrane composition has led to the use of modified diets in some CNS pathological conditions. For example, preterm infants characterized by low levels of C22:6 and fed with formulae diets enriched in this fatty acid, show a recovery of visual function. The administration of C22:6 has also been tested in patients affected by peroxisomal biogenesis disorders which are associated with very low levels of this fatty acid in the brain. During the treatment, C22:6 content increases in red blood cells, and probably in the brain membranes, as considerable neurologic and electrophysiological improvement suggest. A mixture of glyceryltrierucate and glyceryltrioleate has been tested in the demyelinating disease Adrenoleukodistrophy which is characterized by an abnormal accumulation of very long chain fatty acids (VLCFA) in tissues and fluids. The diet is able to lower VLCFA levels in plasma, but its efficacy for myelin damage is debated. Lastly, a diet which reduces the intake of saturated fatty acid and increases the quantity of polyunsaturates is suggested for multiple sclerosis patients since a decrease of linoleic acid in their plasma and erythrocytes has been observed. Such a diet seems able to reduce the severity of the attacks. (85 Refs.)

Nutritional factors in the aetiology of multiple sclerosis: A case-control study in Montreal, Canada

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International Journal of Epidemiology (UnitedKingdom) 1998, 27/5 (845-852)

Background. It has been suggested that nutrition and food patterns, particularly high consumption of animal fat and low intake of fish products, may play a role in the aetiology of multiple sclerosis (MS).

Methods. The relation between nutritional factors and MS was studied among 197 incident cases and 202 frequency matched controls in metropolitan Montreal during 1992-1995. Dietary information was collected by employing a 164-item food frequency questionnaire in a face-to-face interview.

Results. An inverse association was observed between high body mass index (BMI) and the risk of MS, with an odds ratio (OR) of 0.76 (95% confidence interval [CI] 0.61-0.95), per 5-unit increase in BMI, both sexes combined. In addition, taller women showed a greater risk for MS; the OR per 10 cm increase in height was 1.58 (95% CI: 1.06-2.35). In continuous variable analyses, using the difference between the lowest and highest quartile of intake as a unit, a positive association was observed with energy and animal fat intake. The OR per 897 kcal increase was 2.03 (95% CI: 1.13-3.67) and 1.99 (95% CI: 1.12-3.54) per 33 g of animal fat intake above the baseline. A significant protective effect was observed with other nutrients, including vegetable protein, dietary fibre, cereal fibre, vitamin C, thiamin, riboflavin, calcium, and potassium. Similar trends were seen for males and females when analysed separately. With respect to specific foods (as opposed to nutrients), a higher intake of fruit juices was inversely associated with risk (OR = 0.82; 95% CI: 0.74-0.92). A protective effect was also observed with cereal/breads intake for all cases combined (OR = 0.62; 95% CI: 0.40-0.97) and for fish among women only; pork/hot dogs (OR = 1.24; 95% CI: 1.02-1.51) and sweets/candy (OR = 1.29; 95% CI: 1.07-1.55) were positively associated with risk.

Conclusion. The study generally supports a protective role for components commonly found in plants (fruit/vegetables and grains) and an increased risk with high energy and animal food intake.

Multiple sclerosis: Decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D

Goldberg P, Fleming MC, Picard EH

Med. Hypotheses (UK), 1986, 21/2 (193-200)

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of

exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

Vitamin D and multiple sclerosis.

Hayes CE; Cantorna MT; DeLuca HF Department of Biochemistry, University of Wisconsin-Madison 53706, USA.

Proc Soc Exp Biol Med (United States) Oct 1997, 216 (1) p21-7

Recently, it has been clearly demonstrated that exogenous 1,25-dihydroxyvitamin D3, the hormonal form of vitamin D3 , can completely prevent experimental autoimmune encephalomyelitis (EAE), a widely accepted mouse model of human multiple sclerosis (MS). This finding has focused attention on the possible relationship of this disease to vitamin D. Although genetic traits certainly contribute to MS susceptibility, an environmental factor is also clearly involved. It is our hypothesis that one crucial environmental factor is the degree of sunlight exposure catalyzing the production of vitamin D3 in skin, and, further, that the hormonal form of vitamin D3 is a selective immune system regulator inhibiting this autoimmune disease. Thus, under low-sunlight conditions, insufficient vitamin D3 is produced, limiting production of 1,25-dihydroxyvitamin D3, providing a risk for MS. Although the evidence that vitamin D3 is a protective environmental factor against MS is circumstantial, it is compelling. This theory can explain the striking geographic distribution of MS, which is nearly zero in equatorial regions and increases dramatically with latitude in both hemispheres. It can also explain two peculiar geographic anomalies, one in Switzerland with high MS rates at low altitudes and low MS rates at high altitudes, and one in Norway with a high MS prevalence inland and a lower MS prevalence along the coast. Ultraviolet (UV) light intensity is higher at high altitudes, resulting in a greater vitamin D3 synthetic rate, thereby accounting for low MS rates at higher altitudes. On the Norwegian coast, fish is consumed at high rates and fish oils are rich in vitamin D3 . Further, experimental work on EAE provides strong support for the importance of vitamin D3 in reducing the risk and susceptibility for MS. If this hypothesis is correct, then 1,25-dihydroxyvitamin D3 or its analogs may have great therapeutic potential in patients with MS. More importantly, current research together with data from migration studies opens the possibility that MS may be preventable in genetically susceptible individuals with early intervention strategies that provide adequate levels of hormonally active 1,25-dihydroxyvitamin D3 or its analogs. (65 Refs.)

The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis.

Johnson S.

Med Hypotheses 2000 Sep;55(3):239-41

Multiple sclerosis (MS) has a much higher incidence among caucasians that in any other race. Furthermore: females are much more susceptible than males and white females living in colder, wetter areas are much more susceptible than those living in warmer areas. On the other hand, menstruating women have increased copper (Cu) absorption and half-life, so they tend to accumulate more Cu than males. Moreover, rapidly growing girls have an increased demand for zinc (Zn), but their rapidly decreasing production of melatonin results in impaired Zn absorption, which is exacerbated by the high Cu levels. The low Zn levels result in deficient CuZnSuperoxide dismutase (CuZnSOD), which in turn leads to increased levels of superoxide. Menstruating females also often present with low magnesium (Mg) and vitamin B6 levels. Vitamin B6 moderates intracellular nitric oxide (NO) production and extracellular Mg is required for NO release from the cell, so that a deficiency of these nutrients results in increased NO production in the cell and reduced release from the cell. The trapped NO combines with superoxide to form peroxinitrite, an extremely powerful free radical that leads to the myelin damage of MS. Iron (Fe), molybdenum (Mo) and cadmium (Cd) accumulation also increase superoxide production. Which explains MS in males, who tend to accumulate Fe much faster and Cu much less rapidly than females. Since vitamin D is paramount for Mg absorption, the much reduced exposure to sunlight in the higher latitudes may account for the higher incidence in these areas. Moreover, vitamin B2 is a cofactor for xanthine oxidase, and its deficiency exacerbates the low levels of uric acid caused by high Cu levels, resulting in myelin degeneration. Finally Selenium (Se) and vitamin E prevent lipid peroxidation and EPA and DHA upregulate CuZnSOD. Therefore, supplementation with 100 mg MG, 25 mg vit B6, 10 mg vit B2, 15 mg Zn and 400 IU vit D and E, 100 < mgr;g Se, 180 mg EPA and 120 mg DHA per day between 14 and 16 years of age may prevent MS.

Vitamin B12 metabolism and massive-dose methyl vitamin B12 therapy in Japanese patients with multiple sclerosis.

Kira J; Tobimatsu S; Goto I Department of Neurology, Faculty of Medicine, Kyushu University, Fukuoka.

Intern Med (Japan) Feb 1994, 33 (2) p82-6

Serum vitamin B12 levels and unsaturated vitamin B12 binding capacities were measured in 24 patients with multiple sclerosis (MS), 73 patients with other neurological disorders and 21 healthy subjects. There was no decrease in the vitamin B12 levels, however, a significant decrease in the unsaturated vitamin B12 binding capacities was observed in patients with MS when compared with other groups. A massive dose of methyl vitamin B12 (60 mg every day for 6 months) was administered to 6 patients with chronic progressive MS, a disease which usually had a morbid prognosis and widespread demyelination in the central nervous system. Although the motor disability did not improve clinically, the abnormalities in both the visual and brainstem auditory evoked potentials improved more frequently during the therapy than in the pre-treatment period. We

therefore consider that a massive dose methyl vitamin B12 therapy may be useful as an adjunct to immunosuppressive treatment for chronic progressive MS.

CLINICAL CORRESPONDENCE: the effect of magnesium oral therapy on spasticity in a patient with multiple sclerosis.

Rossier P, van Erven S, Wade DT. Rivermead Rehabilitation Centre, Abingdon Road, Oxford OX1 4XD, UK.

Eur J Neurol 2000 Nov;7(6):741-4

The effects of magnesium glycerophosphate oral therapy on spasticity was studied in a 35-year-old woman with severe spastic paraplegia resulting from multiple sclerosis (MS). We found a significant improvement in the spasticity after only 1 week from the onset of the treatment on the modified Ashworth scale, an improvement in the range of motion and in the measures of angles at resting position in lower limbs. No side-effects were reported and there was no weakness in the arms during the treatment.

Vitamin B12 and its relationship to age of onset of Kira J. et al. 1994 multiple sclerosis.

Sandyk R; Awerbuch GI NeuroCommunication Research Laboratories, Danbury, CT 06811.

Int J Neurosci (England) Jul-Aug 1993, 71 (1-4) p93-9

Attention has been focused recently on the association between vitamin B12 metabolism and the pathogenesis of multiple sclerosis (MS). Several recent reports have documented vitamin B12 deficiency in patients with MS. The etiology of this deficiency in MS is unknown. The majority of these patients do not have pernicious anemia and serum levels of the vitamin Are unrelated to the course or chronicity of the disease. Moreover, vitamin B12 does not reverse the associated macrocytic anemia nor are the neurological deficits of MS improved following supplementation with vitamin B12 . It has been suggested that vitamin B12 deficiency may render the patient more vulnerable to the putative viral and/or immunologic mechanisms widely suspected in MS. In the present communication, we report that serum vitamin B12 levels in MS patients are related to the age of onset of the disease. Specifically, we found in 45 MS patients that vitamin B12 levels were significantly lower in those who experienced the onset of first neurological symptoms prior to age 18 years (N = 10) compared to patients in whom the disease first manifested after age 18 (N = 35). In contrast, serum folate levels were unrelated to age of onset of the disease. As vitamin B12 levels were statistically unrelated to chronicity of illness, these findings suggest a specific association between the timing of onset of first neurological symptoms of MS and vitamin B12 metabolism. In addition, since vitamin B12 is required for the formation of myelin and for immune mechanisms, we propose that its deficiency in MS is of critical pathogenetic significance.

Experimental and clinical studies on dysregulation of magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K. Division of Neurological Diseases, Wakayama Medical College, Japan.

Magnes Res 1992 Dec;5(4):295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.

Homocysteine and vitamin B12 in multiple sclerosis

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Biogenic Amines (Netherlands) 1995, 11/6 (479-485)

The levels of cobalamin and homocysteine in patients with multiple sclerosis (MS) were evaluated. The mean value of cobalamin (B12) in serum and cerebrosphinal fluid (CSF) in MS patients were 0.176 +/- 0.0177 and 0.059 +/- 0.003 mumol/l respectively whereas the levels were 0.317 +/- 0.02 and 0.081 +/- 0.005 mumol/l respectively in the healthy subjects. The mean homocysteine (HC) levels in serum and CSF in MS patients were 13.05 +/- 0.54 and 3.07 +/- 0.15 mumol/l respectively as compared to 2.85 +/- 0.15 and 1.06 +/- 0.07 in the healthy subjects. The increased levels of HC and decreased levels in B12 in serum as well as in CSF in MS patients were significant ($p < 0.001$) as compared to healthy subjects. Our finding indicate that MS patients are particularly prone to B12 deficiency resulting into increased levels of HC both in serum and CSF and this even subtle biochemical signs of abnormality seems to justify B6 and B12 treatment.

Measurement of low-molecular-weight antioxidants, uric acid, tyrosine and tryptophan in plaques and white matter from patients with multiple sclerosis.

Langemann H, Kabiersch A, Newcombe J Department of Research, Cantonal Hospital Basel, Switzerland.

Eur Neurol (Switzerland) 1992, 32 (5) p248-52

The levels of the antioxidants ascorbic acid, cysteine, reduced glutathione and alpha-tocopherol, of the free-radical marker uric acid and of the amino acids tyrosine and tryptophan were measured by means of high-pressure liquid chromatography in plaques, adjacent white matter and distant white matter from patients with multiple sclerosis, and in central nervous system tissue from patients without neurological diseases. Cholesterol and DNA were also determined, to check demyelination and cellularity. Uric acid was increased and glutathione correspondingly decreased in plaques; alpha-tocopherol was lowest in plaques and highest in distant white matter in all cases. Ascorbic acid, cysteine, tyrosine and tryptophan were not significantly changed in any tissue. The results provide evidence supporting the involvement of free radicals in multiple sclerosis.

Clinical trials of unsaturated fatty acids in multiple sclerosis

Field E.J.; Joyce G. Crossley House Neurol. Res. Cent., Newcastle upon Tyne NE4 5NS United Kingdom

IRCS Med. Sci. (England), 1981, 9/12 (1081)

The membrane of MS-RBC (multiple sclerosis-erythrocytes) is different from non-MS. Until now it was believed that 6-8 months treatment with gamma-linolenate converted their abnormal properties into normal, as judged by electrophoretic measurements in the presence of LA (linoleic acid) and AA (arachidonic acid). Further experimentation has shown however, such conversion to non-MS type is delayed until 21-24 months after gamma-linolenate feeding, when low doses of LA and AA begin to have the same effect on mobility as they do in normal cells. Thus any clinical trial of PUFA should begin about 2 years after it is instituted - not concluded, as at present. This may account for the relative success of Swank's dietary treatment which spans over 20 years. The long term requirement for essential fatty acids (EFA) to restore membrane normality in MS must be taken into account in planning therapeutic trials.

Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy

Hibbeln JR, Salem N Jr Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA.

American Journal of Clinical Nutrition (USA), 1995, 62/1 (1-9)

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and postpartum depression. We postulate that adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Indirect evidence for nitric oxide involvement in multiple sclerosis by characterization of circulating antibodies directed against conjugated S-nitrosocysteine.

Boullerne AI, Petry KG, Meynard M, Geffard M INSERM U394 Neurobiologie integrative, Bordeaux, France.

J Neuroimmunol (Netherlands) Jul 1995, 60 (1-2) p117-24

Converging data suggest that nitric oxide (NO) production by cytokine-induced immune cells in demyelinating lesions is involved in multiple sclerosis (MS). High levels of NO may complex to suitable amino acids, causing an immune response against the formed neo-epitopes. By testing MS sera with chemically defined nitroso-amino acids conjugated to carrier protein in ELISA, we observed a significant antibody reaction against the S-nitroso-cysteine epitope. The MS antibody response was exclusively of IgM isotype with an avidity of 8 x 10(-7) M. Sera of all clinical MS forms showed a significantly elevated antibody titer versus sera from healthy subjects or from patients affected with other neurological and autoimmune diseases. The detection of circulating antibodies to a conjugated S-nitroso-cysteine epitope provides indirect evidence for NO involvement in MS.

Isoprenoid (CoQ10) biosynthesis in multiple sclerosis.

Steen G, Axelsson H, Bowallius M, Holthuis N, Molander BM

Acta Neurol Scand (Denmark) Sep 1985, 72 (3) p328-35

Recently discovered metabolites in urine have suggested a defect of isoprenoid metabolism in multiple sclerosis. Lymphocyte HMG-CoA reductase was found unaffected however, and so was lymphocyte biosynthesis of geraniol, farnesol and squalene from mevalonolactone. The level of dolichol in white matter of an MS brain was similar to that of a control sample. Serum ubiquinone, on the other hand, was decreased in multiple sclerosis. Ubiquinone in serum was both age-dependent and related to serum cholesterol. Active as well as stable MS displayed

a decreased level of serum ubiquinone, and a reduced ubiquinone-cholesterol ratio. These results are compatible with a deficient ubiquinone biosynthesis in multiple sclerosis.

Abnormality of fatty acid composition of plasma lipid in multiple sclerosis

Sato S, Shirakawa K, Tsubaki T, Sakuragawa N

Brain Nerve (Tokyo) (Japan), 1979, 31/8 (797-801)

It has been reported that the composition of fatty acid is abnormal in the blood of European patients with multiple sclerosis (MS). The purpose of the present paper is to confirm such an abnormality in Japanese MS. The level of linoleic acid was decreased significantly in active stage at seven relapses in four cases of MS. While the level of plasma linoleic acid was decreased the non-essential fatty acids oleate and palmitate showed significant increase in these relapses. In thirteen patients with MS who were in remission, the level of arachidonic acid was decreased. Clinical courses were correlated to linoleic acid levels in four cases of active MS. The level of linoleic acid was decreased at each relapse and returned to normal in remission.

The pineal and regulation of fibrosis: pinealectomy as a model of primary biliary cirrhosis: Roles of melatonin and prostaglandins in fibrosis and regulation of T lymphocytes

Cunnane SC, Manku MS, Horrobin DF

Med. Hypotheses (England), 1979, 5/4 (403-414)

Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity, increased skin pigmentation and elevated cholesterol and alkaline phosphatase levels. It also leads to reduced formation and/or action of prostaglandin (PG) E1 and thromboxane (TX) A2. PGE1 plays an important role in enhancing function of T suppressor lymphocytes. In primary biliary cirrhosis there are increased skin pigmentation, hepatic fibrosis, elevated cholesterol and alkaline phosphatase levels, defective T lymphocytes and hyperactive B lymphocytes. Primary biliary cirrhosis may be a pineal deficiency disease. Serotonin is important in the pineal and the serotonin antagonist methysergide may cause retroperitoneal fibrosis by interfering with pineal function. These is a good deal of other evidence which suggests that melatonin PGE1 and TXA2 are important in the regulation of fibrosis in other situations such as 'collagen' diseases, lithium-induced fibrosis and cardiomyopathies. This suggests that enhancement of formation of PGE1 and of TXA2 may be of value in diseases associated with excess fibrosis and defective T suppressor cell function. PGE1 levels may be raised by zinc, penicillin, penicillamine and essential fatty acids. TXA2 levels may be raised by low dose colchicine. These new approaches to treatment may prove safer and more effective than existing ones. They may be of value in disorders such as cardiomyopathy, Hodgkin's disease and other

lymphomas, multiple sclerosis, Crohn's disease, atopy and other diseases in which defective T cell function is suspected.

Fatty acid patterns of serum lipids in multiple sclerosis and other diseases

Love W.C.; Reynolds M.; Cashel A.; Callaghan N. Clin. Biochem. Lab., Trinity Coll., Dublin Ireland

Biochem.Soc.Trans. (England), 1973, 1/1 (141-143)

The fatty acid composition of phosphatidylcholines (lecithins) from the brains of patients with multiple sclerosis is altered from that of normal brain. Even in non plaque areas there was an increase in the saturated and a decrease in the unsaturated fatty acids. When the fatty acid composition of serum total lipid extracts was analysed a similar observation was made, with the major decrease occurring in the linoleate fraction. The decrease in linoleate in multiple sclerosis was most marked in the cholesterol linoleate fraction, and was also observed in the lipids of erythrocytes and platelets from patients with this disease. These findings led to the reasonable speculation that the decrease in serum linoleate in the active phase of multiple sclerosis may be due to a dietary deficiency or failure to absorb this fatty acid. The linoleate content of serum lipids is decreased in a variety of acute illnesses and is not specific for multiple sclerosis or other neurological disease. However, attention is drawn to the similarity of the fatty acid pattern of serum lipids in acute illness to that of essential fatty acid deficiency. This phenomenon bears further investigation to see whether the decrease in linoleate content precedes or is a consequence of the illness, and draws attention to the possibility that requirements or metabolism of essential fatty acids may be altered significantly by a large variety of acute illnesses.

Magnesium concentration in plasma and erythrocytes in MS

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Acta Neurologica Scandinavica (Denmark), 1995, 92/1 (109-111)

There are few reports of Mg in MS and none dealing with Mg content in erythrocytes. Mg concentration was determined in serum and in erythrocytes with the help of a BIOTROL Magnesium Calmagite colorimetric method (average sensitivity: 0.194 A per mmol/I) and a Hitachi autoanalyzer in 24 MS patients (7 men and 17 women, age 29-60; 37 years on average with the duration of the disease: 3-19; 11 years on average, at clinical disability stages according to the Kurtzke scale: 1-7; 3.2 on average, in remission stage. A statistically significant decrease ($p < 0.001$) of Mg concentration in erythrocytes and no changes in plasma of MS patients were found. The results obtained suggest the presence of changes in membrane of erythrocytes which could be connected with their shorter life and with affection of their function.

Magnesium concentration in brains from multiple sclerosis patients

Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K Division of Neurological Diseases, Wakayama Medical College, Japan.

Acta Neurol. Scand. (Denmark), 1990, 81/3 (197-200)

Magnesium(Mg) concentrations were studied in the brains of 4 patients with definite multiple sclerosis (MS) and 5 controls. The magnesium contents were determined by inductively coupled plasma emission spectrometry in autopsy samples taken from 26 sites of central nervous system tissues, and visceral organs such as liver, spleen, kidney, heart and lung. The average Mg content in the CNS tissues, as well as visceral organs except for spleen, of MS patients showed a significantly lower value than that seen in control cases. The most marked reduction of Mg content was observed in CNS white matter including demyelinated plaques of MS samples. Whether or not these significantly lower Mg contents found in CNS and visceral organs of MS patients may play an essential role in the demyelinating process remain unclear, requiring further studies on MS pathogenesis from the point of metal metabolism.

Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders

Kapaki E, Segditsa J, Papageorgiou C Department of Neurology, Aeginition University Hospital, Athens, Greece.

Acta Neurol. Scand. (Denmark), 1989, 79/5 (373-378)

Zinc (Zn), copper (Cu) and magnesium(Mg) concentrations in cerebrospinal fluid (CSF) and serum were determined with atomic absorption spectrophotometry in 74 patients suffering from various neurological diseases, and in 28 healthy controls. Increased CSF zinc levels were found in the group of peripheral nervous system diseases ($P < 0.01$) and in the cases of different neurological syndromes with increased CSF protein concentration ($P < 0.001$). Increased CSF and serum copper levels were found in the cases with increased CSF protein levels ($P < 0.05$). It is probable that damaged blood-brain-barrier (BBB) permits the passage of the trace elements Zn, Cu and of Mg into the subarachnoid space. Decreased serum Cu levels ($P < 0.01$) were found in the group of multiple sclerosis (MS). The findings are correlated to those of previous communications.

Evaluation of a nutrition education programme for people with multiple sclerosis

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J. Hum. Nutr. Diet. (United Kingdom), 1993, 6/2 (131-147)

A nutrition education programme was designed specifically to meet the needs of people with multiple sclerosis (MS) and implemented in five self-help groups. The programme was evaluated by means of two 7-day weighed food and drink

records carried out before and after the programme, by an attitude questionnaire and subjectively by the dietitians and participants. Although the diets of the 48 participants were good before the programme, there were significant improvements in the mean intakes of added sugar, saturated fatty acids, N-3 PUFA, P/S ratio and energy from N-3 PUFA in both males and females. RNIs for all mean intakes of vitamins and minerals were met by males and females both before and after the programme and intakes were generally better than mean values for the British adult population. Seventy-five per cent of the group took food supplements before the programme and 65% after. The diets of those people who took supplements before the programme were better, compared with those who did not, in terms of fibre, Vitamin-C, saturated fatty acids, N-3 and N-6 PUFAs. The supplemented group also made more significant changes in their diets compared with the unsupplemented group. Attitudes towards diet were found to be positive both before and after the programme. Dietitians and participants subjectively evaluated the programme and their suggested alterations were incorporated into the programme.

On the causes of multiple sclerosis

Hutter C City Hospital, Nottingham, UK.

Med. Hypotheses (United Kingdom), 1993, 41/2 (93-96)

Evidence on aetiology in multiple sclerosis suggests that the prevalence depends on the interaction of two factors, diet and exposure to visible sunlight. The dietary features which may be beneficial include supplementation with fish oils, avoidance of saturated fats, and the associated intake of antioxidants with unsaturated fatty acids. Inhibition, by antioxidants, of the enzyme lipoxygenase inhibits leukotriene synthesis, and the presence of fish oils leads to the production of leukotrienes with less inflammatory properties. This is of particular importance in the retina where leukotrienes might be the underlying cause of retrobulbar neuritis. The antioxidant properties of vitamin A may also lead to inhibition of leukotriene synthesis. Visible solar radiation could be of benefit therefore by releasing vitamin A from visual pigment rhodopsin. The interaction ot these two factors may explain the epidemiological observations on the prevalence of multiple sclerosis.

Lipids and neurological diseases.

Marshall BH

Med Hypotheses 1991 Mar;34(3):272-4

Neurological diseases, such as multiple sclerosis (MS), Sjogren-Larsson syndrome, Reye's syndrome, and Refsum's syndrome (herediopathica atactica polyneuroformis), and many others afflict millions of persons yearly and have no successful treatment available. A common aspect of these diseases appears to be a lipid imbalance involving the essential fatty acids (EFA), linoleic and linolenic, and trace fatty acids which result from faulty lipid metabolism. It is proposed that

treatments for these diseases should be sought through diet and metabolic enzymes rather than drugs.

Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis.

Cunnane SC, Ho SY, Dore-Duffy P, Ells KR, Horrobin DF Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Canada.

Am J Clin Nutr (United States) Oct 1989, 50 (4) p801-6

This study was conducted to investigate the possible differences in erythrocyte lipid composition, which might account for the previously reported increase in erythrocyte membrane zinc levels in patients with multiple sclerosis (MS). Compared with healthy control subjects, plasma lipids in patients with MS contained less sphingomyelin but more phosphatidylserine and the cholesterol-phospholipid ratio was 42% higher in the plasma from MS patients (p less than 0.01). In erythrocytes from MS patients, phosphatidylinositol was lower and erythrocyte cholesterol per milligram protein was significantly lower than concentrations in healthy control subjects (p less than 0.01). Among the long-chain fatty acids, the omega-3 fatty acids were lower in plasma from MS patients and linoleic acid was lower in erythrocyte ghosts from MS patients (p less than 0.01). We conclude that altered levels of cholesterol in plasma and erythrocytes from MS patients may contribute to increased erythrocyte-membrane Zn in MS patients. It cannot be stated with certainty whether the altered fatty acid profiles in MS patients were a function of the disease or of altered fatty acid intake.

Plasma lipids and their fatty acid composition in multiple sclerosis.

Navarro X, Segura R Department of Physiology, Autonomous University of Barcelona, Spain.

Acta Neurol Scand (Denmark) Aug 1988, 78 (2) p152-7

We report an extensive study of the plasma lipid profile and fatty acid composition in 61 multiple sclerosis (MS) patients compared with 61 normal subjects. The main abnormality in the MS was a reduction in the proportion of linoleic and arachidonic acids mostly evident in the HDL and in the cholesteryl esters fraction, with a compensatory increase in saturated acids. The fatty acid abnormalities correlated with the duration of the disease and the degree of disability. Thus, in the MS patients studied there as a deficiency in essential fatty acids, although this metabolic abnormality does not seem specific to MS.

The effect of nutritional counselling on diet and plasma EFA status in multiple sclerosis patients over 3 years.

Fitzgerald G; Harbige LS; Forti A; Crawford MA ARMS Research Unit, Central Middlesex Hospital, Acton, London, UK.

Hum Nutr Appl Nutr 1987 Oct;41(5):297-310

The dietary intake of 83 people with multiple sclerosis (MS) was assessed by the 7-day weighed intake method prior to dietary advice and at 6-monthly intervals thereafter up to 36 months. The P:S ratio of the diet increased from an initial value of 0.8 to 1.5 after 6 months and 1.34 at 36 months. Biochemical investigation of plasma essential fatty acid (EFA) status specifically linoleic, eicosapentanoic and docosahexanoic acids showed significant correlations with diet. Concurrent 6-monthly neurological and physiotherapy assessments were also carried out, the neurological results are discussed in relation to a nutrient scoring system.

Essential fatty acids in the serum and cerebrospinal fluid of multiple sclerosis patients.

Neu IS

Acta Neurol Scand (Denmark) Mar 1983, 67 (3) p151-63

Statistical evaluation of essential fatty acids (determined by gas chromatography) in the serum and cerebrospinal fluid of patients with definite MS and acute CCT showed marked differences as compared to healthy subjects. It was also evident that the decrease of essential fatty acids in MS patients differed from that of CCT patients. Whereas the fatty acid levels in the serum of MS patients revealed only minor differences as compared to the controls and CCT patients, MS patients did show a clear decrease, especially of linoleic and arachidonic acids, in the CSF. This difference was most pronounced in cholesterol esters in the CSF. One absorption study with safflower oil demonstrated normal enteral absorption of essential fatty acids and the ability to cross the blood-CSF barrier.

Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil.

Horrobin DF

Med Hypotheses (England) Mar 1979, 5 (3) p365-78

Multiple sclerosis (MS) is a disease with no known treatment. In view of this and of its distressing nature patients are attracted by any new concepts. As a reaction to this neurologists are sometimes excessively sceptical and fail to consider new approaches seriously. Recent attempts have been made to treat multiple sclerosis with polyunsaturated fatty acids and with colchicine. This approach is not arbitrary and is firmly grounded in fundamental basic scientific concepts. In patients with multiple sclerosis there is evidence of both an abnormality in essential fatty acid metabolism and an abnormality in lymphocyte function. It is now apparent that the fatty acid abnormality may cause the lymphocyte abnormality and that both may be improved by dietary manipulation. There is also evidence that the demyelination may be associated with recurrent inflammatory episodes and with entry of calcium into the cytoplasm. In vitro colchicine has

been shown to have actions compatible with regulation of cytoplasmic calcium and in two diseases characterised by intermittent inflammatory episodes (Behcets syndrome and familial Mediterranean fever) it has been found to prevent or to reduce the severity of such episodes. Preliminary results suggest that combined therapy with evening primrose oil and colchicine may be of considerable value.

Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis.

Nightingale S, Woo E, Smith AD, French JM, Gale MM, Sinclair HM, Bates D, Shaw DA Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne.

Acta Neurol Scand (Denmark) Jul 1990, 82 (1) p43-50

The fatty acid profiles of phosphatidyl ethanolamine (PE) and phosphatidyl choline (PC) of the red blood cells of 30 patients with mild inactive multiple sclerosis (MS) and 30 healthy controls were studied by gas chromatography. The groups were well matched for factors likely to influence tissue lipid levels, including diet. The MS patients showed a significant reduction in PE eicosapentaenoic acid ($p = 0.009$) especially in women, and an increase in both PE dihomo-gamma-linolenic acid ($p = 0.004$) and PC stearic acid ($p = 0.04$). No reduction in linoleic acid was observed in either the PC or PE fractions of the MS subjects. A similar study of the fatty acid profile in adipose tissue in 26 MS and 35 healthy controls found no detectable eicosapentaenoic acid in either group. However, whereas docosahexaenoic acid was not detectable in any MS patient, 40% of the controls had measurable levels varying from to 0.1 to 0.3% of total estimated fatty acid ($p = 0.0003$). No reduction in linoleic acid in MS subjects was observed. Supplementation with oral fish body oil demonstrated that n-3 fatty acids were incorporated into red blood cells over 5 weeks and this occurred equally in MS and controls. The effects of oral supplementation on adipose tissue were studied after 1 and 2 years. Whereas many fatty acids such as linoleic acid were raised at 1 year, but did not rise subsequently, eicosapentaenoic acid and docosahexaenoic acid continued to rise through the 2-year period.

The nutritional regulation of T lymphocyte function.

Horrobin DF, Manku MS, Oka M, Morgan RO, Cunnane SC, Ally AI, Ghayur T, Schweitzer M, Karmali RA

Med Hypotheses (England) Sep 1979, 5 (9) p969-85

Prostaglandin (PG) E1 plays a major role in the regulation of thymus development and T lymphocyte function and the evidence for this is reviewed. The production of PGE1 is dependent on nutritional factors with linoleic acid, gamma-linolenic acid, pyridoxine, zinc and Vitamin-C playing key roles. Inadequate intake of any one of these will lead to inadequate PGE1 formation and defective T lymphocyte function. Megadoses of any one are likely to be only minimally effective in the absence of adequate intakes of the others. By careful attention to diet it should be

possible to activate T lymphocyte function in the large number of diseases including rheumatoid arthritis, various auto-immune diseases, multiple sclerosis, and cancer in which such function is defective. It is possible that T lymphocytes may require both endogenous and exogenous PGE1 in order to function adequately. It is therefore of particular interest that many cancer cells and virally infected cells are unable to make PGE1 because they cannot convert linoleic acid to gamma-linolenic acid. The direct provision of gamma-linolenic or dihomo-gammalinolenic acids in these situations is worthy of full investigation.

Effect of prolonged ingestion of gamma-linolenate by MS patients.

Field EJ, Joyce G

Eur Neurol (Switzerland) 1978, 17 (2) p67-76

The absolute electrophoretic mobility of erythrocytes from MS patients is reduced in the presence of 0.08 mg/ml of linoleic or arachidonic acid, whilst that of normal or other neurological disease patients is increased in the presence of these acids. When an MS patient ingests gamma-linolenate (in capsule form equivalent to 413.4 mg of gamma-linolenic acid and 2.664 g of linoleic acid per day) the reaction of MS erythrocytes begins to change. After 3 or 4 months the reaction becomes normal with arachidonic acid (i.e. mobility is speeded up) and 2 months or so later this occurs also with linoleic acid. Very prolonged administration of gamma-linolenate leads to a markedly increased sensitivity to the effect of prostaglandins (PGE2) on RBC mobility. The observations are interpreted to mean the induction of a biochemical-biophysical change in the membranes, and the significance of this in the aetiology and treatment of multiple sclerosis is discussed.

Experimental and clinical studies on dysregulation of Magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K Division of Neurological Diseases, Wakayama Medical College, Japan.

Magnes Res (England) Dec 1992, 5 (4) p295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A

magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.

Multiple sclerosis and neurotransmission

Ali Qureshi G.; Halawa A.; Baig S.; Siden A.
Clinical Research Center, Dept. Clin. Neuroscience Family Med., Huddinge University Hospital, S-141 57 Stockholm Sweden
Biogenic Amines (Netherlands), 1996, 12/5 (353-376)

In this study, the role of excitatory amino acids (EAA), nitrite (metabolite of nitric oxide), vitamin B12, homocysteine (HC), monoamines, and neuropeptides such as cholecystokinin (CCK) and neuropeptide Y in multiple sclerosis (MS) is defined on the basis of accumulated results obtained in cerebrospinal fluid from 47 MS patients. These results were compared with 25 healthy subjects. These results showed the significant increase of free radical NO, arginine, tryptophan, noradrenaline and HC, and decrease in the levels of Apartate, glutamate, dopamine, vitamin B12, CCK-4 and CCK-8 in MS patients. From these results, the role of NO, HC and deficiency of vitamin B12 are considered as some of the factors attributing to the degeneration of MS.

[Visual, auditory and somatosensory potentials in the diagnosis of vitamin B12 deficiency]

Cheliout-Heraut F, Durand MC, Desterbecq E, Dizien O, de Lattre J
Service d'explorations fonctionnelles, hopital Raymond Poincare, Garches, France.
Neurophysiol Clin 1997;27(1):59-65

We describe visual, brain stem auditory, and somatosensory evoked (VEP, BAEP, SEP) in a 49-year old male patient presenting with subacute degeneration of the spinal cord due to vitamin B12 deficiency. Neurological signs included tetraplegia with a C4-C5 spinal cord compression that was unchanged after surgical decompression. Before treatment, the duration of the bilateral VEP was slightly increased, though their amplitude and morphology were not modified. BAEP were normal. However, abnormalities of SEP with loss of cortical potentials were noticed. Two months after initiation of the treatment, both VEP and SEP recorded in response to median nerve stimulation had improved, but there was still no cortical response to tibial nerve stimulation. Eighteen months later, VEP were normal and recovery of SEP in response to tibial nerve stimulation was observed; however, alterations of peripheral sensory and motor action potentials were still

present. These findings are in good agreement with previously reported pathological changes in patients presenting with subacute combined degeneration. Similar abnormalities have been described in patients with multiple sclerosis. Evoked potentials in this case proved to be useful for the diagnosis and the evaluation of the efficacy of the treatment. These findings also suggest that demyelination of the posterior part of the spinal cord and peripheral axonal degeneration might be the main pathological changes related to vitamin B12 deficiency. The former, but not like the latter, were clearly responsive to the treatment.

Folate, vitamin B12, and neuropsychiatric disorders.

Bottiglieri T
Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas, USA.
Nutr Rev (United States) Dec 1996, 54 (12) p382-90

Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.

1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

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Proceedings of the National Academy of Sciences of the United States of America (USA), 1996, 93/15 (7861-7864)

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease multiple sclerosis (MS). Induced by immunizing B10.PL mice with myelin basic protein (MBP). EAE was completely prevented by the administration of 1,25-dihydroxyvitamin D3 (1,25- (OH)2D3). 1,25-(OH)2D3 could also prevent the progression of EAE when administered at the appearance of the first disability symptoms. Withdrawal of 1,25-(OH)2D3

resulted in a resumption of the progression of EAE. Thus, the block by 1,25-(OH)2D3 is reversible. A deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, 1,25-(OH)2D3 or its analogs are potentially important for treatment of MS.

Measurement of low-molecular-weight antioxidants, uric acid, tyrosine and tryptophan in plaques and white matter from patients with multiple sclerosis.

Langemann H, Kabiersch A, Newcombe J
Department of Research, Cantonal Hospital Basel, Switzerland.
Eur Neurol (Switzerland) 1992, 32 (5) p248-52

The levels of the antioxidants ascorbic acid, cysteine, reduced glutathione and alpha-tocopherol, of the free-radical marker uric acid and of the amino acids tyrosine and tryptophan were measured by means of high-pressure liquid chromatography in plaques, adjacent white matter and distant white matter from patients with multiple sclerosis, and in central nervous system tissue from patients without neurological diseases. Cholesterol and DNA were also determined, to check demyelination and cellularity. Uric acid was increased and glutathione correspondingly decreased in plaques; alpha-tocopherol was lowest in plaques and highest in distant white matter in all cases. Ascorbic acid, cysteine, tyrosine and tryptophan were not significantly changed in any tissue. The results provide evidence supporting the involvement of free radicals in multiple sclerosis.

Clinical trials of unsaturated fatty acids in multiple sclerosis

Field E.J.; Joyce G.
Crossley House Neurol. Res. Cent., Newcastle upon Tyne NE4 5NS United Kingdom
IRCS Med. Sci. (England), 1981, 9/12 (1081)

The membrane of MS-RBC (multiple sclerosis-erythrocytes) is different from non-MS. Until now it was believed that 6-8 months treatment with gamma-linolenate converted their abnormal properties into normal, as judged by electrophoretic measurements in the presence of LA (linoleic acid) and AA (arachidonic acid). Further experimentation has shown however, such conversion to non-MS type is delayed until 21-24 months after gamma-linolenate feeding, when low doses of LA and AA begin to have the same effect on mobility as they do in normal cells. Thus any clinical trial of PUFA should begin about 2 years after it is instituted - not concluded, as at present. This may account for the relative success of Swank's dietary treatment which spans over 20 years. The long term requirement for essential fatty acids (EFA) to restore membrane normality in MS must be taken into account in planning therapeutic trials.

Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy

Hibbeln JR, Salem N Jr
Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA.
American Journal of Clinical Nutrition (USA), 1995, 62/1 (1-9)

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and postpartum depression. We postulate that adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Indirect evidence for nitric oxide involvement in multiple sclerosis by characterization of circulating antibodies directed against conjugated S-nitrosocysteine.

Boullerne AI, Petry KG, Meynard M, Geffard M
INSERM U394 Neurobiologie integrative, Bordeaux, France.
J Neuroimmunol (Netherlands) Jul 1995, 60 (1-2) p117-24

Converging data suggest that nitric oxide (NO) production by cytokine-induced immune cells in demyelinating lesions is involved in multiple sclerosis (MS). High levels of NO may complex to suitable amino acids, causing an immune response against the formed neo-epitopes. By testing MS sera with chemically defined nitroso-amino acids conjugated to carrier protein in ELISA, we observed a significant antibody reaction against the S-nitroso-cysteine epitope. The MS antibody response was exclusively of IgM isotype with an avidity of 8 x 10(-7) M. Sera of all clinical MS forms showed a significantly elevated antibody titer versus sera from healthy subjects or from patients affected with other neurological and autoimmune diseases. The detection of circulating antibodies to a conjugated S-nitroso-cysteine epitope provides indirect evidence for NO involvement in MS.

Isoprenoid (coQ10) biosynthesis in multiple sclerosis.

Steen G, Axelsson H, Bowallius M, Holthuis N, Molander BM
Acta Neurol Scand (Denmark) Sep 1985, 72 (3) p328-35

Recently discovered metabolites in urine have suggested a defect of isoprenoid metabolism in multiple sclerosis. Lymphocyte HMG-CoA reductase was found unaffected however, and so was lymphocyte biosynthesis of geraniol, farnesol and squalene from mevalonolactone. The level of dolichol in white matter of an MS brain was similar to that of a control sample. Serum ubiquinone, on the other hand, was decreased in multiple sclerosis. Ubiquinone in serum was both age-dependent and related to serum cholesterol. Active as well as stable MS displayed a decreased level of serum ubiquinone, and a reduced ubiquinone-cholesterol ratio. These results are compatible with a deficient ubiquinone biosynthesis in multiple sclerosis.

Abnormality of fatty acid composition of plasma lipid in multiple sclerosis

Sato S, Shirakawa K, Tsubaki T, Sakuragawa N
Brain Nerve (Tokyo) (Japan), 1979, 31/8 (797-801)

It has been reported that the composition of fatty acid is abnormal in the blood of European patients with multiple sclerosis (MS). The purpose of the present paper is to confirm such an abnormality in Japanese MS. The level of linoleic acid was decreased significantly in active stage at seven relapses in four cases of MS. While the level of plasma linoleic acid was decreased the non-essential fatty acids oleate and palmitate showed significant increase in these relapses. In thirteen patients with MS who were in remission, the level of arachidonic acid was decreased. Clinical courses were correlated to linoleic acid levels in four cases of active MS. The level of linoleic acid was decreased at each relapse and returned to normal in remission.

The pineal and regulation of fibrosis: pinealectomy as a model of primary biliary cirrhosis: Roles of melatonin and prostaglandins in fibrosis and regulation of T lymphocytes

Cunnane SC, Manku MS, Horrobin DF
Med. Hypotheses (England), 1979, 5/4 (403-414)

Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity, increased skin pigmentation and elevated cholesterol and alkaline phosphatase levels. It also leads to reduced formation and/or action of prostaglandin (PG) E1 and thromboxane (TX) A2. PGE1 plays an important role

in enhancing function of T suppressor lymphocytes. In primary biliary cirrhosis there are increased skin pigmentation, hepatic fibrosis, elevated cholesterol and alkaline phosphatase levels, defective T lymphocytes and hyperactive B lymphocytes. Primary biliary cirrhosis may be a pineal deficiency disease. Serotonin is important in the pineal and the serotonin antagonist methysergide may cause retroperitoneal fibrosis by interfering with pineal function. These is a good deal of other evidence which suggests that melatonin PGE1 and TXA2 are important in the regulation of fibrosis in other situations such as 'collagen' diseases, lithium-induced fibrosis and cardiomyopathies. This suggests that enhancement of formation of PGE1 and of TXA2 may be of value in diseases associated with excess fibrosis and defective T suppressor cell function. PGE1 levels may be raised by zinc, penicillin, penicillamine and essential fatty acids. TXA2 levels may be raised by low dose colchicine. These new approaches to treatment may prove safer and more effective than existing ones. They may be of value in disorders such as cardiomyopathy, Hodgkin's disease and other lymphomas, multiple sclerosis, Crohn's disease, atopy and other diseases in which defective T cell function is suspected.

Fatty acid patterns of serum lipids in multiple sclerosis and other diseases

Love W.C.; Reynolds M.; Cashel A.; Callaghan N.
Clin. Biochem. Lab., Trinity Coll., Dublin Ireland
Biochem.Soc.Trans. (England), 1973, 1/1 (141-143)

The fatty acid composition of phosphatidylcholines (lecithins) from the brains of patients with multiple sclerosis is altered from that of normal brain. Even in non plaque areas there was an increase in the saturated and a decrease in the unsaturated fatty acids. When the fatty acid composition of serum total lipid extracts was analysed a similar observation was made, with the major decrease occurring in the linoleate fraction. The decrease in linoleate in multiple sclerosis was most marked in the cholesterol linoleate fraction, and was also observed in the lipids of erythrocytes and platelets from patients with this disease. These findings led to the reasonable speculation that the decrease in serum linoleate in the active phase of multiple sclerosis may be due to a dietary deficiency or failure to absorb this fatty acid. The linoleate content of serum lipids is decreased in a variety of acute illnesses and is not specific for multiple sclerosis or other neurological disease. However, attention is drawn to the similarity of the fatty acid pattern of serum lipids in acute illness to that of essential fatty acid deficiency. This phenomenon bears further investigation to see whether the decrease in linoleate content precedes or is a consequence of the illness, and draws attention to the possibility that requirements or metabolism of essential fatty acids may be altered significantly by a large variety of acute illnesses.

Magnesium concentration in plasma and erythrocytes in MS

Stelmasiak Z, Solski J, Jakubowska B
Department of Clinical Analytics, School of Medicine, Lublin, Poland.
Acta Neurologica Scandinavica (Denmark), 1995, 92/1 (109-111)

There are few reports of Mg in MS and none dealing with Mg content in erythrocytes. Mg concentration was determined in serum and in erythrocytes with the help of a BIOTROL Magnesium Calmagite colorimetric method (average sensitivity: 0.194 A per mmol/I) and a Hitachi autoanalyzer in 24 MS patients (7 men and 17 women, age 29-60; 37 years on average with the duration of the disease: 3-19; 11 years on average, at clinical disability stages according to the Kurtzke scale: 1-7; 3.2 on average, in remission stage. A statistically significant decrease ($p < 0.001$) of Mg concentration in erythrocytes and no changes in plasma of MS patients were found. The results obtained suggest the presence of changes in membrane of erythrocytes which could be connected with their shorter life and with affection of their function.

Comparative findings on serum IMg2+ of normal and diseased human subjects with the NOVA and KONE ISE's for Mg2+

Altura BT, Bertschat F, Jeremias A, Ising H, Altura BM
Department of Physiology, State University of New York, Health Science Center at Brooklyn 11203.
Scand J Clin Lab Invest Suppl 1994;217:77-81

It is clear now that although different ionophores for ionized Mg (Img2+) have been designed by several groups, each of these has a distinctly different K(MgCa). In view of this, it is important to determine whether each of these ion selective electrodes (ISE's) yield identical results for IMg2+ in sera from healthy and diseased humans. Using such an approach, we determined, in a blinded-and random manner, IMg2+ with both the NOVA and KONE ISE's for IMg2+ in two independent laboratories. No significant differences were found either for sera from healthy human volunteers or diseased patients. We did, however, note several interesting findings: 1. randomly, selected hospitalized patients exhibit a much higher incidence of abnormalities for IMg2+ (57-71%) than that noted previously for total Mg (TMg) measurements; and 2. coronary heart disease, rectal cancer and multiple sclerosis patients exhibit extracellular deficits in ionized free Mg.

Magnesium concentration in brains from multiple sclerosis patients

Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K
Division of Neurological Diseases, Wakayama Medical College, Japan.
Acta Neurol. Scand. (Denmark), 1990, 81/3 (197-200)

Magnesium (Mg) concentrations were studied in the brains of 4 patients with definite multiple sclerosis (MS) and 5 controls. The magnesium contents were determined by inductively coupled plasma emission spectrometry in autopsy samples taken from 26 sites of central nervous system tissues, and visceral organs such as liver, spleen, kidney, heart and lung. The average Mg content in the CNS tissues, as well as visceral organs except for spleen, of MS patients showed a significantly lower value than that seen in control cases. The most marked reduction of Mg content was observed in CNS white matter including demyelinated plaques of MS samples. Whether or not these significantly lower Mg contents found in CNS and visceral organs of MS patients may play an essential role in the demyelinating process remain unclear, requiring further studies on MS pathogenesis from the point of metal metabolism.

Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders

Kapaki E, Segditsa J, Papageorgiou C
Department of Neurology, Aeginition University Hospital, Athens, Greece.
Acta Neurol. Scand. (Denmark), 1989, 79/5 (373-378)

Zinc (Zn), copper (Cu) and magnesium (Mg) concentrations in cerebrospinal fluid (CSF) and serum were determined with atomic absorption spectrophotometry in 74 patients suffering from various neurological diseases, and in 28 healthy controls. Increased CSF zinc levels were found in the group of peripheral nervous system diseases ($P < 0.01$) and in the cases of different neurological syndromes with increased CSF protein concentration ($P < 0.001$). Increased CSF and serum copper levels were found in the cases with increased CSF protein levels ($P < 0.05$). It is probable that damaged blood-brain-barrier (BBB) permits the passage of the trace elements Zn, Cu and of Mg into the subarachnoid space. Decreased serum Cu levels ($P < 0.01$) were found in the group of multiple sclerosis (MS). The findings are correlated to those of previous communications.

Multiple sclerosis: Decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D

Goldberg P, Fleming MC, Picard EH
Med. Hypotheses (UK), 1986, 21/2 (193-200)

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for

younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

Evaluation of a nutrition education programme for people with multiple sclerosis

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J. Hum. Nutr. Diet. (United Kingdom), 1993, 6/2 (131-147)

A nutrition education programme was designed specifically to meet the needs of people with multiple sclerosis (MS) and implemented in five self-help groups. The programme was evaluated by means of two 7-day weighed food and drink records carried out before and after the programme, by an attitude questionnaire and subjectively by the dietitians and participants. Although the diets of the 48 participants were good before the programme, there were significant improvements in the mean intakes of added sugar, saturated fatty acids, N-3 PUFA, P/S ratio and energy from N-3 PUFA in both males and females. RNIs for all mean intakes of vitamins and minerals were met by males and females both before and after the programme and intakes were generally better than mean values for the British adult population. Seventy-five per cent of the group took food supplements before the programme and 65% after. The diets of those people who took supplements before the programme were better, compared with those who did not, in terms of fibre, Vitamin-C, saturated fatty acids, N-3 and N-6 PUFAs. The supplemented group also made more significant changes in their diets compared with the unsupplemented group. Attitudes towards diet were found to be positive both before and after the programme. Dietitians and participants subjectively evaluated the programme and their suggested alterations were incorporated into the programme.

Multiple sclerosis: A diathesis?

Adlam J.P.
Italy
Gazz.Sanit. (Milano) (Italy), 1973, 22/1 (37-39)

The incidence of multiple sclerosis among predisposed subjects is higher in cold climates, and is compounded where trace metals, such as copper, selenium and cobalt, are lacking in the diet. The importance of trace elements in various metabolic processes is discussed, including the etiology of multiple sclerosis. Screening children, removing those at risk to warmer climates and further research into trace metal physiology are recommended.

Lipids and neurological diseases.

Marshall BH
Med Hypotheses 1991 Mar;34(3):272-4

Neurological diseases, such as multiple sclerosis (MS), Sjogren-Larsson syndrome, Reye's syndrome, and Refsum's syndrome (herediopathica atactica polyneuroformis), and many others afflict millions of persons yearly and have no successful treatment available. A common aspect of these diseases appears to be a lipid imbalance involving the essential fatty acids (EFA), linoleic and linolenic, and trace fatty acids which result from faulty lipid metabolism. It is proposed that treatments for these diseases should be sought through diet and metabolic enzymes rather than drugs.

Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis.

Cunnane SC, Ho SY, Dore-Duffy P, Ells KR, Horrobin DF
Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Canada.
Am J Clin Nutr (United States) Oct 1989, 50 (4) p801-6

This study was conducted to investigate the possible differences in erythrocyte lipid composition, which might account for the previously reported increase in erythrocyte membrane zinc levels in patients with multiple sclerosis (MS). Compared with healthy control subjects, plasma lipids in patients with MS contained less sphingomyelin but more phosphatidylserine and the cholesterol-phospholipid ratio was 42% higher in the plasma from MS patients (p less than 0.01). In erythrocytes from MS patients, phosphatidylinositol was lower and erythrocyte cholesterol per milligram protein was significantly lower than concentrations in healthy control subjects (p less than 0.01). Among the long-chain fatty acids, the omega-3 fatty acids were lower in plasma from MS patients and linoleic acid was lower in erythrocyte ghosts from MS patients (p less than 0.01). We conclude that altered levels of cholesterol in plasma and erythrocytes from MS patients may contribute to increased erythrocyte-membrane Zn in MS patients. It cannot be stated with certainty whether the altered fatty acid profiles in MS patients were a function of the disease or of altered fatty acid intake.

Plasma lipids and their fatty acid composition in multiple sclerosis.

Navarro X, Segura R
Department of Physiology, Autonomous University of Barcelona, Spain.
Acta Neurol Scand (Denmark) Aug 1988, 78 (2) p152-7

We report an extensive study of the plasma lipid profile and fatty acid composition in 61 multiple sclerosis (MS) patients compared with 61 normal subjects. The main abnormality in the MS was a reduction in the proportion of linoleic and arachidonic acids mostly evident in the HDL and in the cholesteryl esters fraction, with a compensatory increase in saturated acids. The fatty acid abnormalities correlated with the duration of the disease and the degree of disability. Thus, in the MS patients studied there as a deficiency in essential fatty acids, although this metabolic abnormality does not seem specific to MS.

The effect of nutritional counselling on diet and plasma EFA status in multiple sclerosis patients over 3 years.

Fitzgerald G; Harbige LS; Forti A; Crawford MA
ARMS Research Unit, Central Middlesex Hospital, Acton, London, UK.
Hum Nutr Appl Nutr 1987 Oct;41(5):297-310

The dietary intake of 83 people with multiple sclerosis (MS) was assessed by the 7-day weighed intake method prior to dietary advice and at 6-monthly intervals thereafter up to 36 months. The P:S ratio of the diet increased from an initial value of 0.8 to 1.5 after 6 months and 1.34 at 36 months. Biochemical investigation of plasma essential fatty acid (EFA) status specifically linoleic, eicosapentanoic and docosahexanoic acids showed significant correlations with diet. Concurrent 6-monthly neurological and physiotherapy assessments were also carried out, the neurological results are discussed in relation to a nutrient scoring system.

[Metabolic aspects of multiple sclerosis]

Neu IS
Wien Med Wochenschr (Austria) Jan 31 1985, 135 (1-2) p20-2

According to the present opinion multiple sclerosis (MS) is caused by a concurreance of various factors. This predisposing factor seem to be related to a disturbance of the lipid- and fatty acid metabolism, characterized by decreased concentrations of polyunsaturated fatty acids (PUFA) and essential fatty acids (EFA) in the plasma, the blood cells, the cerebrospinal fluid (CSF) and white matter of the brain in patients with MS. A disturbed absorption of EFA could be excluded. Now the question arises whether there is a disturbed utilisation of EFA with the consequence of biochemical changes in myelin and blood cells. According to lipid-chemical and lipolytic enzymological studies a disturbance of the fatty acid elongation system as well as primary increased activation of the phospholipase A1 is conceivable. According to the demonstrated results the conception of a metabolic immunological caused generalised defect of the biological membranes - especially those of the myelin sheath and platelets - as predisposing factor for the increased platelet aggregation is possible. Even though

these ideas do not yet allow a concrete pathogenetic conclusion, the prostaglandins (PG) might be of importance because their precursors are fatty acids and influence the immune mechanisms. Possibly, new approaches follow from the synopsis of present working hypotheses for an extended biochemical-immunological model of multiple sclerosis. Further immunological and laboratory methods should concentrate on differentiating MS from other diseases of the central nervous system and on diagnosing the disease in its early stage. The results of this work are fully discussed in other publications. Separate prints can be requested from the author.

Essential fatty acids in the serum and cerebrospinal fluid of multiple sclerosis patients.

Neu IS
Acta Neurol Scand (Denmark) Mar 1983, 67 (3) p151-63

Statistical evaluation of essential fatty acids (determined by gas chromatography) in the serum and cerebrospinal fluid of patients with definite MS and acute CCT showed marked differences as compared to healthy subjects. It was also evident that the decrease of essential fatty acids in MS patients differed from that of CCT patients. Whereas the fatty acid levels in the serum of MS patients revealed only minor differences as compared to the controls and CCT patients, MS patients did show a clear decrease, especially of linoleic and arachidonic acids, in the CSF. This difference was most pronounced in cholesterol esters in the CSF. One absorption study with safflower oil demonstrated normal enteral absorption of essential fatty acids and the ability to cross the blood-CSF barrier.

Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil.

Horrobin DF
Med Hypotheses (England) Mar 1979, 5 (3) p365-78

Multiple sclerosis (MS) is a disease with no known treatment. In view of this and of its distressing nature patients are attracted by any new concepts. As a reaction to this neurologists are sometimes excessively sceptical and fail to consider new approaches seriously. Recent attempts have been made to treat multiple sclerosis with polyunsaturated fatty acids and with colchicine. This approach is not arbitrary and is firmly grounded in fundamental basic scientific concepts. In patients with multiple sclerosis there is evidence of both an abnormality in essential fatty acid metabolism and an abnormality in lymphocyte function. It is now apparent that the fatty acid abnormality may cause the lymphocyte abnormality and that both may be improved by dietary manipulation. There is also evidence that the demyelination may be associated with recurrent inflammatory episodes and with entry of calcium into the cytoplasm. In vitro colchicine has

been shown to have actions compatible with regulation of cytoplasmic calcium and in two diseases characterised by intermittent inflammatory episodes (Behcets syndrome and familial Mediterranean fever) it has been found to prevent or to reduce the severity of such episodes. Preliminary results suggest that combined therapy with evening primrose oil and colchicine may be of considerable value.

Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis.

Nightingale S, Woo E, Smith AD, French JM, Gale MM, Sinclair HM, Bates D, Shaw DA
Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne.
Acta Neurol Scand (Denmark) Jul 1990, 82 (1) p43-50

The fatty acid profiles of phosphatidyl ethanolamine (PE) and phosphatidyl choline (PC) of the red blood cells of 30 patients with mild inactive multiple sclerosis (MS) and 30 healthy controls were studied by gas chromatography. The groups were well matched for factors likely to influence tissue lipid levels, including diet. The MS patients showed a significant reduction in PE eicosapentaenoic acid ($p = 0.009$) especially in women, and an increase in both PE dihomo-gamma-linolenic acid ($p = 0.004$) and PC stearic acid ($p = 0.04$). No reduction in linoleic acid was observed in either the PC or PE fractions of the MS subjects. A similar study of the fatty acid profile in adipose tissue in 26 MS and 35 healthy controls found no detectable eicosapentaenoic acid in either group. However, whereas docosahexaenoic acid was not detectable in any MS patient, 40% of the controls had measurable levels varying from to 0.1 to 0.3% of total estimated fatty acid ($p = 0.0003$). No reduction in linoleic acid in MS subjects was observed. Supplementation with oral fish body oil demonstrated that n-3 fatty acids were incorporated into red blood cells over 5 weeks and this occurred equally in MS and controls. The effects of oral supplementation on adipose tissue were studied after 1 and 2 years. Whereas many fatty acids such as linoleic acid were raised at 1 year, but did not rise subsequently, eicosapentaenoic acid and docosahexaenoic acid continued to rise through the 2-year period.

Multiple sclerosis: effect of gamma linolenate administration upon membranes and the need for extended clinical trials of unsaturated fatty acids.

Field EJ, Joyce G
Eur Neurol (Switzerland) 1983, 22 (1) p78-83

Electrophoretic mobility studies of red blood cells from subjects with multiple sclerosis indicate that treatment with unsaturated fatty acids must continue for at least 2 years before normal reactivity is restored by currently available tests. If this applies to myelin also, then clinical trials aimed at treating the recognized

multiple sclerosis subject by polyunsaturated fatty acids really begin after 2 years, and this should be recognized when a trial program is drawn up.

The nutritional regulation of T lymphocyte function.

Horrobin DF, Manku MS, Oka M, Morgan RO, Cunnane SC, Ally AI, Ghayur T, Schweitzer M, Karmali RA
Med Hypotheses (England) Sep 1979, 5 (9) p969-85

Prostaglandin (PG) E1 plays a major role in the regulation of thymus development and T lymphocyte function and the evidence for this is reviewed. The production of PGE1 is dependent on nutritional factors with linoleic acid, gamma-linolenic acid, pyridoxine, zinc and Vitamin-C playing key roles. Inadequate intake of any one of these will lead to inadequate PGE1 formation and defective T lymphocyte function. Megadoses of any one are likely to be only minimally effective in the absence of adequate intakes of the others. By careful attention to diet it should be possible to activate T lymphocyte function in the large number of diseases including rheumatoid arthritis, various auto-immune diseases, multiple sclerosis, and cancer in which such function is defective. It is possible that T lymphocytes may require both endogenous and exogenous PGE1 in order to function adequately. It is therefore of particular interest that many cancer cells and virally infected cells are unable to make PGE1 because they cannot convert linoleic acid to gamma-linolenic acid. The direct provision of gamma-linolenic or dihomo-gammalinolenic acids in these situations is worthy of full investigation.

Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis.

Bates D, Fawcett PR, Shaw DA, Weightman D
Br Med J (England) Nov 18 1978, 2 (6149) p1390-1

One hundred and sixteen patients with acute remitting multiple sclerosis (MS) took part in a double-blind controlled trial of treatment with polyunsaturated fatty acids and were randomly allocated to one of four groups. Two groups received linoleic acid, one alone as a spread and one with gamma-linolenic acid in capsules (Naudicelle); and two control groups received oleic acid, one as a spread and one in capsules. Rates of clinical deterioration and frequencies of attacks were not significantly different between treated and control groups. Exacerbations were shorter and less severe in patients receiving a high dose of linoleic acid than in controls, but those receiving a lower dose--that is, Naudicelle--showed no such difference. Thus supplementing the diet with 20 g linoleic acid marginally affected the duration and severity of relapses of MS but had no effect on overall disability. The dose of Naudicelle used provided insufficient supplementation.

Effect of prolonged ingestion of gamma-linolenate by MS patients.

Field EJ, Joyce G
Eur Neurol (Switzerland) 1978, 17 (2) p67-76

The absolute electrophoretic mobility of erythrocytes from MS patients is reduced in the presence of 0.08 mg/ml of linoleic or arachidonic acid, whilst that of normal or other neurological disease patients is increased in the presence of these acids. When an MS patient ingests gamma-linolenate (in capsule form equivalent to 413.4 mg of gamma-linolenic acid and 2.664 g of linoleic acid per day) the reaction of MS erythrocytes begins to change. After 3 or 4 months the reaction becomes normal with arachidonic acid (i.e. mobility is speeded up) and 2 months or so later this occurs also with linoleic acid. Very prolonged administration of gamma-linolenate leads to a markedly increased sensitivity to the effect of prostaglandins (PGE2) on RBC mobility. The observations are interpreted to mean the induction of a biochemical-biophysical change in the membranes, and the significance of this in the aetiology and treatment of multiple sclerosis is discussed.

Experimental and clinical studies on dysregulation of magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K
Division of Neurological Diseases, Wakayama Medical College, Japan.
Magnes Res (England) Dec 1992, 5 (4) p295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing

the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.

22. Osteoporosis

Preventative and curative options include:

Calcium. magnesium, zinc, manganese, vitamin D3, DHEA, soy extract, ipriflavone, progesterone cream, vitamin K, GLA/DHA, fish oil

Efficacy of ipriflavone in established osteoporosis and long-term safety.

Agnusdei D, Bufalino L. Institute of Internal Medicine and Medical Pathology, University of Siena, Italy.

Calcif Tissue Int 1997;61 Suppl 1:S23-7

Ipriflavone (i.p.), an isoflavone derivative, is currently used in several countries for prevention and treatment of osteoporosis. Recently, 149 elderly, osteoporotic women (65-79 years) with prevalent vertebral fractures were enrolled in two Italian, multicenter, double-blind, 2-year studies. Women were randomly allocated to receive either oral i.p. (200 mg T.I.D. at meals) or matching placebo, plus 1 g oral calcium daily. One hundred eleven subjects completed the 2-year treatment period. A significant increase in forearm bone mineral density (BMD), measured by dual photon absorptiometry (DPA), was obtained after i.p. treatment. Women receiving the placebo showed only a limited bone loss during the treatment period, probably due to calcium supplement; however, a significant between-treatment difference was obtained in both studies. Urinary hydroxyproline was significantly decreased in i.p.-treated patients, suggesting a reduction in bone turnover rate. A reduction of incident vertebral fractures was observed in i.p.-treated women compared with control subjects. A significant improvement of bone pain and mobility has also been pointed out in one of the studies. To date, 2769 patients have been treated with i.p., for a total of 3132 patient/years, in 60 clinical studies performed in Italy, Japan, and Hungary and reviewed for long-term safety assessment. The incidence of adverse reactions in ipriflavone-treated patients (14.5%) was similar to that observed in subjects receiving the placebo (16.1%). Side effects were mainly gastrointestinal. Few patients presented reversible modifications of laboratory parameters. The data from the above studies show that long-term treatment with i.p. may be considered safe, and may increase bone density and possibly prevent fractures in elderly patients with established osteoporosis.

Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial.

Alexandersen P, Toussaint A, Christiansen C, Devogelaer JP, Roux C, Fechtenbaum J, Gennari C, Reginster JY; Ipriflavone Multicenter European Fracture Study. Center for Clinical and Basic Research, Ballerup Byvej 222, 2750 Ballerup, Denmark. pa@ccbr.dk

JAMA 2001 Mar 21;285(11):1482-8

CONTEXT: Data on the efficacy and safety of ipriflavone for prevention of postmenopausal bone loss are conflicting. OBJECTIVES: To investigate the effect of oral ipriflavone on prevention of postmenopausal bone loss and to assess the safety profile of long-term treatment with ipriflavone in postmenopausal osteoporotic women. DESIGN AND SETTING: Prospective, randomized, double-blind, placebo-controlled, 4-year study conducted in 4 centers in Belgium, Denmark, and Italy from August 1994 to July 1998. PARTICIPANTS: Four hundred seventy-four postmenopausal white women, aged 45 to 75 years, with bone mineral densities (BMDs) of less than 0.86 g/cm(2). INTERVENTIONS: Patients were randomly assigned to receive ipriflavone, 200 mg 3 times per day (n = 234), or placebo (n = 240); all received 500 mg/d of calcium. MAIN OUTCOME MEASURES: Efficacy measures included spine, hip, and forearm BMD and biochemical markers of bone resorption (urinary hydroxyproline corrected for creatinine and urinary CrossLaps [Osteometer Biotech, Herlev, Denmark] corrected for creatinine), assessed every 6 months. Laboratory safety measures and adverse events were recorded every 3 months. RESULTS: Based on intent-to-treat analysis, after 36 months of treatment, the annual percentage change from baseline in BMD of the lumbar spine for ipriflavone vs placebo (0.1% [95% confidence interval (CI), -7.9% to 8.1%] vs 0.8% [95% CI, -9.1% to 10.7%]; P =.14), or in any of the other sites measured, did not differ significantly between groups. The response in biochemical markers was also similar between groups (eg, for hydroxyproline corrected for creatinine, 20.13 mg/g [95% CI, 18.85-21.41 mg/g] vs 20.67 mg/g [95% CI, 19.41-21.92 mg/g]; P =.96); urinary CrossLaps corrected for creatinine, 268 mg/mol (95% CI, 249-288 mg/mol) vs 268 mg/mol (95% CI, 254-282 mg/mol); P =.81. The number of women with new vertebral fracture was identical or nearly so in the 2 groups at all time points. Lymphocyte concentrations decreased significantly (500/microL (0.5 x 10(9)/L]) in women treated with ipriflavone. Thirty-one women (13.2%) in the ipriflavone group developed subclinical lymphocytopenia, of whom 29 developed it during ipriflavone treatment. Of these, 15 (52%) of 29 had recovered spontaneously by 1 year and 22 (81%) of 29 by 2 years. CONCLUSIONS: Our data indicate that ipriflavone does not prevent bone loss or affect biochemical markers of bone metabolism. Additionally, ipriflavone induces lymphocytopenia in a significant number of women.

Beverage choices affect adequacy of children's nutrient intakes.

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Arch Pediatr Adolesc Med 2000 Nov;154(11):1148-52

OBJECTIVE: To assess the relationship between beverage choices and the adequacy of nutrient intakes among children and adolescents. DESIGN: Beverages reported in 24-hour recall records were classified as milk, 100% juice, fruit-flavored drinks, or carbonated sodas. Recommended intakes were based on

Recommended Dietary Allowances or Dietary Reference Intakes. PARTICIPANTS: Four thousand seventy children aged 2 to 5, 6 to 11, and 12 to 17 years participating in the 1994-96 Continuing Survey of Food Intakes by Individuals. STATISTICAL ANALYSIS: The likelihood of achieving recommended intakes of selected nutrients on the day of recall was assessed with multiple logistic regression including ounces of milk, juice, fruit-flavored drinks, and carbonated sodas in the model while controlling for sex, age in years, race/ethnic group, household income, and total energy intake. RESULTS: Milk consumption was positively (P<.0001) associated with the likelihood of achieving recommended vitamin A, folate, vitamin B(12), calcium, and magnesium intakes in all age strata. Juice consumption was positively (P< or =. 001) associated with achieving recommended vitamin C and folate intakes in all age strata and magnesium intakes among children aged 6 years and older. Carbonated soda consumption was negatively (P< or =. 01) associated with achieving vitamin A intake in all age strata, calcium in children younger than 12 years, and magnesium in children aged 6 years and older. CONCLUSION: Beverage choice can have a significant effect on the nutrient adequacy of the diets of children and adolescents.

Management of osteoporosis. An overview.

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Drugs Aging (New Zealand) 1998, 12 Suppl 1 p25-32

Osteoporosis is a common disease associated with aging and menopause, and is becoming a major health and socioeconomic problem worldwide. The 2 major determinants of risk of osteoporosis are peak bone mass (reached in the third decade of life) and bone loss thereafter. There is substantial evidence that bone mass is of major importance for the strength of bone and the risk of fracture. The measurement of bone mass in the third decade of life is therefore a potentially useful tool in assessing the individual risk of fracture. Moreover, biochemical markers of bone formation and resorption may be of some use in predicting oss and the response to therapy. Since the most well-defined risk factor for osteoporosis is the cessation of ovarian estrogen production at menopause, estrogen replacement therapy (ERT) is the treatment of choice for postmenopausal bone loss. While the benefits of ERT in preventing bone loss and reducing the incidence of fractures are well established, such therapy is contraindicated in some women and is not an acceptable option for others. Other widely used treatments for osteoporosis that have been utilised to prevent bone loss include calcitonin and bisphosphonates, calcium supplementation, ossein-hydroxyapatite compound, vitamin D analogues, sodium fluoride, parathyroid hormone, anabolic steroids and growth hormone. While ERT is presently the best option for the prevention of bone loss, a regimen of ERT combined with lifestyle changes (e.g., exercise and diet) as well as other bone-preserving drugs may increase bone mass in postmenopausal women to a greater extent than ERT alone (44 references).

Improved bone metabolism in female elite athletes after vitamin K supplementation.

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Int J Sports Med 1998 Oct;19(7):479-84

In female elite athletes strenuous exercise may result in hypoestrogenism and amenorrhoea. As a consequence, a low peak bone mass and rapid bone loss are often seen in relatively young athletes. In postmenopausal women, increased intake of vitamin K may result in an increase of serum markers for bone formation, a decrease of urinary markers for bone resorption, and a decrease in urinary calcium loss. In the present paper we report an intervention study among eight female athletes, four of whom had been amenorrhoeic for more than one year, whereas the others had been using oral contraceptives. All participants received vitamin K supplementation (10 mg/day) during one month, and various bone markers were measured before and after treatment. At baseline the athletes not using oral contraceptives were biochemically vitamin K-deficient as deduced from the calcium binding capacity of the circulating bone protein osteocalcin. In all subjects increased vitamin K was associated with an increased calcium-binding capacity of osteocalcin. In the low-estrogen group vitamin K supplementation induced a 15-20% increase of bone formation markers and a parallel 20-25% decrease of bone resorption markers. This shift is suggestive for an improved balance between bone formation and resorption.

Daily oral magnesium supplementation suppresses bone turnover in young adult males.

Dimai HP, Porta S, Wirnsberger G, Lindschinger M, Pamperl I, Dobnig H, Wilders-Truschnig M, Lau KH. Department of Endocrinology, University of Graz Medical School, Austria.

J Clin Endocrinol Metab (United States) Aug 1998, 83 (8) p2742-8

This study examined the effects of daily oral magnesium (Mg) supplementation on bone turnover in 12 young (27-36 yr old) healthy men. Twelve healthy men of matching age, height, and weight were recruited as the control group. The study group received orally 15 mmol Mg (Magnosolv powder, Asta Medica) daily in the early afternoon with 2-h fasting before and after Mg intake. Fasting blood and second void urine samples were collected in the early morning on days 0, 1, 5, 10, 20, and 30, respectively. Total and ionized Mg2+ and calcium (Ca2+), and intact PTH (iPTH) levels were determined in blood samples. Serum biochemical markers of bone formation (i.e. C-terminus of type I procollagen peptide and osteocalcin) and resorption (i.e. type I collagen telopeptide) and urinary Mg level adjusted for creatinine were measured. In these young males, 30 consecutive days of oral Mg supplementation had no significant effect on total circulating Mg level, but caused a significant reduction in the serum ionized Mg+ level after 5 days of

intake. The Mg supplementation also significantly reduced the serum iPTH level, which did not appear to be related to changes in serum Ca2+ because the Mg intake had no significant effect on serum levels of either to tal or ionized Ca2+. There was a strong positive correlation between serum iPTH and ionized Mg2+ ($r = 0.699$; $P < 0.001$), supporting the contention that decreased serum iPTH may be associated with the reduction in serum ionized Mg2+. Mg supplementation also reduced levels of both serum bone formation and resorption biochemical markers after 1-5 days, consistent with the premise that Mg supplementation may have a suppressive effect on bone turnover rate. Covariance analyses revealed that serum bone formation markers correlated negatively with ionized Mg2+ ($r = -0.274$ for type I procollagen peptide and -0.315 for osteocalcin), but not with iPTH or ionized Ca2+. Thus, the suppressive effect on bone formation may be mediated by the reduction in serum ionized Mg2+ level (and not iPTH or ionized Ca2+). In summary, this study has demonstrated for the first time that oral Mg supplementation in normal young adults caused reductions in serum levels of iPTH, ionized Mg2+, and biochemical markers of bone turnover. In conclusion, oral Mg supplementation may suppress bone turnover in young adults. Because increased bone turnover has been implicated as a significant etiological factor for bone loss, these findings raise the interesting possibility that oral Mg supplementation may have beneficial effects in reducing bone loss associated with high bone turnover, such as age-related osteoporosis.

Vitamin K intake and hip fractures in women: a prospective study.

Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. diane.feskanich@channing.harvard.edu

Am J Clin Nutr 1999 Jan;69(1):74-9

BACKGROUND: Vitamin K mediates the gamma-carboxylation of glutamyl residues on several bone proteins, notably osteocalcin. High serum concentrations of undercarboxylated osteocalcin and low serum concentrations of vitamin K are associated with lower bone mineral density and increased risk of hip fracture. However, data are limited on the effects of dietary vitamin K. OBJECTIVE: We investigated the hypothesis that high intakes of vitamin K are associated with a lower risk of hip fracture in women. DESIGN: We conducted a prospective analysis within the Nurses' Health Study cohort. Diet was assessed in 72327 women aged 38-63 y with a food-frequency questionnaire in 1984 (baseline). During the subsequent 10 y of follow-up, 270 hip fractures resulting from low or moderate trauma were reported. RESULTS: Women in quintiles 2-5 of vitamin K intake had a significantly lower age-adjusted relative risk (RR: 0.70; 95% CI: 0.53, 0.93) of hip fracture than women in the lowest quintile (< 109 microg/d). Risk did not decrease between quintiles 2 and 5 and risk estimates were not altered when other risk factors for osteoporosis, including calcium and vitamin D intakes, were added to the models. Risk of hip fracture was also inversely associated with lettuce consumption (RR: 0.55; 95% CI: 0.40, 0.78) for one or more servings per day compared with one or fewer servings per week), the food that contributed the most to dietary vitamin K intakes. CONCLUSIONS: Low

intakes of vitamin K may increase the risk of hip fracture in women. The data support the suggestion for a reassessment of the vitamin K requirements that are based on bone health and blood coagulation.

Effect of ipriflavone-a synthetic derivative of natural isoflavones-on bone mass loss in the early years after menopause.

Gennari C; Agnusdei D; Crepaldi G; Isaia G; Mazzuoli G; Ortolani S; Bufalino L; Passeri M. Internal Medicine and Medical Pathology Institute, University of Siena, Italy.

Menopause (United States) Spring 1998, 5 (1) p9-15

OBJECTIVE: We studied whether oral administration of ipriflavone, a synthetic derivative of naturally occurring isoflavones, could prevent bone loss occurring shortly after menopause. DESIGN: Fifty-six women with low vertebral bone density and with postmenopausal age less than five years were randomly allocated to receive either ipriflavone, 200 mg three times daily, or placebo. All subjects also received 1,000 mg elemental calcium daily. RESULTS: Vertebral bone density declined after two years in women taking only calcium (4.9 +/- 1.1%, SEM, p = 0.001), but it did not change in those receiving (-0.4 +/- 1.1%, n.s.). A significant (p = 0.010) between-treatment difference was evidenced at both year 1 and year 2. At the end of the study, urine hydroxyproline/creatinine excretion was higher in the control group than in the ipriflavone group, as compared to no difference at baseline. Five patients taking ipriflavone and five taking placebo experienced gastrointestinal discomfort or other adverse reactions, but only one and four subjects, respectively, had to discontinue the study. CONCLUSIONS: Ipriflavone prevents the rapid bone loss following early menopause. This effect is associated with a reduction of bone turnover rate.

Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and IL-6 levels in women.

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Calcif Tissue Int 2000 Jun;66(6):414-8

Data from animal and in vitro studies suggest that the growth-promoting effects of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) may be mediated by stimulation of insulin-like growth factor-I (IGF-I) and/or inhibition of interleukin 6 (IL-6), a cytokine mediator of bone resorption. This study tests the hypotheses that there are effects of age on serum DHEAS, IGF-I, and IL-6 levels, and that levels of IGF-I and IL-6 are related to DHEAS levels. The study included 102 women: 27 premenopausal and 75 postmenopausal, including 35 postmenopausal women with osteoporosis, as defined by bone mineral density scores by dual X-ray energy absorptiometry. DHEAS levels decreased significantly with age ($r = -0.52$, $P < 0.0001$) and IGF-I levels decreased

significantly with age (r = -0.49, P < 0.0001). IL-6 levels increased significantly with age (r = 0.36, P = 0.008). IGF-I was positively correlated to DHEAS levels (r = 0.43, P < 0. 0001, n = 102) and IL-6 levels were negatively correlated to DHEAS levels (r = -0.32, P = 0.021, n = 54). Levels of DHEAS and IGF-I were correlated with T scores of the spine and some hip sites. In a multiple variable model to predict DHEAS, age was an important predictor (P < 0.001), but osteoporosis status, IGF-I, and IL-6 were not. The median DHEAS level was lower in the postmenopausal osteoporotic women (67 microg/dl, n = 35) than in the nonosteoporotic postmenopausal women (106.3 microg/dl, n = 40, P = 0. 03), but this was not significant after correction for age. Age accounted for 32% of the variance in DHEAS levels. In summary, DHEAS levels decreased with age and had a positive association with IGF-I levels and a negative association with IL-6 levels. DHEA deficiency may contribute to age-related bone loss through anabolic (IGF-I) and anti-osteolytic (IL-6) mechanisms.

The effect of an ipriflavone-containing supplement on urinary N-linked telopeptide levels in postmenopausal women.

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J Womens Health Gend Based Med 2000 Nov;9(9):995-8

Osteoporosis is a significant health concern to our aging population. We report here the results of a pilot placebo-controlled trial of a dietary supplement containing ipriflavone, calcium, and vitamin D on a urinary marker of bone breakdown in postmenopausal women. Seven postmenopausal women not currently receiving hormone replacement therapy received either an ipriflavone-containing supplement or placebo for 3 months. Urinary N-linked telopeptides, a marker of bone breakdown, declined by 29% in those receiving the supplement, whereas an increase in this marker was observed in the group receiving the placebo. No changes were observed in salivary hormone measurements. Although our sample size was small, to the best of our knowledge, this is the first report that demonstrates changes in N-linked telopeptide levels as a result of consuming an ipriflavone-containing product. Our findings confirm those of other researchers that demonstrate the usefulness of ipriflavone at slowing the progression of bone loss and suggest that measuring N-linked telopeptides may be a useful tool to assess therapeutic efficacy.

IL-6, DHEA and the ageing process.

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Mech Ageing Dev 1997 Feb;93(1-3):15-24

The age-related increase in circulating IL-6 levels in humans which has been attributed to a decline in DHEA production by the adrenal gland is currently attracting attention because of its possible relevance to the aetiology and

management of a number of age-related clinical disorders. The potential importance of these observations and suggestions has prompted us to perform more detailed studies on the relationship between IL-6 and DHEA. Using immunoassay techniques we have found in normal healthy individuals over the age of 40 an inverse relationship between plasma DHEA levels and the presence of detectable levels of IL-6 (more than 1 pg/ml). In vitro, studies also revealed that low dose (10(-6)-10(-8) M) of DHEA and DHEAS inhibited the production of IL-6 in unstimulated human spleen cell suspension cultures whilst enhancing its release by explant cultures of the same tissue. In contrast they had no effect on immunoglobulin production. These studies suggest that there is a real, but complex relationship between IL-6 production and DHEA levels which warrants further investigation.

The effect of vitamin K supplementation on circulating osteocalcin (bone Gla protein) and urinary calcium excretion.

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Ann Intern Med 1989 Dec 15;111(12):1001-5

STUDY OBJECTIVE: To determine whether vitamin K administration affects urinary calcium excretion in postmenopausal women. DESIGN: Before- and after-trials with a 2-week treatment period. SUBJECTS: Healthy postmenopausal women (55 to 75 years old) were recruited from the convents in and around Maastricht. Controls (25 to 40 years old) were healthy premenopausal volunteers. INTERVENTION: Daily administration of 1 mg of vitamin K for 2 weeks. MEASUREMENTS: Serum immunoreactive osteocalcin: hydroxylapatite binding (HAB) capacity of serum immunoreactive osteocalcin; excretion of calcium, hydroxyproline, and creatinine in the urine during the last 2 h of a 16-h fasting period. RESULTS: In premenopausal women, no effect of vitamin K administration was seen. In the postmenopausal group, vitamin K induced increased serum immunoreactive osteocalcin concentration; normalization of the HAB capacity of serum immunoreactive osteocalcin (this marker was less than 50% that of the controls in the pretreatment samples); a decrease in urinary calcium excretion, notably in the "fast losers" of calcium; and a parallel decrease in urinary hydroxyproline excretion in the fast losers of calcium. CONCLUSIONS: The serum immunoreactive osteocalcin level may vary with vitamin K status. This variance should be taken into consideration if osteocalcin is used as a marker for osteoblast activity. Vitamin K is one factor that may play a role in the loss of bone mass in postmenopausal osteoporosis.

Vitamin K-induced changes in markers for osteoblast activity and urinary calcium loss.

Knapen MH, Jie KS, Hamulyak K, Vermeer C. Department of Biochemistry, University of Limburg, Maastricht, The Netherlands.

Calcif Tissue Int 1993 Aug;53(2):81-5

The objective of this study was to identify subjects in whom vitamin K has an effect on markers for calcium and bone metabolism and to detect hitherto-unnoticed correlations between vitamin K-induced changes in these markers. Participants in our studies were apparently healthy women, in whom we measured serum-immunoreactive osteocalcin (irOC) before and after adsorption to hydroxylapatite; total serum alkaline phosphatase (T-AP) and bone-specific alkaline phosphatase (B-AP); and fasting urinary calcium and creatinine. We describe a trial among 145 women who were treated with vitamin K (1 mg/day) for 2 weeks, and a prospective placebo-controlled trial among two groups each of 70 postmenopausal women with a treatment period of 3 months. It turned out that in elderly women vitamin K induced increased levels of serum irOC with a high affinity for hydroxylapatite (irOCbound), whereas that with low affinity (irOCfree) remained unaffected. In placebo-treated women the ratio irOCfree/irOCbound shifted from 0.38 to 0.65 around the 50th year of age. This shift was not found in vitamin K-treated women. After 3 months of treatment the vitamin K-induced changes in irOCbound were correlated with changes in B-AP, whereas irOCfree was correlated to urinary calcium excretion. In fast losers of urinary calcium vitamin K induced a 30% decrease of calcium excretion. The hypothesis is put forward that irOCbound may be a marker for bone formation, that serum irOCfree may be a marker for bone resorption, and that the serum irOCfree/irOCbound ratio may become a marker for skeletal remodeling. (ABSTRACT TRUNCATED AT 250 WORDS.)

[New spine and non-spine fractures in 871 women/year treated with oral pamidronate plus calcium and vitamin D supplements.] [Article in Spanish]

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Medicina (B Aires) 1997;57 Suppl 1:32-6

A sample of 871.3 patients/year was conformed by 205 postmenopausal women, aged 64.8 +/- 18.2 years (mean +/- SD), followed up during 51 +/- 12 months. All have osteoporosis, diagnosis assessed through radiological findings of at least one atraumatic fracture or vertebral crush ("severe osteoporosis" according to the new WHO classification). Each woman received 100 mg/day oral pamidronate (enteric coated soft gelatin capsules), half an hour before breakfast. Additional calcium and vitamin D were supplemented as follows: Total daily calcium = 1 g provided by diet and/or calcium carbonate. Vitamin D equivalent to 400-1200 IU/day. All patients were recommended to improve their physical activity, at least by walking exercise. Clinical examination radiological, bone mineral density (BMD) and biochemical studies were periodically performed. But, fracture indicence was the end-point of the study. Same was related to the 1,673 fall episodes recorded in the sample. In addition, height loss, lumbar BMD, proximal femur BMD, are also reported. Data has been cross-sectional collected in March 1995. All patients improved the symptomatology, specifically pain. This, and the good tolerability of the treatments proved to be considerably favorable for their compliance. Within the observation period, only 12 patients decreased their height (5.85%; mean = 0.85 cm; range = 0.5-2.0 cm). Lumbar spine BMD increased in 90% of 48

women. Mean gain after 2 years was 5.3 +/- 1.0% ($p < 0.001$). Proximal femur increased in 78% of other 32 women. Mean gain 6.3 +/- 0.7% ($p < 0.001$) after 2 years. A total of 78 new fractures were recorded, 47 vertebral crush, 29 forearm fractures and 2 hip fractures. Its incidence related to the fall episodes was of 2.8; 1.7 and 0.12% respectively. When compared with a historical estimated data, from an untreated population (Cummings SR et al, 1994), both, the total number of new fractures and the new hip fractures were significantly lower ($p < 0.01$) in our treated population than the reference data. Pamidronate, in oral doses of 100 mg/day, adequately supplemented with calcium and vitamin D, proved to be effective and a well tolerated therapy. The low rate of height's loss, BMD significant increases in subgroups of patients and the low rate of new fractures, strongly support the use of the compound to treat severe osteoporotic women. To our knowledge, this is the first time, that the new fracture incidence is related to the fall frequency reported in a bisphosphonate treated sample.

Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women.

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Am J Clin Nutr 1998 Dec;68(6 Suppl):1375S-1379S

The effects of soy protein (40 g/d) containing moderate and higher concentrations of isoflavones on blood lipid profiles, mononuclear cell LDL receptor messenger RNA, and bone mineral density and content were investigated in 66 free-living, hypercholesterolemic, postmenopausal women during a 6-mo, parallel-group, double-blind trial with 3 interventions. After a control period of 14 d, during which subjects followed a National Cholesterol Education Program Step I low-fat, low-cholesterol diet, all subjects were randomly assigned to 1 of 3 dietary groups: Step I diet with 40 g protein/d obtained from casein and nonfat dry milk (CNFDM), Step I diet with 40 g protein/d from isolated soy protein containing 1.39 mg isoflavones/g protein (ISP56), or Step I diet with 40 g protein/d from isolated soy protein containing 2.25 mg isoflavones/g protein (ISP90). Total and regional bone mineral content and density were assessed. Non-HDL cholesterol for both ISP56 and ISP90 groups was reduced compared with the CNFDM group ($P < 0.05$). HDL cholesterol increased in both ISP56 and ISP90 groups ($P < 0.05$). Mononuclear cell LDL receptor mRNA was increased in subjects consuming ISP56 or ISP90 compared with those consuming CNFDM ($P < 0.05$). Significant increases occurred in both bone mineral content and density in the lumbar spine but not elsewhere for the ISP90 group compared with the control group ($P < 0.05$). Intake of soy protein at both isoflavone concentrations for 6 mo may decrease the risk factors associated with cardiovascular disease in postmenopausal women. However, only the higher isoflavone-containing product protected against spinal bone loss.

Progesterone as a bone-trophic hormone.

Prior JC.

Endocr Rev 1990 May;11(2):386-98

Critical analysis of the reviewed data indicate that progesterone meets the necessary criteria to play a causal role in mineral metabolism. This review provides the preliminary basis for further molecular, genetic, experimental, and clinical investigation of the role(s) of progesterone in bone remodeling. Much further data are needed about the interrelationships between gonadal steroids and the "life cycle" of bone. Feldman et al., however, may have been prophetic when he commented; "If this anti-glucocorticoid effect of progesterone also holds true in bone, then postmenopausal osteoporosis may be, in part, a progesterone deficiency disease."

Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis.

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J Bone Miner Res 2000 Mar;15(3):515-21

We attempted to investigate whether vitamin K2 (menatetrenone) treatment effectively prevents the incidence of new fractures in osteoporosis. A total of 241 osteoporotic patients were enrolled in a 24-month randomized open label study. The control group (without treatment; n = 121) and the vitamin K2-treated group (n = 120), which received 45 mg/day orally vitamin K2, were followed for lumbar bone mineral density (LBMD; measured by dual-energy X-ray absorptiometry [DXA]) and occurrence of new clinical fractures. Serum level of Glu-osteocalcin (Glu-OC) and menaquinone-4 levels were measured at the end of the follow-up period. Serum level of OC and urinary excretion of deoxypyridinoline (DPD) were measured before and after the treatment. The background data of these two groups were identical. The incidence of clinical fractures during the 2 years of treatment in the control was higher than the vitamin K2-treated group (chi2 = 10.935; p = 0.0273). The percentages of change from the initial value of LBMD at 6, 12, and 24 months after the initiation of the study were -1.8 +/- 0.6%, -2.4 +/- 0.7%, and -3.3 +/- 0.8% for the control group, and 1.4 +/- 0.7%, -0.1 +/- 0.6%, and -0.5 +/- 1.0% for the vitamin K2-treated group, respectively. The changes in LBMD at each time point were significantly different between the control and the treated group (p = 0.0010 for 6 months, p = 0.0153 for 12 months, and p = 0.0339 for 24 months). The serum levels of Glu-OC at the end of the observation period in the control and the treated group were 3.0 +/- 0.3 ng/ml and 1.6 +/- 0.1 ng/ml, respectively (p < 0.0001), while the serum level of OC measured by the conventional radioimmunoassay (RIA) showed a significant rise (42.4 +/-6.9% from the basal value) in the treated group at 24 months (18.2 +/- 6.1% for the controls;p = 0.0081). There was no significant change in urinary DPD excretion in the treated group. These findings suggest that vitamin K2 treatment effectively prevents the occurrence of new fractures, although the vitamin K2-treated group

failed to increase in LBMD. Furthermore, vitamin K2 treatment enhances gamma-carboxylation of the OC molecule.

Effect of recombinant human growth hormone in elderly osteoporotic women.

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Clin Endocrinol (Oxf) 1999 Dec;51(6):715-24

OBJECTIVE: Bone mineral density and growth hormone (GH) secretion rate both decline during normal human ageing. We evaluated the effects of recombinant human GH on markers of body composition and bone turnover in an open study in 8 elderly osteoporotic women aged 68-75 years (mean age 71 years). DESIGN: Subjects were treated with GH as a single daily subcutaneous injection (0.125 IU/kg/week for the first 4 weeks and subsequently 0.25 IU/kg/week) for 48 weeks. RESULTS: GH treatment caused a rapid (within 2 weeks) increase in serum levels of IGF-I and IGF-binding protein-3 (IGFBP-3) which was sustained throughout the study. Markers of bone formation and resorption were both gradually increased up to 24 weeks of GH treatment. The bone formation markers, osteocalcin (OC) and bone alkaline phosphatase, remained high during GH treatment, while the bone resorption marker, deoxypyridinoline (D-Pyr), tended to return to baseline levels after 24 weeks of GH therapy. GH treatment for 48 weeks caused a significant increase in hand grip and a decrease in waist/hip ratio. The mean percentage changes in bone mineral density (BMD) of mid-radius and lumbar spine were + 2.1% and + 1.2%, respectively, although they were not statistically significant. GH treatment was well tolerated and no major side-effects except mild oedema and joint pain were found. Since GH treatment produced durable increases in bone formation markers, BMD continued to be monitored after discontinuation of GH treatment for another 48 weeks, during which significant increases in radial and lumbar BMD (8.1 +/- 2.1 and 3.8 +/- 1.4% above pre- treatment values, respectively) were recorded. CONCLUSION: These results indicate that GH attenuates the decrease in muscle strength and bone mass as well as the gain of abdominal fat with ageing in elderly women. The present data provide useful information about the application of GH treatment in elderly women.

Vitamin K and bone health.

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Nutrition 2001 Oct;17(10):880-7; erratum, Nutrition 2001 Nov-Dec;17(11-12):1024

In the past decade it has become evident that vitamin K has a significant role to play in human health that is beyond its well-established function in blood clotting.

There is a consistent line of evidence in human epidemiologic and intervention studies that clearly demonstrates that vitamin K can improve bone health. The human intervention studies have demonstrated that vitamin K cannot only increase bone mineral density in osteoporotic people but also actually reduce fracture rates. Further, there is evidence in human intervention studies that vitamins K and D, a classic in bone metabolism, works synergistically on bone density. Most of these studies employed vitamin K(2) at rather high doses, a fact that has been criticized as a shortcoming of these studies. However, there is emerging evidence in human intervention studies that vitamin K(1) at a much lower dose may also benefit bone health, in particular when coadministered with vitamin D. Several mechanisms are suggested by which vitamin K can modulate bone metabolism. Besides the gamma-carboxylation of osteocalcin, a protein believed to be involved in bone mineralization, there is increasing evidence that vitamin K also positively affects calcium balance, a key mineral in bone metabolism. The Institute of Medicine recently has increased the dietary reference intakes of vitamin K to 90 microg/d for females and 120 microg/d for males, which is an increase of approximately 50% from previous recommendations.

Effect of ipriflavone--a synthetic derivative of natural isoflavones--on bone mass loss in the early years after menopause.

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Internal Medicine and Medical Pathology Institute, University of Siena, Italy.
Menopause (United States) Spring 1998, 5 (1) p9-15

OBJECTIVE: We studied whether oral administration of ipriflavone, a synthetic derivative of naturally occurring isoflavones, could prevent bone loss occurring shortly after menopause.

DESIGN: Fifty-six women with low vertebral bone density and with postmenopausal age less than five years were randomly allocated to receive either ipriflavone, 200 mg three times daily, or placebo. All subjects also received 1,000 mg elemental calcium daily.

RESULTS: Vertebral bone density declined after two years in women taking only calcium (4.9 +/- 1.1%, SEM, p = 0.001), but it did not change in those receiving (-0.4 +/- 1.1%, n.s.). A significant (p = 0.010) between-treatment difference was evidenced at both year 1 and year 2. At the end of the study, urine hydroxyproline/creatinine excretion was higher in the control group than in the ipriflavone group, as compared to no difference at baseline. Five patients taking ipriflavone and five taking placebo experienced gastrointestinal discomfort or other adverse reactions, but only one and four subjects, respectively, had to discontinue the study.

CONCLUSIONS: Ipriflavone prevents the rapid bone loss following early menopause. This effect is associated with a reduction of bone turnover rate.

Growth, development and differentiation: A functional food science approach

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British Journal of Nutrition (United Kingdom), 1998, 80/Suppl. 1 (S5-S45)

Few other aspects of food supply and metabolism are of greater biological importance than the feeding of mothers during pregnancy and lactation, and of their infants and young children. Nutritional factors during early development not only have short-term effects on growth, body composition and body functions but also exert long-term effects on ealth, disease and mortality risks in adulthood. as well as development of neural functions and behaviour, a phenomenon called 'metabolic programming'. The interaction of nutrients and gene expression may form the basis of many of these programming effects and needs to be investigated in more detail. The relation between availability of food ingredients and cell and tissue differentiation and its possible uses for promoting health and development requires further exploration. The course of pregnancy, childbirth and lactation as well as human milk composition and the short- and long term outcome of the child are influenced by the intake of foods and particularly micronutrients, e.g. polyunsaturated fatty acids, Fe, Zn and I. Folic acid supplementation from before conception through the first weeks of pregnancy can markedly reduce the occurrence of severe embryonic malformations; other potential benefits of modulating nutrient supply on maternal and child health should be further evaluated. The evaluation of dietary effects on child growth requires epidemiological and field studies as well as evaluation of specific cell and tissue growth. Novel substrates, growth factors and conditionally essential nutrients (e.g. growth factors, amino acids, polyunsaturated fatty acids) may be potentially useful redients in functional foods and need to be assessed carefully. Intestinal growth, maturation, and adaptation as well as long-term function may be influenced by food ingredients such as oligosaccharides, gangliosides, high-molecular-mass glycoproteins, bile salt-activated lipase, pre- and probiotics. There are indications for some beneficial effects of functional foods on the developing immune response, for example induced by antioxidant vitamins, trace elements, fatty acids, arginine, nucleotides, and altered antigen contents in infant foods. Peak bone mass at the end of adolescence can be increased by dietary means, which is expected to be of long-term importance for the prevention of osteoporosis at older ages. Future studies should be directed to the combined effects of Ca and other constituents of growing bone, such as P, Mg and Zn, as well as vitamins D and K, and the trace elements F and B. Pregnancy and the first postnatal months are critical time periods for the growth and development of the human nervous system, processes for which adequate substrate supplies are essential. Early diet seems to have long-term effects on sensory and cognitive abilities as well as behaviour. The potential beneficial effects of a balanced supply

of n Zn and polyunsaturated fatty acids should be further evaluated. Possible long-term effects of early exposure to tastes and flavours on later food choice preferences may have a major impact on public health and need to be further elucidated. The use of biotechnology and recombinant techniques may offer the opportunity to include various bioactive substances in special dietary products, such as human milk proteins, peptides, growth factors, which may have beneficial physiological effects, particularly in infancy and early childhood.

Osteoporosis in rheumatoid arthritis - Loss of bone mass in the early stage of the disease and the possibility to influence it by calcium and vitamin D

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Ceska Revmatologie (Czech Republic), 1998, 6/2 (39-47)

The authors present a report on an investigation implemented in the framework of a grant. The objective was to investigate patients with rheumatoid arthritis in the early stage of the disease and assess the rate of loss of bone mass and the possibility to influence it by the most frequently used and most economical treatment with calcium and vitamin D. Already in the early stage of the disease after a maximum of three years the mean bone density (BMD) is by 0.5 to 0.9 units of the T-score below the mean in healthy people or even much lower. During a two-year follow upod in all patients (with a negligible exception) a further significant drop of the BMD was recorded, on average by 5%, i.e. 2.5% per year. This rate of loss of bone mass is important from the aspect of premature development of osteoporosis . Examination of markers of bone turnover revealed an increased osteoresorption without increased new formation. On average it was small, but in some cases it was marked. Calcium therapy (1000 mg/day and vitamin D 8000 u./day) suppressed signs of enhanced osteoresorption, but did not affect the loss of bone mass. The trial proceeds now beyond the framework of the grant in order to assemble data over a longer period of time and confront them with some parameters of the basic disease.

The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density

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Journal of Bone and Mineral Research (USA), 1997, 12/7 (1049-1057)

Previous studies of the vitamin D receptor (VDR) polymorphisms and bone mineral density (BMD) have suggested that there may be differences in calcium absorption among groups of women with different VDR genotypes, and that the association may be stronger in younger women. To investigate the association between the VDR polymorphisms and BMD, this study was undertaken in the Framingham Study Cohort and a group of younger volunteers. Subjects from the Framingham Study (ages 69-90 years) included those who underwent BMD testing and who had genotyping for the VDR alleles (n = 328) using polymerase chain reaction methods and restriction fragment length polymorphisms with BsmI (B absence, b presence of cut site). A group of younger volunteer subjects (ages 18-68) also underwent BMD testing and VDR genotyping (n = 94). In Framingham Cohort subjects with the bb genotype, but not the Bb or BB genotypes, there were significant associations between calcium intake and BMD at five of six skeletal sites, such that BMD was 7-12% higher in those with dietary calcium intakes greater than 800 mg/day compared with those with intakes <500 mg/day. The data also suggested that BMD was higher in persons with the bb genotype only in the group with calcium intakes above 800 mg/day. No significant differences were found in the Framingham Cohort for age-, sex-, and weight-adjusted BMD at any skeletal site between those with the BB genotype and those with the bb genotype regardless of 25-hydroxyvitamin D levels or country of origin. In the younger volunteers, BMD of the femoral neck was 5.4% higher ($p < 0.05$) in the bb genotype group compared with the BB group and 11% higher ($p < 0.05$) in males with the bb genotype compared with the BB group. There were no significant differences at the lumbar spine. In this study, the association between calcium intake and BMD appeared to be dependent upon VDR genotype. The finding of an association between dietary calcium intake and BMD only in the bb genotype group suggests that the VDR genotype may play a role in the absorption of dietary calcium. Studies that do not consider calcium intake may not detect associations between VDR genotype and BMD. In addition, the association between VDR alleles and BMD may become less evident in older subjects.

The effect of 1,25(OH)2 vitamin D3 on CD4+/CD8+ subsets of T lymphocytes in postmenopausal women

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Life Sciences (USA), 1997, 61/2 (147-152)

The effect of exogenous 1,25(OH)2 vitamin D3 (1,25(OH)2D3) on the CD3+, CD4+ and CD8+ subsets (counts/ul) of T lymphocytes was investigated in two randomized groups of post menopausal women. Group one (16 subjects) received 1ug/day of the secosteroid for 14 days, while group two (14 participants) was treated with 2 ug/day for the same period. The placebo group comprised another 10 postmenopausal women. Compliance of the treatment was controlled by serum intact parathyroid hormone (PTH) levels, which markedly declined at the end of

the treatment ($p<0.01$ for both doses). The vitamin D status of the women before the treatment was defined by serum 25(OH) vitamin D (25(OH)D) levels. The lower dose of the secosteroid did not change any of the measured immune parameters. After a higher dose of 1,25(OH)2 D3 the mean values of CD3+ and CD8+ increased ($p<0.05$ for the both parameters), but no changes in total lymphocytes and the CD4+ subset were observed. There were no correlations between the immune response DeltaCD3+, DeltaCD4+ and DeltaCD8+) and basal circulating 25(OH)D. Briefly, then, 1,25(OH)2D3 slighly but significantly increases CD3+ and CD8+ subsets independently on the initial vitamin D status of the postmenopausal women.

Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of five currently available calcium salts in healthy male volunteers

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Clinical Rheumatology (Belgium), 1997, 16/3 (249-253)

Several calcium supplements are currently available and many of them are marketed without proper comparison of the bioavailability of the actual preparations. The aim of the present trial was to evaluate and compare the acute changes in serum calcium (Ca) and parathyroid hormone (PTH) levels following the oral administration of a vehicle and of five calcium salts currently prescribed in Western Europe. No significant changes in serum Ca or PTH levels were observed after administration of the vehicle. All calcium salts induced significant increases in serum Ca and decreases in serum PTH compared to baseline values. Comparison of the six response curves revealed a significantly greater increase in serum Ca and a greater decrease in serum PTH after each of the calcium salts than observed after the vehicle. However, no statistically significant differences were observed between the different calcium salts for serum Ca increments. The decrease in serum PTH observed after administration of an ossein-hydroxyapatite complex was significantly less important than after the four other calcium salts, even if statistically different than after vehicle. When assessing the area under the curve (AUC) of PTH values, we observed that calcium carbonate and citrate induce a significantly greater decrease in serum PTH than the other calcium salts which are, however, statistically more active than the vehicle. Serum PTH is decreased under the lower limit of the normal range (10 pg/ml), between t60 and t120 for calcium carbonate and citrate and between t60 and t90 for calcium gluconolactate while the mean PTH values remain within the normal range throughout the study with calcium pidolate, the ossein-hydroxyapatite complex and the vehicle. In conclusion, all calcium preparations significantly increase serum calcium and decrease serum parathormone, ompared to what is observed after oral intake of a vehicle. However, significant differences in suppression of

parathormone are observed between the different calcium preparations and might h of importance for their clinical use.

1-alpha-hydroxyvitamin D3 treatment decreases bone turnover and modulates calcium-regulating hormones in early postmenopausal women

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Bone (USA), 1997, 20/6 (557-562)

50 Japanese women within 10 years after menopause (mean age 52.5 years) were studied to determine the effects of 0.75 microg of 1-alpha-hydroxyvitamin D3 (1-alpha-(OH)D3) with calcium (150 mg/day) (treated group: N = 25) and calcium only (control group: N = 25) for 12 months on bone mass and metabolism. Their L2-4 BMD measurements were 1.5 SD below the mean value of Japanese young, normal women, L2-4 BMDs increased significantly in the treated group (+2.1%; $p < 0.01$), but decreased significantly in controls (-2.l%; $p < 0.01$). Although serum calcium and creatinine remained unchanged in both groups, phosphorus levels increased significantly in the treated group ($p < 0.01$). Urinary calcium/creatinine (Cr) increased in both groups. Urinary pyridinoline/Cr and deoxypyridinoline/Cr decreased significantly in the treated group ($p < 0.05$), but not in the control group. Serum osteocalcin levels remained unchanged in both groups, Intact parathyroid hormone levels decreased significantly ($p < 0.05$) and calcitonin levels significantly increased in the treated group ($p < 0.05$), but these changes were not observed in the control group. These data clearly demonstrate that 0.75 microg of 1-alpha-(OH)D3 maintained bone mass by reducing bone resorption by modulation of calcium-regulating hormones. Temporarily increased urinary calcium excretion was observed in control group, but did not appear to be effective in modulating bone turnover.

Role of dietary lipid and antioxidants in bone metabolism

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Nutrition Research (USA), 1997, 17/7 (1209-1228)

Recent investigations and clinical studies suggest that dietary lipids and antioxidant nutrients influence bone formation and cartilage biology. In animals, bone modeling appears to be optimal when (n-3) fatty acids are supplied in thediet to moderate the metabolic and physiologic effects of (n- 6) fatty acids. In osteoporosis, greater osteoclastic activity results in excessive mineral loss and bone destruction. New evidence supports the idea that dietary fatty acids and

antioxidants can attenuate osteoclastic activity to reduce the severity of osteolytic diseases of the bone and joint. Moreover,(n-6) fatty acids may aggravate the deficiency of antioxidant enzyme protective systems in epiphyseal cartilage of long bones. For example, vitamin E was reported to increase in vivo trabecular bone formation rate and to restore collagen synthesis in chondrocytes enriched with linoleic acid. This review presents new information that documents a role for dietary lipids and antioxidants in supporting bone formation and cartilage function for optimal health.

The response to calcitriol therapy in postmenopausal osteoporotic women is a function of initial calcium absorptive status

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Calcified Tissue International (USA), 1997, 61/1 (6-9)

Calcitriol is used in the treatment of osteoporosis but the indications for its use have not been clearly defined. Because it stimulates calcium absorption, we have tended to select osteoporotic patients with low calcium absorption for this therapy and now report the results. We measured the hourly fractional rate of calcium absorption (alpha) with 45Ca and fasting urinary calcium /creatinine (Ca/Cr) and hydroxyproline/creatinine (OHPr/Cr) in 103 postmenopausal women aged 68 (0.67SE) years with vertebral compression fractures (77) or forearm or vertebral bone density below the young normal range (26). They were given 0.25 microg daily of calcitriol (Rocaltrol, Roche, Basle, Switzerland) with a 1g calcium supplement daily for 6-12 weeks, when the biochemical tests were repeated. Initial OHPr/Cr was inversely related to initial alpha (P=0.001) and positively to initial Ca/Cr (P<0.001). alpha rose on therapy from 0.47 (0.018) to 0.59 (0.018) per hour (P<0.001) and OHPr/Cr fell in the whole group from 19.1 (0.83) to13.8 (0.58) (P< 0.001). The change in alpha on therapy (corrected for the 'regression to the mean effect') was inversely related to initial alpha (P<0.001) as was the change in OHPr/Cr (P=0.001). There was no relationship, however, between initial Ca/Cr and either the rise in alpha or the fall in OHPr/Cr on therapy. The data support the concept that low calcium absorption is a cause of negative calcium balance in postmenopausal osteoporosis and that the effectiveness of calcitriol therapy is inversely related to the initial rate of calcium absorption.

Postprandial parathyroid hormone response to four calcium-rich foodstuffs

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We studied the effects of four calcium-rich foodstuffs on postprandial parathyroid hormone secretion. Four hundred milligrams calcium from either Emmental cheese, milk, sesame seeds, spinach, or calcium salt (calcium lactate gluconate + calcium carbonate) or no additional calcium (control session) were given to nine female volunteers immediately after a first blood sample (at 0900) in random order with a light standardized meal containing 37 mg Ca. Blood samples were taken at 0900 (before the calcium load), 1000, 1100, 1300, and 1500 at every study session. Urine was collected during the sessions. Serum ionized calcium, phosphate, magnesium, intact parathyroid hormone, and urinary calcium excretion were measured. The serum ionized calcium concentration increased significantly after ingesting cheese (P=0.004, contrast analysis) or calcium salt (P=0.05, contrast analysis) compared with the control session. Compared with the control session, the serum phosphate concentration increased after the cheese session (P=0.004, contrast analysis) and after the milk session (P=0.02, contrast analysis). Calcium salt (P=0.007, contrast analysis) and cheese (P=0.002, contrast analysis) caused a significant decline in serum intact parathyroid hormone compared with the control session. The urinary calcium excretion with cheese was 141% (P=0.001), with milk was 107% (P=0.004), and with calcium salt was 75% (P= 0.02) above that of the control session. Our results show that calcium from sesame seeds and spinach does not cause an acute response in calcium metabolism. Our results indicate that fermented cheese could be a better dietary source of calcium than milk when the metabolic effects of the foodstuffs are considered.

Complementary medical treatment for Colles' fracture: A comparative, randomized, longitudinal study

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Calcified Tissue International (USA), 1997, 60/6 (567-570)

In 45 women with Colles' fracture, two types of complementary medical treatment (calcitonin with calcium (SCT+Ca) and calcium alone (Ca)) were compared with placebo. Consecutive patients were assigned randomly to one of the three study groups at the time of inclusion in the study: 15 women (68.6 +/- 5.7 years) were given 100IU/day IM of SCT plus 1200 mg of elemental Ca for 10 successive days each month; 15 women (71.7 +/- 6.1 years) were given only 1200 mg of elemental Ca for 10 days each month; and 15 women (66.9 +/-7.9 years) were treated with placebo. Biochemical and radiogrammetric studies were made at baseline and after 1 year of treatment. In the SCT+Ca group tartrate-resistant acid phosphatase decreased (Wilcoxon test, P =0.014) and the metacarpal index and the cortical and total area (CA/TA) ratio increased (both P =0.001). In the group treated with Ca alone, no changes were observed. In the placebo group, the metacarpal index and CA/TA decreased (P = 0.015 and P = 0.007, respectively). Ca alone, at the dosage used here, inhibited bone loss after Colles' fracture. The addition of SCT to Ca

administration not only impeded bone loss but significantly increased cortical bone mass.

Calcium and vitamin D in the prevention and treatment of osteoporosis

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Journal of Clinical Rheumatology (USA), 1997, 3/2 Suppl. (S52-S56)

An increasing prevalence of calcium and/or vitamin Ddeficiency in the general population (especially, but not only, in elderly subjects) has been emphasized in recent epidemiologic studies. These deficiencies could be responsible for accelerated bone loss mediated by secondary hyperparathyroidism and increased bone turnover and could explain the dramatic increase of the incidence of osteoporotic fractures with age. High calcium intake in prepubertal girls seems to be associated with higher peak bone mass in late adolescence. Calcium supplementation could slow bone turnover and bone loss in particular subsets of patients, including calcium- deficient postmenopausal women and elderly patients. A specific antifracture effect of calcium supplementation in postmenopausal osteoporotic patients has not been established, but a calcium-plus-low-dose-vitamin D3 supplementation has been suggested to decrease the peripheral fracture incidence (especially hip fracture) in elderly institutionalized women. After a critical review of these data, some practical recommendations are suggested.

Calcium intake and fracture risk: Results from the study of osteoporotic fractures

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The relation between dietary calcium, calcium, and vitamin D supplements and the risk of fractures of the hip (n = 332), ankle (n = 210), proximal humerus (n = 241), wrist (n = 467), and vertebrae (n = 389) was investigated in a cohort study involving 9,704 US white women aged 65 years or older. Baseline assessments took place in 1986-1988 in four US metropolitan areas. Dietary calcium intake was assessed at baseline with a validated food frequency questionnaire. Data on new nonvertebral fractures were collected every 4 months during a mean of 6.6

years of follow-up; identification of new vertebral fractures was based on comparison of baseline and follow-up radiographs of the spine done a mean of 3.7 years apart. Results were adjusted for numerous potential confounders, including weight, physical activity, estrogen use, protein intake, and history of falls, osteoporosis, and fractures. There were no important associations between dietary calcium intake and the risk of any of the fractures studied. Current use of calcium supplements was associated with increased risk of hip (relative risk = 1.5, 95% confidence interval 1.1-2.0) and vertebral (relative risk = 1.4, 95% confidence interval 1.1-1.9) fractures; current use of Tums antacid tablets was associated with increased risk of fractures of the proximal humerus (relative risk = 1.7, 95% confidence interval 1.3-2.4). There was no evidence of a protective effect of vitamin D supplements. Although a true adverse effect of calcium supplements on fracture risk cannot be ruled out, it is more likely that our findings are due to inadequately controlled confounding by indications for use of supplements. In conclusion, this study did not find a substantial beneficial effect of calcium on fracture risk.

Effect of dietary calcium on urinary oxalate excretion after oxalate loads

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An experimental model that allowed differentiation between endogenously and exogenously derived urinary oxalate was used to assess the effect of different forms and doses of ingested calcium on oxalate absorption and excretion. In replication 1 (R-1), subjects participated in three oxalate load (OL) tests: baseline (OL alone), calcium carbonate (OL with concomitant calcium carbonate ingestion), and calcium citrate malate (CCM) (OL with concomitant CCM ingestion). The calcium salts each provided 300 mg elemental Ca. OLs consisted of 180 mg unlabeled and 18 mg 1,2(13C2)oxalic acid. In R-2, subjects participated in four OL tests: baseline (OL alone) and OLs administered concomitantly with 100, 200, or 300 mg Ca. Timed urine samples after the OL were collected at 2-h intervals for the initial 6 h and samples were pooled into 9-h aliquots for the remaining 18 h of the 24 h period. In R-1, 24-h mean exogenous oxalate decreased ($P < 0.05$) after the OL from 36.2 mg (baseline) to 16.1 mg (after calcium carbonate) and to 14.3 mg (after CCM) whereas endogenous oxalate remained relatively constant. Mean 24-h oxalate absorption decreased significantly from that at the time of the baseline treatment (18.3%) after both calcium carbonate (8.1%) and CCM (7.2%) treatments. In R-2, mean 24-h oxalate absorption was significantly lower after 200 (5.9%) and 300 (7.6%) mg Ca than after 100 mg Ca (9.1%) and the OL alone (11.3%). Concomitant meal ingestion significantly decreased oxalate absorption in the absence of dietary calcium but not in association with the 300-mg Ca treatment. The overall data provide definitive evidence that dietary calcium can reduce oxalate absorption and excretion. Calcium carbonate and CCM were equally effective in this regard and a

minimum of 200 mg elemental Ca maximized this effect in conjunction with an oxalic acid intake of 198 mg.

1alpha-Hydroxyvitamin D2 partially dissociates between preservation of cancellous bone mass and effects on calcium homeostasis in ovariectomized rats

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Calcified Tissue International (USA), 1997, 60/5 (449-456)

Vitamin D metabolites can prevent estrogen depletion-induced bone loss in ovariectomized (OVX) rats. Our aim was to compare the bone-protective effects of 1alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3), 1alpha,25-dihydroxyvitamin D2 (1,25(OH)2D2), 1alpha-hydroxyvitamin D3 (1alpha(OH)D3), and 1alpha-hydroxyvitamin D2 (1alpha(OH)D2) in OVX rats.1alpha(OH)D3 and 1alpha(OH)D2 are thought to be activated in the liver toform 1,25(OH)2D3 and 1,25(OH) 2D2, respectively. Forty-four 12-week-old female Fischer-344 rats were either OVX or sham- operated (SHAM). Groups of OVX rats (n = 7 each) received vehicle alone, 1,25(OH)2D3, 1,25(OH)2D2, 1alpha(OH)D3, or 1alpha(OH)D2, starting 2 weeks after surgery. All vitamin D metabolites were administered orally at a dose of 15 ng/day/rat. Urine and blood samples were collected 6, 9, 12, and 16 weeks after surgery. Serum samples were analyzed for total calcium and phosphate. Calcium, phosphate, creatinine, and free collagen cross-links (ELISA) were determined in urine. After tetracycline double labeling, the rats were sacrificed 16 weeks postsurgery, and the proximal tibiae and the first lumbar vertebrae were processed undecalcified for static and dynamic bone histomorphometry.1,25(OH)2D3 and, to a slightly lesser extent, 1,25 (OH) 2D2 elevated vertebral cancellous bone mass in OVX rats to a level beyond that observed in SHAM animals, and both compounds increased serum calcium and urinary calcium excretion to similar extents. 1alpha(OH)D3 and 1alpha(OH)D2 resulted in a 64% and 84%, respectively, inhibition of ovariectomy-induced vertebral cancellous bone loss. In the proximal tibial metaphysis, all vitamin D metabolites tested could only partially prevent post-OVX trabecular bone loss, with a tendency for 1alpha(OH)D3 to be the least active compound. The effects of 1alpha(OH)D3 and 1alpha(OH)D2 on calcium homeostasis differed markedly, however. The mean increase in urinary calcium excretion over the whole experiment was fivefold for 1alpha(OH)D3, whereas the corresponding increase for 1lpha(OH)D2 was only twofold. We conclude that, compared with 1alpha(OH)D3, 1alpha(OH)D2 combined at least equal or higher bone-protective activity in OVX rats with distinctly less pronounced effects on calcium homeostasis. This effect was not due to a differential action of the corresponding main activation products, 1,25(OH)2D3 and 1,25(OH)2D2.

A high dietary calcium intake is needed for a positive effect on bone density in Swedish postmenopausal women

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Osteoporosis International (United Kingdom), 1997, 7/2 (155-161)

The importance of dietary calcium for bone health is unclear, partly since most investigations have dealt only with a fairly narrow range of calcium intake. In the present population-based observational study with longitudinal dietary assessment, we investigated women with a mean age of 60 years and with a consistently high (range 1417-2417, mean 1645 mg, n = 40), intermediate (80-1200, mean 1006 mg, n = 35) or low (400-550, mean 465 mg, n = 40) estimated daily consumption of calcium. Measurements of bone mineral density (BMD) of the lumbar spine, femoral neck and total body were performed by dual-energy X-ray absorptiometry, as well as ultrasound of the heel. In a multivariate analysis, with adjustment for energy intake the risk factors for osteoporosis (age, body mass index, physical activity, menopausal age, use of estrogens, smoking and former athletic activity), the group with the highest calcium intake had higher values for BMD than the others at all measured sites. The average mean difference compared with the low and the intermediate calcium group was 11% for the femoral neck, 8-11% for the lumbar spine and 5-6% for total body BMDs. In univariate analyses and multivariate models which did not include energy intake, the differences between the groups were less pronounced. The women in the intermediate calcium group had approximately the same mean BMD values as those in the low calcium group. These findings support the view that only a high calcium intake (3% highest percentiles in the studied population) protects against osteoporosis in Swedish postmenopausal women.

Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1alpha-hydroxyvitamin D3 and calcium supplementation

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Stroke (USA), 1997, 28/4 (736-739)

Background and Purpose: It has been demonstrated that bone mass was significantly reduced on the hemiplegic side of stroke patients, which might increase their risk of hip fracture. We evaluated the efficacy of 1alpha-hydroxyvitamin D3 (1alpha(OH)D3) and supplemental elemental calcium in maintaining bone mass and decreasing the incidence of hip fractures after hemiplegic stroke.

Methods: In a randomized study, 64 patients with hemiplegia after stroke with a mean duration of illness of 4.8 years received either 1 microg 1alpha(OH)D3 daily (treatment group, n=30) or an inactive placebo (placebo group, n=34) for 6 months and were observed for this duration. Both groups received 300 mg of

elemental calcium daily. The bone mineral density (BMD) and metacarpal index (MCI) in the second metacarpals were determined by computed x-ray densitometry. The incidence of hip fractures in these patients was recorded.

Results: BMD on the hemiplegic side decreased by 2.4% in the treatment group and 8.9% in the placebo group (P=.0021), while BMD on the intact side increased by 3.5% and decreased by 6.3% in the treated and placebo groups, respectively (P=.0177). In the treatment group, the difference in BMD between hemiplegic and nonhemiplegic sides decreased significantly compared with that before randomization. This difference increased in the placebo group. We observed a similar improvement in MCI in the treatment group but not in the placebo group. Four patients in the placebo group suffered a hip fracture compared with none in the treatment group (P=.0362).

Conclusions: Treatment with 1alpha(OH)D3 and supplemental elemental calcium can reduce the risk of hip fractures and can prevent further decreases in BMD and MCI on the hemiplegic side of patients with a long-standing stroke. Treatment also may improve these indices on the intact side.

Effects of growth hormone (GH) replacement on bone metabolism and mineral density in adult onset of GH deficiency: Results of a double-blind placebo-controlled study with open follow-up

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It's known that GH stimulates bone turnover and GH-deficient adults have a lower bone mass than healthy controls. In order to evaluate the influences of GH replacement therapy on markers of bone turnover and on bone mineral density (BMD) in patients with adult onset GH deficiency, a double-blind placebo-controlled study of treatment with recombinant human GH (rhGH; mean dose 2.4IU daily) in 20 patients for 6 months and an extended open study of 6 to12 months were conducted. Eighteen patients, fourteen men and four women, with a mean age of 44 years with adult onset GH deficiency were evaluated in the study. Compared with placebo, after 6 months serum calcium (2.39 + or - 0.02 vs 2.32 +or- 0.02 mmol/l, P=0.037) and phosphate (0.97 + or -0.06 vs 0.75 + or - 0.05 mmol/l, P=0.011) increased and the index of phosphate excretion (0.03 +or - 0.03 vs 0.19 + or - 0.02, P<0.001) decreased significantly, and there was a significant increase in the markers of bone formation (osteocalcin, 64.8 + or -11.8 vs 17.4 +or -1.8 ng/ml, P<0.001; procollagen type I carboxyterminal propeptide (PICP), 195.3 plus or minus 26.4 vs 124.0 + or - 15.5 ng/ml, P=0.026) as well as those of bone resorption (type I collagen carboxyterminal telopeptide (ICTP), 8.9 plus or minus 1.2 vs 3.3 + or - 0.5 ng/ml, P<0.001; urinary hydroxyproline, 0.035 + or - 0.006 vs 0.018 + or - 0.002 mg/100 ml glomerular filtration rate, P=0.009). BMD did not change during this period of time. IGF-I was significantly higher in treated patients (306.5 + or - 45.3 vs 88.7 + or - 22.5 ng/ml, P<0.001). An analysis of the

data compiled from 18 patients treated with rhGH for12 months revealed similar significant increases in serum calcium and phosphate, and the markers of bone turnover (osteocalcin, PICP, ICTP, urinary hydroxyproline). Dual energy x-ray absorptiometry (DXA)-measured BMD in the lumbar spine (1.194 + or - 0.058 vs 1.133 + or - 0.046 g/cm2, P=0.015), femoral neck (1.009 plus or minus 0.051 vs 0.936 + or - 0.034 g/cm2, P=0.004), Ward=s triangle (0.881 + or - 0.055 vs 0.816 + or - 0.04 g/cm2, P=0.019) and the trochanteric region (0.869 + or - 0.046 vs 0.801 + or - 0.033 g/cm2, P=0.005) increased significantly linearly (compared with the individual baseline values). At 12 months, BMD in patients with low bone mass (T-score < -1.0 S.D.) increased more than in those with normal bone mass (lumbar spine 11.5 vs 2.1%, P=0.030, and femoral neck 9.7 vs 4.2%, P= 0.055). IGF-I increased significantly in all treated patients. In conclusion, treatment of GH-deficient adults with rhGH increases bone turnover for at least 12 months, BMD in the lumbar spine and the proximal femur increases continuously in this time (open study) and the benefit is greater in patients with low bone mass. Therefore, GH-deficient patients exhibiting osteopenia or osteoporosis should be considered candidates for GH supplementation. However, long-term studies are needed to establish that the positive effects on BMD are persistent and are associated with a reduction in fracture risk.

Decreased serum IGF-I and dehydroepiandrosterone sulphate may be risk factors for the development of reduced bone mass in postmenopausal women with endogenous subclinical hyperthyroidism

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Postmenopausal women with endogenous subclinical hyperthyroidism seem to have reduced bone mass, which does not correlate with serum thyroid hormone levels. Relative insufficiencies of IGF-I and dehydroepiandrosterone sulphate (DHEAS) might be additional risk factors for low bone density in these patients. We measured IGF-I, IGF-binding protein-3 (IGFBP-3) and DHEAS levels together with bone mineral density (BMD) of the femoral neck and lumbar spine in women with an autonomously functioning thyroid nodule. Sixty-three women were classified as subclinical hyperthyroid (31 pre- and 32 postmenopausal) and 39 as overt hyperthyroid (16 pre- and 23 postmenopausal) and results were compared with data obtained from 41age- matched euthyroid healthy women. In premenopausal women BMD was reduced only in the overt hyperthyroid group, and only in the spine, to 92% (P < 0.05). Serum IGF-I as well as IGFBP-3 were increased in the manifest hyperthyroid group, to 157% (P < 0.001) and 129% (P < 0.05) respectively, whereas DHEAS levels did not change in either premenopausal patient group. In postmenopausal women BMD was significantly reduced both in the subclinical hyperthyroid group (spine to 90% and femoral neck to 88%; P < 0.05), as well as in the hyperthyroid group (spine to 78% and femoral neck to 86%; P < 0.01). In contrast to premenopausal women, serum IGF-I and IGFBP-3 did not change in the two groups who were postmenopausal and

serum DHEAS levels were reduced to 58% ($P < 0.001$) in both postmenopausal groups with subclinical as well as overt hyperthyroidism. In the same two groups of patients, serum IGF-I and DHEAS levels correlated with BMD (femoral neck; both $r = 0.50$, $P < 0.05$). In conclusion, women with a solitary autonomous thyroid nodule with subclinical hyperthyroidism have reduced BMD only if they are postmenopausal. This is probably due to the effect of subtle increases in thyroid hormone production together with lack of oestrogen protection of the skeleton. But additional risk factors for the development of enhancd bone loss might be a state of relative IGF-I and DHEAS insufficiency in these patients as well as in postmenopausal women with overt hyperthyroidism.

Osteoporosis: Prevention, diagnosis, and management

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American Journal of Medicine (USA), 1997, 102/1 A (35S-39S)

Osteoporosis is a public health scourge that is usually eminently preventable. Some risk factors, such as low calcium intake, vitamin D deficiency, and physical inactivity, are amenable to early interventions that will help maximize peak bone density. Other risk factors subject to modification are cigarette smoking and excessive consumption of protein, caffeine, and alcohol. Hip fractures are the most serious outcome of osteoporosis, with enormous personal and public health consequences. The ongoing Study of Osteoporotic Fractures has identified additional independent predictors of hip fracture risk, including maternal hip fracture, absence of significant weight gain since age 25, height, hyperthyroldism, use of long- acting benzodiazepines or anticonvulsants, spending <4 hours a day on one's feet, inability to rise from a chair without using one's arms, poor visual depth perception and contrast sensitivity, and tachycardia. In an individual perimenopausal woman, the risk of osteoporotic fracture and the urgency of estrogen replacement therapy can be best estimated on the basis of bone mineral density, as measured by dual-energy x-ray absorptiometry, coupled with the presence or absence of existing fractures and clinical risk factors evident from the history and physical examination. Estrogen, calcitonin, and bisphosphonates have all been proved effective in retarding postmenopausal bone loss and therefore reducing the risk of fracture. The use of sodium fluoride is more controversial, although a recent study has suggested a possible role for slow-release fluoride combined with high-dose calcium supplementation.

Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes

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Vitamin D deficiency, which causes osteomalacia, may also be important in the pathogenesis of age-related osteoporosis. We studied serum vitamin D metabolites in 52 young women (mean age: 30 + or - 3 y; range: 25-35y), 64 elderly free-living women (mean age: 71 + or - 4 y; range: 65-82 y) and 60 elderly women living in nursing homes (mean age: 84 plus or minus 9 y; range: 61-102 y). Mean serum 25-hydroxyvitamin D (calcidiol) was 10.8 plus or minus 4.4 nmol/L (27 + or - 11 ng/mL) in women living in nursing homes and was similar to that of free- living young (11.3 plus or minus 4.2 nmol/L, or 28 + or - 10 ng/mL) and elderly (11.5 plus or minus 3.2 nmol/L, or 29 plus or minus 8 ng/mL) women. Vitamin D deficiency (defined as serum calcidiol < 4.8 nmol/L, or 12 ng/mL) occurred in 8% of women living in nursing homes, in 6% of the young women, and in 1.6% of the free-living elderly women. Serum calcidiol was significantly correlated with vitamin D intake ($r = 0.25$, $P < 0.05$) and inversely correlated with serum intact parathyroid hormone (iPTH) ($r = -0.16$, $P < 0.03$). Serum iPTH increased with age and secondary hyperparathyroidism was observed in 17% of the women living in nursing homes. Calcium absorption declined with age, but calcium absorption and serum 1alpha,25-dihydroxyvitamin D (calcitriol) were significantly lower in women living in nursing homes, which probably contributed to the secondary hyperparathyroidism. In conclusion, normal serum calcidiol may avoid the problem of osteomalacia, but it does not correct malabsorption of calcium. Although calcitriol corrects the malabsorption of calcium, it remains to be seen whether higher amounts of vitamin D can normalize the calcium malabsorption of aging.

Effect of 1,25(OH)2 vitamin D3 on circulating insulin-like growth factor-I and beta2 microglobulin in patients with osteoporosis

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Calcified Tissue International (USA), 1997, 60/3 (236-239)

To test the hypothesis that growth factors mediate the stimulatory effect of 1,25(OH)2 vitamin D3 (1,25(OH)2D3) on bone remodeling in osteoporosis, the authors studied the effect of the secosteroid administration in two closes (1 microg and day and 2 microg/day) for 14 days on circulating insulin-like growth factor-I (IGF-I), beta2 microglobulin, anti osteocalcin in 18 osteoporotic women. The biological effectiveness of the treatment was controlled by a decline of serum intact parathyroid hormone. Compared with the values before treatment, 1,25(OH)2D3 increased means of plasma IGF I, beta2 microglobulin, and serum osteocalcin significantly: however, the effects were only apparent after the higher dose of the drug (169 + or - 26 versus 134 + or - 28 ng/ml, $P < 0.01$; 2.08 + or - 0.1 versus 1.92 plus or minus 0.1 microg/ml, $P < 0.05$; and 8.5 plus or minus 1.3 versus 5.4 + or - 1.1 ng/ml, $P < 0.01$, respectively). The authors conclude that exogenous 1,25(OH)2D3 promotes the production of IGF-I and beta2 microglobulin in osteoporotic patients in parallel to the marker of osteoblastic function, osteocalcin, which supports the tested hypothesis.

Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women

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Journal of Bone and Mineral Research (USA), 1997, 12/2 (241-247)

It's well established that genetic factors contribute to bone turnover and bone density. Evidence exists suggesting that a major part of this genetic influence may be due to polymorphisms in the vitamin D receptor (VDR) gene. However, it=s not clear whether the VDR genotype effect persists in elderly women. In the present study, the relationship between the BsmI, ApaI, and TaqI polymorphisms in the VDR gene, and the bone mineral density (BMD) at the lumbar spine, the femoral neck (FN), and the proximal radius was investigated in a large group of elderly women (75.5 plus or minus 5.0 years) of Caucasian origin and in 84 Type I osteoporotic women (66.6 + or - 8.4 years). We did not find a correlation between the VDR genotypes and BMD in elderly women. However, a significantly higher FN-BMD was observed in obese (body mass index (BMI) > 30 kg/m2) versus nonobese (BMI < 30 kg/m2) women ($p < 0.01$). This relationship was observed for all BsmI genotypes. Furthermore, the FN-BMD of nonobese women with bb BsmI genotype was 5% higher than that of women with the BB genotype ($p = 0.04$). We conclude that the VDR gene polymorphisms influence the FN-BMD in nonobese postmenopausal women. In a second part of the study, possible correlations between the VDR gene polymorphisms and osteoporosis Type I were analyzed. Our data could not reveal any association between these parameters.

Connections between phospho-calcium metabolism and bone turnover. Epidemiologic study on osteoporosis (second part)

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Italy
Minerva Medica (Italy), 1996, 87/12 (565-576)

Background. The recent development of highly accurate and precise osseous mass quantitative evaluation methodology, permits the conduction, in the sphere of osteoporosis, of epidemiologic investigations no longer limited solely to fracture complications, but also based on the definition of osseous mass. Fractures being only complications, possible but not certain, of the advanced stages of the disease, the studies based on their incidence allow one to underestimate the global entity of prevalence and incidence, besides building only a partially useful reference in view of primary and secondary prevention.

Methods. The main points of our study are the following:

1) Evaluation of the incidence of the primary risk factors for osteoporosis as they appear in the literature, on the bone mass values of examined subjects, utilizing static mineralometric data as a reference standard;

2) Study of biohumoral data relative to phospho-calcium metabolism and to sexual function, to show the possibility of their use as early identifying markers of subjects at risk; reference values represented by dynamic mineralometric data. The principal conclusions that emerged in the course of the study are the following.

Results.In relation to the use of phospho-calcium metabolic biohumoral and hormonal variables, as a predictive function on the variations of bone turnover, the variables:osteocalcin, alkaline phosphatase, alkaline phos-phatase bone isoenzyme, hydroxyprolinuria/creatininuria, have resulted significantly different in the comparison between high and low turnover subjects. The degree of quantitative correlation of such variables with the entity of percentage decrement of bone mass has been modest. The overall value of R-square of the predictive model, besides the variables mentioned the value of bone mass at 1degreecontrol visit, was 0.38(osteocalcin:0 .27; osteocalcin+hydroxyprolinuria /creatininuria: 0.33; preceding variables + bone mass at 1st control: 0.36; preceding variables + alkaline phosph-atase:0.37; preceding variables +alkaline phosphatase bone isoenzyme:0.38).

Conclusions.The single value osteocalcin may furnish indications on the future variations of bone turnover and consequently on the early identification of the subjects at risk for osteoporosis at high turnover; the addition of the other variables indicated in our predictive model allows an increase of the possibilities of individualizing of these subjects.

Treatment of post-menopausal osteoporosis with recombinant human growth hormone and salmon calcitonin: A placebo controlled study

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Clinical Endocrinology (United Kingdom), 1997, 46/1 (55-61)

Objective: The usefulness of GH in the treatment of post-menopausal osteoporosis (PMO) is still debated. We have studied the effects of recombinant human GH (rhGH) given alone or in combination with salmon calcitonin (sCT)in the treatment of PMO.

Patients: Thirty women with established PMO (aged 61.1 + or - 4.4 years) were divided into 3 groups of 10 and randomly assigned to 3 treatment sequences: rhGH (12 IU/day) s.c. for 7 days, followed by sCT (50 IU/day) s.c. for 21 days and by 61 days without treatment (group 1); placebo for 7 days, followed by sCT for 21 days and by 61 days without treatment (group 2); rhGH for 7 days,

followed by placebo for 21 days, and by 61 days without treatment (group 3). Each cycle was repeated 8 times (24 months).

Measurements: At days 0, 8, 29 and 90 of each cycle, serum IGF-I, calcium, phosphate, osteocalcin, alkaline phosphatase and urinary excretion of calcium, hydroxyproline and pyridinoline cross-links (Pyr) were measured. At months 0, 6, 12, 18 and 24, bone mineral density (BMD) was measured by dual-photon absorptiometry (DPA), at lumbar spine (LS), femoral shaft (F) and distal radius (DR).

Results: A significant increase in serum osteocalcin and urinary calcium, hydroxyproline and Pyr was detected after each rhGH period. In group 1, BMD at lumbar spine increased by 2.5% at year 2; in contrast, significant ($p < 0.05$) decreases in BMD-LS values were found in patients treated with CT and placebo (group 2) and with OH and placebo (group 3). BMD-F did not show any significant change in patients of group 2, but a significant ($p < 0.05$) decrease was found in groups 1 and 3. BMD-DR did not show any significant change with respect to baseline in any of the three groups. No significant difference between the three groups was found in bone mass at the three different regions.

Conclusions: Our study demonstrates that treatment with rhGH increases bone turnover in postmenopausal osteoporotic women. Combined treatment with rhGH and CT over a period of 24 months is able to maintain bone mass at lumbar spine and distal radius, but induces a decline at femoral shaft; therefore, it does not seem particularly useful in the therapy of post-menopausal osteoporosis. :

Effect of measuring bone mineral density on calcium intake

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Japanese Journal of Geriatrics (Japan), 1996, 33/11 (840-846)

The diet in Japan has improved, but calcium intake has not increased for the past ten years, and it remains insufficient. To prevent osteoporosis, instruction in nutrition is directed at increasing calcium intake. We studied the effect of measuring bone mineral density on calcium intake in people receiving nutrition education. Intake of other nutrients was also measured. The subjects were 87 healthy women living in an agricultural region (Yamanashi Prefecture). They were members of a group formed to improve the diet of people in their area. For three days in October 1992 and in August 1994 food-weight records were obtained. A total of 76 of the 87 women chose to have their bone mineral density measured. The measurements before the first nutrition assessment in 1992. The intake of almost all nutrients tended to be greater in 1994 than in 1992. Calcium intake exceeded the minimum daily requirement (600mg). Calcium intake increased between 1992 and 1994 only in the subjects whose bone mineral density had been measured. Calcium intake decreased in the other subjects. Therefore, nutrition education programs aimed at preventing osteoporosis may be more

effective if bone mineral density is measured. In addition, an appropriate balance of other nutrients can be maintained as the intake of calcium is increased.

Osteoporosis: Its pediatric causes and prevention opportunities

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Primary Care Update for Ob/Gyns (USA), 1997, 4/1 (15-20)

Osteoporosis is the most common metabolic bone disease in western societies, and is characterized by a reduction of bone mass leading to the increased susceptibility to fractures. With increases in life expectancy and in the number of elderly people, bone loss and fractures are becoming more common in the United States and throughout the world. As a consequence, an epidemic of bone fractures among the elderly is expected. In this respect, it is obvious that the emphasis should be on the development of strategies for maximizing bone gain and preventing bone loss and subsequent osteoporosis. This paper discusses the concepts that are the foundation for primary prevention of osteoporosis: the measures that should be implemented during childhood and adolescence, with the goal of optimizing bone mass in young adulthood. Some important concepts, such as peak bone mass and calcium intake threshold, as well as the original studies of adolescent females and their bone mass acquisition are presented. It becomes clear that osteoporosis could have its roots during growth, and it should be treated as such. Teenagers should therefore be targeted as a population at risk, and preventive measures should be implemented by means of adequate calcium intake, proper diet, and exercise programs aimed at increasing peak bone mass.

Estimated dietary calcium intake and food sources for adolescent females: 1980-92

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Journal of Adolescent Health (USA), 1997, 20/1 (20-26)

Purpose: To estimate dietary calcium intake of three groups of adolescent females ages 11-12 years, 13-14 years, and 15-18 years during four separate 2-year time periods from the years 1980-92; and to identify their food sources of calcium.

Methods: Nutrient intake survey based on 14-day food consumption records collected from four national representative samples of 4,000 United States households.

Results: Dietary calcium consumption declined significantly ($p < .01$) over the 10-year period for the 15-18 year olds. Calcium intake was significantly lower for 13-14 year olds compared to the youngest age group, and for 15-18 year olds

when compared to the two younger age groups for all four study periods ($p < .01$). Over 90% of all adolescent females consumed < 100% of the RDA for calcium during all data collection periods. The percentage of adolescent females who consumed less than two- thirds of the RDA increased with age. Seventy-seven percent of 15-18 year olds consumed below this level from 1990-92. Milk and milk products were the best food sources of calcium contributing over one-half of the calcium to the diet. This percentage declined over time and with age to 44% for the 15-18 year old females in 1990. This drop can be attributed to a 7-12% decline in fluid milk consumption for the 11-12 year olds and 15-18 year olds, respectively.

Conclusions: Estimates indicate that dietary calcium intakes fall far short of both the Recommended Dietary Allowance (RDA) and National Institutes of Health (NIH) recommendations. Intakes have declined over time, with age, and appear to be related to a decline in fluid milk consumption. Efforts to increase calcium consumption among adolescent females appear critical. Clear recommendations to consume a minimum of three servings everyday of lowfat or nonfat dairy products such as milk and yogurt are needed to help this population meet daily calcium requirements.

The importance of genetic and nutritional factors in responses to vitamin D and its analogs in osteoporotic patients

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Calcified Tissue International (USA), 1997, 60/1 (119-123)

The effects of vitamin D and its analogs on fractures and bone mass have been clarified by clinical observations for more than 10 years. Reviewing the results of six clinical trials on osteoporotic fractures using activated vitamin D analogs, there appeared to be a negative correlation between basal levels of calcium intake and the incidence of vertebral fractures in the control groups. For example, when daily calcium intake was about 600 mg, there were approximately 800 vertebral fractures per 1000 persons a year in the controls. When daily calcium intake was above 1000 mg, the incidence was less than 400 fractures per 1000 persons a year. The incidence of fractures de-creased by about half in the activated vitamin D-treated group compared with the control group, but the most marked preventive effects of activated vitamin D on fractures were obtained in clinical studies, with daily calcium intakes of 400-800 mg. The effects of vitamin D analogs on bone mass were reported in the clinical studies, but the results are not consistent. However, these studies suggest that the effects of both 1,25(OH)2D3 and 1-alpha(OH)D3 on bone mass were dose dependent, and the doses were low in clinical studies in which good results were not obtained. Significant effects on bone mass were obtained when more than 0.6 microg of 1,25(OH)2D3, or more than 0.75 microg of 1-alpha(OH)D3 was administered, with increase in the urinary calcium level being within the acceptable range. Reported data indicate that both nonactivated vitamin D and activated vitamin D reduce the serum

parathyroid hormone level. However, activated vitamin D administration is more effective, and is able to reduce bone resorption in postmenopausal, osteoporotic patients with a vitamin D-sufficient status. Recent studies concerning the polymorphism of the vitamin D-receptor gene emphasize that sensitivity to active vitamin D varies between genotypes. In the bb type, sensitivity to active vitamin D is high, and calcium absorption efficiency in the intestine under low calcium conditions increases with increase in the serum 1,25(OH)2D level. A significant increase in lumbar bone mineral density was obtained after administration of activated vitamin D to osteoporotic patients of bb type. However, in the genotype with the B factor, sensitivity to active vitamin D was low, and the rate of increase of bone density was low. These data suggest that nutritional and genetic factors are critical when using active vitamin D and its analogs in the treatment of osteoporosis.

The pathogenesis of age-related osteoporotic fracture: Effects of dietary calcium deprivation

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Journal of Clinical Endocrinology and Metabolism (USA), 1997, 82/1 (260-264)

The pathogenesis of osteoporotic fracture after the menopause is uncertain. We studied the effects of a 4-day low calcium diet on 17 subjects with vertebral osteoporotic fracture and 17 age-matched controls with a bone density within the young normal range and without fracture. At baseline, the osteoporotic patients were well matched to normal subjects in terms of calcium intake and absorption and renal function, but had higher bone turnover and relative secondary hyperparathyroidism. After the low calcium diet, the rise in calcitriol was deficient in the osteoporotic subjects. These data are consistent with the suggested pathogenesis of type II or age- related osteoporosis and show that in these subjects with osteoporotic fracture there was a primary defect in calcitriol production that resulted in secondary hyperparathyroidism. This defect may be the cause of the high bone turnover and may play an important role in the development of bone loss in these subjects.

Increased catabolism of 25-hydroxyvitamin D in patients with partial gastrectomy and elevated 1,25-dihydroxyvitamin D levels. Implications for metabolic bone disease

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Journal of Clinical Endocrinology and Metabolism (USA), 1997, 82/1 (209-212)

Serum vitamin D metabolites and PTH were measured in seven subjects with a history of previous partial gastrectomy (PGX) and metabolic bone disease. The elimination tone-quarter of (3H)25-hydroxyvitamin D3 ((3H)25OHD3) in serum was assessed after an iv pulse dose of 5 microCi (26,27-3H)25OHD3. Median serum 25OHD3 was 37.5 (27.5-101.3) nmol/L, (normal range (NR) 10.8-58.5 nmol/L), mean serum 1,25-dihydroxyvitamin D (1,25-(OH)2D3) was raised at 175 + or - 72 pmol/L, (NR 48-120 pmol/L) and mean PTH was also high, 67 + or - 27 ng/L, (NR 10- 60 ng/L). Serum tone-quarter (3H)25OHD3 ranged from 10.9-21.2 days. A strong negative correlation existed between tone-quarter (3H)25OHD3 and serum 1,25- (OH)2D3 (Spearman's rank correlation coefficient ($r = -0.82$, $P = 0.002$)) and PTH) Spearman's rank correlation coefficient ($r = -0.81$, $P = 0.001$)). Four subjects who had high initial PTH concentrations (60-115 ng/L) and elevated 1,25-(OH)2D levels (162300 pmol/L) were reassessed after calcium supplementation to suppress secondary hyperparathyroidism (2degreeHPT). In this subgroup, after-treatment PTH fell from 82 + or - 24 to 52 + or B 24 ng/L (mean plus or minus SD), not significant; 1,25-(OH)2D fell from 210 plus or minus 61 to 116 plus or minus 28 pmol/L, $P = 0.015$; and tone-quarter (3H)25OHD3 increased from 13.2 + or - 1.9 to 18.9 plus or minus 3.1 days, $P = 0.012$. Patients with PGX and evidence of 2degreeHPT with elevated 1,25(OH)2D have a reduced tone-quarter (3H)25OHD3, and this may explain the increased susceptibility of the subjects to osteomalacia. Calcium supplementation suppresses 2degreeHPT, increases tone-quarter (3H)25OHD3 and may protect against PGX osteoporosis and osteomalacia.

Can the fast bone loss in osteoporotic and osteopenic patients be stopped with active vitamin D metabolites?

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Calcified Tissue International (USA), 1997, 60/1 (115-118)

The aim of this study was to evaluate whether fast trabecular bone loss in osteoporotic and osteopenic patients can effectively be treated with active vitamin D metabolites. Thirty-one osteoporotic and osteopenic patients were monitored between 4 and 22 months before and between 8 and 18 months during the treatment. Fast bone losers were designated as osteoporotic or osteopenic patients with a loss of trabecular bone density in the radius of 3% or more calculated for 1 year. For this differentiation, the high precise peripheral quantitative computed tomography system (DENSISCAN 1000) was used (reproducability 0.3% in mixed collectives). The pretreatment loss and the 'gain' under treatment with active vitamin D metabolites was calculated for 1 year. The treatment consisted of either 0.5 microg calcitriol daily or 1 microg of alfacalcidol daily. Before treatment, the trabecular bone loss in the radius/ year was -6.6 + or - 0.5% (mean + or - SEM). After treatment with vitamin D metabolites, the trabecular bone gain in the radius/year was 0.01 + or - 0.6% (mean + or - SEM). The difference was highly significant ($P < 0.001$). In contrast to this, the loss of cortical bone density before treatment was -1.8 + or - 0.3% (mean + or - SEM) and the reduced loss

after treatment -0.2 + or - 0.4% (mean plus or minus SEM), both values calculated for 1 year. This difference was less significant ($P < 0.05$). This study shows that the treatment with active vitamin D metabolites is very effective in slowing fast trabecular bone loss in osteoporotic and osteopenic patients.

Is there a differential response to alfacalcidol and vitamin D in the treatment of osteoporosis?

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Calcified Tissue International (USA), 1997, 60/1 (111-114)

There is a decline in serum 25 hydroxyvitamin D (25OHD), 1,25 dihydroxyvitamin D (1,25(OH)2D), and calcium absorption with advancing age, which may lead to secondary hyperparathyroidism and bone loss. Studies show a relationship between serum 25OHD and bone density in older men and women, with an inverse correlation between bone density and parathyroid hormone (PTH). Vitamin D supplementation in this age group improves calcium absorption, suppresses PTH, and decreases bone loss. Vitamin D many also reduce the incidence of hip and other nonvertebral fractures, particularly in the frail elderly who are likely to have vitamin D deficiency. Patients with established vertebral osteoporosis have lower calcium absorption than age- matched control subjects, possibly due to reduced serum 1,25(OH)2D or to relative resistance to the action of vitamin D on the bowel. Malabsorption of calcium in women with vertebral crush fractures does not usually respond to treatment with physiological doses of vitamin D, but can be corrected by pharmacological doses of vitamin D or by low doses of calcitriol or alfacalcidol. In a recent randomized, controlled study in 46 elderly women with radiological evidence of vertebral osteoporosis, alfacalcidol 0.25 microg twice daily improved calcium absorption, decreased serum PTH, and reduced alkaline phosphatase, whereas vitamin D2 5001000 IU daily had no effect over the 6-month study period. Studies of the effect of the vitamin D metabolites in the management of elderly women with established vertebral osteoporosis have yielded conflicting results, but suggest that alfacalcidol and calcitriol may decrease spinal bone loss and reduce the incidence of vertebral fractures. Although vitamin D supplementation decreases bone loss and fracture risk in the frail elderly, vitamin D metabolites may prove more useful in the treatment of elderly women with vertebral osteoporosis.

Rationale for active vitamin D analog therapy in senile osteoporosis

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Calcified Tissue International (USA), 1997, 60/1 (100-105)

Osteoporosis is diagnosed when bone density decreases below the fracture threshold, a change that is associated with decreased biomechanical integrity and fracture. There are two types of primary osteoporosis: postmenopausal osteoporosis and senile osteoporosis. Postmenopausal osteoporosis is due to some combinations of a low peak bone density and a high rate of bone loss during the early postmenopausal years. The bone loss is primarily due to estrogen deficiency, which leads to increases in resorbing cytokines and a consequent increase in bone resorption. The pathogenesis of senile osteoporosis is less well understood and includes factors in addition to estrogen deficiency. A potential etiological factor is the vitamin D deficiency that occurs with advancing age. Severe vitamin D deficiency in the adult leads to osteomalacia, whereas a mild deficiency, which is common in the elderly, is rarely associated with mineralization defects but instead could lead to development of secondary hyperparathyroidism and osteoporosis. There are basically two types of vitamin D deficiency: (1) primary vitamin D deficiency which is due to a deficiency of vitamin D, the parent compound of the active metabolite 1,25(OH)2D3; and (2) a deficiency of 1,25(OH)2D3 action resulting from either decreased production of 1,25(OH)2D3 by the kidney or from decreased responsiveness to 1,25(OH)2D3 of target tissues, i.e., resistance. Both types of deficiencies could occur with aging, and both have been implicated as potential causes of senile osteoporosis. In this paper, we would like to advance the hypothesis that the age-related deficiency in 1,25(OH)2D3 action plays a role in the pathogenesis of senile osteoporosis. We will provide evidence to support the concept that a deficiency of 1,25(OH)2D3 action exists in the elderly, which plays a role in age-related bone loss, and that this deficiency of 1,25(OH)2D3 action can be successfully treated with 1,25(OH)2D3 or 1alpha-hydroxy vitamin D3 (1alpha(OH)D3).

Efficacy and safety of long-term, open-label treatment of calcitriol in postmenopausal osteoporosis: A retrospective analysis

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Current Therapeutic Research - Clinical and Experimental (USA), 1996, 57/11 (857-868)

To assess the efficacy and safety of calcitriol treatment in postmenopausal osteoporotic patients, a retrospective study was made of 340 women (mean age plus or minus SD, 63 plus or minus 7.7 years) with established postmenopausal osteoporosis characterized by calcium malabsorption who received long-term, open-label treatment with calcitriol 1 microg/d. The patients were separated into subgroups based on the length of calcitriol therapy (1 to 14 years). The previously reported data of 25 postmenopausal osteoporotic women (mean age + or - SD, 64 plus or minus 7.2 years), untreated for a period of 2 years, were used as a control group. Calcitriol promoted a significant increase in intestinal calcium absorption at all treatment durations, with no clinically significant changes in serum calcium or creatinine levels. Urinary calcium increased in a statistically significant manner

and was always higher than at baseline as long as calcitriol was administered, without modifying blood urea nitrogen and serum creatinine levels. Urinary hydroxyproline excretion was generally unchanged, indicating that the increased calcium excretion was due to increased intestinal absorption rather than bone catabolism. Measured by using a visual analog scale, pain decreased markedly and statistically significantly during treatment in all groups. There was a slight but progressive mean height loss during the study, although this was only 2 cm in the patients treated for 9 years or more. Measurements of bone mineral density (BMD) showed that both total body BMD and spine BMD were largely unchanged during treatment, whereas the decrease in BMD in the untreated osteoporotic patients was more than 2%. The occurrence of nontraumatic clinically relevant fractures decreased noticeably in comparison with the period preceding calcitriol treatment.

Magnesium deficiency: Possible role in osteoporosis associated with gluten-sensitive enteropathy

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Osteoporosis International (United Kingdom), 1996, 6/6 (453-461)

Osteoporosis and magnesium (Mg) deficiency often occur in malabsorption syndromes such as gluten-sensitive enteropathy (GSE). Mg deficiency is known to impair parathyroid hormone (PTH) secretion and action in humans and will result in osteopenia and increased skeletal fragility in animal models. We hypothesize that Mg depletion may contribute to the osteoporosis associated with malabsorption. It was our objective to determine Mg status and bone mass in GSE patients who were clinically asymptomatic and on a stable gluten-free diet, as well as their response to Mg therapy. Twenty-three patients with biopsy-proven GSE on a gluten-free diet were assessed for Mg deficiency by determination of the serum Mg, red blood cell (RBC) and lymphocyte free Mg2+, and total lymphocyte Mg. Fourteen subjects completed a 3-month treatment period in which they were given 504-576 mg MgCl2 or Mg lactate daily. Serum PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and osteocalcin were measured at baseline and monthly thereafter. Eight patients who had documented Mg depletion (RBC Mg2+ < 150 microM) underwent bone density measurements of the lumbar spine and proximal femur, and 5 of these patients were followed for 2 years on Mg therapy. The mean serum Mg, calcium, phosphorus and alkaline phosphatase concentrations were in the normal range. Most serum calcium values fell below mean normal and the baseline serum PTH was high normal or slightly elevated in 7 of the 14 subjects who completed the 3-month treatment period. No correlation with the serum calcium was noted, however. Mean serum 25-hydroxyvitamin D, 1,25-dihydroxy vitamin D and osteocalcin concentrations were also normal. Despite only 1 patient having hypomagnesemia, the RBC Mg2+ (153 + or - 6.2 microM; mean plus or minus SEM) and lymphocyte Mg2+ (182 plus or minus 5.5 microM) were significantly lower than normal (202 + or - 6.0 microM, P < 0.001, and 198 + or - 6.8 microM, p < 0.05, respectively). Bone

densitometry revealed that 4 of 8 patients had osteoporosis of the lumbar spine and 5 of 8 had osteoporosis of the proximal femur (T-scores less than or equal to -2.5). Mg therapy resulted in a significant rise in the mean serum PTH concentration from 44.6 + or - 3.6 pg/ml to 55.9 plus or minus 5.6 pg/ml ($p < 0.05$). In the 5 patients given Mg supplements for 2 years, a significant increased in bone mineral density was observed in the femoral neck and total proximal femur. This increase in bone mineral density correlated positively with a rise in RBC Mg^{2+}. This study demonstrates that GSE patients have reduction in intracellular free Mg^{2+}, despite being clinically asymptomatic on a gluten-free diet. Bone mass also appears to be reduced. Mg therapy resulted in a rise in PTH, suggesting that the intracellular Mg deficit was impairing PTH secretion in these patients. The increase in bone density in response to Mg therapy suggests that Mg depletion may be one factor contributing to osteoporosis in GSE.

Effects of vitamin B12 on cell proliferation and cellular alkaline phosphatase activity in human bone marrow stromal osteoprogenitor cells and UMR106 osteoblastic cells

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Metabolism: Clinical and Experimental (USA), 1996, 45/12 (1443-1446)

Pernicious anemia has recently been recognized as one of the risk factors for osteoporosis and bone fractures, but the underlying pathophysiologic mechanism is still unknown. To determine whether vitamin B12 has any direct effect on osteoblasts, we studied the effects of vitamin B12 on the proliferation and alkaline phosphatase activity in human bone marrow stromal osteoprogenitor cells (hBMSC) and UMR106 osteoblastic cells. Vitamin B12 at concentrations as low as 10-12 mol/L significantly stimulated (3H)-thymidine incorporation in both types of cells, but concentrations higher than 10-12 mol/L did not produce a greater effect.Vitamin B12 in the concentration range from 10-12 to 10-8 mol/L concentration- dependently increased alkaline phosphatase activity in both hBMSC and UMR106 cells. Based on these results, we suggest that a suppressed activity of osteoblasts may contribute to osteoporosis and fractures in patients with vitamin B12 deficiency.

Calcium metabolism in the elderly

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Giornale di Gerontologia (Italy), 1996, 44/2 (91-96)

The aging process is characterized by several alterations in calcium metabolism and by a negative calcium balance. Total body calcium is reduced in the elderly. Since 99% of total body calcium is localized in the bone this reduction is associated with a reduction in progressive bone mass, increased fragility of the skeleton, and with increased risk of fractures. The reduction in calcium with aging is paradoxically associated with an accumulation of calcium within the cells and soft tissues. From a metabolic point of view, the aging process is associated with several alterations in calcium homeostasis. Calcium intake, calcium absorption, and renal calcium conservation are all reduced in the aged. Calciotropic hormone levels undergo alterations with age. 25(OH)2 levels tend to decrease with age due to reduced vitamin D intake and as a result of a reduction in exposure to the sun. PTH levels in response to the status of calcium deprivation and the reduction of serum ionized calcium progressively tend to increase with age. Aging is also associated with an increase in bone turnover, as documented by the increased levels of the serum and urinary markers of bone formation and bone reabsorption. This increase in bone remodeling is directly related to the reduction in bone mass and the increased risk of fractures. Calcium supplements together with drugs able to reduce bone turnover, may contribute to the normalizing of the calcium balance, and reducing the risk of fractures in the elderly.

Hormones, vitamins, and growth factors in cancer treatment and prevention: A critical appraisal

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BACKGROUND. Hormones, hormone agonists, hormone antagonists, vitamins and their synthetic analogues, and growth factors are currently the most widely used anticancer drugs. Although in many cases they provide dramatic results, in other cases their effects are conflicting. A critical appraisal of the effects of these drugs is needed.

METHODS. To evaluate the potential therapeutic and preventive roles of these drugs as well as their areas of controversy, data published in the literature in the last two decades are reviewed in this article, and the author's personal findings are also reviewed.

RESULTS.Hormones, hormone agonists, hormone antagonists, vitamins and their synthetic analogues, growth factors, and cytokines are replacing conventional cancer therapies (chemotherapy, surgical therapy, and radiation therapy) for many purposes, and recently became the 'fourth arm' of cancer treatment. However, their mechanisms of action have not yet been elucidated. This article critically reviews the mechanisms of their action on cancer cells (specifically, DNA, RNA, oncogenes, and antioncogenes); their role in cancer cell division, cell cycle, apoptosis, and angiogenesis; and their relation to human cancers. Since hormones,

vitamins, growth factors (GFs), and GF receptors play a cardinal role in multistage carcinogenesis, using monoclonal antibodies to develop novel hormone antagonists, vitamin synthetic analogues, and GF inhibitors will be of paramount significance for neoadjuvant systemic therapy and cancer prevention.

CONCLUSIONS. It is hoped that the data presented in this review regarding the role of hormones, hormone agonists, hormone antagonists, vitamins, growth factors, and growth factor inhibitors will provide a rationale for designing effective new cancer chemoprevention strategies and clinical trials.

Therapy of osteoporosis: Calcium, vitamin D, and exercise

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American Journal of the Medical Sciences (USA), 1996, 312/6 (278-286)

Calcium supplementation has long been regarded as a fundamental part of the prevention and treatment of postmenopausal osteoporosis, but it is only in recent years that clear evidence has emerged demonstrating its impact on bone mass. Calcium supplementation does not completely arrest postmenopausal bone loss but slows the rate of decline by 30 to 50%. The effect of calcium supplementation on fracture incidence in postmenopausal women has not been established. Vitamin D deficiency is common in the frail elderly, particularly in countries where fortification or food with this vitamin is not practiced. Treatment of vitamin D deficiency has been associated with significant reductions in the number of hip fractures. The role of the potent vitamin D metabolites, calcitriol and alphacalcidol, in the management of postmenopausal osteoporosis is not clear. Although some studies show substantial benefits in bone density or fracture rate from the use of these compounds, the published data are inconsistent. In general, hormone replacement therapy and the potent bisphosphonates produce greater effects on bone density and there is a greater consistency among the results of the published studies of these other interventions. Controlled trials of exercise interventions in postmenopausal women show that exercise can positively influence bone density by a few percent. Exercise interventions in the elderly have been reported to decrease fall frequency by 10%. This latter effect may have a greater impact on fracture frequency than the modest benefits of exercise on bone density.

Pathophysiology of osteoporosis

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USA
American Journal of the Medical Sciences (USA), 1996, 312/6 (251-256)

As with many chronic diseases that express themselves late in life, osteoporosis is distinctly multifactorial both in etiology and in pathophysiology. Osteoporotic fractures occur because of a combination of injury and intrinsic bony fragility. The injury comes most often from a combination of falls, poor postural reflexes that fail to protect bony parts from impact, and reduced soft tissue padding over bony prominences. The bony fragility itself is a composite of geometry, low mass density, severance of microarchitectural connections in trabecular structures, and accumulated fatigue damage. Reduced bone mass, in turn, is caused by varying combinations of gonadal hormone deficiency, inadequate intakes of calcium and vitamin D, decreased physical activity, comorbidity, and the effects of drugs used to treat various unrelated medical conditions. Finally, the often poor outcome from hip fracture in the elderly is partly caused by associated protein- calorie malnutrition. An adequate preventive program for osteoporotic fracture must address as many of these factors as possible, ie, it must be as multifaceted as the disease is multifactorial.

Involutional osteoporosis in the elderly

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Giornale di Gerontologia (Italy), 1996, 44/2 (85-89)

Involutional osteoporosis (IO) is a multifactorial disorder resulting in bone fragility and fractures due to bone loss. Estrogen deficiency is known to be a dominant contributor to the postmenopausal bone loss. The mode of action of estrogen on bone tissue has been recently clarified by the demonstration of estrogen receptors in bone cells suggesting a direct effect of estrogens on bone tissue. However, over the years, other theories have been proposed to explain the pathophysiological mechanism underlying IO. These involve the calcium regulating hormones: calcitonin (CT), vitamin D metabolites and parathyroid hormone (IPTH). Studies have shown that women have lower serum CT levels, decreased secretory reserve than men, and that estrogens can increase CT secretion in pre- and postmenopausal women. Another important determinant of postmenopausal bone loss is an impaired intestinal calcium absorption. This phenomenon appears to be the result of two defects: increased intestinal resistance to 1,25 (OH)2D3 action and, later in life, impaired conversion of 25 (OH)D to 1,25 (OH)2D. A third hypothesis to explain estrogen effect on bone suggests that estrogens may modulate the sensitivity of bone to PTH-induced bone resorption. Several studies have shown that PTH activity increases with age. This finding is the probable cause of the increase in bone turnover rate and, because of the coexistence of an age-related imbalance in bone remodeling, would lead to increase bone loss. Finally, recent studies have shown that some local factors, such as citokines and skeletal growth factors may play a role in the control of bone remodeling and bone loss.

Dietary calcium intake and its relation to bone mineral density in patients with inflammatory bowel disease

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Journal of Internal Medicine (United Kingdom), 1996, 240/5 (285-292)

Objectives. To investigate calcium intake and its association with bone mineral density (BMD) and the type and extent of the disease in patients with inflammatory bowel disease (IBD).

Setting. University hospital clinic.

Subjects. A total of 152 unselected IBD patients and 73 healthy controls.

Measurements. Dietary calcium intake was assessed with a food frequency questionnaire and BMD of the lumbar spina and proximal femur was measured.

Results. The IBD patients had lower dietary calcium intake (1034 (SD 493) mg) than the controls (1334 (514) mg, $P < 0.001$). The difference was significant in the males (1047 (552) mg and 1575 (586) mg, respectively, $P < 0.001$), but not in the females (1020 (422) mg and 1112 (303) mg). The dietary daily calcium intake was below 1000 mg in 53% of the patients and 27% of the controls ($P = 0.0004$) and below 400 mg in 9.2% of the patients and none of the controls ($P = 0.007$). The calcium intake was not associated with the severity or the type of IBD. Seventy-one (47%) patients and eight (11%) controls avoided lactose in their diet ($P < 0.001$). In the IBD patients, no association between the calcium intake and BMD was detected, whereas in the controls a positive correlation between the calcium intake and the BMD of the proximal femur was found.

Conclusions, Calcium intakes below the recommendations are seen more often in the IBD patients than in the healthy controls, but in the IBD patients the calcium intake is not associated with BMD in a cross-sectional study. A low-lactose diet is common among IBD patients. To reduce the risk of inadequate calcium intake, unnecessary dietary restrictions concerning, e.g. milk products, should be avoided for these patients.

Clinical practice guidelines for the diagnosis and management of osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/8 (1113-1129)

Objective: To recommend clinical practice guidelines for the assessment of people at risk for osteoporosis, and for effective diagnosis and management of the condition.

Options: Screening and diagnostic methods: risk-factor assessment, clinical evaluation, measurement of bone mineral density, laboratory investigations.

Prophylactic and corrective therapies: calcium and vitamin D nutritional supplementation, physical activity and fall-avoidance techniques, ovarian hormone therapy, bisphosphonate drugs, other drug therapies. Pain-management medications and techniques.

Outcomes: Prevention of loss of bone mineral density and fracture; increased bone mass; and improved quality of life.

Evidence: Epidemiologic and clinical studies and reports were examined, with emphasis on recent randomized controlled trials. Clinical practice in Canada and elsewhere was surveyed. Availability of treatment products and diagnostic equipment in Canada was considered.

Values: Cost-effective methods and products that can be adopted across Canada were considered. A high value was given to accurate assessment of fracture risk and osteoporosis, and to increasing bone mineral density, reducing fractures: and fracture risk and minimizing side effects of diagnosis and treatment.

Benefits, harms and costs: Proper diagnosis and management of osteoporosis minimize injury and disability, improve quality of life for patients and reduce costs to society. Rationally targeted methods of screening and diagnosis are safe and cost effective. Harmful side effects and costs of recommended therapies are minimal compared with the harms and costs of untreated osteoporosis. Alternative therapies provide a range of choices for physicians and patients.

Recommendations: Population sets at high risk should be identified and then the diagnosis confirmed through bone densitometry. Dual-energy x-ray absorptiometry is the preferred measurement technique. Radiography can be an adjunct when indicated. Calcium and vitamin D nutritional supplementation should be at currenly recommended levels. Patients should be counselled in fall-avoidance techniques and exercises. Immobilization should be avoided. Guidelines for management of acute pain are listed. Ovarian hormone therapy is the therapy of choice for osteoporosis prevention and treatment in post menopausal women. Bisphosphonates are an alternative therapy for women with established osteoporosis who cannot or prefer not to take ovarian hormone therapy.

Validation: These guidelines were reviewed and approved by the Scientific Advisory Board of the Osteoporosis Society of Canada, in consultation with individual family and general practitioners.

Vitamin D metabolites and analogs in the treatment of osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/7 (955-961)

Objective: To review recent findings on the skeletal actions of vitamin D and to examine results of the latest clinical trials of vitamin D in the treatment of osteoporosis.

Options: The vitamin D analog 1-alpha hydroxycholecalciferol (1alpha-OH-D3); the vitamin D metabolite calcitriol.

Outcomes: Fracture and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures and improved quality of life associated with vitamin D therapies.

Evidence: Relevant laboratory and clinical studies and reports were examined. Greatest reliance was placed on recent large-scale, randomized, controlled trials; others were noted and their methods critiqued. Clinical practice in Japan was also considered.

Values: Reducing fractures, increasing bone mineral density and minimizing side effects of treatment were given a high value. Benefits, harms and costs: Vitamin D maintains the dynamic nature of bone and so presumably helps to keep it healthy. Calcitriol and 1alpha-OH-D3 may be effective in increasing bone mass and preventing fractures in osteoporosis. Calcitriol may be an alternative treatment in the prevention and management of corticosteroid-induced osteoporosis. Possible side effects of vitamin D analogs and metabolites are hypercalcemia, hypercalciuria, renal calcification and renal stones.

Recommendations: The use of 1alpha-OH-D3 for the treatment of osteoporosis in Canada cannot be supported without larger and longer randomized, controlled clinical trials. Calcitriol appears to prevent vertebral fractures in patients with osteoporosis. More information is needed on its mechanism of action and efficacy in preventing hip fractures. Future studies should focus on comparisons with other effective therapies and on determining whether its effect on fractures is greater than that achieved through improved vitamin D nutrition. Patients taking calcitriol at dose levels required for antifracture effects should be monitored for serum and urine calcium response to the drug. Calcitriol should not be given to atients whose calcium intake is at current generally recommended levels. At present, prescription of calcitriol for the treatment of osteoporosis should be reserved for physicians with a special interest in the treatment of metabolic bone disease.

Validation: These recommendations were developed by the Scientific Advisory Board of the Osteoporosis Society of Canada at its 1995 Consensus Conference.

Calcium nutrition and osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/7 (935-939)

Objective: To recommend appropriate levels of calcium intake in light of the most recent studies.

Options: Dietary calcium intake, calcium supplementation, calcium and vitamin D supplementation; ovarian hormone therapy in postmenopausal women.

Outcomes: Fracture and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures and improved quality of life associated with osteoporosis prevention.

Evidence: Relevant clinical studies and reports were examined, in particular those published since the 1988 Osteoporosis Society of Canada position paper on calcium nutrition. Only studies in humans were considered, including controlled, randomized trials and prospective studies, using bone mass and fractures as end-points. Studies in early and later phases of skeletal growth were noted. The analysis was designed to eliminate menopause as a confounding variable.

Values: Preventing osteoporosis and maximizing quality of life were given a high value. Benefits, harms and costs: Adequate calcium nutrition increases bone mineral density during skeletal growth and prevents bone loss and osteoporotic fractures in the elderly. Risks associated with high dietary calcium intake are low, and a recent study extends this conclusion to the risk of kidney stones. Lactase-deficient patients may substitute yogurt and lactase-treated milk for cow's milk. True milk allergy is probably rare; its promotion of diabetes mellitus in susceptible people is being studied.

Recommendations: Current recommended intakes of calcium are too low. Revised intake guidelines designed to reduce bone loss and protect against osteoporotic fractures are suggested. Canadians should attempt to meet their calcium requirements principally through food sources. Pharmaceutical calcium supplements and a dietician's advice should be considered where dietary preferences or lactase deficiency restrict consumption of dairy foods. Further research is necessary before recommending the general use of calcium supplements by adolescents. Calcium suplementation cannot substitute for hormone therapy in the prevention of postmenopausal bone loss and fractures. Adequate amounts of vitamin D are necessary for optimal calcium absorption and bone health. Elderly people and those who use heavy sun screens should have a dietary intake of 400 to 800 IU of vitamin D per day.

Interrelationships of food, nutrition, diet and health: The national association of state universities and land grant colleges white paper

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Nutrition and food science have each enhanced the development of an abundant, nutritious, safe food supply. A healthy diet should contain all of the required nutrients and sufficient calories to balance energy expenditure and provide for growth and maintenance throughout the life cycle. Importantly, dietary factors are associated with 5 of the 10 leading causes of death, including coronary heart disease, certain types of cancer, stroke, noninsulin dependent diabetes mellitus and atherosclerosis. National health care expenditures for 1990 totaled $666 billion of which 30% are related to inappropriate diet. Identification of external factors that contribute to premature death would aid preventive efforts, improve the quality of life, and reduce health care costs. Even though genetic predisposition increases susceptible people's risk for many of these chronic diseases, these conditions may be diminished or prevented by improvements in the American diet. Each stage of the life cycle has specific nutrient needs. Throughout infancy, childhood and adolescence nutrients are requited to meet the growth processes as well as cognitive function. During pregnancy nutrients are required for both mother and developing infant needs. Adult nutrition focuses on tissue maintenance, nutrient and energy needs, and disease prevention. As the population of elderly increase in number and greater age, nutritional needs must be met to minimize certain disease states and assure the quality of life. Nutrition associated health risks have been identified for coronary heart disease, cancer and diabetes mellitus. Recommendations for each includes a decrease in dietary fat, awareness of caloric intake and enhancement of nutrient density including an increase in fruit and vegetables. These recommendations also impact obesity and diminish the compounding of other disease states affected by excessive body weight. Calcium intake at early ages affects development of bone density and manifestation of osteoporosis. Current gaps in knowledge are also ientified that could improve health. Numerous nutrients are being examined for their regulation of specific gene expressions and in the processes of transcription and translation. To offer food products with greater nutrient density or improved functional health ingredients, modification of existing foods is needed to assure an improved diet. Policies to improve health require integration of nutrition needs with economic growth and development, agriculture and food production, processing, marketing, health care and education, and includes changing life styles and food choices. Increased research support is required to achieve national health goals with emphasis on nutrition and food sciences. Education methods must be improved to better inform consumers, to encourage food producers and manufacturers to produce healthier foods, to assure training of future professionals and to provide legislators with the basis to make informed decisions. Recommendations to CFERR aye identified. Improved quality and availability of nutritious foods will result in a healthier, more productive population. A decrease in the occurrence and duration of chronic diseases should diminish the cost of health care and allow

these resources to further benefit the nation. International concerns about undernutrition include 780 million people who are malnourished, lacking sufficient food to meet their basic nutritional needs for protein and energy, and 2 billion people who subsist on diets lacking essential nutrients needed for growth, development and physiological maintenance. National concerns about undernutrition exist based on incomplete data identified by indices of hunger and characterized by an increased demand for food assistance for women, children and the elderly. Major health problems in the US impacted by diet and nutrition include coronary heart disease, atherosclerosis, some types of cancer, non-insulin dependent diabetes mellitus, hypertension, hyperlipidemia, osteoporosis and obesity. Conservative estimates suggest improved nutriion could reduce health care costs by 10% (or more), potentially saving the US $15-20 billion annually. The disciplines of food science and nutrition can provide the means to carry out research, enhance education (train professionals and educate the public), and contribute to improved public policy.

Effect of Vitamin D receptor gene polymorphism on vitamin D therapy for postmenopausal bone loss

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In order to assess the effect of vitamin D receptor (VDR) gene polymorphisms on vitamin D3 therapy for postmenopausal bone loss. Thirty-four Japanese postmenopausal women, administer ed vitamin D3 (Alfarol(R)1.0microg/day) and Ca(2.0g/day) for 18 months, were analyzed by RFLP Bone mineral density (BMI) at the lumbar spine (L2-4) and Os-calcis were measured every 6 months by dual energy X-ray absorptiometry (DXA) and single energy X-ray absorptiometry (SXA) VDR gene allelic polymorphisms were assessed by Bsm 1 endonuclease restriction after specific PCR amplification. Genotypic polymorphism was defined as BB, bb and Bb. The genotypes were BB in 1 (3.1%) Bb in 13 (40.6%) and bb in 18 (56.3%). The women in these two major VDR genotype groups (Bb and bb) were similar in their backgrounds (interms of age, menopausal age, body mass index, and BMD in premedication), but the VDR genotype was associated the percent of change in BMD after treatment. In Group-Bb, the mean percent increases in L2-4 BMD were 3.2%, 4.9% and 4.1% at 6, 12 and 18 months. In contrast, in Group-bb they were 0.8%, 1.8% and 4.2% at the same points. Analysis of VDR alleles may prove useful in selecting the vitamin D therapy for osteopenia before treatment.

The preparation and stability of compound active calcium tablets

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Chinese Pharmaceutical Journal (China), 1996, 31/8 (474-477)

Objective: To prepare compound active calcium tablets and evaluate their stability.

Method: The optimal formulation of the tablets was found with orthogonal experiment design. The stability of the tablets was investigated by shelf-life and accelerated experiment.

Results: The prepared tablets rapidly disentigrated in 15 min, and showed good stability under various experimental conditions.

Conclusion: The compound active calcium tablets will play an important part in prevention and treatment of late middle age or older osteoporosis.

Nutrition and women's health

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Current Problems in Obstetrics, Gynecology and Fertility (USA), 1996, 19/4 (112-166)

With the rapid changes that are occurring in our health care system, interventions that enhance patients' health will prove to be the most satisfactory and provide the most cost savings over time. Data support a strong relationship between diet and health and disease. Although life expectancy in the United States is increasing in women, longevity is also associated with increasing morbidity. As a nation, we may live longer, but not necessarily better, lives. Dietary modification can improve health and reduce disease incidence; thus advice on good nutrition and appropriately selected vitamin and mineral supplements becomes paramount. Because women are the primary providers of meals to their families, a woman's food selections have an impact not only on her health but also on the health of her entire family. Accumulating evidence suggests that maternal nutrition, intrauterine events, birth weight and weight at 1 year of age all have an impact on adult morbidity and mortality. In females, body weight and body composition affect sexual maturation, onset of menstruation, ovulation, and fertility. With pregnancy, further body compositional changes occur with increased deposition of fat stores, especially in the hips and thighs. Recurring pregnancy, a sedentary lifestyle, and an abundance of food contribute to obesity, which is on the rise in the United States. With menopause, a decline in fat-free mass, bone mass, and lean tissue occurs. This loss in lean tissue includes not only muscle but also neuronal and connective tissue. Furthermore, with menopause fat is redistributed in the body with an increase in truncal deposition of adipose tissue, which is associated with an increased risk of coronary heart disease (CHD) and breast

cancer. These risk factors can be attenuated through appropriate diet, hormone replacement therapy, and exercise, which emphasizes resistance training. One approach to an appropriate diet would focus on 'culturally based' dietary patterns. A Mediterranean-based diet, an Asian- based diet, or othr ancestral-based diets have recently been suggested. These dietary patterns are associated with the decreased incidence of many chronic diseases and the maintenance of long-term health. The type of fat in the diet influences many aspects of health. Saturated fats, whether derived from animal or vegetable sources, are associated with increased risk for cardiovascular disease and certain cancers. Fats derived from fish oils appear to be cardioprotective and are associated with decreased incidence of breast cancer in epidemiologic and animal studies. Monounsaturated fats, such as those found in olive oil, appear to decrease serum triglycerides and may reduce the risk for breast cancer. A greater consumption of vegetables and fruit is associated with a decreased incidence of heart disease and many types of cancer. The protective factors in plant-derived foods include fiber, folic acid, antioxidant vitamins, carotenoids, and nonnutritive chemoprotective factors such as genistein, deidzen, and lignans. Plant- derived foods are also high in magnesium and calcium, which are associated with cardioprotection, reduced risk for certain cancers, and attenuation of osteoporosis. The ideal diet is based on the eating habits of our ancestors. It emphasizes the use of unrefined food products and drastically reduces the consumption of highly processed flours and grains and simple sugars that are added to most foods. Optimal recommendations include the daily consumption of large amounts of fresh fruits and vegetables. Animal-based protein would be replaced with plant protein and fish. Selective supplementation with vitamins and minerals would be encouraged for patients who are unwilling or unable to modify their eating habits and where scientific data support their use.

Current treatment options for osteoporosis

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The goals of treatment for patients with osteoporosis are to maintain normal bone and to prevent the deterioration of normal bone to osteoporotic bone. Achievement of these goals, combined with a successful approach to prevention of falls, may substantially decrease the incidence and risk of fractures. Strategies for osteoporosis therapy include patient strategies (e.g., administration of calcium, exercise), drug therapy to stimulate bone formation (e.g., fluoride, anabolic steroids), and drugs to inhibit bone resorption (e.g., estrogen replacement therapy, calcitonin, bisphosphonates).

A comparison of the effects of alfacalcidol treatment and vitamin D2 supplementation on calcium absorption in elderly women with vertebral fractures

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Although vitamin D supplementation in the frail elderly improves calcium absorption, suppresses parathyroid hormone, decreases bone loss and reduces the risk of fractures, such treatment may be ineffective in patients with vertebral osteoporosis, because of impaired vitamin D metabolism or resistance to the action of vitamin D metabolites on the bowel. We have therefore performed a randomized, single masked study comparing the effects of alfacalcidol treatment (0.25 microg twice daily) and vitamin D2 supplementation (500-1000 units daily) on calcium absorption and bone turnover in 46 elderly women (median age 69 years, range 64-79 years) with radiological evidence of vertebral fractures. Serum 25-hydroxyvitamin D increased significantly after 3 and 6 months of treatment with vitamin D2 ($p < 0.001$), but was unchanged in the group receiving alfacalcidol. Serum 1,25-dihydroxyvitamin D did not change significantly in either group over the study period. Fractional 45Ca absorption increased after 3 months of treatment with alfacalcidol ($p < 0.05$), but was unchanged with vitamin D2. There was also a reduction in plasma intact parathyroid hormone and serum alkaline phosphatase after 6 months of treatment with alfacalcidol ($p < 0.05$) which was not seen in the group receiving vitamin D2. Our study shows that vitamin D2 supplementation is ineffective in stimulating calcium absorption in elderly women with vertebral osteoporosis. By increasing calcium absorption in such patients, alfacalcidol may prove more effective than vitamin D in the management of vertebral osteoporosis.

The effect of calcium supplementation and Tanner Stage on bone density, content and area in teenage women

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One hundred and twelve Caucasian girls, 11.9 + or - 0.5 years of age at entry, were randomized into a 24-month, double-masked, placebo-controlled trial to determine the effect of calcium supplementation on bone mineral content, bone area and bone density. Supplementation was 500 mg calcium as calcium citrate

malate (CCM) per day. Controls received placebo pills, and compliance of both groups averaged 72%. Bone mineral content, bone mineral area and bone mineral density of the lumbar spine and total body were measured by dual energy X-ray absorptiometry (DXA). Calcium intake from dietary sources averaged 983 mg/day for the entire study group. The supplemented group received, on average, an additional 360 mg calcium/day from CCM. At baseline and after 24 months, the two groups did not differ with respect to anthropometric measurements, urinary reproductive hormone levels or any measurement of pubertal progression. The supplemented group had greater increases of total body bone measures: content 39.9% versus 35.7% ($p = 0.01$), area 24.2% versus 22.5% ($p = 0.15$) and density 12.2% versus 10.1% ($p = 0.005$). Region-of-interest analyses showed that the supplemented group had greater gains compared with the control group for bone mineral density, content and area. In particular, in the lumbar spine and pelvis, the gains made by the supplemented group were 12%-24% greater than the increases made by the control group. Bone acquisition rates in the two study groups were further compared by subdividing the groups into those with below- or above-median values for Tanner score and dietary calcium intake. In subjects with below-median Tanner scores, bone acquisition was not affected by calcium supplementation or dietary calcium level. However, the calcium supplemented subjects with above-median Tanner had higher bone acqusition rates than the placebo group with above-median Tanner scores. Relative to the placebo group, the supplemented group had increased yearly gains of bone content, area and density which represented about 1.5% of adult female values. Such increases, if held toadult skeletal maturity, could provide protection against future risk of osteoporotic fractures.

The role of vitamin D in the pathogenesis and treatment of osteoporosis

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Journal of Rheumatology (Canada), 1996, 23/Suppl. 45 (15-18)

It is well recognized that patients with postmenopausal osteoporosis usually exhibit some degree of calcium malabsorption and commonly have low serum concentrations of 1,25-dihydroxyvitamin D (calcitriol). Administration of calcitriol has been shown to normalize calcium absorption in patients with osteoporosis and, over the long term may have a stimulating effect on bone formation. Clinical trials have shown a significant reduction in osteoporotic fractures among calcitriol-treated patients. Hypercalcemia and hypercalciuria are infrequent complications of calcitriol therapy with physiologic doses (0.25 microg twice daily), and are most commonly related to excessive calcium intake (i.e., > 1000 mg daily).

Nutritional and biochemical studies on vitamin D and its active derivatives

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Yakugaku Zasshi (Japan), 1996, 116/6 (457-472)

We have performed nutritional and biochemical studies on vitamin D and its active derivatives and the following results are obtained. 1. Since recent studies have revealed that dietary supplement of vitamin D (D2 and D3) and calcium is effective for preventing osteoporosis, a simplified routine method for determination of vitamin D in foods is established and applied to the assay on the contents of vitamin D in various kinds of Japanese foods. 2. A simplified routine method for simultaneous determination of vitamin D and its metabolites in the plasma and milk is established and applied to nutritional and clinical studies. 3. Physiological activities of two kinds of novel vitamin D3 derivatives, 22-oxa-1alpha,25-dihydroxyvitamin D3 (22-oxa-1,25(OH)2D3, OCT) and 2beta-(3-hydroxypropoxy)-1,25(OH)2D3 (ED- 71) have been studied. OCT, which has less calcemic and stronger cell differentiation activities than 1,25(OH)2D3, is a candidate for curing leukemia and other cancers without hypercalcemia. We have clarified that the property is due to its weak binding affinity for vitamin D binding protein and rapid turn-over in the body and rapid excretion into bile. On the other hand, ED-71, which has stronger effects on intestinal calcium absorption and longer bone turn-over than 1,25(OH)2D3, is a candidate for curing osteoporosis. We have clarified that the properties are due to stronger binding affinity for DBP and longer half-life than 1,25(OH)2D3.

Osteoporosis and calcium ingest

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Bone mineral content related to calcium ingest is analyzed in 200 women through a case-control design. 75 were diagnosed of osteoporosis and the remaining 125 had normal bone mineral content. The age ranged between 48 and 55 years old, with climateric period lower than 18 months. Bone mass determination was carried out with double fotonic absortion densitomerty. The calcium ingest study was fulfilled through 24 hours before remind, with personal interview. It was repeated 4 times in a one year period. There were significant differences and also a positive correlation in bone mass related to calcium ingest even in trabecular or cortical bone.

Lower serum 25-hydroxyvitamin D is associated with increased bone resorption markers and lower bone density at the proximal femur in normal females: A population-based study

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Subclinical vitamin D deficiency is considered to be a risk factor for osteoporosis. Therefore, we studied vitamin D status and bone mineral density (BMD) in an age- and sex-stratified population based sample (209 males and 206 females aged between 50 and 80 years). In addition, urinary excretion of pyridinium crosslinks of collagen was determined in order to monitor bone resorption. We found a seasonal variation of serum 25-hydroxyvitamin D (25(OH)D) levels with higher values detected in the summer (27 +/- 10 ng/ml) and lower values measured in the winter (17 +/- 9 ng/ml). Further analyses were performed separately for winter and summer, respectively. We also excluded subjects taking osteotropic medication. In men, we found no significant relationship between vitamin D status and bone density or pyridinium crosslinks. In women, we found significant positive correlations between 25(OH)D and proximal femur BMD in winter ($r = 0.21$, $p < 0.05$) and in summer ($r = 0.36$, $p < 0.01$). The association between 25(OH)D and proximal femur BMD persisted after correction for age and body mass index. Serum 25(OH)D and urinary pyridinium crosslinks were inversely correlated in females in winter ($r = -0.24$, $p < 0.02$) and in summer ($r = -0.32$, $p < 0.02$). Our data support the hypothesis that already moderately low serum levels of 25(OH)D within the 'normal' range lead to osteopenia via increased bone resorption.

Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: A 3 year followup

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Journal of Rheumatology (Canada), 1996, 23/6 (995-1000)

Objective. To determine the efficacy and safety of vitamin D 50,000 units/week and calcium 1,000 mg/day in the prevention of corticosteroid induced osteoporosis.

Methods. A minimized double blind, placebo controlled trial in corticosteroid treated subjects in a tertiary care university affiliated hospital. The sample was 62 subjects with polymyalgia rheumatica, temporal arteritis, asthma, vasculitis, or systemic lupus erythematosus. The primary outcome measure was the percentage change in bone mineral density (BMD) of the lumbar spine in the 2 treatment groups from baseline to 36 mo followup.

Results. BMD of the lumbar spine in the vitamin D and calcium treated group decreased by a mean (SD) of 2.6% (4.1%) at 12 mo, 3.7% (4.5%) at 24 mo, and 2.2% (5.8%) at 36 mo. In the placebo group there was a decrease of 4.1% (4.1%) at 12 mo, 3.8% (5.6%) at 24 mo, and 1.5% (8.8%) at 36 mo. The observed

differences between groups were not statistically significant. The difference at 36 mo was -0.693% (95% CI -5.34, 3.95).

Conclusion. Vitamin D and calcium may help prevent the early loss of bone seen in the lumbar spine as measured by densitometry of the lumbar spine. Longterm vitamin D and calcium in those undergoing extended therapy with corticosteroids does not appear to be beneficial.

Influence of life style in the MEDOS study

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MEDOS is a case-control study where 9,000 persons were interviewed with an extensive questionnaire, either at time of fracture or in age-matched controls. Both men and ium intake in the diet, urinary excretion of calcium, serum calcium, serum phosphate, serum parathormone and calcitonin. In children (10-14 years) with lactase deficiency and osteoporosis the mean value of calcium intake was smaller (540-670 mg per day) than in patients of the lactase-normal group (on average 820 mg per day). In children osteoporosis has developed 2-10 years after the hypolactasia diagnosis. In the group of postmenopausal women (50-60 years) calcium intake was smaller in the lactase-deficient group with osteoporosis (average 630 mg per day), in the lactase-normal group in postmenopausal women calcium intake was normal (about 1200 mg per day). Urinary excretion of calcium (per 24 h) and other laboratory analyses did not differ in patients with hypolactasia from patients of the lactase-normal group. Lactase deficiency appears to be one of several factors that predispose the development of osteoporosis, probably through diminished calcium intake.

Roles of diet and physical activity in the prevention of osteoporosis

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In recent years, much attention has been directed toward the prevention of osteoporosis, since this disease has become a leading cause of morbidity and mortality in elderly women. Research has demonstrated that the prevention of osteoporosis and osteoporosis-related fractures may best be achieved by initiating sound health behaviors early in life and continuing them throughout life. Evidence

suggests that osteoporosis is easier to prevent than to treat. In fact, healthy early life practices, including the adequate consumption of most nutrients, regular physical activity, and other healthy behaviors, contribute to greater bone mineral measurements and optimal peak bone mass by the fourth decade of life of females, and, perhaps, also of males. Several reports have shown that the adequate consumption of nutrients, calcium in particular, during the pre-pubertal and early post-pubertal years of females contribute to increased peak bone mass. Indeed, skeletal benefits from long-term calcium supplementation have been reported for females at practically every period of the life cycle. Vitamin D, which may be either consumed or produced endogenously through the action of sunlight, promotes calcium absorption and thereby enhances bone mineralization. Thus, the adequate consumption of calcium, in conjunction with vitamin D, in early life will likely optimize peak bone mass, and adequate intakes of these two nutrients should continue through the remainder of life to help maintain bone mass. On the other hand, excess phosphorus consumption may deter bone mineral accrual because of the resultant elevation of serum parathyroid hormone levels. Additionally, high intakes of protein, sodium, and caffeine may decrease bone mineral mass through increased urinary excretion of calcium. Vitamin K may also have an important positive effect on the development and maintenance of bone through its role in promoting carboxylations of the matrix protein, osteocalcin. In conclusion, the prevention of osteoporosis needs to begin during the pre-ubertal years and it should be continued throughout life. Bone mass can better be maintained later in life through adequate consumption of several nutrients with specific roles in calcium and bone metabolism, regular physical activity, and the practice of a healthy lifestyle. Mechanisms through which the nutrients and exercise affect bone mass will be explored.

Vitamin D in the treatment of osteoporosis revisited

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Proceedings of the Society for Experimental Biology and Medicine (USA), 1996, 212/2 (110-115)

Interest in vitamin D treatment for osteoporosis has recently been revived because of the focus in various parts of the world on the elderly population, which is predominantly vitamin D deficient, in addition to postmenopausal osteoporosis due to estrogen withdrawal, which has been the central theme of osteoporosis research for many years. Combined use of other agents along with vitamin D has fortified the therapeutic armory against osteoporosis. The recent suggestion of a role of vitamin D receptor polymorphism in the development and progress of osteoporosis, possibly by interfering with its expected action, provoked intense discussions on the role of vitamin D in the pathogenesis and treatment of osteoporosis. Vitamin D receptor polymorphism may explain some of the racial differences in the incidence of osteoporosis and its complications. Responses to vitamin D treatment may also be predicted by vitamin D receptor allelic analysis, though the currently proposed allelic patterns are yet far from being widely

accepted. The outlook for vitamin D treatment for osteoporosis may require insight into vitamin D receptor, not only for vitamin D's given form, but also for a possible future form designed to intervene at the genomic level.

Prevention of bone loss in cardiac transplant recipients: A comparison of biphosphonates and vitamin D

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Transplantation (USA), 1996, 61/10 (1495-1499)

Bone mineral density is already abnormally reduced at the moment of cardiac transplantation and bone loss occurs at an impressive rate in the first postoperative year. The aim of the study was to compare two prophylactic medical regimens as to their efficacy in mitigating hone loss after transplantation. Forty-eight consecutive recipients were randomized to receive either alternating calcium carbonate and disodium etidronate (group A) or a daily supplement of calcium carbonate and alphacalcidol (group B). Bone mineral density measurements were performed immediately before hospital discharge and 6, 12, and 24 months after surgery using dual energy X-ray absorptiometry. Clinical events were recorded and roentgenograms of the spine were performed postoperatively and 1 and 2 years later. In both treatment groups bone loss remained significant at the level of the lumbar spine in the first postoperative year ($P<0.005$) and at the level of the femoral neck in the first ($P<0.005$) and the second ($P<0.05$) year after transplantation. Six months after transplantation, however, patients receiving alphacalcidol had a significant reduction in bone loss at the level of the lumbar spine ($P=0.047$) and at the level of the femoral neck ($P=0.043$). At the level of the femoral neck this decrease in bone loss was even more pronounced in the second postoperative year ($P<0.001$). In the group of patients treated with disodium etidronate, 4 recipients needed additional hospitalizations for treatment of symptomatic fractures at the level of the lumbar spine or the femoral neck. No such events happened in recipients receiving vitamin D supplements. Prophylactic administration of calcium carbonate and alphacalcidol after cardiac transplantation reduces bone loss and seems to decrease osteoporotic complications.

Prophylaxis of osteoporosis with calcium, estrogens and/or eelcatonin: Comparative longitudinal study of bone mass

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Maturitas (Ireland), 1996, 23/3 (327-332)

Objective: To evaluate three different therapeutic regimens for the prevention of osteoporosis in natural and surgical postmenopausal women who had been found to have rapid bone loss in analytical studies.

Methods: A total of 104 naturally or surgically postmenopausal women were studied, and subsequently followed-up during 1 year for avoidance of the influence of seasonal variation on bone mass, a factor overlooked in several studies. They were randomized into four groups of 26 patients each: the untreated control group (mean age 50 + or - 5 years); the hormonal replacement treatment (HRT) group (mean age 48 plus or minus 6 years), which was treated for 24 days each month with transdermal 17beta-estradiol, 50 mg/day, together with medroxiprogesterone, 10 mg during 12 days; the calcium group (mean age 50 + or - 4 years), which was treated with elemental calcium, 1 g/day; and the calcitonin group (mean age 50 plus or minus 5 years), which was treated for 10 days each month with eel calcitonin, 40 IU/day and with elemental calcium, 500 mg/day. Full-body bone densitometry, for measuring total body bone mineral content (TBBMC), was carried out in all the women at baseline and 1 year. TBBMC was corrected for body weight by dividing its value by body weight (TBBMC/W).

Results: After 1 year TBBMC/W was lower in every group: -2.14% ($P < 0.001$) in the control group; -0.14% (P = NS) in the HRT group ($P < 0.05$ vs. controls); -0.18% (P = NS) in the calcium group ($P < 0.05$ vs. controls); and -0.06% (P = NS) in the calcitonin group ($P < 0.01$ vs. controls; $P < 0.05$ vs. calcium and HRT).

Conclusions: These findings show that all three treatments are effective in the prevention of postmenopausal loss of bone mass.

Open-label, controlled study on the metabolic and absorptiometric effects of calcitriol in involutional osteoporosis

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Clinical Drug Investigation (New Zealand), 1996, 11/5 (270-277)

Calcitriol 0.5 microg twice daily, in combination with a low dietary calcium intake, was administered for 2 years to 35 women (mean age 64.6 + or - 8.3 years) with involutional osteoporosis; 45 women (mean age 63.5 + or - 8.7 years) with osteoporosis ingested dietary calcium 1000 mg/day and were considered a control group. Total body bone mineral density (BMD) and BMD of major anatomical areas were measured (Lunar DPX). In the calcitriol group, significant increases in serum and urinary calcium levels were observed after 12 and 24 months; urinary hydroxyproline excretion did not change significantly. No differences in blood urea nitrogen or serum creatinine were observed during calcitriol therapy, and none of the patients experienced symptomatic renal lithiasis. Increases in total body, spine and leg BMD were observed after 12 and 24 months of calcitriol therapy (+0.63%, +1.15% and +0.56%, and +0.85%, +1.37% and +0.35%,

respectively). In the control group, total body BMD and BMD of the spine, trunk, arms and legs decreased significantly. The mean percentage BMD differences between the 2 study groups were statistically significant. In the control group, spinal height declined progressively and significantly from baseline (-1.61% and -3.02% after 12 and 24 months, respectively), while in calcitriol-treated patients the decrease was less marked (-1.11% and -1.15%, respectively): the difference between the 2 groups was statistically significant ($p < 0.01$) after 24 months. In conclusion, calcitriol 1 microg/day plus a low dietary calcium intake may be considered safe and effective in patients with involutional osteoporosis.

Nutritional prevention of aging osteoporosis

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Cahiers de Nutrition et de Dietetique (France), 1996, 31/2 (98-101)

Aging is accompanied by a decrease in bone mass, with the risk of developing osteoporosis, of which the consequence is atraumatic fractures. These fractures, particularly those of the proximal femur, are associated with an important socioeconomic impact.Calcium supplements contribute to prevent bone loss in the elderly. On the other hand, protein repletion administered to compensate highly frequent malnutrition in the elderly can decrease medical complications following a fracture of the proximal femur, and exerts a favorable influence on bone mineral density.

Effects of 2 years' treatment of osteoporosis with 1alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: A placebo-controlled, double-blind prospective study

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Endocrine Journal (Japan), 1996, 43/2 (211-220)

A two-year double-blind study monitored and evaluated the effects of 1alpha-hydroxy vitamin D3 (1alpha(OH)D3) on the lumbar (L2-4BMD) and total body bone mineral densities (TBBMD) and occurrence of fracture in 113 female osteoporotic patients receiving 0.75 microg/day of 1alpha(OH)D3 (n=57) or a placebo (n=56) with calcium supplementation in both groups. L2-4BMD increased 1.81% and 2.32% after one and 2 years in the 1alpha(OH)D3 group, but decreased 1.89% ($P<0.05$) and 0.28% in the placebo group. A significant difference ($P<0.01$) existed between the two groups after one year. TBBMD decreased significantly in the placebo group by 3.34% ($P<0.01$) and 3.52% after one and 2 years. Six new fractures occurred in the control group, but only two in the 1alpha(OH)D3 group (Odd's ratio=0.343, 95% confidence range; 0.0648-

1.815). There were no serious adverse effects of the 1alpha(OH)D3 treatment. It was concluded that two-year treatment with 1alpha(OH)D3 increased the lumbar BMD and inhibited the decrease in TBBMD. Although it was not significant, new fracture occurrence in the 1alpha(OH)D3 group was around 1/3 of that in the control group.

Energy and nutrient intake in patients with CF

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Monatsschrift fur Kinderheilkunde (Germany), 1996, 144/4 (396-402)

Background: Nutritional assessment and management remain important issues in the treatment of CF patients despite newer developments as lung transplantation, inhalation with DNase and gene therapy.

Methods: The nutritional status of 26 patients (mean age 15,8 years; 16 male; 46% homozygous, 38% heterozygous for DeltaF 508, remaining unknown; 3 pancreas sufficient, Shwachman score intermediate to excellent) of our CF clinic was analyzed using a three days protocol, the precise weighing method and comparison of data with the official dietary recommendations.

Results: The average energy intake was below the 130% officially recommended and the fat intake was below the aimed 40% of total energy intake. The regression analysis revealed positive correlations between energy intake and SDS(Height) and Shwachman score and SDS(Weight) respectively. Food contained an insufficient amount of unsaturated fatty acids. Water soluble vitamins were supplemented adequately besides folic acid, but intake of fat soluble vitamins E and A often was insufficient despite extra Vitamin-Capsules. Every second patient did not take enough minerals as calcium, magnesium or iron.

Conclusions: This analysis underlines how important the regular assessment of the nutritional status can be for the individual nutritional management of CF patients even if clinical symptoms of deficiencies could not be detected. An increase of fat intake as a main source of energy, essential fatty acids and fat soluble vitamins has to be encouraged as well as the increased use of milk and milk products for the prevention of osteoporosis. Iron and folic acid are further critical nutrients.

1,25-Dihydroxyvitamin D3 enhances the enzymatic activity and expression of the messenger ribonucleic acid for aromatase cytochrome P450 synergistically with dexamethasone depending on the vitamin D receptor level in cultured human osteoblasts

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Endocrinology (USA), 1996, 137/5 (1860-1869)

Not every postmenopausal woman with a low level of estrogen suffers from osteoporosis, and no correlation of bone density with serum estrogen level, but a significant correlation with adrenal androgens, is often noted. Vitamin D3 has been reported to be osteoclastic in vitro, whereas the effectiveness of vitamin D3 for the treatment of osteoporosis is clinically relevant. To study the roles of these factors in the development of osteoporosis, we characterized aromatase activity converting androgens to estrogens in human osteoblasts, because postmenopausal women maintain considerable levels of adrenal androgens. Glucocorticoids at 10-9-10-7 M transiently induced the expression and enzymatic activity of aromatase cytochrome P450 (P450(AROM)) in primary cultured osteoblasts, and the K(m) value for androstenedione (4.7 + or -2.9 nM) was lower than that in adipose tissue and skin. Human osteoblasts showed a promoter specificity different from that found in other tissues. 1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3) alone did not induce aromatase activity, but enhanced and maintained glucocorticoid-induced P450(AROM) gene expression. This synergistic effect was not observed by other sex steroids or retinoic acids. The enhancement of P450(AROM) activity by 1,25(OH)2D3 varied from 0.94-fold (no enhancement) to 2.40-fold (maximal enhancement) among the individual human osteoblasts examined, but the magnitude of the enhancement was significantly correlated with the level of vitamin D receptor messenger RNA ($P < 0.05$). Cycloheximide did not abolish the synergistic effect of 1,25(OH)2D3, suggesting that de hove protein synthesis is not required for the synergism with 1,25-(OH)2D3. These results suggest that bone tissue can synthesize estrogen from adrenal androgens by a unique aromatase activity depending on the level of vitamin D receptor expressed.

Effects of hormonal therapies and dietary soy phytoestrogens on vaginal cytology in surgically postmenopausal macaques

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Fertility and Sterility (USA), 1996, 65/5 (1031-1035)

Objective: To evaluate the effects of conjugated equine estrogens, medroxyprogesterone acetate (MPA), conjugated equine estrogens combined with MPA, tamoxifen, and soybean estrogens on vaginal cytology in surgically postmenopausal cynomolgus macaques (Macaca fascicularis).

Design: Randomized long-term experimental trial.

Setting: Cytologic samples were taken from animals in two long-term randomized studies of the effects of hormonal and dietary effects on atherosclerosis.

Patients: Surgically postmenopausal cynomolgus macaques.

Interventions: Conjugated equine estrogens, MPA, conjugated equine estrogens combined with MPA, tamoxifen, and soybean estrogens were given via the diet, at doses scaled from those given to women.

Main Outcome Measure: Vaginal cytologic maturation index.

Results: Conjugated equine estrogens elicited a marked maturation effect, which was antagonized partially by the addition of MPA. Tamoxifen produced a lesser estrogenic response. The cytologic pattern in animals given soybean estrogens or MPA alone did not differ from that of controls.

Conclusion: Soybean estrogens at the doses given do not exert an estrogenic effect on the vagina of macaques. Conjugated equine estrogens are potent inducers of vaginal keratinization in this model; tamoxifen has a lesser effect. Medroxyprogesterone acetate partially antagonizes the effects of conjugated equine estrogens, and has no effect when given alone. The results support the possibility that soybean estrogens may be a 'tissue-selective' estrogen with minimal effects on the reproductive tract.

Evaluation of acceptability, tolerance and observance of a new calcium-vitamine D combination

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Rhumatologie (France), 1996, 48/2 (37-42)

The aim of this trial was to assess in 190 patients randomized in two identical groups the tolerance and acceptability of a new calcium-vitamin D combination, OROCAL (R) Vitamine D3 (chewable tablets containing calcium 500 mg and vitamine D3 400 IU) in order to compare it with the same doses of calcium (1 g/day) and vitamin D (800 IU/day), obtained by taking two SANDOCAL (R) 500 mg bags and two STEROGYL (R) drops/day. After 10 weeks, patients were asked about the acceptability of the treatments and the occurrence of adverse effects. They had also to answer before and after treatment a guestionnaire listing 10 gastrointestinal symptoms. The observance and the acceptability have been better under OROCAL (R) Vitamine D3, with drop out 3 times less numerous under this combination than under the SANDOCAL (R) + STEROGYL (R) solution. The number of patients with a gastrointestinal symptom and the total number of these symptoms were statistically higher in the SANDOCAL (R) + STEROGYL (R) group, this association being more frequently responsible for flatulences, probably because the solution is effervescent.

Effects of vitamin K on bone mass and bone metabolism

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Journal of Nutrition (USA), 1996, 126/4 SUPPL. (1187S-1191S)

Vitamin K is involved in blood coagulation and in bone metabolism via the carboxylation of glutamate residues in (hepatic) blood coagulation factors and (osteoblastic) bone proteins. The bioavailability of nutritional vitamin K depends on the type of food, the dietary fat content, the length of the aliphatic side chain in the K-vitamer and probably also the genetically determined polymorphism of apolipoprotein E. Although undercarboxylation of blood coagulation factors is very rare, undercarboxylated osteocalcin (bone Gla-protein) is frequently found in postmenopausal women. Supplementation of these women with extra vitamin K causes the markers for bone formation to increase. In parallel, a decrease of the markers for bone resorption is frequently seen. Insufficient data are available to conclude that the regular administration of vitamin K concentrates will reduce the loss of bone mass in white women at risk for developing postmenopausal osteoporosis.

Calcium and vitamin D nutritional needs of elderly women

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Journal of Nutrition (USA), 1996, 126/4 Suppl. (1165S-1167S)

Because osteoporosis is irreversible, the most effective approach to reduce morbidity and mortality from this disease is to maximize peak bone mass and minimize bone loss. This presentation reviews the evidence that calcium and vitamin D influence rates of bone loss in postmenopausal women. In the first five or more years after menopause, women lose bone very rapidly. During this period, high dose calcium supplementation modestly reduces cortical loss from long bones but has minimal effect on more trabecular sites such as the spine. In addition, vitamin D appears to enhance the effectiveness of supplemental calcium. Late postmenopausal women are generally more responsive to added calcium, and those with the lowest dietary calcium intakes benefit the most. In calcium-replete women, supplementation with vitamin D reduces bone loss and fracture incidence. Available evidence indicates that postmenopausal women should consume 1000-1500 mg of calcium and 400 to 800 IU of vitamin D per day to minimize bone loss.

Vitamin D and bone health

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Vitamin D plays an essential role in maintaining a healthy mineralized skeleton for most land vertebrates including humans. Sunlight causes the photoproduction of vitamin D3 in the skin. Once formed, vitamin D3 is metabolized sequentially in the liver and kidney to 1,25-dihydroxy vitamin D. The major biological function of 1,25-dihydroxyvitamin D is to keep the serum calcium and phosphorus concentrations within the normal range to maintain essential cellular functions and to promote mineralization of the skeleton. Most foods do not contain any vitamin D. Foods fortified with vitamin D have a variable amount present and cannot be depended on as a sole source of vitamin D nutrition. Exposure to sunlight provides most humans with their vitamin D requirement. Aging, sunscreen use and the change in the zenith angle of the sun can dramatically affect the cutaneous production of vitamin D3. Vitamin D insufficiency and vitamin D deficiency is now being recognized as a major cause of metabolic bone disease in the elderly. Vitamin D deficiency not only causes osteomalacia but can exacerbate osteoporosis. It is generally accepted that an increase in calcium intake to 1000-1500 mg/d along with an adequate source of vitamin D of at least 400 IU/d is important for maintaining good bone health.

Heated oyster shell-seaweed calcium (AAA Ca) on osteoporosis

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Calcified Tissue International (USA), 1996, 58/4 (226-230)

A randomized, prospective, double-blind lest was curried out to compare the effects of heated oyster shell-seaweed calcium (AAA Ca), calcium carbonate, and placebo in 58 elderly, hospitalized women with the mean age of 80 divided into three groups. Group A received 900 mg/day Ca as AAA Ca. Group B 900 mg/day Ca as CaCO3, and Group C placebo besides regular hospital diet containing approximately 600 mg Ca/day for 24 months. From the 25th to the 30th month, all groups were given AAA Ca. Lumbar spine and radial bone mineral density (BMD) were measured at 3-month intervals. Urinary Ca/Cr and serum alkaline phosphatase, intact and midportion serum parathyroid hormone (PTH), and calcitonin were also measured at intervals. From the 6th to the 24th month of the study, the ratio of lumbar spine BMD (L2-L4 by DPX, Lunar) to the basal pretest value was consistently mid significantly higher in Group A than Group C but not higher in Group B than in Group C. PTH, measured 12 months after the beginning of the study, was lower in Group A than in Group C, but no significant difference

was found between Groups B and C. At 3 months after the placebo was switched to AAA Ca in Group C. serum PTH was significantly decreased from the level during placebo supplement. Morning urine Ca/Cr decreased in Groups A after 18 months and in B after 12 months, but not in C. Serum alkaline phosphatase decreased in Group A significantly compared with Group C, but not in Group B. AAA Ca appears to be effective for increasing BMD in elderly subjects.

The lack of influence of long-term potassium citrate and calcium citrate treatment in total body aluminum burden in patients with functioning kidneys

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Journal of the American College of Nutrition (USA), 1996, 15/1 (102-106)

Background: It has been suggested that citrate salts might enhance aluminum (Al) absorption from a normal diet, posing a threat of Al toxicity even in subjects with normal renal function. We have recently reported that in normal subjects and patients with moderate renal failure, short-term treatment with tricalcium dicitrate (Ca,Cit2) does not significantly change urinary and serum Al levels. However, we have not assessed total body Al stores in patients on long-term citrate treatment.

Objective: The objective of this study was to ascertain body content of Al non-invasively using the increment in serum and urinary Al following the intravenous administration of deferoxamine (DFO) in patients with kidney stones and osteoporotic women undergoing long-term treatment with potassium citrate (K3Cit) or Ca3Cit2, respectively.

Methods: Ten patients with calcium nephrolithiasis and five with osteoporosis who were maintained on potassium citrate (40 mEq/day or more) or calcium citrate 800 mg calcium/day (40 mEq citrate) for 2 to 8 years, respectively, and 1 h normal volunteers without a history of regular aluminum-containing antacid use participated in the study. All participants completed the 8 days of study, during which they were maintained on their regular home diet. Urinary Al excretion was measured during a two-day baseline before (Days 5, 6) and for 1 day (Day 7) immediately following a single intravenous dose of DFO (40 mg/kg). Blood for Al was obtained before DFO administration, and at 2, 5 and 24 hours following the start of the infusion.

Results: The median 24-hour urinary Al excretion (microg/day) at baseline versus post-DFO value was 15.9 vs. 44.4 in the normal subjects and 13.3 vs. 35.7 in the patients. These values were all within normal limits and did not change significantly following DFO infusion ($p = 0.003$ and $p = 0.0001$, respectively). The median change of 17.1 microg/day in urinary Al in the normal subjects was not significantly different from the 18.7 microg/day change measured in the patient group (p 0.30). Similarly, no change in the mean serum Al was detected at

any time following the DFO infusion, either in the patient or control group (patients 4.1 to 4.3 ng/ml, controls 7.4 to 4.6 ng/ml).

Conclusion: The results suggest that abnormal total body retention of Al does not occur during long term citrate treatment in patients with functioning kidneys.

Dietary soybean protein prevents bone loss in an ovariectomized rat model of osteoporosis

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Journal of Nutrition (USA), 1996, 126/1 (161-167)

The purpose of this study was to examine whether soybean protein isolate prevents bone loss induced by ovarian hormone deficiency. Thirty-two 95-d- old Sprague-Dawley rats were randomly assigned to four treatment groups (sham-operated (sham); ovariectomized (ovx); ovx + soybean; ovx + 17beta- estradiol (E2)) and killed after 30 d. Rats in the sham, ovx and ovx + 17beta- estradiol groups were fed a casein-based diet, and the soybean group was fed soybean protein isolate instead of casein; the diets were otherwise comparable. Rats in the ovx group had significantly lower densities of the right femur ($P < 0.001$) and the fourth lumbar vertebra ($P < 0.05$) than rats in the sham group. These lower bone densities were not observed in animals receiving 17beta-estradiol or fed soybean. The ovx group also had significantly ($P < 0.01$) greater serum concentrations of 1,25-dihydroxycholecalciferol than the other three groups. Our findings suggest that dietary soybean protein is effective in preventing bone loss due to ovarian hormone deficiency. Because serum activities of both alkaline phosphatase and tartrate-resistant acid phosphatase were significantly greater in the ovx group and in the ovx + soybean group but not in the group receiving 17beta-estradiol, compared with sham animals, this confirms that ovariectomy enhances and 17beta-estradiol suppresses the rate of bone turnover. Despite the higher rate of bone turnover in the soybean-fed animals, the vertebral and femoral bone densities of these rats were significantly greater than those of rats in the ovx group, suggesting that formation exceeded resorption. Further studies are needed to clarify whether this protective effect on bone is due to the protein itself or to the presence of isoflavones in soybean protein.

Bone mineral density in mother-daughter pairs: Relations to lifetime exercise, lifetime milk consumption, and calcium supplements

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American Journal of Clinical Nutrition (USA), 1996, 63/1 (72-79)

This study investigated associations between lifetime milk consumption, calcium intake from supplements, lifetime weight bearing exercise, and bone mineral density (BMD) among 25 elderly women (mean age 72 y) and their premenopausal daughters (mean age 41 y).The BMD of the total, axial, and peripheral skeleton was measured by dual energy X-ray absorptiometry. Lifetime milk consumption, supplemental calcium intake, and weight-bearing exercise were estimated retrospectively by questionnaire and interview. In multiple linear-regression analyses, mothers' total and peripheral BMD were positively associated with supplemental calcium intake after age 60 y, body weight, current estrogen replacement therapy (ERT), and past oral contraceptive (OC) use, and negatively associated with age and height (all $P < 0.05$). Mothers' axial BMD was positively correlated with body weight and past OC use. Among daughters, lifetime weight-bearing exercise was a predictor of total and peripheral BMD, whereas total lean mass was a predictor of axial BMD. Mothers' lifetime milk consumption was positively associated with that of their daughters. Mothers' and daughters' peripheral BMD values were positively correlated after adjustment for daughters' exercise, and mothers' age, body weight, and ERT. These results suggest that calcium supplementation and exogenous estrogen positively influence bone mass in postmenopausal years. Our findings lend support to recommendations for physical activity as a means of osteoporosis prevention. In the age groups studied, the effects of behavioral and hormonal factors on BMD appeared to dominate over familial similarity, which suggests thai women may successfully enhance their genetically determined bone mass through weight-bearing exercise, post menopausal ERT, and adequate calcium intake.

Whey protein stimulated the proliferation and differentiation of osteoblastic MC3T3-E1 cells.

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Biochem Biophys Res Commun 1996 Jun 14;223(2):445-9

We examined the effects of whey protein on osteoblastic MC3T3-E1 cells. This protein caused dose-dependent increases in [3H]thymidine incorporation and DNA content in the cells. It also increased the total protein and hydroxyproline contents in the cells. These activities were heat resistant when the protein was heated at 75 degrees C to 90 degrees C for 10 min. Heat-treated whey protein was first fractionated on a Mono S column, and the active fraction (basic protein fraction) was then applied to Superose 12. The molecular weights of the active components were approximately 10,000 and 14,000 Da, as determined with gel filtration. The inner solution of an everted gut-sac incubated in a solution of intact BP (basic protein), pepsin-digested BP or pepsin/pancreatin-digested BP also stimulated the [3H]thymidine incorporation. Thus these active components can possibly permeate or be absorbed by the intestines. We propose the possibility that the active component in the whey protein plays an important role in bone formation by activating osteoblasts.

23. Parkinson's Disease

Preventative and curative options include:

L-tyrosine, NADH, acetyl-L-carnitine, niacinamide, ginkgo biloba, ginseng, licorice root, royal jelly, freeze-dried liver, MSM, calcium, phosphatidylserine, co-enzyme Q10, vitamin C, vitamin E, grape seed extract, gamma tocopherol, magnesium, tryptophan, lecithin, melatonin, DHEA, pregnenolone, bee pollen, chlorella, spirulina, probiotic.

Protective effect of melatonin in a chronic experimental model of Parkinson's disease.

Antolin I, Mayo JC, Sainz RM, del Brio Mde L, Herrera F, Martin V, Rodriguez C. Departmento de Morfologia y Biologia Celular, Facultad de Medicina, Universidad de Oviedo, C/ Julian Claveria, 33006 Oviedo, Asturias, Spain.

Brain Res. 2002 Jul 12;943(2):163-73.

Parkinson's disease is a chronic condition characterized by cell death of dopaminergic neurons mainly in the substantia nigra. Among the several experimental models used in mice for the study of Parkinson's disease 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced parkinsonism is perhaps the most commonly used. This neurotoxin has classically been applied acutely or sub-acutely to animals. In this paper we use a chronic experimental model for the study of Parkinson's disease where a low dose (15 mg/kg bw) of MPTP was administered during 35 days to mice to induce nigral cell death in a non-acute way thus emulating the chronic condition of the disease in humans. Free radical damage has been implicated in the origin of this degeneration. We found that the antioxidant melatonin (500 microg/kg bw) prevents cell death as well as the damage induced by chronic administration of MPTP measured as number of nigral cells, tyrosine hydroxylase levels, and several ultra-structural features. Melatonin, which easily passes the blood-brain barrier and lacks of any relevant side-effect, is proposed as a potential therapy agent to prevent the disease and/or its progression.

The effect of dehydroepiandrosterone sulfate administration to patients with multi-infarct dementia.

Azuma T, Nagai Y, Saito T, Funauchi M, Matsubara T, Sakoda S. The Second Department of Internal Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.

J Neurol Sci. 1999 Jan 1;162(1):69-73

We measured cerebrospinal fluid (CSF) levels of dehydroepiandrosterone sulfate (DHEAS) by radioimmunoassay in seven patients with multi-infarct dementia (MID), fourteen age- and gender-matched non-demented patients with a history of cerebral infarction and fifteen age- and gender-matched patients without neurological disorders. The levels of DHEAS in CSF of patients with MID were significantly lower than those in non-demented patients with a history of cerebral infarction or those in patients without neurological disorders. Daily intravenous administration of 200 mg DHEAS for 4 weeks markedly increased serum and CSF levels of DHEAS in seven MID patients, improved decrease of daily activities and emotional disturbances in three patients and EEG abnormalities in two patients. The DHEAS therapy may provide a beneficial effect on MID patients.

Mitochondria, NO and neurodegeneration.

Beal MF. Neurochemistry Laboratory, Neurology Service/WRN 408, Massachusetts General Hospital, Boston, USA.

Biochem Soc Symp. 1999;66:43-54.

A role for mitochondrial dysfunction in neurodegenerative disease is gaining increasing support. Mitochondrial dysfunction may be linked to neurodegenerative diseases through a variety of different pathways, including free-radical generation, impaired calcium buffering and the mitochondrial permeability transition. This can lead to both apoptotic and necrotic cell death. Recent evidence has shown that there is a mitochondrial defect in Friedreich's ataxia, which leads to increased mitochondrial iron content, that appears to be linked to increased free-radical generation. There is evidence that the point mutations in superoxide dismutase which are associated with amyotrophic lateral sclerosis may contribute to mitochondrial dysfunction. There is also evidence for bioenergetic defects in Huntington's disease. Studies of cybrid cell lines have implicated mitochondrial defects in both Parkinson's disease and Alzheimer's disease. If mitochondrial dysfunction plays a role in neurodegenerative diseases then therapeutic strategies such as coenzyme Q10 and creatine may be useful in attempting to slow the disease process.

Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3,tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice.

Beal MF, Matthews RT, Tieleman A, Shults CW. Neurology Service, Massachusetts General Hospital, Boston, MA, USA.

Brain Res. 1998 Feb 2;783(1):109-14.

We investigated whether oral administration of coenzyme Q10 (CoQ10) could attenuate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in one-year-old mice. Four groups of one-year-old, male C57BL/6 mice received a either standard diet or a diet supplemented with CoQ10 (200 mg/kg/day) for five

weeks. After four weeks, one group that had received the standard diet and one group that had received the CoQ10 supplemented diet were treated with MPTP. The four groups continued on their assigned diets for an additional week prior to sacrifice. Striatal dopamine concentrations were reduced in both groups treated with MPTP, but they were significantly higher (37%) in the group treated with CoQ10 and MPTP than in the group treated with MPTP alone. The density of tyrosine hydroxylase immunoreactive (TH-IR) fibers in the caudal striatum was reduced in both MPTP-treated groups, but the density of TH-IR fibers was significantly (62%) greater in the group treated with CoQ10 and MPTP than in the group treated with MPTP alone. Our results indicate that CoQ10 can attenuate the MPTP-induced loss of striatal dopamine and dopaminergic axons in aged mice and suggest that CoQ10 may be useful in the treatment of Parkinson's disease.

Niacin depletion in Parkinsonian patients treated with L-dopa, benserazide and carbidopa.

Bender DA, Earl CJ, Lees AJ.

Clin Sci (Lond) 1979 Jan;56(1):89-93

1. Benserazide and carbidopa, decarboxylase inhibitors used in the treatment of Parkinson's disease, have been shown to inhibit the enzyme kynurenine hydrolase in rat and mouse liver. This results in reduced synthesis of nicotinamide coenzymes from tryptophan, and hence an increased reliance on dietary niacin. 2. Pellagra might be expected as a result of this inhibition of endogenous synthesis of nicotinamide nucleotides, but has not been reported in patients treated with either drug. 3. The urinary excretion of N1-methyl-nicotinamide, a product of nicotinamide nucleotide metabolism, is considerably reduced in patients treated with dopa alone or in combination with an inhibitor of peripheral dopa decarboxylase, to as low as 40% of the control value. This means that many of these patients could be classified as 'at risk' of niacin deficiency, even if not frankly deficient. 4. Patients treated with dopa plus a decarboxylase inhibitor, but not those treated with dopa alone, also show a reduced excretion of xanthurenic acid, and an increased excretion of kynurenine, as would be expected after inhibition of the kynurenine pathway, and possibly indicative of marginal vitamin B6 deficiency.

L-tryptophan: a rational anti-depressant and a natural hypnotic?

Boman B. Department of Veterans' Affairs, Repatriation Hospital, Concord NSW.

Aust N Z J Psychiatry. 1988 Mar;22(1):83-97.

L-tryptophan is an essential amino acid which is the metabolic precursor of serotonin. Because of the evidence that serotonin deficiency may be an aetiological factor in some sorts of affective disorder and that serotonin is important in the biochemistry of sleep, L-tryptophan has been suggested as a "rational" anti-depressant and as a "natural" hypnotic. This paper reviews the

biochemistry and pharmacology of L-tryptophan as well as the literature of the clinical trials that have been conducted with it and suggests that, by itself, L-tryptophan may be useful in mild cases of depression accompanied by endogenous features and cases of bipolar disorder resistant to standard treatments. It also potentiates the monoamine oxidase inhibitors and possibly the serotonergic tricyclic drugs. L-tryptophan may improve the depressed mood of Parkinsonian patients and has a clinically useful hypnotic action. There is evidence it may be useful in organic mental disorders induced by levodopa. Dosage schedules, contraindications and complications are discussed.

Melatonin attenuates MPP+-induced neurodegeneration and glutathione impairment in the nigrostriatal dopaminergic pathway.

Chen ST, Chuang JI, Hong MH, Li EI. Department of Anatomy, National Cheng Kung University, Tainan, Taiwan.

J Pineal Res. 2002 May;32(4):262-9.

In this study we selected a rat model of Parkinson's disease (PD) by using intrastriatal infusion of the 1-methyl-4-phenyl-pyridinium ion (MPP+) to investigate the neuroprotective action of melatonin and its inhibitory activity on MPP+-impaired glutathione (GSH) system in the nigrostriatal system. Results show that MPP+ caused not only a severe neuronal injury in the striatum and in the ipsilateral substantia nigra (SN), but it also induced a significant decrease in GSH levels and an increase in the GSSG/GSH ratio 3 days after intrastriatal MPP+ infusion. Intraperitoneal co-administration of melatonin (10 mg/kg, five times) significantly attenuated MPP+-induced nigrostriatal neurotoxicity and GSH impairment. Depletion of cytosolic GSH by L-buthionine sulfoximine (BSO) did not cause neuronal damage by itself. It, however, when co-administrated with MPP+, potentiated the GSH reduction in the striatum, without aggravating nigrostriatal neurodegeneration induced by MPP+. Moreover, the MPP+-caused neuronal damage was positively correlated with a rising ratio of GSSG/GSH, but not with a drop of GSH. These results suggest that the MPP+-triggered oxidative stress may play a more important role than the loss of the antioxidant GSH in determining neuronal injury. Interestingly, the neuronal damage and oxidative stress elicited by co-treatment of BSO with MPP+ were effectively reduced by melatonin. Our results hence provide direct evidence showing that melatonin attenuates MPP+-induced nigrostriatal dopaminergic injury by its ability to impede the increase of GSSG/GSH ratio; therefore melatonin may have therapeutic implications in PD.

Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease.

Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, Mattson MP. Laboratory of Neurosciences, National Institute on Aging Gerontology Research Center, Baltimore, Maryland 21224, USA.

J Neurochem. 2002 Jan;80(1):101-10.

Although the cause of Parkinson's disease (PD) is unknown, data suggest roles for environmental factors that may sensitize dopaminergic neurons to age-related dysfunction and death. Based upon epidemiological data suggesting roles for dietary factors in PD and other age-related neurodegenerative disorders, we tested the hypothesis that dietary folate can modify vulnerability of dopaminergic neurons to dysfunction and death in a mouse model of PD. We report that dietary folate deficiency sensitizes mice to MPTP-induced PD-like pathology and motor dysfunction. Mice on a folate-deficient diet exhibit elevated levels of plasma homocysteine. When infused directly into either the substantia nigra or striatum, homocysteine exacerbates MPTP-induced dopamine depletion, neuronal degeneration and motor dysfunction. Homocysteine exacerbates oxidative stress, mitochondrial dysfunction and apoptosis in human dopaminergic cells exposed to the pesticide rotenone or the pro-oxidant Fe(2+). The adverse effects of homocysteine on dopaminergic cells is ameliorated by administration of the antioxidant uric acid and by an inhibitor of poly (ADP-ribose) polymerase. The ability of folate deficiency and elevated homocysteine levels to sensitize dopaminergic neurons to environmental toxins suggests a mechanism whereby dietary folate may influence risk for PD.

Oxidative stress and antioxidant therapy in Parkinson's disease.

Ebadi M, Srinivasan SK, Baxi MD. Department of Pharmacology, University of Nebraska College of Medicine, Omaha 68198-6260, USA.

Prog Neurobiol. 1996 Jan;48(1):1-19.

Parkinson's disease, known also as striatal dopamine deficiency syndrome, is a degenerative disorder of the central nervous system characterized by akinesia, muscular rigidity, tremor at rest, and postural abnormalities. In early stages of parkinsonism, there appears to be a compensatory increase in the number of dopamine receptors to accommodate the initial loss of dopamine neurons. As the disease progresses, the number of dopamine receptors decreases, apparently due to the concomitant degeneration of dopamine target sites on striatal neurons. The loss of dopaminergic neurons in Parkinson's disease results in enhanced metabolism of dopamine, augmenting the formation of H2O2, thus leading to generation of highly neurotoxic hydroxyl radicals (OH.). The generation of free radicals can also be produced by 6-hydroxydopamine or MPTP which destroys striatal dopaminergic neurons causing parkinsonism in experimental animals as well as human beings. Studies of the substantia nigra after death in Parkinson's disease have suggested the presence of oxidative stress and depletion of reduced glutathione; a high level of total iron with reduced level of ferritin; and deficiency of mitochondrial complex I. New approaches designed to attenuate the effects of oxidative stress and to provide neuroprotection of striatal dopaminergic neurons in Parkinson's disease include blocking dopamine transporter by mazindol, blocking NMDA receptors by dizocilpine maleate, enhancing the survival of neurons by giving brain-derived neurotrophic factors, providing antioxidants such as vitamin E, or inhibiting monoamine oxidase B (MAO-B) by selegiline. Among all of these experimental therapeutic refinements, the use of selegiline has been most successful in that it has been shown that selegiline may have a neurotrophic

factor-like action rescuing striatal neurons and prolonging the survival of patients with Parkinson's disease.

An open trial of high-dosage antioxidants in early Parkinson's disease.

Fahn S. Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York.

Am J Clin Nutr 1991 Jan;53(1 Suppl):380S-382S

High dosages of tocopherol and ascorbate were administered to patients with early Parkinson's disease as a preliminary open-labeled trial for the eventual controlled double-blind study evaluating antioxidants as a test of the endogenous toxin hypothesis of the etiology of Parkinson's disease. The primary endpoint of the trial was the need to treat patients with levodopa. The time when levodopa became necessary in the treated patients was compared with another group of patients followed elsewhere and not taking antioxidants. The time when levodopa became necessary was extended by 2.5 y in the group taking antioxidants. The results of this pilot study suggest that the progression of Parkinson's disease may be slowed by the administration of these antioxidants. A large multicenter, controlled clinical trial currently underway in North America evaluating tocopherol and deprenyl has the potential to confirm these results.

A pilot trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's disease.

Fahn S. Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY.

Ann Neurol 1992;32 Suppl:S128-32

High dosages of a combination of alpha-tocopherol and ascorbate were administered to patients with early Parkinson's disease as an open-labeled trial and pilot study to test the endogenous toxic hypothesis of the etiology of Parkinson's disease. Patients receiving concomitant amantadine and anticholinergics were allowed to participate, but those receiving levodopa or dopamine agonists were not. The study was begun prior to the availability of deprenyl. The primary end point of the trial was progression of the disease until patients needed treatment with levodopa or a dopamine agonist. The time when levodopa became necessary in the treated patients was compared to another group of patients followed elsewhere who did not receive antioxidants. The time when levodopa became necessary was extended by 2.5 years in the group receiving alpha-tocopherol and ascorbate. Results of this pilot study suggest that the progression of Parkinson's disease may be slowed by administration of these antioxidants. Controlled clinical trials using double-blind randomization techniques are required to confirm these results.

Normalization of brain serotonin by L-tryptophan in levodopa-treated rats.

Fahn S, Snider S, Prasad AL, Lane E, Makadon H.

Neurology. 1975 Sep;25(9):861-5.

To test possible biochemical mechanisms by which L-tryptophan may reverse mental side effects of levodopa therapy in parkinsonism we administered levodopa, 250 mg per kilogram intraperitoneally, alone and with L-tryptophan, 500 mg per kilogram intraperitoneally, to rats pretreated with the peripheral dopa decarboxylase inhibitor, carbidopa (25 mg per kilogram). Rats were decapitated 0.5, 1, and 2 hours following amino acid injection and brain levels of amino acids, amines, and acid metabolites were determined. As expected, levodopa alone reduced tryptophan and serotonin and increased dopa and dopamine at the 1 and 2 hour intervals. Concurrent administration of L-tryptophan did not significantly alter the increased dopa and dopamine but did restore serotonin levels to within normal range at all time points. If similar events occur in parkinsonian patients, normalization of brain serotonin and not competitive reduction of brain dopa and dopamine may be the basis for the improvement in mental status.

Frontal dysfunction in early Parkinson's disease.

Farina E, Cappa SF, Polimeni M, Magni E, Canesi M, Zecchinelli A, Scarlato G, Mariani C. Istituto di Clinica Neurologia, University of Milan, Italy.

Acta Neurol Scand 1994 Jul;90(1):34-8

Recent studies have suggested that patients with Parkinson's disease (PD) share many of the behavioral deficits found following lesions to the pre-frontal cortex. We assessed the performance of a group of 22 mildly impaired, not-demented parkisonians (I or II Hoehn & Yahr stage) in a test of classification and recall of pictures of familiar objects, which has been demonstrated to be sensitive to frontal damage in patients with unilateral cerebral excision. Parkinsonians utilized fewer categories than normal controls for object classification, while no significant difference was found in the immediate and delayed recall scores. These results support the contention that a subclinical dysfunction of frontal type may be present even in the early stages of PD. A subanalysis of the data suggests that this dysfunction could possibly be aggravated by anticholinergic drugs.

In vivo elevation of extracellular potassium in the rat amygdala increases extracellular glutamate and aspartate and damages neurons.

Fujikawa DG, Kim JS, Daniels AH, Alcaraz AF, Sohn TB. Experimental Neurology Laboratory, Sepulveda VA Medical Center, CA 91343, USA.

Neuroscience. 1996 Oct;74(3):695-706.

It is well known that high potassium (K+) solutions introduced by microdialysis into normal brain increase the extracellular concentration of the excitatory amino acid glutamate, and in vitro studies suggest that a high exogenously applied glutamate concentration can produce excitotoxic neuronal death. However, only

recently were in vivo studies undertaken to determine whether high-K+ exposure damages neurons. We implanted microdialysis probes into rat amygdalae bilaterally, and after a 2-h baseline period exposed one side to a modified Krebs-Ringer-bicarbonate solution containing 100 mmol/l KCl for 30,50 and 70 min, followed by a 2-h recovery period, and 70 min and 3 h without a recovery period. Of 100.9 +/- 2.0 mmol/l KCl, 12.0 +/- 1.0% was extracted by amygdalar tissue in vivo. Election of the extracellular K+ concentration in the amygdale for 70 min or longer without a recovery period produced extensive neuronal damage and edematous-appearing neuropil in the tissue dialysed, as well as loss of normal neurons. Histological evidence of edema subsided in the groups with a 2-h recovery period. Although the number of damaged neurons was not significantly higher in the group with a 70 min high-K+ exposure and 2-h recovery period, the number of normal neurons was reduced, suggesting cell loss. During 70-min high-K+ exposure, the extracellular glutamate concentration increased to 242-377% of baseline during the first 60 min, and extracellular aspartate rose to 162-213% during the first 50 min; extracellular taurine rose even higher, to 316-567% of baseline, and glutamine fell to 14-27% of baseline. Extracellular serine was decreased at 20, 50 and 70 min of high-K+ exposure; extracellular glycine was unchanged. The elevated extracellular glutamate and aspartate concentrations suggest that exposure of the amygdala to high extracellular K+ may produce cell death through an excitotoxic process, and point the way to future studies to define the specific mechanisms involved.

Dementias: the role of magnesium deficiency and an hypothesis concerning the pathogenesis of Alzheimer's disease.

Glick JL. Bionix Corporation, Potomac, Maryland 20854.

Med Hypotheses. 1990 Mar;31(3):211-25.

Evidence is presented indicating that dementias are associated with a relative insufficiency of Magnesium (Mg) in the brain. Such insufficiency may be attributable to low intake or retention of Mg; high intake of a neurotoxic metal, such as aluminum (Al), which inhibits activity of Mg-requiring enzymes; or impaired transport of Mg and/or enhanced transport of the neurotoxic metal into brain tissue. It is proposed that Alzheimer's disease (AD) involves a defective transport process, characterized by both an abnormally high incorporation of Al and an abnormally low incorporation of Mg into brain neurons. The hypothesis is advanced that an altered serum protein contributes to the progression of AD by having a greater affinity for Al than for Mg, in contrast to the normal protein, which binds Mg better than Al. The altered protein crosses the blood-brain barrier more efficiently than the normal protein and competes with the normal protein in binding to brain neurons. Binding of the altered protein to the target neurons would both facilitate Al uptake and impede Mg uptake. Evidence suggests that albumin is the serum protein that is altered.

Case-control study of early life dietary factors in Parkinson's disease.

Golbe LI, Farrell TM, Davis PH. Department of Neurology, University of Medicine and Dentistry of New Jersey, New Brunswick 08903.

Arch Neurol. 1988 Dec;45(12):1350-3.

Studies of the amyotrophic lateral sclerosis parkinsonism dementia complex of Guam direct suspicion to a heat-labile component of vegetables found in greatest concentration in seeds. We therefore surveyed patients with Parkinson's disease (PD) regarding early adult consumption of fruits and vegetables usually eaten raw, with seeds that are swallowed or scraped with the teeth. We administered a pretested questionnaire by telephone to 81 nondemented patients with PD and to a same-sex married sibling without PD. The patients and their siblings were asked whether they or their spouse (as an internal standard) had been more likely to eat each of 17 food items between marrying and age 40 years. No item was associated with the presence of PD. Unexpectedly associated with the absence of PD were preference for nuts (odds ratio, 0.39), salad oil or dressing (pressed from seeds) (odds ratio, 0.30), and plums (odds ratio, 0.24). These three items have higher vitamin E content than the other 14 items in our questionnaire. Our data are consistent with the hypothesis that vitamin E, as an antioxidant, may have prophylactic value against PD.

Effects of oral L-tyrosine administration on CSF tyrosine and homovanillic acid levels in patients with Parkinson's disease.

Growdon JH, Melamed E, Logue M, Hefti F, Wurtman RJ.

Life Sci 1982 Mar 8;30(10):827-32

To determine whether 1-tyrosine administration can enhance dopamine synthesis in humans as it does in rats, we measured levels of tyrosine and the major dopamine metabolite, homovanillic acid, in lumbar spinal fluids of 23 patients with Parkinson's disease before and during ingestion of 100 mg/kg/day of tyrosine. Nine patients took 100 mg/kg/day of probenecid in six divided doses for 24 hours prior to each spinal tap; 14 patients did not receive probenecid. L-tyrosine administration significantly increased CSF tyrosine levels in both groups of patients (p less than .01) and significantly increased homovanillic acid levels in the group of patients pretreated with probenecid (p less than .02). These data indicate that l-tyrosine administration can increase dopamine turnover in patients with disorders in which physicians wish to enhance dopaminergic neurotransmission.

Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study.

Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Institute of Social Medicine, Faculty of Medicine, Otto-von-Guericke University, Magdeburg, Germany.

Neurology 1996 Sep;47(3):644-50

In a case-control study, we compared the past dietary habits of 342 Parkinson's disease (PD) patients recruited from nine German clinics with those of 342 controls from the same neighborhood or region. Data were gathered with a structured interview and a self-administered food-frequency questionnaire. Nutrient intakes were calculated from the reported food intakes through linkage with the German Federal Food Code and analyzed using multivariate conditional logistic regression to control for total energy intake, educational status, and cigarette smoking. At the macronutrient level, patients reported higher carbohydrate intake than controls after adjustment for total energy intake, smoking, and educational status (OR = 2.74, 95% confidence interval [CI]: 1.30-6.07, for the highest versus lowest quartile, p trend = 0.02). This was reflected in higher monosaccharide and disaccharide intakes at the nutrient level. There was no difference between patients and controls in protein and fat intake after adjustment for energy intake. We found an inverse association between the intakes of beta-carotene (OR = 0.67, 95% CI: 0.37-1.19, p trend = 0.06) and ascorbic acid (OR = 0.60, 95% CI: 0.33-1.09, p trend = 0.04) by patients, although only the trend for ascorbic acid intake reached statistical significance. There was no difference between groups for alpha-tocopherol intake after adjustment for energy intake. We also found that patients reported a significantly lower intake of niacin than controls (OR = 0.15, 95% CI: 0.07-0.33, p trend < 0.00005). Our results suggest that if antioxidants play a protective role in this disease, the amounts provided by diet alone are insufficient. Although the interpretation of the inverse association between niacin intake and PD is complicated by the high niacin content in coffee and alcoholic beverages, which were also inversely associated with PD in this study, the strength of this association and its biologic plausibility warrant further investigation.

Exogenous glutamate enhances glutamate receptor subunit expression duringselective neuronal injury in the ventral arcuate nucleus of postnatal mice.

Hu L, Fernstrom JD, Goldsmith PC. Reproductive Endocrinology Center, Department of Ob/Gyn and Reproductive Sciences, University of California, San Francisco, CA 94143-0556, USA.

Neuroendocrinology. 1998 Aug;68(2):77-88.

Administration of high doses of glutamate (Glu) leads to selective neurodegeneration in discrete brain regions near circumventriclular organs of the early postnatal mouse. The arcuate nucleus-median eminence complex (ARC-ME) appears to be the most Glu-sensitive of these brain regions, perhaps because of the intimate relationships between its neurons and specialized astroglial tanycytes. To investigate the mechanism of Glu-induced neuronal loss, we administered graded doses of the sodium salt of glutamate (MSG) to postnatal mice, measured their plasma Glu concentrations, and performed microscopic analyses of the ARC-ME region 5 h after treatment. Nursing, 7-day-old mouse pups (CD1, Charles River, Hollister, Calif.) were injected subcutaneously with

single doses of 0.1-0.5 or 1.0-4.0 mg of MSG per g BW, or with water vehicle alone. Mice were decapitated 5 h later and the brains immediately fixed by immersion in buffered aldehydes. Frontal vibratome tissue sections at comparable levels of the ARC-ME were examined by light microscopy. A dose of 4.0 mg MSG/g BW caused neurodegeneration throughout the ARC region, while 1.0 mg/g MSG resulted in less extensive damage. Injection of 0.2 mg MSG/g BW, which raised plasma Glu concentrations 17-fold after 15 min, was the minimum dose tested at which nuclear and cytoplasmic changes were observed in a small group of subependymal neurons near the lateral recesses of the third ventricle. Higher doses of 0.3-0.5 mg MSG caused injury to additional neurons situated farther laterally, but damage remained confined to the ventral region of the ARC nucleus. Ultrastructural examination showed some subependymal neurons with pyknotic nuclei, reduced cytoplasmic volume, and swollen subcellular organelles, while others had fragmented and condensed nuclear material. Immunostaining for tyrosine hydroxylase indicated that dopamine neurons were spared at the threshold dose, but suffered damage after higher doses of MSG. Immunostaining for Glu receptor subtypes revealed that 0.2 mg MSG/g BW enhanced neuronal expression of NMDAR1 and of GluR2/4, and that higher doses of MSG preferentially increased NMDAR1 expression in injured neurons. These results extend previous reports of Glu sensitivity in the ARC-ME region of 7-day postnatal mice. A dose of 0.2 mg MSG/g BW s.c. causes clear but discrete injury to specific subependymal neurons of undetermined phenotype near the base of the third ventricle. Slightly higher doses of MSG evoke damage of additional neurons confined to the ventral region of the ARC traversed by tanycytes. These same greater amounts of MSG promote dose-related increase in the expression of NMDAR1 more than of GluR2/4 in injured ARC neurons, suggesting that elevated Glu receptor levels may contribute to or be related to neuronal cell death. Taken together with previous findings, the data suggest that Glu responsitivity in the ARC-ME of the postnatal mouse may result from transient developmental conditions involving the numerical ratios and juxtaposition between tanycytes and neurons, expression of Glu receptors, and perhaps other ontogenetic factors which may not persist in the mature adult.

Serum levels of coenzyme Q10 in patients with Parkinson's disease.

Jimenez-Jimenez FJ, Molina JA, de Bustos F, Garcia-Redondo A, Gomez-Escalonilla C, Martinez-Salio A, Berbel A, Camacho A, Zurdo M, Barcenilla B, Enriquez de Salamanca R, Arenas J. Department of Medicine-Neurology, University of Alcala, Alcala de Henares, Madrid, Spain. Fjimenezj@meditex.es

J Neural Transm. 2000;107(2):177-81.

We compared serum levels of coenzyme Q10 and the coenzyme Q10/cholesterol ratio in 33 patients with Parkinson's disease (PD) and 31 matched controls. The mean serum coenzyme Q10 levels did not differ significantly between the 2 study groups. Coenzyme Q10 levels were not correlated with age, age at onset, duration of the disease, scores of the Unified Parkinson Disease Rating Scale (UPDRS) or the Hoehn and Yahr staging in the PD group. The coenzyme Q10/cholesterol ratio had a significant correlation (although low) with duration of the disease (r = -

0.46), total UPDRS score (r = -0.39), motor examination of the UPDRS (r = 0.45). These values were not influenced significantly by therapy with levodopa or dopamine agonists. The normality of serum coenzyme Q10 and coenzyme Q10/cholesterol ratio suggest that these values are not related with the risk for PD.

Thiamin mono- and pyrophosphatase activities from brain homogenate of Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia patients.

Laforenza U, Patrini C, Poloni M, Mazzarello P, Ceroni M, Gajdusek DC, Garruto RM. Institute of Human Physiology, University of Pavia, Italy.

J Neurol Sci 1992 Jun;109(2):156-61

Thiamin-pyrophosphatase (TPPase) and thiamin-monophosphatase (TMPase) were determined using a spectrophotometric method at various pH values (5.5, 7.5, and 9.0) in brain tissue obtained at autopsy from amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) patients from Guam and from Guamanian patients who died from other diseases (controls). TPPase separation by thin-layer polyacrylamide gel isoelectric focusing (IEF) was also performed using both gray and white matter. TPPase content, chemically determined at pH 9.0, was found to be significantly reduced in the frontal cortex of ALS and PD patients compared to controls. TMPase content, on the contrary, was unchanged. IEF analysis showed 9 clear-cut bands with TPPase activity in the pH range 5.4-7.2 and a broad band at pH 4.7-5.2. The enzymatic activity was higher in gray than in white matter. In one patient the pattern was clearly different, with two additional bands observed at pH 7.1 and 6.7, and thought to be due to genetic microheterogeneity.

Dehydroepiandrosterone (DHEA) reduces neuronal injury in a rat model of global cerebral ischemia.

Li H, Klein G, Sun P, Buchan AM. Alberta Stroke Program, Department of Clinical Neurosciences, Foothills Hospital, University of Calgary, AB T2N 2T9, Calgary, Canada.

Brain Res. 2001 Jan 12;888(2):263-266.

Introduction: Many studies report an inverse correlation between levels of DHEA and neurological diseases. Exogenous DHEA protects hippocampal neurons against excitatory amino acid induced neurotoxicity. The purpose of this experiment is to evaluate the effect of DHEA in an animal model of transient but severe forebrain ischemia. Methods: At thirteen days prior to induction of ischemia, male Wistar rats were implanted with various doses of DHEA-placebo, 25 mg, 50 mg or 100 mg. Forebrain ischemia was induced for 10 min using a modified four-vessel occlusion technique, with hippocampal neuronal injury assessed at 7 days post-ischemically and expressed as a percentage of total cells. Results: Both normal and necrotic hippocampal CA(1) cells were counted. Percentages of hippocampal injury observed were 88+/-13% in animals treated

with placebo, 84+/-8% in the 25 mg DHEA group, and 60+/-7% in the 50 mg DHEA group. Animals treated with 100 mg DHEA displayed a significant (P<0.05) reduction of hippocampal CA(1) cell injury at 60+/-7% Conclusion: Treatment with a high dose, but not a low or moderate dose, of DHEA implantation reduces hippocampal CA(1) neuronal injury following severe but transient forebrain ischemia.

[Treatment of complicated Parkinson disease with a solution of levodopa-carbidopa and ascorbic acid] [Article in Spanish]

Linazasoro G, Gorospe A. Unidad de Trastornos del Movimiento. Clinica Quiron, San Sebastian.

Neurologia. 1995 Jun-Jul;10(6):220-3.

We prescribed a solution of levodopa-carbidopa and ascorbic acid (LCAAS) to 21 Parkinsonian patients with motor complications. Eight patients continued the treatment for a mean period of 16.8 months, experiencing substantial increases in the number of hours with good functional capacity. Bothersome symptoms such as dystonia and akathisia in off periods disappeared in all cases in which they had been present and LCAAS was tolerated (in 6 of the 8 patients who continued in the study and in 4 who abandoned treatment late). Intake of other anti-Parkinsonian drugs was reduced. Thirteen patients abandoned the study, citing exacerbation of biphasic dyskinesia as the main reason. We conclude that LCAAS is a useful therapy in some Parkinsonian patients whose motor complications are not managed with conventional drug treatment. Screening of patients is probably of utmost importance to ensure that LCAAS is not administered to patients who already suffer intense biphasic dyskinesia.

Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study.

Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Gertrude H. Sergievsky Center, New York, NY 10032, USA.

Ann Neurol 1996 Jan;39(1):89-94

Oxidative stress plays an important role in the pathogenesis of Parkinson's disease (PD). In a population-based, case-control study we examined whether dietary intake of antioxidants and other oxidative compounds was associated with PD. Dietary intake was assessed by a semiquantitative food-frequency questionnaire in 110 PD case patients and 287 control subjects. A higher caloric intake was observed in patients with PD and did not vary with increasing duration of symptoms. Energy-adjusted fat intake was significantly higher among patients with PD than control subjects (p for trend = 0.007). Intake of protein (p for trend = 0.17) and carbohydrates (p for trend = 0.46) did not differ in patients and control subjects. Analyses of the primary sources of fat indicated that increasing intake of animal fats were strongly related to PD (odds ratio, 5.3; 95% confidence interval, 1.8-15.5; p for trend = 0.001). No significant differences were observed

for intake of vitamins with antioxidant activity. An increase in the consumption of animal fats among patients with PD is consistent with the hypothesis that oxidative stress and lipid peroxidation are important in the pathogenesis of this disease. No effect of vitamins with antioxidant activity, either from food or supplements, was observed.

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects.

Matthews RT, Yang L, Browne S, Baik M, Beal MF. Neurochemistry Laboratory, Neurology Service, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA.

Proc Natl Acad Sci U S A. 1998 Jul 21;95(15):8892-7.

Coenzyme Q10 is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Feeding with coenzyme Q10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of coenzyme Q10 resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q10 increases both brain and brain mitochondrial concentrations. They provide further evidence that coenzyme Q10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.

The role of glutamatergic transmission in the pathogenesis of levodopa-induced dyskinesias. Potential therapeutic approaches.

Merims D, Ziv I, Sherki Y, Djaldetti R, Melamed E. Department of Neurology, Rabin Medical Center, Belinson Campus, Petah Tikva.

Neurol Neurochir Pol. 2001;35 Suppl 3:65-8.

Dyskinesias are the most frequent adverse effect of chronic levodopa therapy in patients with Parkinson's disease (PD). Current pharmacological treatment for this problem is unsatisfactory. Recently, there is evidence for the role of glutamate in the basal ganglia neuronal circuitry in the generation of dyskinesias. If indeed glutamatergic overactivity beyond the dopaminergic synapses plays a role in the pathogenesis of these involuntary movements, there is hope that its suppression may be beneficial without causing loss of levodopa efficacy and parkinsonian deterioration. Indeed, NMDA receptor antagonists such as amantadine and dextrometorphan can reduce such dyskinesias. We tested the efficacy of riluzole, an inhibitor of glutamatergic transmission in the inhibition of levodopa-induced dyskinesias.

Rotations induced by L-dopa in parkinsonian rats are reduced by an ingestion of amino acids.

Mizuta E, Kuno S. Department of Neurology, Utano National Hospital, Kyoto, Japan.

J Neural Transm Park Dis Dement Sect. 1993;6(3):211-4.

We studied the effect of amino acid load on L-dopa-induced rotational behavior in rats with unilateral lesion of the nigrostriatal pathway. Pretreatment of rats with an ingestion of high concentration of amino acids significantly reduced the number of rotations induced by subcutaneously injected L-dopa. These results provide the experimental basis for clinical observations that dietary protein affects the response to L-dopa in parkinsonian patients.

Influence of reduced nicotinamide adenine dinucleotide on the production of interleukin-6 by peripheral human blood leukocytes.

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Neuroimmunomodulation. 2001;9(4):203-8.

OBJECTIVE: Recently, therapy with nicotinamide adenine dinucleotide (NADH) revealed positive effects on neurodegenerative disorders associated with inflammation of the CNS, such as Parkinson's disease or Alzheimer's disease. Pathophysiologically, focal CNS inflammation seems to be accompanied by an unbalanced cytokine production, pointing to an involvement of the immune system. Therefore, the aim of our study was to investigate whether NADH could influence cytokine release of peripheral blood leukocytes (PBLs) with special reference to interleukin-6 (IL-6).

METHODS: PBLs from 18 healthy donors were incubated in vitro with different concentrations of NADH to generate dose-response curves. As a control, mitogen-treated cells and unstimulated cells were included.

RESULTS: In PBLs from the 18 healthy donors, NADH significantly stimulated the dose-dependent release of IL-6, ranging from 6.25 to 400 microg/ml, compared to medium-treated cells (p < 0.001). An amount of 1,000 pg/ml IL-6 was induced by NADH concentrations ranging from 3.1 to >25 microg/ml.

CONCLUSIONS: It is concluded that NADH possesses cytokine-modulating effects on peripheral blood cells. The biological relevance of these data is discussed in the context of the recent use of NADH for the treatment of several neurodegenerative disorders. Copyright 2002 S. Karger AG, Basel

Toxic effects of L-DOPA on mesencephalic cell cultures: protection with antioxidants.

Pardo B, Mena MA, Casarejos MJ, Paino CL, De Yebenes JG. Departamento de Investigacion, Hospital Ramon y Cajal, Madrid, Spain.

Brain Res. 1995 Jun 5;682(1-2):133-43.

The toxicity of L-3,4-dihydroxyphenylalanine (L-DOPA) was studied in neuronal cultures from rat mesencephalon. The survival and function of DA neurons were assessed by the number of tyrosine hydroxylase-positive (TH+) cells and 3H-DA uptake and those non-DA neurons by the exclusion of Trypan blue and the high-affinity 3H-GABA uptake. L-DOPA was toxic for both DA and non-DA neurons. DA neurons were more severely affected than non-DA neurons after short periods of treatment and with exposure to a low dose of L-DOPA (25 vs. 100 microM) and less selectively affected after 1 or 2 days of treatment. After incubation with L-DOPA, a disruption of the neuritic network and an overall deterioration were observed, more evident for TH+ cells in the whole culture. Auto-oxidation to quinones is responsible in part for L-DOPA toxicity in non-DA neurons since the levels of quinones correlated well with the severity of cell death in the cultures. The damage of DA neurons took place before the rising of quinones, suggesting that quinones are not essential in L-DOPA toxicity for DA neurons. Antioxidants, such as ascorbic acid and sodium metabisulfite, completely prevented L-DOPA-induced quinone formation as well as the death of non-DA neurons. In contrast, they could only partially prevent the damage produced by L-DOPA in DA neurons. Mazindol, a selective inhibitor of DA uptake, protected TH+ cells from L-DOPA.

L-tryptophan administration in L-dopa-induced hallucinations in elderly Parkinsonian patients.

Rabey JM, Vardi J, Askenazi JJ, Streifler M.

Gerontology. 1977;23(6):438-44.

L-tryptophan (L-T) was added at a dose of 150-450 mg daily to eight Parkinsonian patients who developed visual hallucinations with paranoidal features under L-dopa (L-D) treatment (112.5-75 mg daily) in combination with alpha-methyldopa hydrazine (12.5-75 mg daily). In six patients L-T ameliorated the symptomatology by arresting the visual paranoidal hallucinations or diminishing their frequency and relieving the psychomotor agitation. As a 'side effect', L-T produced new 'pleasurable', 'LSD-like' visual images in three patients. In two patients, in whom L-T did not affect the mental disturbances, amelioration was obtained only by phenothiazines. Theoretical considerations on the role of dopamine in the genesis of visual hallucinations and mental disturbances emphasizes the benefit of L-T administration in this 'organomental' syndrome.

L-dopa competes with tyrosine and tryptophan for human brain uptake.

Riederer P.

Nutr Metab. 1980;24(6):417-23.

Tyrosine and tryptophan have been assayed spectrofluorometrically in postmortem human brain areas of patients with Parkinson's disease treated orally with or without 3,4-dihydroxyphenylalanine (L-dopa) plus the peripherally acting decarboxylase inhibitor benserazide. Tyrosine as well as tryptophan decrease significantly after treatment with L-dopa, thus showing a competitive action of L-dopa to other aromatic amino acids on human brain uptake. It is suggested that some of the side effects of L-dopa treatment in Parkinson's disease are due to a disturbance in the brain and neural uptake of other, specially aromatic and branched-chain amino acids. An influence of L-dopa administration on protein synthesis also cannot be excluded.

Neuroprotective effect of vitamin E on the early model of Parkinson's disease in rat: behavioral and histochemical evidence.

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Brain Res. 2001 Feb 16;892(1):211-7.

There is strong evidence that oxidative stress participates in the etiology of Parkinson's disease (PD). We designed this study to investigate the neuroprotective effect of vitamin E in the early model of PD. For this purpose, unilateral intrastriatal 6-hydroxydopamine (12.5 microg/5 microl) lesioned rats were pretreated intramuscularly with D-alpha-tocopheryl acid succinate (24 I.U./kg, i.m.) 1 h before and three times per week for 1 month post-surgery. Apomorphine- and amphetamine-induced rotational behavior was measured postlesion fortnightly. A parallel tyrosine hydroxylase immunoreactivity and wheat germ agglutinin-horse radish peroxidase (WGA-HRP) tract-tracing study was performed to evaluate the vitamin E pretreatment efficacy. Tyrosine hydroxylase-immunohistochemical analyses showed a reduction of 18% in ipsilateral substantia nigra pars compacta (SNC) cell number of the vitamin E-pretreated lesioned (L+E) group comparing with contralateral side. The cell number dropped to 53% in the lesioned (L+V) group. In addition, retrograde-labeled neurons in ipsilateral SNC were reduced by up to 30% in the L+E group and 65% in the L+V group. Behavioral tests revealed that there are 74% and 68% reductions in contraversive and ipsiversive rotations in the L+E group, respectively, as compared with the L+V group. Therefore repeated intramuscular administration of vitamin E exerts a rapid protective effect on the nigrostriatal dopaminergic neurons in the early unilateral model of PD.

Interaction between sodium ascorbate and dopamine.

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Free Radic Biol Med. 1998 Dec;25(9):1013-20.

The interaction between sodium ascorbate and dopamine was investigated by three different parameters: radical intensity, prooxidant action, and cytotoxicity induction. Sodium ascorbate and dopamine produced the doublet and quartet ESR signals under alkaline conditions (pH 8.0-9.5), respectively. Addition of increasing concentrations of sodium ascorbate completely scavenged the dopamine radical and replaced the latter with its own radical. Similarly, dopamine slightly, but significantly reduced the radical intensity of sodium ascorbate. These two compounds stimulated the methionine oxidation and hydrogen peroxide generation in culture medium, but in combination, their stimulation activities were weakened. Both of these two compounds dose-dependently reduced the viable cell number of human oral squamous carcinoma HSC-4 cells, and their cytotoxic activity was significantly reduced by catalase. When these two compounds were mixed together before adding to HSC-4 cells, both of their cytotoxic activities were diminished. The present study demonstrates the interaction between sodium ascorbate and dopamine, which might modify their biological activities and generation of nerve disorders such as Parkinson's disease.

L-tryptophan in neuropsychiatric disorders: a review.

Sandyk R. Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY 10461.

Int J Neurosci. 1992 Nov-Dec;67(1-4):127-44.

Animal data indicate that serotonin (5-HT) is a major neurotransmitter involved in the control of numerous central nervous system functions including mood, aggression, pain, anxiety, sleep, memory, eating behavior, addictive behavior, temperature control, endocrine regulation, and motor behavior. Moreover, there is evidence that abnormalities of 5-HT functions are related to the pathophysiology of diverse neurological conditions including Parkinson's disease, tardive dyskinesia, akathisia, dystonia, Huntington's disease, familial tremor, restless legs syndrome, myoclonus, Gilles de la Tourette's syndrome, multiple sclerosis, sleep disorders, and dementia. The psychiatric disorders of schizophrenia, mania, depression, aggressive and self-injurious behavior, obsessive compulsive disorder, seasonal affective disorder, substance abuse, hypersexuality, anxiety disorders, bulimia, childhood hyperactivity, and behavioral disorders in geriatric patients have been linked to impaired central 5-HT functions. Tryptophan, the natural amino acid precursor in 5-HT biosynthesis, increases 5-HT synthesis in the brain and, therefore, may stimulate 5-HT release and function. Since it is a natural constituent of the diet, tryptophan should have low toxicity and produce few side effects. Based on these advantages, dietary tryptophan supplementation has been used in the management of neuropsychiatric disorders with variable success. This review summarizes current clinical use of tryptophan supplementation in neuropsychiatric disorders.

L-tryptophan supplementation in Parkinson's disease.

Sandyk R, Fisher H. Department of Neurology, University of Arizona, Tucson 85724.

Int J Neurosci. 1989 Apr;45(3-4):215-9.

Two female Parkinsonian patients with levodopa-induced "On-Off" responded dramatically to administration of L-tryptophan supplementation. This report highlights the role of serotonergic deficiency in the pathophysiology of Parkinson's disease and of levodopa-induced motor fluctuations, and suggests that L-tryptophan supplementation may be useful in ameliorating motor complications of chronic levodopa therapy in the disease. The possibility that L-tryptophan supplementation with initiation of levodopa therapy may be useful in preventing levodopa-induced motor complications is discussed.

Pyridoxine improves drug-induced parkinsonism and psychosis in a schizophrenic patient.

Sandyk R, Pardeshi R. Department of Psychiatry College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, NY 10032.

Int J Neurosci. 1990 Jun;52(3-4):225-32.

Drug-induced Parkinsonism is a common serious side-effect of neuroleptic therapy. In cases of irreversible drug-induced Parkinsonism, pharmacological management is notoriously difficult. A schizophrenic patient with severe neuroleptic-induced Parkinsonism and Tardive Dyskinesia is presented in whom administration of pyridoxine (vitamin B6) (100 mg/d) resulted in dramatic and persistent attenuation of the movement disorders as well as reduction of psychotic behavior. Since pyridoxine deficiency is associated with marked reduction of cerebral serotonin concentrations and pineal melatonin production in rats, the effects of pyridoxine on the movement disorder and psychosis may have been mediated largely by enhancing serotonin and melatonin functions. An additional effect of excess pyridoxine administration on GABA and dopamine activity cannot be excluded. Pyridoxine has been reported to attenuate the severity of levodopa-induced dyskinesias in patients with Parkinson's disease and it is suggested that pyridoxine supplementation should be considered in psychiatric patients with drug-induced movement disorders including persistent Parkinsonism. An underlying pyridoxine deficiency in these patients may exacerbate the psychotic behavior and additionally, potentially increase the risk of drug-induced movement disorders.

Coenzyme Q10 and nicotinamide and a free radical spin trap protect against MPTP neurotoxicity.

Schulz JB, Henshaw DR, Matthews RT, Beal MF. Neurochemistry Laboratory, Massachusetts General Hospital, Boston 02114, USA.

Exp Neurol. 1995 Apr;132(2):279-83.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) produces Parkinsonism in both experimental animals and in man. MPTP is metabolized to 1-methyl-4-

phenylpridinium, an inhibitor of mitochondrial complex I. MPTP administration produces ATP depletions in vivo, which may lead to secondary excitotoxicity and free radical generation. If this is the case then agents which improve mitochondrial function or free radical scavengers should attenuate MPTP neurotoxicity. In the present experiments three regimens of MPTP administration produced varying degrees of striatal dopamine depletion. A combination of coenzyme Q10 and nicotinamide protected against both mild and moderate depletion of dopamine. In the MPTP regimen which produced mild dopamine depletion nicotinamide or the free radical spin trap N-tert-butyl-alpha-(2-sulfophenyl)-nitrone were also effective. There was no protection with a MPTP regimen which produced severe dopamine depletion. These results show that agents which improve mitochondrial energy production (coenzyme Q10 and nicotinamide) and free radical scavengers can attenuate mild to moderate MPTP neurotoxicity.

Ascorbic acid stimulates DOPA synthesis and tyrosine hydroxylase gene expression in the human neuroblastoma cell line SK-N-SH.

Seitz G, Gebhardt S, Beck JF, Bohm W, Lode HN, Niethammer D, Bruchelt G. Department of Hematology and Oncology, Children's Hospital, University of Tubingen, Germany.

Neurosci Lett. 1998 Mar 6;244(1):33-6.

Ascorbic acid is well known to induce noradrenaline synthesis in sympathetic nervous cells. In a series of experiments we found that incubation of the neuroblastoma cell line SK-N-SH with ascorbic acid (100-500 microM) for 2 h results in a significantly enhanced synthesis of 3,4-dihydroxyphenylalanine (DOPA) and dopamine. Additionally, cDNA-polymerase chain reaction (cDNA-PCR) analysis of relative mRNA levels corresponding to the enzymes involved in catecholamine synthesis revealed a 3-fold increase of tyrosine hydroxylase gene expression after 5 days of incubation with ascorbic acid (200 microM), whereas expression of dopamine-beta-hydroxylase was found to be unaltered. In summary the data give evidence that ascorbic acid leads to enhanced DOPA production in SK-N-SH cells by two different mechanisms: at the metabolic level after short-term incubation and by increasing the tyrosine hydroxylase gene expression after long-term incubation. Based on these data we suppose that enhancement of DOPA synthesis by ascorbic acid may be useful in the treatment of early Parkinson's disease.

Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects.

Shults CW, Haas RH, Passov D, Beal MF. Neurology Service, Veterans Affairs Medical Center, San Diego, CA 92161, USA.

Ann Neurol. 1997 Aug;42(2):261-4.

The activities of complex I and complex II/III in platelet mitochondria are reduced in patients with early, untreated Parkinson's disease. Coenzyme Q10 is the electron acceptor for complex I and complex II. We found that the level of coenzyme Q10 was significantly lower in mitochondria from parkinsonian patients than in mitochondria from age- and sex-matched control subjects and that the levels of coenzyme Q10 and the activities of complex I and complex II/III were significantly correlated.

Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients.

Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH. Department of Neurosciences, University of California, San Diego, La Jolla, USA.

Neurology. 1998 Mar;50(3):793-5.

We report a pilot study of three oral doses of coenzyme Q10 (CoQ10) (200 mg administered two, three, or four times per day for 1 month) in 15 subjects with Parkinson's disease. Oral CoQ10 caused a substantial increase in the plasma CoQ10 level. It was well tolerated, but at the highest dose (200 mg four times per day) mild, transient changes in the urine were noted. CoQ10 did not change the mean score on the motor portion of the Unified Parkinson's Disease Rating Scale. There was a trend toward an increase in complex I activity in the subjects.

A possible role of coenzyme Q10 in the etiology and treatment of Parkinson's disease.

Shults CW, Haas RH, Beal MF. Department of Neurosciences, University of California, San Diego, La Jolla 92093, USA.

Biofactors. 1999;9(2-4):267-72.

Parkinson's disease (PD) is a degenerative neurological disorder. Recent studies have demonstrated reduced activity of complex I of the electron transport chain in brain and platelets from patients with PD. Platelet mitochondria from parkinsonian patients were found to have lower levels of coenzyme Q10 (CoQ10) than mitochondria from age/sex-matched controls. There was a strong correlation between the levels of CoQ10 and the activities of complexes I and II/III. Oral CoQ10 was found to protect the nigrostriatal dopaminergic system in one-year-old mice treated with MPTP, a toxin injurious to the nigrostriatal dopaminergic system. We further found that oral CoQ10 was well absorbed in parkinsonian patients and caused a trend toward increased complex I activity. These data suggest that CoQ10 may play a role in cellular dysfunction found in PD and may be a potential protective agent for parkinsonian patients.

Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline.

Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M; Parkinson Study Group. Department of Neurosciences, Mail Code 0662, University of California-San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0662, USA. cshults@ucsd.edu

Arch Neurol. 2002 Oct;59(10):1541-50.

BACKGROUND: Parkinson disease (PD) is a degenerative neurological disorder for which no treatment has been shown to slow the progression.

OBJECTIVE: To determine whether a range of dosages of coenzyme Q10 is safe and well tolerated and could slow the functional decline in PD.

DESIGN: Multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging trial.

SETTING: Academic movement disorders clinics.

PATIENTS: Eighty subjects with early PD who did not require treatment for their disability.

INTERVENTIONS: Random assignment to placebo or coenzyme Q10 at dosages of 300, 600, or 1200 mg/d.

MAIN OUTCOME MEASURE: The subjects underwent evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and 1-, 4-, 8-, 12-, and 16-month visits. They were followed up for 16 months or until disability requiring treatment with levodopa had developed. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit.

RESULTS: The adjusted mean total UPDRS changes were +11.99 for the placebo group, +8.81 for the 300-mg/d group, +10.82 for the 600-mg/d group, and +6.69 for the 1200-mg/d group. The P value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was.09, which met our prespecified criteria for a positive trend for the trial. A prespecified, secondary analysis was the comparison of each treatment group with the placebo group, and the difference between the 1200-mg/d and placebo groups was significant (P =.04).

CONCLUSIONS: Coenzyme Q10 was safe and well tolerated at dosages of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q10 than in those assigned to placebo, and the benefit was greatest in subjects receiving the highest dosage. Coenzyme Q10 appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

Autoxidation and neurotoxicity of 6-hydroxydopamine in the presence of some antioxidants: potential implication in relation to the pathogenesis of Parkinson's disease.

Soto-Otero R, Mendez-Alvarez E, Hermida-Ameijeiras A, Munoz-Patino AM, Labandeira-Garcia JL. Departamento de Bioquimica y Biologia Molecular, Facultad de Medicina, Universidad de Santiago de Compostela, Spain. bnsoto@uscmail.usc.es

J Neurochem. 2000 Apr;74(4):1605-12.

6-Hydroxydopamine (6-OHDA) is a dopaminergic neurotoxin putatively involved in the pathogenesis of Parkinson's disease (PD). Its neurotoxicity has been related to the production of reactive oxygen species. In this study we examine the effects of the antioxidants ascorbic acid (AA), glutathione (GSH), cysteine (CySH), and N-acetyl-CySH (NAC) on the autoxidation and neurotoxicity of 6-OHDA. In vitro, the autoxidation of 6-OHDA proceeds rapidly with the formation of H2O2 and with the participation of the H2O2 produced in the reaction. The presence of AA induced a reduction in the consumption of O2 during the autoxidation of 6-OHDA and a negligible presence of the p-quinone, which demonstrates the efficiency of AA to act as a redox cycling agent. The presence of GSH, CySH, and NAC produced a significant reduction in the autoxidation of 6-OHDA. In vivo, the presence of sulfhydryl antioxidants protected against neuronal degeneration in the striatum, which was particularly remarkable in the case of CySH and was attributed to its capacity to remove the H2O2 produced in the autoxidation of 6-OHDA. These results corroborate the involvement of oxidative stress as the major mechanism in the neurotoxicity of 6-OHDA and the putative role of CySH as a scavenger in relation to PD.

[Intestinal microflora and concomitant gastrointestinal diseases in patients with chronic hepatitis B and C] [Article in Russian]

Sozinov AS, Anikhovskaia IA, Baiazitova LT, Enaleeva DSh, Zinkevich OD, Salakhov IM, Tkacheva SV, Likhoded VG. State Medical University, Research Institute of Epidemiology and Microbiology, Kazan, Russia.

Zh Mikrobiol Epidemiol Immunobiol. 2002 Jan-Feb;(1):61-4.

In chronic viral hepatitis B and C the development of intestinal dysbacteriosis and high occurrence of concomitant diseases of the gastrointestinal tract were observed. In cases of increased dysbacteriosis degree and in the presence of concomitant diseases the blood plasma of patients exhibited higher activity in reaction with the of amebocytes lysate obtained from crabs of the genus Limulus. A suggestion was made that the endotoxin of Gram negative intestinal microflora could probably play some role in the development of pathological processes in chronic viral hepatitis B and C.

Effect of antimicrobial agents on the ecological balance of human microflora.

Sullivan A, Edlund C, Nord CE. Department of Microbiology, Pathology, and Immunology, Huddinge University Hospital, Karolinska Institutet, and Soderkoping Hogskola, Stockholm, Sweden.

Lancet Infect Dis. 2001 Sep;1(2):101-14.

The normal microflora acts as a barrier against colonisation of potentially pathogenic microorganisms and against overgrowth of already present opportunistic microorganisms. Control of growth of opportunistic microorganisms is termed colonisation resistance. Administration of antimicrobial agents, therapeutically or as prophylaxis, causes disturbances in the ecological balance between the host and the normal microflora. Most studies on the impact of antimicrobial agents on normal microflora have been carried out on the intestinal flora. Less is known on the effects on oropharyngeal, skin, and vaginal microflora. Disturbances in the microflora depend on the properties of the agents as well as of the absorption, route of elimination, and possible enzymatic inactivation and/or binding to faecal material of the agents. The clinically most common disturbances in the intestinal microflora are diarrhoea and fungal infections that usually cease after the end of treatment. A well-balanced microflora prevents establishment of resistant microbial strains. By using antimicrobial agents that do not disturb colonisation resistance, the risk of emergence and spread of resistant strains between patients and dissemination of resistant determinants between microorganisms is reduced. In this article, the potential ecological effects of administration of antimicrobial agents on the intestinal, oropharyngeal, and vaginal microflora are summarised. The review is based on clinical studies published during the past 10 years.

Parkin is linked to the ubiquitin pathway.

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J Mol Med. 2001 Sep;79(9):482-94.

Autosomal recessive juvenile parkinsonism (AR-JP) is one of the most common forms of familial Parkinson's disease. AR-JP is characterized by selective and massive loss of dopaminergic neurons in the substantia nigra of the midbrain and absence of Lewy bodies, the pathological hallmark of idiopathic Parkinson's disease. Parkin, the causative gene of AR-JP, encodes a 52-kDa protein that is a RING-type ubiquitin (Ub) protein ligase (E3) collaborating with a Ub-conjugating enzyme (E2) belonging to a cognate class of UbcH7 or UbcH8. Analysis of parkin mutations in AP-JP patients reveals that the functional loss of parkin as an E3 enzyme is the molecular basis of AR-JP. Thus it is now clear that AR-JP is due to failure of proteolysis mediated by the Ub-proteasome system and accumulation of as yet unidentified protein(s) causes nigral neuronal death without formation of Lewy bodies. These findings should shed new light on the mechanisms underlying neurodegeneration in sporadic Parkinson's disease as well as AR-JP.

Role of human microflora in health and disease.

Tancrede C. Institut Gustave-Roussy, Villejuif, France.

Eur J Clin Microbiol Infect Dis. 1992 Nov;11(11):1012-5.

The human host and its microbial flora constitute a complex ecosystem whose equilibrium serves as a remarkable example of reciprocal adaptation. Intestinal bacteria play an important role in the development of the immune system. The normal intestinal flora is responsible for resistance to colonization by exogenous pathogenic microorganisms. Nevertheless, it also constitutes a reservoir of potentially pathogenic bacteria in close contact with the host. These bacteria are responsible for opportunistic infections in immunocompromised hosts. The equilibrium of the flora can be upset by antibiotics, leading to infections as a result of proliferation of antibiotic-resistant pathogenic bacteria.

Ceroid/lipofuscin-loaded human fibroblasts show decreased survival time and diminished autophagocytosis during amino acid starvation.

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Exp Gerontol. 1999 Dec;34(8):943-57.

To test whether heavy accumulation of ceroid/lipofuscin can disturb important functions of the lysosomal system, AG-1518 human fibroblasts, ceroid/lipofuscin-loaded (following prolonged culture at normobaric hyperoxia) or not, were exposed to amino acid starvation. Ceroid/lipofuscin-loading resulted in decreased cellular survival. Also, there was an inverse relationship between amounts of ceroid/lipofuscin and the survival time of individual cells within the same cultures. Ceroid/lipofuscin-loaded fibroblasts displayed diminished autophagocytotic capacity, as demonstrated by electron microscopy and by treatment of cell cultures with NH4Cl (which inhibits autophagocytotic degradation by increasing intralysosomal pH) for 1 week before ensuing starvation. The latter treatment increased survival of control cells (due to deposition of nondegraded autophagocytosed material before start of starvation), but not that of ceroid/lipofuscin-loaded cells. Moreover, when NH4Cl treatment was combined with starvation, both groups of cells showed approximately the same shortened survival times, testifying to the causal relationship between diminished autophagocytosis and decreased survival of starving ceroid/lipofuscin-loaded cells. We hypothesize that large amounts of undegradable ceroid/lipofuscin within the acidic vacuolar compartment may interfere with lysosomal function, resulting in poor renewal of long-lived proteins and worn-out/damaged organelles, decreased adaptability, and cell death.

Modulation of the host flora.

van Furth R, Guiot HF. Department of Infectious Diseases, University Hospital, Leiden, The Netherlands.

Eur J Clin Microbiol Infect Dis. 1989 Jan;8(1):1-7.

Modulation of the bacterial flora of patients with a high risk of acquiring an infection can be achieved in several ways. The approach used in the Leiden University Hospital is based on selective elimination of the aerobic bacteria in the oropharyngeal cavity and intestinal tract, leaving the anaerobic flora intact. This kind of selective modulation of the host flora has an advantage in that it does not affect the colonization resistance provided by bacterial antagonism, which prevents colonization by resistant but potentially pathogenic bacteria or fungi. The elimination of aerobic bacteria combined with nursing in protective isolation and consumption of food with few bacteria has led to a significant reduction of the incidence of major and fatal infections in patients during episodes of severe granulocytopenia. From these results it may be concluded that the objective of selective antibiotic modulation, namely, the prevention of infections, can be achieved with this approach.

Chronic low-dose glutamate is toxic to retinal ganglion cells. Toxicity blocked by memantine.

Vorwerk CK, Lipton SA, Zurakowski D, Hyman BT, Sabel BA, Dreyer EB. Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA 02114, USA.

Invest Ophthalmol Vis Sci. 1996 Jul;37(8):1618-24.

PURPOSE: It is well known that acute exposure to high concentrations of glutamate is toxic to central mammalian neurons. However, the effect of a chronic, minor elevation over endogenous glutamate levels has not been explored. The authors have suggested that such chronic exposure may play a role in glaucomatous neuronal loss. In the current study, they sought to explore whether a chronic, low-dose elevation in vitreal glutamate was toxic to retinal ganglion cells and whether this toxicity could be prevented with memantine, a glutamate antagonist.

METHODS: Rats were injected serially and intravitreally with glutamate to induce chronic elevations in glutamate concentration. A second group of rats was treated with intraperitoneal memantine and glutamate. Control groups received vehicle injection with or without concurrent memantine therapy. After 3 months, the animals were killed, and ganglion cell survival was evaluated.

RESULTS: Intravitreal injections raised the intravitreal glutamate levels from an endogenous range of 5 to 12 microM glutamate to 26 to 34 microM. This chronic glutamate elevation killed 42% of the retinal ganglion cells after 3 months. Memantine treatment alone had no effect on ganglion cell survival. However, when memantine was given concurrently with low-dose glutamate, memantine was partially protective against glutamate toxicity.

CONCLUSIONS: These data suggest that minor elevations in glutamate concentration can be toxic to ganglion cells if this elevation is maintained for 3

months. Furthermore, memantine is efficacious at protecting ganglion cells from chronic low-dose glutamate toxicity.

Calcium and vitamin D metabolism in Guamanian Chamorros with amyotrophic lateral sclerosis and parkinsonism-dementia.

Yanagihara R, Garruto RM, Gajdusek DC, Tomita A, Uchikawa T, Konagaya Y, Chen KM, Sobue I, Plato CC, Gibbs CJ Jr.

Ann Neurol 1984 Jan;15(1):42-8

We evaluated 16 Guamanian Chamorros with amyotrophic lateral sclerosis and 33 patients with parkinsonism-dementia for disturbances of calcium and vitamin D metabolism. The serum immunoreactive parathyroid hormone level was mildly elevated in 6 patients with amyotrophic lateral sclerosis and in 5 patients with parkinsonism-dementia. There were significant positive correlations between serum immunoreactive parathyroid levels and duration of illness in male patients with motor neuron disease, but not in female patients or in patients with parkinsonism-dementia. Intestinal absorption of calcium, as assessed by serum and urinary activity of calcium 47 following oral administration, was decreased in 2 patients with amyotrophic lateral sclerosis and in 4 patients with parkinsonism-dementia, all of whom had low levels of serum 1,25-dihydroxyvitamin D. Reductions in cortical bone mass were striking in patients with motor neuron disease. A significant negative correlation was found between the percentage of cortical area of the second metacarpal bone and muscle atrophy and weakness, and significant positive correlations were found between degree of immobility and ratio of urinary hydroxyproline to creatinine in patients with amyotrophic lateral sclerosis and parkinsonism-dementia. In general, abnormalities in calcium metabolism were subtle. Thus, if the demonstrated deposition of metals, particularly calcium and aluminum, in central nervous system tissues of Guamanians with these two conditions is a cause of the diseases and of the early appearance of neurofibrillary tangles in neurons, the accumulation has apparently occurred long before onset of symptoms, and detectable abnormalities of calcium and vitamin D metabolism may already have been corrected.

Detection of subclinical ascorbate deficiency in early Parkinson's disease.

Yapa SC. Bury Health Authority, Lancs.

Public Health. 1992 Sep;106(5):393-5.

From mid-October 1989 to mid-July 1990 all newly admitted residents to Bury Local Authority Residential Homes were comprehensively medically screened. In a series of 100 residents eight had early Parkinson's disease (six of them hitherto undiagnosed). Seven showed evidence of Vitamin C deficiency. Of the seven showing evidence of deficiency, four suffered from early Parkinson's disease. Of the 93 without evidence of Vitamin C deficiency only four had Parkinson's disease. This indicates a significantly higher prevalence of Parkinson's disease in the group with Vitamin C deficiency (P less than 0.001 using Fisher's exact).

Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting.

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Cell Mol Neurobiol. 2001 Dec;21(6):605-16.

To review the interaction between melatonin and the dopaminergic system in the hypothalamus and striatum and its potential clinical use in dopamine-related disorders in the central nervous system. Medline-based search on melatonin-dopamine interactions in mammals. Melatonin. the hormone produced by the pineal gland at night. influences circadian and seasonal rhythms, most notably the sleep-wake cycle and seasonal reproduction. The neurochemical basis of these activities is not understood yet. Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla-pons, and retina). Antidopaminergic activities of melatonin have been demonstrated in the striatum. Dopaminergic transmission has a pivotal role in circadian entrainment of the fetus, in coordination of body movement and reproduction. Recent findings indicate that melatonin may modulate dopaminergic pathways involved in movement disorders in humans. In Parkinson patients melatonin may, on the one hand, exacerbate symptoms (because of its putative interference with dopamine release) and, on the other, protect against neurodegeneration (by virtue of its antioxidant properties and its effects on mitochondrial activity). Melatonin appears to be effective in the treatment of tardive dyskinesia. a severe movement disorder associated with long-term blockade of the postsynaptic dopamine D2 receptor by antipsychotic drugs in schizophrenic patients. The interaction of melatonin with the dopaminergic system may play a significant role in the nonphotic and photic entrainment of the biological clock as well as in the fine-tuning of motor coordination in the striatum. These interactions and the antioxidant nature of melatonin may be beneficial in the treatment of dopamine-related disorders.

24. Thyroid Deficiency

Preventative and curative options include:

Vitamin A, vitamin B complex, vitamin B12, vitamin C, vitamin E, coenzyme Q10, magnesium, manganese, selenium, zinc, tyrosine, DHEA, soy protein

Use of soy protein supplement and resultant need for increased dose of levothyroxine.

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Endocr Pract 2001 May-Jun;7(3):193-4

Objective: To report a case of difficulty in achieving suppressive serum levels of thyroid hormone because of malabsorption of exogenous levothyroxine attributable to daily ingestion in close temporal relationship to the intake of a soy protein-containing food supplement. Methods: We present the relevant history and laboratory data of the current case and provide supportive documentation from the literature. Results: A 45-year-old woman who had hypothyroidism after a near-total thyroidectomy and radioactive iodine ablative therapy for papillary carcinoma of the thyroid required unusually high oral doses of levothyroxine to achieve suppressive serum levels of free thyroxine (T4) and thyrotropin (thyroid-stimulating hormone or TSH). She had routinely been taking a "soy cocktail" protein supplement immediately after her levothyroxine. Temporal separation of the intake of the soy protein cocktail from the administration of the levothyroxine resulted in attainment of suppressive serum levels of free T4 and TSH with use of lower doses of levothyroxine. Conclusion: Administration of levothyroxine concurrently with a soy protein dietary supplement results in decreased absorption of levothyroxine and the need for higher oral doses of levothyroxine to attain therapeutic serum thyroid hormone levels.

Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism.

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N Engl J Med. 1999 Feb 11;340(6):424-9.

BACKGROUND: Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown.

METHODS: We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 microg of the usual dose of thyroxine was replaced by 12.5 microg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period.

RESULTS: The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone-binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments.

CONCLUSIONS: In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

Homocysteine, hypothyroidism, and effect of thyroid hormone replacement.

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Thyroid. 1999 Dec;9(12):1163-6.

Elevation of total plasma concentration of homocysteine (t-Hcy) is an important and independent risk factor for cardiovascular disease. Hypothyroidism is possibly also associated with an increased risk for coronary artery disease, which may be related to atherogenic changes in lipid profile. Because hypothyroidism decreases hepatic levels of enzymes involved in the remethylation pathway of homocysteine, we prospectively evaluated fasting and postload t-Hcy in patients before and after recovery of euthyroidism. Fasting and postload t-Hcy levels were higher in 40 patients with peripheral hypothyroidism (14 with autoimmune thyroiditis and 26 treated for thyroid cancer) in comparison with those of 26

controls (13.0 +/- 7.5 vs. 8.5 +/- 2.6 micromol/L, < .01, respectively, and 49.9 +/- 37.3 vs. 29.6 +/- 8.4 micromol/L < .001, respectively). On univariate analysis, fasting Hcy was positively related to thyrotropin (TSH) and inversely related to folates. Multivariate analysis confirmed TSH as the strongest predictor of t-Hcy independent of age, folate, vitamin B12, and creatinine. Thyroid hormone replacement significantly decreased fasting but not postload t-Hcy. We conclude that t-Hcy is elevated in hypothyroidism. The association of hyperhomocysteinemia and lipid abnormalities occurring in hypothyroidism may represent a dynamic atherogenic state. Thyroid hormone failed to completely normalize t-Hcy. Potential benefit of treatment with folic acid in combination with thyroid hormone replacement has to be tested given that hypothyroid patients were found to have lower levels of folate.

Selenium decreases thyroglobulin concentrations but does not affect the increased thyroxine-to-triiodothyronine ratio in children with congenital hypothyroidism.

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J Clin Endocrinol Metab 2001 Mar;86(3):1160-1163

Compared with euthyroid controls, patients with congenital hypothyroidism (CH) who are receiving L-T(4) treatment show elevated serum TSH relative to serum T(4) concentrations and increased T(4)/T(3) ratio. These abnormalities could be the consequence of impaired activity of the selenoenzymes deiodinases on which patients with CH rely to convert the ingested L-T(4) into active T(3). Eighteen patients (0.5-15.4 yr), diagnosed with CH in infancy, received selenomethionine (SeM, 20-60 microg selenium/day) for 3 months. The study took place in Belgium, a country where selenium intake is borderline. Compared with the values observed in age- and sex-matched euthyroid controls, patients with CH had decreased selenium, thyroglobulin and T(3) concentrations and increased TSH, reverse T(3), and T(4) concentrations and T(4)/T(3) ratio at baseline. Selenium supplementation caused a 74% increase in plasma selenium values but did not affect the activity of the selenoenzyme glutathione peroxidase used as a marker of selenium status. SeM abolished the TSH difference observed between CH patients and euthyroid controls at baseline and caused a significant decrease in thyroglobulin values. Thyroid hormone concentrations were not affected by SeM. In conclusion, our data suggest that selenium is not a limiting factor for peripheral T(4)-to-T(3) conversion in CH patients. In contrast, we find indirect evidence that SeM improves thyroid hormones feedback at the hypothalamo-pituitary level and decreases stimulation of the residual thyroid tissue, possibly suggesting greater intracellular T(4)-to-T(3) conversion.

Effects of selenium deficiency on thyroid necrosis, fibrosis and proliferation: a possible role in myxoedematous cretinism.

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Eur J Endocrinol 1995 Jul;133(1):99-109

It has been suggested that selenium deficiency is a co-factor to iodine deficiency in the pathogenesis of myxoedematous cretinism. The mechanism proposed is that the generation of hydrogen peroxide is greatly increased in iodine-deficient thyroid glands, and that selenium is involved in the control of hydrogen peroxide and its derived free radicals. This study was carried out to investigate the effect of the possibly impaired cellular defence mechanism associated with selenium deficiency on thyroid necrosis and tissue repair. For this purpose, we studied thyroid tissue from selenium- (SE-) and/or iodine-deficient (I-) rats before and after an acute toxic iodine overload. In thyroids, necrotic cells were numerous. Acute iodine administration increased this effect. Necrosis was associated with transient infiltration of inflammatory cells. In I-SE+ thyroids the tissue resumed its normal appearance. In I-SE- thyroid glands, the iodide toxicity was stronger, with greater necrosis and inflammatory reaction. The inflammation resolved but was replaced by fibrotic tissue. Fifteen days after the toxic overload, the connective tissue volume was twice the control value. Before iodide overload, the proportion of dividing cells was equal in I-SE+ and I-SE- thyroids. Three days after the iodide overload, this proportion was increased in I-SE+ thyroids but reduced in the I-SE- thyroids. Overall, the I-SE- thyroids had four times fewer dividing cells than the I-SE+ thyroids. In summary, selenium deficiency coupled to iodine deficiency increased necrosis, induced fibrosis and impeded compensatory epithelial cell proliferation. These results are compatible with histological and functional description of thyroid tissue from myxoedematous cretins.

Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism.

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Clin Endocrinol (Oxf). 2001 Feb;54(2):197-204.

OBJECTIVE: Hyperhomocysteinaemia is a risk factor for premature atherosclerotic vascular disease and venous thrombosis. The aim of the present study was to assess plasma total homocysteine (tHCys) concentrations in hypo- as well as hyperthyroid patients before and after treatment, and to evaluate the role of potential determinants of plasma tHCys levels in these patients.

DESIGN: Prospective follow up study.

PATIENTS: Fifty hypothyroid and 46 hyperthyroid patients were studied in the untreated state and again after restoration of euthyroidism.

MEASUREMENTS: Fasting plasma levels of tHCys and its putative determinants (plasma levels of free thyroxine (fT4), folate, vitamin B(12), renal function, sex, age, smoking status and the C677T polymorphism in the

methylenetetrahydrofolate reductase (MTHFR) gene were measured before and after treatment.

RESULTS: Restoration of the euthyroid state decreased both tHCys (17.6 +/- 10.2-13.0 +/- 4.7 micromol/l; < 0.005) and creatinine (83.9 +/- 22.0-69.8 +/- 14.2 micromol/l; <0.005) in hypothyroid patients and increased both tHCys (10.7 +/- 2.5-13.4 +/- 3.3 micromol/l; < 0.005) and creatinine (49.0 +/- 15.4-66.5 +/- 15.0 micromol/l; < 0.005) in hyperthyroid patients (values as mean +/- SD). Folate levels were lower in the hypothyroid group compared to the hyperthyroid group (11.7 +/- 6.4 and 15.1 +/- 7.6 nmol/l; < 0.05). Pretreatment tHCys levels correlated with log fT(4) (r = - 0.47), folate (r = - 0.21), plasma creatinine (r = 0.45) and age (r = 0.35) but not with C677T genotype. Multivariate analysis indicated that pretreatment log(fT(4)) levels and age accounted for 28% the variability of pre-treatment tHCys (tHCys = 14.2-5.50 log(fT(4)) + 0.14 age). After treatment the logarithm of the change (Delta) in fT(4) (expressed as the post-treatment fT(4)/pre-treatment fT(4) ratio) accounted for 45% of the variability in change of tHCys (tHCys = - 0.07-4.94 log (fT(4))); there was no independent contribution of changes in creatinine which was, however, strongly related to changes in tHCys (r = 0.61).

CONCLUSIONS: Plasma tHCys concentrations increased in hypothyroidism and decreased in hyperthyroidism. Plasma fT(4) is an independent determinant of tHCys concentrations. Lower folate levels and a lower creatinine clearance in hypo-thyroidism, and a higher creatinine clearance in hyperthyroidism only partially explain the changes in tHCys.

Anti-thyroid isoflavones from soybean: isolation, characterization, and mechanisms of action.

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Biochem Pharmacol 1997 Nov 15;54(10):1087-96

The soybean has been implicated in diet-induced goiter by many studies. The extensive consumption of soy products in infant formulas and in vegetarian diets makes it essential to define the goitrogenic potential. In this report, it was observed that an acidic methanolic extract of soybeans contains compounds that inhibit thyroid peroxidase- (TPO) catalyzed reactions essential to thyroid hormone synthesis. Analysis of the soybean extract using HPLC, UV-VIS spectrophotometry, and LC-MS led to identification of the isoflavones genistein and daidzein as major components by direct comparison with authentic standard reference isoflavones. HPLC fractionation and enzymatic assay of the soybean extract showed that the components responsible for inhibition of TPO-catalyzed reactions coeluted with daidzein and genistein. In the presence of iodide ion, genistein and daidzein blocked TPO-catalyzed tyrosine iodination by acting as alternate substrates, yielding mono-, di-, and triiodoisoflavones. Genistein also inhibited thyroxine synthesis using iodinated casein or human goiter thyroglobulin as substrates for the coupling reaction. Incubation of either

isoflavone with TPO in the presence of H2O2 caused irreversible inactivation of the enzyme; however, the presence of iodide ion in the incubations completely abolished the inactivation. The IC50 values for inhibition of TPO-catalyzed reactions by genistein and daidzein were ca. 1-10 microM, concentrations that approach the total isoflavone levels (ca. 1 microM) previously measured in plasma from humans consuming soy products. Because inhibition of thyroid hormone synthesis can induce goiter and thyroid neoplasia in rodents, delineation of anti-thyroid mechanisms for soy isoflavones may be important for extrapolating goitrogenic hazards identified in chronic rodent bioassays to humans consuming soy products.

Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism.

Hussein WI, Green R, Jacobsen DW, Faiman C. The Cleveland Clinic Foundation, Ohio 44195, USA.

Ann Intern Med. 1999 Sep 7;131(5):348-51.

BACKGROUND: Hyperhomocysteinemia is an independent risk factor for coronary, peripheral, and cerebrovascular disease. Elevated plasma homocysteine levels were described in a preliminary report on primary hypothyroidism.

OBJECTIVE: To determine whether restoration of euthyroidism by L-thyroxine replacement therapy would reduce or normalize plasma homocysteine levels.

DESIGN: Prospective cohort study.

SETTING: Outpatient endocrinology department of a tertiary center.

PATIENTS: 14 patients (10 women and 4 men; 25 to 77 years of age): 4 with newly diagnosed chronic (Hashimoto) hypothyroidism and 10 who had been rendered acutely hypothyroid (thyroid-stimulating hormone level < 25 mU/L) by total thyroidectomy for thyroid carcinoma.

MEASUREMENTS: Total plasma homocysteine levels were measured at baseline and 3 to 9 months later, after euthyroidism had been attained by L-thyroxine replacement therapy.

RESULTS: Median baseline plasma homocysteine levels in both sexes (women, 11.65 micromol/L [range, 7.2 to 26.5 micromol/L]; men, 15.1 micromol/L [range, 14.1 to 16.3 micromol/L]) were higher (P = 0.002) than those in healthy female (n = 35) and male (n = 36) volunteers (women, 7.52 micromol/L [range, 4.3 to 14.0 micromol/L]; men, 8.72 micromol/L [range, 5.94 to 14.98 micromol/L]). Eight patients (57%) had baseline plasma homocysteine levels that exceeded the upper limit of sex-specific reference ranges. Upon attainment of euthyroidism, all patients had a diminution in plasma homocysteine levels. The median overall change of -5.5 micromol/L (range, -15.4 to -1.8 micromol/L) corresponds to a

difference of -44% (range, -58% to -13%) (< 0.001). Homocysteine levels returned to normal in 7 of the 8 patients with elevated pretreatment values.

CONCLUSIONS: Hypothyroidism may be a treatable cause of hyperhomocysteinemia, and elevated plasma homocysteine levels may be an independent risk factor for the accelerated atherosclerosis seen in primary hypothyroidism.

Homocysteine and restenosis after percutaneous coronary intervention.

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J Med Assoc Thai. 2001 Dec;84 Suppl 3:S636-44.

Numerous clinical studies in Western and Asian countries suggest that individuals with elevated blood levels of homocysteine have an increased risk of atherosclerosis, myocardial infarction, cerebral infarction, and deep vein thrombosis. Homocysteine is also known to induce both atherogenic and thrombogenic mediators in cultured vascular cells so that homocysteine may influence the damage of endothelial cells, promote smooth muscle cell growth, induce atherogenic mediators and thrombus formation after coronary angioplasty. The association between homocysteine and restenosis after percutaneous coronary intervention (PCI) has been discussed. In this study, the relationship between plasma homocysteine levels and restenosis after PCI to investigate whether plasma homocysteine levels may be a predictor of restenosis after PCI was examined. One hundred consecutive patients who underwent successful PCI were enrolled and plasma homocysteine level was measured in all patients prior to PCI. Plasma for homocysteine level was obtained in 99 of 100 patients who had angioplasty. The mean plasma homocysteine concentration in the enrolled patients was 13.61 +/- 6.04 micromol/L. The minimum and maximum of plasma homocysteine were 4.40 micromol/L and 50.00 micromol/L, respectively. In healthy subjects, the normal reference range of homocysteine level is 5-15 micromol/L However, recent data suggest that some patients may be at increased cardiovascular and cerebrovascular risk at levels as low as 12 micromol/L. For this reason, both cut off points of homocysteine level < or = 15 micromol/L or < or = 12 micromol/L to identify the high homocysteine level group were used. Of 99 patients, high homocysteine level (< or = 15 micromol/L) was established in 9 patients with restenosis versus 20 patients without restenosis. If the cut off point of homocysteine level < or = 12 micromol/L was used, high homocysteine level was established in 14 patients with restenosis versus 39 patients without restenosis. From both cut off points of homocysteine level, there was no correlation between plasma homocysteine level and the restenosis group. (< 0.05).

Plasma total homocysteine levels in hyperthyroid and hypothyroid patients.

Nedrebo BG, Ericsson UB, Nygard O, Refsum H, Ueland PM, Aakvaag A, Aanderud S, Lien EA. Department of Internal Medicine, University Hospital of Bergen, Norway.

Metabolism. 1998 Jan;47(1):89-93.

We found a higher plasma concentration of total homocysteine (tHcy), an independent risk factor for cardiovascular disease, in patients with hypothyroidism (mean, 16.3 micromol/L; 95% confidence interval [CI], 14.7 to 17.9 micromol/L) than in healthy controls (mean, 10.5 micromol/L; 95% CI, 10.1 to 10.9 micromol/L). The tHcy level of hyperthyroid patients did not differ significantly from that of the controls. Serum creatinine was higher in hypothyroid patients and lower in hyperthyroid patients than in controls, whereas serum folate was higher in hyperthyroid patients compared with the two other groups. In multivariate analysis, these differences did not explain the higher tHcy concentration in hypothyroidism. We confirmed the observation of elevated serum cholesterol in hypothyroidism, which together with the hyperhomocysteinemia may contribute to an accelerated atherogenesis in these patients.

Low selenium status in the elderly influences thyroid hormones.

Olivieri O, Girelli D, Azzini M, Stanzial AM, Russo C, Ferroni M, Corrocher R. Institute of Medical Pathology, University of Verona, Italy.

Clin Sci (Lond). 1995 Dec;89(6):637-42.

1. Iodothyronine 5'-deiodinase, which is mainly responsible for peripheral triiodothyronine (T3) production, has recently been demonstrated to be a selenium-containing enzyme. In the elderly, reduced peripheral conversion of thyroxine (T4) to T3 and overt hypothyroidism are frequently observed. 2. We measured serum selenium and erythrocyte glutathione peroxidase (as indices of selenium status), thyroid hormones and thyroid-stimulating hormone in 109 healthy euthyroid subjects (52 women, 57 men), carefully selected to exclude abnormally low thyroid hormone levels induced by acute or chronic diseases or calorie restriction. The subjects were subdivided into three age groups. To avoid conditions of under-nutrition or malnutrition, dietary records were obtained for a sample of 24 subjects, randomly selected and representative of the whole population for age and sex. 3. In order to properly assess the influence of selenium status on iodothyronine 5'-deiodinase type I activity, a double-blind placebo-controlled trial was also carried out on 36 elderly subjects, resident at a privately owned nursing home. 4. In the free-living population, a progressive reduction of the T3/T4 ratio (due to increased T4 levels) and of selenium and erythrocyte glutathione peroxidase activity was observed with advancing age. A highly significant linear correlation between T4, T3/T4 and selenium was observed in the population as a whole (for T4, $R = -0.312$, < 0.002; for T3/T4 ratio, $R = 0.32$, < 0.01) and in older subjects (for T4, $R = -0.40$, < 0.05; for T3/T4 ratio, $R = 0.54$, < 0.002). 5. The main result of the double-blind placebo-controlled trial was a significant improvement of selenium indices and a decrease

in the T4 level in selenium-treated subjects; serum selenium, erythrocyte glutathione peroxidase activity and thyroid hormones did not change in placebo-treated subjects. 6. We concluded that selenium status influences thyroid hormones in the elderly, mainly modulating T4 levels.

Selenium deficiency and hypothyroidism: a new etiology in the differential diagnosis of hypothyroidism in children.

Pizzulli A, Ranjbar A.

Biol Trace Elem Res 2000 Dec;77(3):199-208

Three female children presented with different clinical symptoms that could be related to impaired thyroid function. They underwent an accurate pediatric-endocrinologic diagnosis. Laboratory tests revealed no pathological findings, except latent hypothyroidism and selenium deficiency. Hypothyroidism was diagnosed by elevated basal TSH and by a pathological i.v.-TRH-stimulation test. After treating the children with sodium selenite orally for 4 wk, their metabolism had returned to normal and we saw a marked improvement of all clinical symptoms. For the first time, we have been able to describe hypothyroidism caused exclusively by selenium deficiency, the pathophysiology of which may be expressed as a malfunction of human 5'-deiodinases.

Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease.

Robinson K, Mayer EL, Miller DP, Green R, van Lente F, Gupta A, Kottke-Marchant K, Savon SR, Selhub J, Nissen SE, et al. Department of Cardiology, Cleveland Clinic Foundation, OH 44195, USA.

Circulation. 1995 Nov 15;92(10):2825-30.

BACKGROUND: High plasma homocysteine is associated with premature coronary artery disease in men, but the threshold concentration defining this risk and its importance in women and the elderly are unknown. Furthermore, although low B vitamin status increases homocysteine, the link between these vitamins and coronary disease is unclear.

METHODS AND RESULTS: We compared 304 patients with coronary disease with 231 control subjects. Risk factors and concentrations of plasma homocysteine, folate, vitamin B12, and pyridoxal 5'-phosphate were documented. A homocysteine concentration of 14 mumol/L conferred an odds ratio of coronary disease of 4.8 (< .001), and 5-mumol/L increments across the range of homocysteine conferred an odds ratio of 2.4 (< .001). Odds ratios of 3.5 in women and of 2.9 in those 65 years or older were seen (< .05). Homocysteine correlated negatively with all vitamins. Low pyridoxal 5'-phosphate (< 20 nmol/L) was seen in 10% of patients but in only 2% of control subjects (< .01), yielding an odds ratio of coronary disease adjusted for all risk factors, including high homocysteine, of 4.3 (< .05).

CONCLUSIONS: Within the range currently considered to be normal, the risk for coronary disease rises with increasing plasma homocysteine regardless of age and sex, with no threshold effect. In addition to a link with homocysteine, low pyridoxal-5'-phosphate confers an independent risk for coronary artery disease.

Serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and pregnenolone sulfate concentrations in patients with hyperthyroidism and hypothyroidism.

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Clin Chem. 2000 Apr;46(4):523-8.

BACKGROUND: Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) have been suggested to have protective effects against cardiovascular disease, cancer, immune-modulated diseases, and aging. We examined serum concentrations of DHEA, DHEA-S, and pregnenolone sulfate (PREG-S) in patients with thyroid dysfunction.

METHODS: Steroids extracted with methanol from serum sample were separated into an unconjugated fraction (DHEA) and a monosulfate fraction (DHEA-S and PREG-S), using a solid-phase extraction and an ion-exchange column. After separation of unconjugated steroids by HPLC, the DHEA concentration was measured by enzyme immunoassay. The monosulfate fraction was treated with arylsulfatase, and the freed steroids were separated by HPLC. The DHEA and PREG fractions were determined by gas chromatography-mass spectrometry, and the concentrations were converted into those of DHEA-S and PREG-S.

RESULTS: Serum concentrations of DHEA, DHEA-S, and PREG-S were all significantly lower in patients with hypothyroidism (n = 24) than in age- and sex-matched healthy controls (n = 43). By contrast, in patients with hyperthyroidism (n = 22), serum DHEA-S and PREG-S concentrations were significantly higher, but the serum DHEA concentration was within the reference interval. Serum concentrations of these three steroids correlated with serum concentrations of thyroid hormones in these patients. Serum albumin and sex hormone-binding globulin concentrations were not related to these changes in the concentration of steroids.

CONCLUSIONS: Serum concentrations of DHEA, DHEA-S, and PREG-S were decreased in hypothyroidism, whereas serum DHEA-S and PREG-S concentrations were increased but DHEA was normal in hyperthyroidism. Thyroid hormone may stimulate the synthesis of these steroids, and DHEA sulfotransferase might be increased in hyperthyroidism.