

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 (asparagine, 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 liquid chromatography, 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

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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

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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 amino 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 subgroups, 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

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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

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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.

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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

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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. Copyright 1998 Elsevier Science B.V. All rights reserved.

Plant sterols and sterolins: a review of their immune-modulating properties.

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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 β -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 $\text{Na}^+/\text{Ca}^{++}$ 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.

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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.

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.

Beta-carotene in HIV infection.

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J Acquir Immune Defic Syndr 1993 Mar;6(3):272-6

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.

Defer MC, Dugas B, Picard O, Damais C. U313 INSERM, Centre de Recherche des Cordeliers, Paris, France.

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 $< \text{or} = 1,300/\text{mm}^3$) 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-ammoniobutanoate) 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) intravenous L-carnitine (6 g/day) 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 CD8-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 für 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 cysteine and methionine concentrations. Cysteine cannot be replaced by a corresponding increase of the extracellular cysteine 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.

Ehrenpreis ED, Carlson SJ, Boorstein HL, Craig RM. Department of Gastroenterology, Cleveland Clinic Florida, Ft. Lauderdale 33309.

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.

Flora K, Hahn M, Rosen H, Benner K. Division of Gastroenterology, Oregon Health Sciences University, Portland 97201-3098, USA.

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 ($p < 0.001$) 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.

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 noncytotoxic 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, $P < 0.0001$ 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.

Hori K, Hatfield D, Maldarelli F, Lee BJ, Clouse KA. Division of Cytokine Biology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20852, USA.

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. Division 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.

Look MP, Rockstroh JK, Rao GS, Kreuzer KA, Spengler U, Sauerbruch T. Department of General Internal Medicine, University of Bonn, Germany.

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*.

Merali S, Vargas D, Franklin M, Clarkson AB. Department of Medical and Molecular Parasitology, New York University School of Medicine, New York, New York 10010, USA. merals01@popmail.med.nyu.edu

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 1.40×10^7 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 $0.5 \times 10^9/l$ 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.

Mutomba MC, Yuan H, Konyavko M, Adachi S, Yokoyama CB, Esser V, McGarry JD, Babior BM, Gottlieb RA. Department of Molecular and Experimental Medicine, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

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.

Remacha AF, Riera A, Cadafalch J, Gimferrer E. Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

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.

Rivas CI, Vera JC, Guaiquil VH, Velasquez FV, Borquez-Ojeda OA, Carcamo JG, Concha II, Golde DW. Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.

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.

Romero-Alvira D, Roche E. Servicio de Cardiología, Residencia General de la Seguridad Social, Hospital Miguel Servet, Zaragoza, Spain.

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 ($p < 10^{-4}$). Decreased rGSH levels were demonstrated in non-inflamed mucosa ($p < 0.01$) 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 ($p < 0.01$) and, along with gamma GT, in inflamed mucosa ($p < 10^{-4}$). 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.

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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.

Lactoferrin. Antiviral activity of lactoferrin.

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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.

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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 (≥ 23.5 $\mu\text{mol/l}$) 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 $\mu\text{mol/l}$). Similar trends were observed for each vitamin with mortality as the outcome, but neither vitamin was associated with CD4+ cell decline to ≤ 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.

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Free Radic Biol Med 2000 Mar 15;28(6):979-86

The release of superoxide ($\text{O}_2^{\cdot-}$) and hydrogen peroxide (H_2O_2), induced by tumor necrosis factor- α (TNF- α) or interleukin-1 β (IL-1 β), 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_2O_2 but not $\text{O}_2^{\cdot-}$ detectable in the extracellular medium. Inhibition of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by diphenyliodonium (DPI) or phenylarsine oxide (PAO),

largely prevents O₂(^{•-}) production, whereas H₂O₂ remains above the amount accounted for by disproportion of residual O₂(^{•-}). Thus, a fraction of H₂O₂ 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 H₂O₂ is inactive and catalase does not affect the activation induced by TNF-alpha, it is concluded that only intracellularly generated H₂O₂ 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.

Vendemiale G, Altomare E, Trizio T, Le Grazie C, Di Padova C, Salerno MT, Carrieri V, Albano O. Institute of Medical Clinic I, University of Bari, Italy.

Scand J Gastroenterol 1989 May;24(4):407-15

S-Adenosyl-L-methionine (S-AMe) 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 S-AMe (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. S-AMe 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. S-AMe 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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Department of Nutrition, School of Medicine, University of
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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 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.

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) intravenous 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 CD8-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 ($CD4 < 200/\mu\text{mol}$) 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-Methylxanthine 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, accounting 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/lymphocyte because of certain kinds of diseases as advanced AIDS are risk population of adverse dapsone reactions. Routinely determining human acetylator 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 glutathione 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 similar 2- 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 similar 2-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, similar 1.5-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 noncytotoxic 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 asymptomatic 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 oxide (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 found 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-ammoniumbutanoate) 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 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.

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 IIIIB 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 similar 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 <7 nmol/l and CD4+ cell counts $<0.5 \times 10^9/l$ 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

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 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 the mean 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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Mancini M; Littarru GP

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Medical School, Italy.

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 angiocardigraphy. 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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University of Texas Medical Branch, Galveston 77551, USA.

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.

Danysz A; Oledzka K; Bukowska-Kiliszek M
Department of Pharmacology, Pharmaceutical Research Institute Rydygiera,
Warszawa, Poland.
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.

Okamoto H; Kawaguchi H; Togashi H; Minami M; Saito H; Yasuda H
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.

Greenberg S; Frishman WH

Department of Medicine, Mt. Sinai Hospital and Medical Center, New York, New York

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 trials worldwide.

Coenzyme Q10: a new drug for myocardial ischemia?

Greenberg SM; Frishman WH

Department of Medicine, Mt. Sinai Hospital and Medical School, New York, New York

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. Administration 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, and clonidine also inhibited CoQ10-NADH-oxidase. Reserpine did not inhibit either CoQ10-enzyme, and methyldopa was a very weak 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]

Resch KL; Ernst E
Postgraduate Medical School, University of Exeter, UK.
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.

Silagy CA; Neil HA
Department of General Practice, Flinders University of South Australia, Adelaide.
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 than 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.

Estrada CA; Young MJ

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.

McMahon FG; Vargas R

Clinical Research Center, New Orleans, LA 70112.
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 ≥ 115 mm Hg). Sitting blood pressure fell 7/16 ($\pm 3/2$ 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., ≤ 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.

Auer W; Eiber A; Hertkorn E; Hoehfeld E; Koehrl U; Lorenz A; Mader F; Merx W; Otto G; Schmid-Otto B; et al
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 \pm 2.3% versus high NaCl -7.1 \pm 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 \pm 7% versus high NaCl 36 \pm 8%, $P < .05$) but not in the salt-resistant patients (low NaCl 51 \pm 6% versus high NaCl 58 \pm 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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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 anesthetized 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.

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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.

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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.

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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.

Adachi M; Nara Y; Mano M; Yamori Y
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 Ca^{2+} ($[Ca^{2+}]_i$) and Mg^{2+} ($[Mg^{2+}]_i$) 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). $[Ca^{2+}]_i$ was significantly lower and $[Mg^{2+}]_i$ was significantly higher in Mg group than in the control group. Further, $[Ca^{2+}]_i$ was positively and $[Mg^{2+}]_i$ was negatively correlated with SBP. These results suggest that dietary Mg supplementation modifies $[Ca^{2+}]_i$ and $[Mg^{2+}]_i$, 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 $\mu\text{mol/l}$) 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 \pm 4.4 mmHg) compared with WKY (n=10; 124 \pm 1.2 mmHg, $P < 0.0001$). DHA (1-100 $\mu\text{mol/l}$) relaxed aortic rings from WKY (-3.3 \pm 0.7 to -13 \pm 2.3%, $P < 0.001$) and from SHR (-6.5 \pm 1.8 to -22.9 \pm 4%, $P < 0.01$) in a concentration-dependent manner. EPA (1-100 $\mu\text{mol/l}$) evoked greater relaxation in SHR (-10.1 \pm 2.0 to -33 \pm 3.9%, $P < 0.01$) than in WKY (-2.9 \pm 1.1 to -18.3 \pm 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 $\mu\text{mol/l}$) induced greater responses in intact SHR rings (-10.1 \pm 2.0 to -14.5 \pm 3.1%) than in de-endothelialized SHR rings (0 to -2.1 \pm 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 + docosahexaenoic 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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20007, USA.

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 \pm SE): ANG II ($n = 7$), before = 102 \pm 4, during = 133 \pm 3 mmHg, AVP ($n = 8$), before = 110 \pm 7, during = 136 \pm 5 mmHg, PE ($n = 6$), before = 111 \pm 6, during = 141 \pm 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.

Laurant P; Demolombe B; Berthelot
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

Carrier 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 μM 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

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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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Department of Medicine, Oregon Health Sciences University, Portland.

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.

Altura BM; Altura BT

Department of Physiology, State University of New York, Health Science Center at Brooklyn 11203.

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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Department of Medicine, Howard University Medical Center, Washington, DC.

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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Department of Medicine, Oregon Health Sciences University, Portland 97201.
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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Medical Hospital and Research Centre, Moradabad, India.

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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Department of Medicine, University of the Witwatersrand Medical School, Johannesburg, South Africa.

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

Ascherio A; Rimm EB; Giovannucci EL; Colditz GA; Rosner B; Willett WC; Sacks F; Stampfer MJ

Department of Epidemiology, Harvard School of Public Health, Boston, MA. 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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Department of Pharmacology and Toxicology, University of Helsinki, Finland.
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).

Lowik MR; Hofman Z; Kok FJ; Wedel M; Hulshof KF; Odink J; Schaafsma G
Department of Human Nutrition, TNO-CIVO Toxicology and Nutrition Institute,
Zeist, The Netherlands.

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.

Hattori K; Sano H; Kubota Y; Kawahara J; Miki T; Suzuki H; Fukuzaki H
First Department of Internal Medicine, Kobe University School of Medicine,
Japan.

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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Medical Hospital and Research Centre, Uttar Pradesh, India.
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 intraluminal 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; *Pseuedanum 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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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 l⁻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 mitochondrial CoQ10-enzymes. These enzymes are indispensable for the bioenergetics 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.

Ghosh SK; Ekpo EB; Shah IU; Girling AJ; Jenkins C; Sinclair AJ
Wrexham Maelor Hospital, Clwyd, UK.
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.

Knekt P; Reunanen A; Jarvinen R; Seppanen R; Heliovaara M; Aromaa A
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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.

Pongpaew P; Tungtrongchitr R; Lertchavanakul A; Vudhivai N; Supawan V; Vudhikes S; Prayurahong B; Tawprasert S; Kwanbunjan K; Migasena P; et al
Department of Tropical Nutrition and Food Science, Faculty of Tropical Medicine, Mahidol University.
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

Holbrook TL; Barrett-Connor E
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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 multicollinearity in the Western diet.

Nitric oxide and the regulation of blood pressure in the hypertension-prone and hypertension-resistant Sabra rat.

Rees D; Ben-Ishay D; Moncada S
Wellcome Research Laboratories, Beckenham, Kent, UK.
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.

Reunanen A; Knekt P; Marniemi J; Maki J; Maatela J; Aromaa A
National Public Health Institute, Helsinki, Finland.
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 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 renovasculopathy 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-morpholinopyridone, 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 spectrophotometry.

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. 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 Ca^{2+} -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.)