

LE Magazine June 2001

ABSTRACTS

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Melatonin references

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Policosanol

Protective effect of policosanol on atherosclerotic lesions in rabbits with exogenous hypercholesterolemia.

Policosanol is a mixture of higher aliphatic alcohols purified from sugar cane wax, with cholesterol-lowering effects demonstrable in experimental models and in patients with type II hypercholesterolemia. The protective effects of policosanol on atherosclerotic lesions experimentally induced by lipofundin in rabbits and rats and spontaneously developed in stump-tail monkeys have been described. The present study was conducted to determine whether policosanol administered orally to rabbits with exogenous hypercholesterolemia also protects against the development of atherosclerotic lesions. Male New Zealand rabbits weighing 1.5 to 2 kg were randomly divided into three experimental groups which received 25 or 200 mg/kg policosanol (N = 7) orally for 60 days with acacia gum as vehicle or acacia gum alone (control group, N = 9). All animals received a cholesterol-rich diet (0.5%) during the entire period. Control animals developed marked hypercholesterolemia, macroscopic lesions and arterial intimal thickening. Intima thickness was significantly less (32.5 +/- 7 and 25.4 +/- 4 microm) in hypercholesterolemic rabbits treated with policosanol than in controls (57.6 +/- 9 microm). In most policosanol-treated animals, atherosclerotic lesions were not present, and in others, thickness of fatty streaks had less foam cell layers than in controls. We conclude that policosanol has a protective effect on the atherosclerotic lesions occurring in this experimental model.

Braz J Med Biol Res 2000 Jul;33(7):835-40

A double-blind, placebo-controlled study of the effects of policosanol in patients with intermittent claudication.

This study was undertaken to evaluate the efficacy and tolerability of policosanol, a new cholesterol-lowering drug with concomitant antiplatelet effects, in patients with intermittent claudication. After a baseline period of 6 weeks, 62 patients were randomized to receive, under double-blind conditions, either placebo (31 patients) or policosanol (31), 10 mg twice daily. Walking distances in a treadmill (constant speed 3.2 km/hr, slope 10 degrees) were assessed before and after 6 months of treatment. Both groups were similar at randomization. Policosanol increased significantly ($p < 0.01$) the initial claudication distance from 132.5 +/- 13.5 m (baseline) to 205.7 +/- 36.3 m (after therapy) and the absolute claudication distance ($p < 0.0001$) from 229.5 +/- 22.0 m to 365.4 +/- 46.9 m; meanwhile both variables remained unchanged in the placebo group ($p < 0.05$). The reduction of lower limb symptoms showed a greater benefit in the policosanol group. There was no significant change in either group in the ankle/arm pressure ratio. The treatment was well tolerated. There were 10 discontinuations (seven placebo, three policosanol) from the study. Six withdrawals occurred because of adverse events (AE); all were in placebo patients. There were five serious vascular AEs in the placebo group but none in the policosanol group ($p < 0.05$). Overall, 12/31 (38.7%) placebo patients and 3/31 (9.7%) policosanol patients experienced AEs after randomization, which showed a lesser incidence of AEs in the policosanol group ($p < 0.01$). The present study demonstrates a beneficial effect of policosanol in patients with intermittent claudication.

Angiology 1999 Feb;50(2):123-30

Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors.

INTRODUCTION: This study was undertaken to evaluate the efficacy, safety, and tolerability of policosanol, a new cholesterol-lowering drug, in patients with type II hypercholesterolemia and additional coronary risk factors. **PATIENTS AND METHODS:** After 5 weeks of a standard step-1 lipid-lowering diet, 437 patients were randomized to receive, under double-blind conditions, 5 mg policosanol or placebo once a day with the evening meal for 12 weeks and 10 mg policosanol or placebo for the next 12 weeks. **RESULTS:** Both groups were similar at randomization. Policosanol (5 and 10 mg/day) significantly reduced ($P < .001$) serum low-density lipoprotein cholesterol (18.2% and 25.6%, respectively) and cholesterol (13.0% and 17.4%), and it significantly raised ($P < .01$) high-density lipoprotein cholesterol (15.5% and 28.4%). Triglycerides remained unchanged after the first 12 weeks and

lowered significantly (5.2%; $P < .01$) at study completion. Policosanol was safe and well tolerated, and no drug-related disturbances were observed. Two male patients who received placebo died during the study--one because of a myocardial infarction and the other because of a cardiac arrest that occurred during a surgical intervention. There were 11 serious adverse events (5.1%) in 10 patients who received placebo (4.6%), 7 of which were vascular, compared with no serious adverse events reported in patients receiving policosanol ($P < .01$). CONCLUSIONS: Subjects in the group treated with policosanol did not have serious adverse events during the 24-week study. This study shows that policosanol is effective, safe, and well tolerated in patients with hypercholesterolemia and concomitant coronary risk factors.

Clin Pharmacol Ther 1999 Apr;65(4):439-47

Oral administration of policosanol inhibits in vitro copper ion-induced rat lipoprotein peroxidation.

Policosanol, a new cholesterol-lowering agent, is a mixture of higher aliphatic primary alcohols isolated from sugar cane (*Saccharum officinarum* L.) wax, which prevents the onset of spontaneously and experimentally induced atherosclerotic lesions in experimental models. Because the oxidation of low-density lipoprotein (LDL) may play a role in the pathogenesis of atherosclerosis, we investigate the effect of policosanol on copper oxidative susceptibility of rat lipoprotein fractions (VLDL + LDL). Rats fed normal diet were treated with policosanol (250-500 mg/kg/day) for up to 4 weeks. EDTA-free lipoprotein particles were oxidized in a cell-free system by the addition of copper ions, and conjugated dienes generation was monitored by changes of optical density at 234 nm. Thiobarbituric acid-reactive substances (TBARS) content and lysine-amino group reactivity were investigated. After administration, there was no change in cholesterol, triglycerides, and phospholipid content of lipoprotein fractions; however, policosanol significantly prolongs the lag time and reduces the propagation rate of diene generation. Also, policosanol reduces TBARS content and increases lysine reactivity in lipoprotein fractions treated with Cu^{2+} . In conclusion, policosanol, in addition to its cholesterol-lowering effect, has other properties that enables it to reduce the potential of lipoprotein to undergo lipid peroxidation. Such effect can be considered of promissory value in the management of atherosclerosis.

Physiol Behav 1999 Aug 1;67(1):1-7

Comparative effects of policosanol and two HMG-CoA reductase inhibitors on type II hypercholesterolemia.

BACKGROUND: Policosanol is a new cholesterol lowering agent derived from sugar cane. AIM: To compare the cholesterol lowering efficacy of policosanol with HMG CoA inhibitors. PATIENTS AND METHODS: Patients with a LDL cholesterol over 160 mg/dl were studied. If, after 6 weeks of diet, cholesterol persisted elevated, they were doubly blind randomized to receive policosanol 10 mg/day (55 patients), lovastatin 20 mg/day (26 patients) or simvastatin 10 mg/day (25 patients). Serum cholesterol was measured again after eight weeks of therapy. RESULTS: Initial demographic and laboratory data were similar among treatment groups. A 24% LDL cholesterol reduction was obtained with policosanol, compared with a 22% reduction with lovastatin and a 15% reduction with simvastatin. HDL cholesterol significantly increased in patients on policosanol and did not change in the other treatment groups. Adverse effects of policosanol were mild and unspecific. No changes in hepatic enzymes were observed. CONCLUSIONS: Policosanol is a safe and effective cholesterol reducing agent.

Rev Med Chil 1999 Mar;127(3):286-94

Long-term therapy with policosanol improves treadmill exercise-ECG testing performance of coronary heart disease patients.

This study examined the effects of long-term lipid-lowering therapy with policosanol on the clinical evolution, and exercise-ECG testing responses of 45 coronary heart disease (CHD) patients with myocardial ischemia, documented by exercise 201Tl-myocardial perfusion scintigraphy, in an overall randomized, double-blind, placebo-controlled trial, made for different test endpoints. Fifteen patients were treated with 5 mg of policosanol twice daily; another 15 patients were administered the same drug dose plus 125 mg aspirin; and the other 15 patients received placebo plus equal aspirin dose. They were followed for 20 months, previous baseline observations, with treadmill exercise-ECG, besides serum lipid test. Beneficial changes on proportions among the 2 policosanol groups and the placebo group, showed an increment on functional capacity class, a decrement on rest and exercise angina, and a significant decrease in cardiac events, and in ischemic ST segment response, especially in the policosanol plus aspirin group ($p = 0.05$, $\chi^2(2df) = 5.8$; $p = 0.04$, $p = 0.02$; Fisher). After treatment, sets of mean changes revealed an increase on maximum oxygen uptake, and a decline on double product simultaneously in both policosanol groups ($p < \text{or} = 0.02$, $p < \text{or} = 0.002$; Pillais, Hotellings' T2), while the placebo group was impaired. Aerobic functional capacity percent showed an increment in policosanol groups ($p < \text{or} = 0.05$, paired T). Lipid levels improved as other endpoints already reported. A supposed ergogenic effect of octacosanol, policosanol's main active compound, was not detected with this design. These results show that policosanol-treated CHD patients improved clinical evolution, and exercise-ECG responses, owing to the amelioration of myocardial ischemia, even more when administered with aspirin.

Int J Clin Pharmacol Ther 1998 Sep;36(9):469-73

Effect of policosanol on arterial blood pressure in rats. Study of the pharmacological interaction with nifedipine and propranolol.

BACKGROUND: Policosanol is a natural mixture of higher aliphatic primary alcohols isolated from sugar cane wax (*Saccharum officinarum*, L) with cholesterol-lowering effects demonstrated in experimental models and in patients with type II hyperlipoproteinemia. The purpose of this study is to determine the effect of policosanol on arterial blood pressure and its interaction with propranolol and nifedipine. **METHODS:** Single doses of policosanol (25, 50 and 200 mg/kg) orally administered to spontaneously hypertensive rats (SHR) did not significantly change arterial pressure. **RESULTS:** The study on pharmacological interactions between policosanol (200 mg/kg) and both antihypertensive agents revealed that pretreatment with high doses of policosanol significantly increased propranolol-induced hypotensive effects, while the effects of nifedipine remained unchanged. **CONCLUSIONS:** Our results show that policosanol does not antagonize the hypotensive effect of beta-blockers but it can increase the hypotensive effect of beta-blockers without modifying cardiac frequency.

Arch Med Res 1998 Spring;29(1):21-4

A 12-month study of policosanol oral toxicity in Sprague Dawley rats.

Policosanol is a natural mixture of higher aliphatic primary alcohols. Oral toxicity of policosanol was evaluated in a 12-month study in which doses from 0.5 to 500 mg/kg were given orally to Sprague Dawley (SD) rats (20/sex/group) daily. There was no treatment-related toxicity. Thus, effects on body weight gain, food consumption, clinical observations, blood biochemistry, hematology, organ weight ratios and histopathological findings were similar in control and treated groups. This study supports the wide safety margin of policosanol when administered chronically.

Toxicol Lett 1994 Jan;70(1):77-87

Effect of policosanol on lipofundin-induced atherosclerotic lesions in rats.

Policosanol is a mixture of higher aliphatic alcohols isolated from sugar cane wax, showing cholesterol-lowering effects and preventing the development of lipofundin-induced lesions in New Zealand rabbits. This study was conducted to determine whether policosanol orally administered to rats also protects against the development of lipofundin-induced atherosclerotic lesions. Fifty four male Wistar rats were randomly distributed amongst a negative control group, a positive control group intravenously injected with lipofundin for eight days, and four experimental groups also injected with lipofundin, but orally receiving policosanol at 0.5, 2.5, 5 and 25 mg kg⁻¹, respectively. Policosanol treatment was orally administered once-a-day for eight days, while control groups similarly received equivalent amounts of vehicle. A significant reduction of the atherosclerotic lesions in the treated animals was observed. It is concluded that policosanol has a protective effect on lipofundin-induced aortic lesions in Wistar rats.

J Pharm Pharmacol 1995 Apr;47(4):289-91

Effects of policosanol chronically administered in male monkeys (*Macaca arctoides*).

Policosanol, administered orally, has shown a cholesterol-lowering effect in different experimental models. Because lipid-lowering therapy is administered chronically, it is necessary to know the effects of these drugs after long-term administration. 18 adult male *Macaca arctoides* monkeys were used to study the cholesterol-lowering effects and possible toxicity produced by oral administration of policosanol (0.25, 2.5 and 25 mg/kg) for 54 wk. After 8 wk, a significant reduction of serum total cholesterol and low-density lipoprotein cholesterol was observed in policosanol-treated animals when compared with the controls; this effect persisted throughout the study. The animals' behavioural repertoire, physical condition, haematology and blood biochemistry, as well as spermogram analysis and electrocardiography, were monitored during the study; ophthalmological and pathological anatomy examinations were performed at the end of the administration period. No drug-related toxicity was detected by any examination. The results gave further evidence of the marked and persistent cholesterol-lowering effects of policosanol that had been observed in different experimental models. There was a significant reduction of spontaneous aortic atherosclerotic lesions in treated animals compared with controls. Policosanol (0.25-25 mg/kg) administered orally for 54 wk brought about a persistent reduction in blood cholesterol levels and was very safe and well tolerated during long-term administration.

Food Chem Toxicol 1994 Jun;32(6):565-75

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Vitamin E

Effects of vitamin E on lipid peroxidation in healthy persons.

CONTEXT: Oxidative stress may play a role in the development or exacerbation of many common diseases. However, results of prospective controlled trials of the effects of antioxidants such as vitamin E are contradictory. **OBJECTIVE:** To assess the effects of supplemental vitamin E on lipid peroxidation in vivo in healthy adults. **DESIGN:** Randomized, double-blind, placebo-controlled trial conducted March 1999 to June 2000. **SETTING:** A general clinical research center in a tertiary referral academic medical center. **PARTICIPANTS:** Thirty healthy men and women aged 18 to 60 years. **INTERVENTIONS:** Participants were randomly assigned to receive placebo or alpha-tocopherol dosages of 200, 400, 800, 1200, or 2000 IU/d for 8 weeks (n = 5 in each group), followed by an 8-week washout period. **MAIN OUTCOME MEASURES:** Three indices of lipid peroxidation, urinary 4-hydroxynonenal (4-HNE) and 2 isoprostanes, iPF(2alpha)-III and iPF(2alpha)-VI, measured by gas chromatography/mass spectrometry and compared among the 6 groups at baseline, 2, 4, 6, and 8 weeks, and 1, 3, and 8 weeks after discontinuation. **RESULTS:** Circulating vitamin E levels increased in a dose-dependent manner during the study. No significant effect of vitamin E on levels of urinary 4-HNE or either isoprostane was observed. Mean (SEM) baseline vs week 8 levels of iPF(2alpha)-III were 154 (20.1) vs 168 (22.3) pg/mg of creatinine for subjects taking placebo; 165 (19.6) vs 234 (30.1) pg/mg for those taking 200 IU/d of vitamin E; and 195 (26.7) vs 213 (40.6) pg/mg for subjects taking 2000 IU/d. Corresponding iPF(2alpha)-VI levels were 1.43 (0.6) vs 1.62 (0.4) ng/mg of creatinine for subjects taking placebo; 1.64 (0.3) vs 1.24 (0.8) ng/mg for those taking 200 IU/d of vitamin E; and 1.83 (0.3) vs 1.94 (0.9) ng/mg for those taking 2000 IU/d. Baseline vs week 8 levels of 4-HNE were 0.5 (0.04) vs 0.4 (0.05) ng/mg of creatinine for subjects taking placebo; 0.4 (0.06) vs 0.5 (0.02) ng/mg with 200 IU/d of vitamin E; and 0.2 (0.02) vs 0.2 (0.1) ng/mg with 2000 IU/d. **CONCLUSIONS:** Our results question the rationale for vitamin E supplementation in healthy individuals. Specific quantitative indices of oxidative stress in vivo should be considered as entry criteria and for dose selection in clinical trials of antioxidant drugs and vitamins in human disease.

JAMA 2001 Mar 7;285(9):1178-82

Vitamin E regulation of mitochondrial superoxide generation.

The mitochondrion is the greatest source, as well as the target, of reactive oxygen species (ROS). Increasing evidence indicates that vitamin E can act as a biological modifier independently of its antioxidant activity. Experimental evidence available shows that vitamin E is capable of dose-dependently regulating mitochondrial generation of superoxide and hydrogen peroxide. Vitamin E may modulate mitochondrial production and levels of superoxide by preventing electron leakage, by mediating the superoxide generation systems directly and/or by scavenging superoxide generated. By downregulating mitochondrial generation of superoxide and related ROS, vitamin E not only attenuates oxidative damage but also modulates the expression and activation of signal transduction pathways and other redox-sensitive biological modifiers.

Biol Signals Recept 2001 Jan-Feb;10(1-2):112-24

Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin.

PURPOSE: The anticancer activity of omega-3 polyunsaturated fatty acids (omega-3 PUFA) has been shown in a large number of studies. This study was undertaken to analyze the combined effect of omega-3 PUFA and antioxidative vitamins on the level of spontaneous metastatic dissemination. The supportive effect of this dietary combination on chemotherapy with cisplatin (CP) was determined in parallel. **METHODS:** C57BL/6J mice bearing the Lewis lung carcinoma 3LL were fed ad libitum one of three isocaloric diets containing 5% soybean oil supplemented with 40 mg/kg alpha-tocopherol acetate (SO diet), or 4% fish oil plus 1% corn oil, and basal amounts of vitamin E (FO diet) or FO diet supplemented with vitamins E and C (FO+E+C diet). These diets were tested in combination with the conventional cytotoxic agent CP in a series of regimens. Tumor growth, feed consumption, body weight, lung metastasis and lung histology were followed. **RESULTS:** Both the FO dietary groups showed significantly lower tumor development than the SO group in all examined parameters, indicating that omega-3 PUFA have anticancer activity. However, the FO diet, in comparison with the FO+E+C diet induced a significantly slower rate of tumor growth, and lower metastatic load, as reflected in lung weight. The decrease in the anticancer activity of FO by the addition of vitamins E and C suggests that in situ oxidation of omega-3 PUFA underlies their anticancer action. It is thus proposed that oxidized omega-3 PUFA accumulates in the membranes and the cytosol of tumor cells, reducing their vitality and eventually leading to their death. No signs of anorexia or cachexia were observed in either FO group, in contrast to the SO group. CP treatment with the SO diet had no apparent therapeutic effect, while with the FO diets it reduced the metastatic load. The best regimen of this combined

treatment was FO diet followed by CP treatment with FO diet supplemented with vitamins E and C after resection of the primary growth. This regimen could be translated to a combined therapy for human cancer. CONCLUSIONS: Diets enriched with omega-3 PUFA may have beneficial anticancer effects in particular when containing only basal amounts of antioxidants such as vitamin E or C. Furthermore, the addition of drugs which promote oxidation of omega-3 PUFA, such as ferrous salts (e.g. as prescribed for the treatment of anemia), may further increase these effects. However, the supportive effect of omega-3 PUFA in chemotherapy (e.g. with CP) increases when vitamins E and C are also included.

Cancer Chemother Pharmacol 2001;47(1):34-40

Vitamin E analog modulates UVB-induced signaling pathway activation and enhances cell survival.

We have recently shown that exposure of human keratinocytes to physiologic doses of ultraviolet B (UVB) activates epidermal growth factor receptor (EGFR)/extracellular-regulated kinases 1 and 2 (ERK1/2) and p38 signaling pathways via reactive oxygen species, an effect that can be modulated by antioxidants. Trolox, a water-soluble vitamin E analog, is among the antioxidants that are currently being investigated for their preventive and protective potential against harmful effects of UV radiation to the skin. We found that Trolox inhibits both basal and UVB-induced intracellular H₂O₂ generation in primary keratinocytes in a concentration-dependent manner. Trolox did not significantly affect UVB-induced phosphorylation of EGFR. Stronger inhibition was observed for ERK1/2 activation at lower, and for p38 activation at higher, concentrations of Trolox added to cells before exposure to UVB. Similarly different effects were found with regard to length of pretreatment with Trolox before UVB exposure-increasing inhibition for ERK1/2 activation at shorter, and for p38 activation at longer, pretreatment intervals. UVB-induced c-jun-N-terminal kinase activation was potently suppressed by Trolox. Also, increasing the pretreatment time of Trolox decreased the rate of cell death following UVB. In conclusion, UVB-induced signaling pathway activation is differentially modulated by Trolox. Further investigation into the time-dependent biologic activation of Trolox and its metabolic products, and modulation of signal transduction with cell outcome should facilitate development of rational strategies for pharmacologic applications.

Free Radic Biol Med 2001 Feb 15;30(4):425-32

Acute effects of oats and vitamin E on endothelial responses to ingested fat.

OBJECTIVE: To assess the effects of oats and vitamin E on endothelial function following a high-fat meal in healthy adults as measured by brachial artery reactivity studies (BARS). METHODS: A total of 25 men and 25 women (N=50) were recruited from a community population to participate in this randomized, crossover study. All subjects were free of known vascular disease, and female subjects were postmenopausal. Subjects underwent BARS before and after a high-fat meal (50 gm fat) on three occasions 1 week apart, one each with vitamin E 800 IU, oatmeal containing 3 gm beta-glucan, or a comparable bowl of wheat cereal serving as a placebo, in random sequence. The ultrasonographer was blinded to treatment status. RESULTS: Endothelial function, as measured by brachial artery peak flow during one minute of post-occlusive hyperemia, declined significantly from baseline when the high-fat meal was consumed with the wheat cereal (-13.4%; p=0.02). There was no difference in brachial artery flow change before and after a high-fat meal with oats (+0.37%; p=0.77) or a high-fat meal with vitamin E (+1.87%; p=0.42). No significant differences in flow-mediated vasodilation before and after the high-fat meal were detected among the three supplements. CONCLUSIONS: Endothelial dysfunction induced by acute fat ingestion in healthy adults is apparently prevented by concomitant ingestion of oats or vitamin E, but not wheat. Nutrient distribution and meal composition may have important implications for cardiovascular health.

Am J Prev Med 2001 Feb;20(2):124-9

Does vitamin E decrease heart attack risk?

The hypothesis that oxidative stress has a role in atherosclerosis rests on a large body of experimental work carried out in animal models of heart disease. The situation is more complex in humans, in that the results from vitamin E supplementation trials have been conflicting. Nonetheless, there is emerging information that alpha-tocopherol may play a critical role in maintaining the function of key cellular components in the atherosclerotic process through its ability to inhibit the activity of protein kinase C, a key player in many signal transduction pathways. alpha-Tocopherol modulates pathways of platelet aggregation, endothelial cell nitric oxide production, monocyte/macrophage superoxide production and smooth muscle cell proliferation. Regulation of adhesion molecule expression and inflammatory cell cytokine production by alpha-tocopherol has also been reported. More studies are required to relate alpha-tocopherol intakes to optimal tissue responses in humans.

J Nutr 2001 Feb;131(2):395S-7S

Vitamin E inhibition of platelet aggregation is independent of antioxidant activity.

Vitamin E is the principal lipid-soluble antioxidant in human plasma, and some studies indicate that it may provide cardiovascular protection. To investigate putative mechanisms for vitamin E in this regard, the effect of vitamin E on vascular function and platelet aggregation was examined. In animal models of endothelial dysfunction, vitamin E improved the activity of endothelium-derived

nitric oxide, and this effect was not dependent upon the antioxidant protection of LDL. In fact, vitamin E improved endothelial function in part due to the inhibition of protein kinase C (PKC) stimulation. This activity of vitamin E was examined in platelets, and vitamin E inhibited platelet aggregation in part through a mechanism that involves PKC. Moreover, the platelet inhibitory activity of vitamin E was independent of its antioxidant action because platelet inhibition was still observed with isoforms of vitamin E that were devoid of antioxidant activity.

J Nutr 2001 Feb;131(2):374S-377S

Effect of dietary vitamin E supplementation on vascular reactivity of thoracic aorta in streptozotocin-diabetic rats.

The present study evaluated the effect of dietary vitamin E supplementation (1,000 mg/kg chow) on the alterations in vascular reactivity of streptozotocin-diabetic aorta of Wistar rats. After 12 weeks of treatment, thoracic aortic rings of rats were mounted in organ baths and contractile responses to phenylephrine and 5-hydroxytryptamine and relaxant responses to acetylcholine, calcium ionophore and sodium nitroprusside were assessed. Plasma vitamin E concentration as measured by HPLC was markedly decreased in diabetic rats and increased with dietary vitamin E supplementation. Induction of diabetes significantly impaired endothelium-dependent relaxations to acetylcholine and calcium ionophore in aortic rings, but did not change endothelium-independent relaxation to sodium nitroprusside. Vitamin E significantly improved the impaired endothelium-dependent relaxations, further it decreased the enhanced contractile response to phenylephrine and 5-hydroxytryptamine in diabetic rings. The mechanical denudation of endothelium or the chemical inhibition of endothelium-dependent relaxation with N(omega)-nitro-L-arginine methyl ester (100 micromol/l) significantly increased phenylephrine contractility in control rings and the rings of diabetic rats treated with vitamin E; such a difference was not observed in diabetic rats fed with normal diet. Liver and lung malondialdehyde concentrations, as an index of lipid peroxidation, were increased in diabetic rats and significantly decreased with vitamin E supplementation. It is concluded that dietary supplementation of vitamin E improved endothelial dysfunction in insulin-dependent model of uncontrolled diabetes, probably decreasing membranous lipid peroxidation.

Pharmacology 2001 Jan;62(1):56-64

Cypermethrin-induced oxidative stress in rat brain and liver is prevented by vitamin E or allopurinol.

Considering that the involvement of reactive oxygen species (ROS) has been implicated in the toxicity of various pesticides, this study was designed to investigate the possibility of oxidative stress induction by cypermethrin, a Type II pyrethroid. Either single (170 mg/kg) or repeated (75 mg/kg per day for 5 days) oral administration of cypermethrin was found to produce significant oxidative stress in cerebral and hepatic tissues of rats, as was evident by the elevation of the level of thiobarbituric acid reactive substances (TBARS) in both tissues, either 4 or 24 h after treatment. Much higher changes were observed in liver, increasing from a level of 60% at 4 h up to nearly 4 times the control at 24 h for single dose. Reduced levels (up to 20%) of total glutathione (total GSH), and elevation of conjugated dienes (approximately 60% in liver by single dose at 4 h) also indicated the presence of an oxidative insult. Glutathione-S-transferase (GST) activity, however, did not differ from control values for any dose or at any time point in cerebral and hepatic tissues. Pretreatment of rats with allopurinol (100 mg/kg, ip) or vitamin E (100 mg/kg per day, ig, for 3 days and a dose of 40 mg/kg on the 4th day) provided significant protection against the elevation of TBARS levels in cerebral and hepatic tissues, induced by single high dose of oral cypermethrin administration within 4 h. Thus, the results suggest that cypermethrin exposure of rats results in free radical-mediated tissue damage, as indicated by elevated cerebral and hepatic lipid peroxidation, which was prevented by allopurinol and vitamin E.

Toxicol Lett 2001 Jan 3;118(3):139-46

Endogenous ascorbate regenerates vitamin E in the retina directly and in combination with exogenous dihydrolipoic acid.

Vitamin E (alpha-tocopherol) is the major lipid-soluble antioxidant of retinal membranes whose deficiency causes retinal degeneration. Its antioxidant function is realized via scavenging peroxy radicals as a result of which phenoxyl radicals of alpha-tocopherol are formed. Our hypothesis is that alpha-tocopherol phenoxyl radicals can be reduced by endogenous reductants in the retina, providing for alpha-tocopherol recycling. The results of this study demonstrate for the first time that: (i) endogenous ascorbate (vitamin C) in retinal homogenates and in rod outer segments is able to protect endogenous alpha-tocopherol against oxidation induced by UV-irradiation by reducing the phenoxyl radical of alpha-tocopherol, (ii) in the absence of ascorbate, neither endogenous nor exogenously added glutathione (GSH) is efficient in protecting alpha-tocopherol against oxidation; (iii) GSH does not substantially enhance the protective effect of ascorbate against alpha-tocopherol oxidation; (iv) exogenous dihydrolipoic acid (DHLA), although inefficient in direct reduction of the alpha-tocopherol phenoxyl radical, is able to enhance the protective effect of ascorbate by regenerating it from dehydroascorbate. Thus, regeneration of alpha-tocopherol from its phenoxyl radical can enhance its antioxidant effectiveness in the retina. The recycling of alpha-tocopherol opens new avenues for pharmacological approaches to enhance antioxidants of the retina.

Curr Eye Res 1995 Mar;14(3):181-9

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ABSTRACTS

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Homocysteine

Vegan diet-based lifestyle program rapidly lowers homocysteine levels.

BACKGROUND: Plasma homocysteine levels have been directly associated with cardiac disease risk. Current research raises concerns as to whether comprehensive lifestyle approaches including a plant-based diet may interact with other known modulators of homocysteine levels. **METHODS:** We report our observations of homocysteine levels in 40 self-selected subjects who participated in a vegan diet-based lifestyle program. Each subject attended a residential lifestyle change program at the Lifestyle Center of America in Sulphur, Oklahoma and had fasting plasma total homocysteine measured on enrollment and then after one week of lifestyle intervention. The intervention included a vegan diet, moderate physical exercise, stress management and spirituality enhancement sessions, group support, and exclusion of tobacco, alcohol and caffeine. Vitamin B supplements known to reduce blood homocysteine levels were not provided. **RESULTS:** Subjects' mean homocysteine levels fell 13%: from 8.66 micromol/L (SD 2.7 micromol/L) to 7.53 micromol/L (SD 2.12 micromol/L; $P < 0.0001$). Subgroup analysis showed that homocysteine decreased across a range of demographic and diagnostic categories. **Conclusions.** Our results suggest that broad-based lifestyle interventions favorably impact homocysteine levels. Furthermore, analysis of Lifestyle Center of America program components suggests that other factors in addition to B vitamin intake may be involved in the observed homocysteine lowering.

Prev Med 2000 Mar;30(3):225-33

Inhibition of endothelial cell thromboresistance by homocysteine.

Homocysteine (HC) is a highly reactive thiol intermediate in amino acid metabolism, which can modify the function of endothelial cells in a myriad of ways. In vitro, homocysteine can inhibit the thromboresistance properties of the endothelial cell by induction of procoagulant factors, inactivation of natural anticoagulant systems, and suppression of vasodilatory and platelet-modulating factors. HC also inhibits the fibrinolytic system by impairing the ability of the endothelial cell to bind tissue plasminogen activator (t-PA), by interacting directly with the t-PA binding "tail" domain of its endothelial cell receptor, annexin II. Moreover, HC influences endothelial cell gene expression as exemplified by induction of the elongation factor-1 family of polypeptides, which promote polypeptide chain elongation during mRNA translation. Induction of EF-1 subunits alpha, beta, gamma and delta by homocysteine is associated with increased turnover of at least one free thiol-containing protein, suggesting that up-regulation of these subunits may represent a mechanism for replacement of damaged or modified proteins. A more complete understanding of the diverse effects of homocysteine on endothelial cell function may provide important clues to the precise role homocysteine may play in the initiation and progression of vascular disease.

J Nutr 2000 Feb;130(2S Suppl):373S-376S

Serum homocysteine concentration as an indicator of survival in patients with acute coronary syndromes.

BACKGROUND: Circulating homocysteine levels are predictive of survival in patients with stable coronary artery disease. The prognostic value of serum homocysteine levels, obtained in the acute phase in patients with myocardial infarction or unstable angina, is unknown. **OBJECTIVES:** To test the hypothesis that circulating homocysteine levels, obtained during the first 24 hours following hospital admission in patients with acute coronary syndromes, are predictive of long-term mortality. **METHODS:** To test this hypothesis we performed a prospective inception cohort study at a teaching hospital in Gothenburg, Sweden. A total of 579 patients (179 women and 400 men; median age, 67 years) were included (Q-wave myocardial infarction in 163 patients, non-Q-wave myocardial infarction in 210 patients, unstable angina pectoris in 206 patients). **Main Outcome Measure:** All-cause mortality. **RESULTS:** During a median follow-up of 628 days, 65 patients died. The serum homocysteine level (mean [SD]) was significantly lower in long-term survivors ($n = 514$) than in nonsurvivors ($n=65$) (12.3 [7.0] vs 14.3 [5.9] pmol/L; $P=.003$). The relative risk (all-cause mortality) for patients with homocysteine levels in the upper quartile was 2.4 (95% confidence interval, 1.5-4.0) compared with that of patients in the 3 lower quartiles. After adjustment for relevant confounders, the relative risk estimate remained significant (relative risk= 1.69; 95% confidence interval, 1.02-2.80). In a stepwise model the homocysteine level provided prognostic information additional to that of patient age, diabetes mellitus, and diuretic usage prior to hospital admission ($P=.03$). **CONCLUSION:** The serum homocysteine level on hospital admission is an independent predictor of long-term survival in patients with acute coronary syndromes.

Folate Depletion and Elevated Plasma Homocysteine Promote Oxidative Stress in Rat Livers.

This study was designed to determine whether nutritional folate depletion exerts hepatic oxidative stress in relation to elevated plasma homocysteine. To mimic various extents of folate depletion status in vivo, male Wistar rats were fed an amino acid-defined diet containing either 8 (control), 2, 0.5, or 0 mg folic acid/kg diet. After a 4-wk feeding period, the plasma and hepatic folate concentrations of the rats decreased significantly with each decrement of dietary folate. Folate depletion did not significantly affect two major liver antioxidants: reduced glutathione and alpha-tocopherol. Conversely, folate depletion decreased Cu-Zn superoxide dismutase and glutathione peroxidase activities, but had no effect on catalase activity in liver homogenates. Lipid peroxidation products, as measured by thiobarbituric acid-reactive substances, were significantly higher in livers of folate-depleted rats than in those of the controls. This occurrence of hepatic oxidative stress in folate-depleted rats was confirmed by demonstrating an increased susceptibility of livers of folate-depleted rats to lipid peroxidation induced by additional H₂O₂ or Fe²⁺ treatments compared with the controls. Decreasing dietary folate intake resulted in graded increases in plasma homocysteine concentrations of folate-depleted rats. Elevated plasma homocysteine and decreased plasma and hepatic folate concentrations in folate-depleted rats were all strongly and significantly correlated with increased liver lipid peroxidation ($|r| \geq 0.58$, $P < 0.0003$). These data demonstrate that folate depletion and elevated plasma homocysteine promote oxidative stress in rat livers.

J Nutr 2001 Jan;131(1):33-38

The effect of diet on plasma homocysteine concentrations in healthy male subjects.

OBJECTIVE: To determine the effect of habitual omnivorous and vegetarian diets on folate and vitamin B12 status and the subsequent effect on homocysteine concentration. DESIGN: Cross-sectional comparison of free-living habitual meat-eaters and habitual vegetarians. SETTING: The study was conducted at RMIT University, Melbourne. SUBJECTS: One hundred and thirty-nine healthy male subjects (vegans n=18, ovolacto vegetarians n=43, moderate meat-eaters n=60 and high meat-eaters n=18) aged 20-55 who were recruited in Melbourne. OUTCOME MEASURES: Fasting plasma or serum from each subject was analysed for folate, vitamin B12 and homocysteine concentration. A semi-quantitative Food Frequency Questionnaire was completed by a subset of subjects from each group to determine methionine intake. RESULTS: The two meat eating groups consumed significantly greater levels of methionine ($P < 0.001$). There was no clear trend in plasma folate status between groups, however the plasma vitamin B12 concentration decreased progressively from the high-meat-eating group to vegans ($P < 0.05$). An inverse trend was observed with plasma homocysteine concentration, with vegans showing the highest levels and high meat eaters the lowest ($P < 0.05$). CONCLUSIONS: Dietary methionine intake has no observable effect on plasma homocysteine concentration. In habitual diets, where folate intake is adequate, lowered vitamin B12 intake from animal foods leads to depleted plasma vitamin B12 concentration with a concomitant increase in homocysteine concentration. The suggested mechanism is the failure to transfer a methyl group from methyl tetrahydrofolate by vitamin B12 in the remethylation of homocysteine to methionine.

Eur J Clin Nutr 1999 Nov;53(11):895-9

Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population.

BACKGROUND: Elevated blood concentrations of total homocysteine (tHcy) have been implicated in the pathogenesis of atherosclerotic cardiovascular disease. Previous studies identified suboptimal nutritional status and dietary intake of folate, vitamin B-6, and vitamin B-12 as determinants of elevated tHcy. OBJECTIVE: We identified other nutritional factors associated with tHcy in 260 retired schoolteachers in the Baltimore metropolitan area. DESIGN: We performed observational analyses of baseline and 2-4-month follow-up data collected in a study designed to test the feasibility of conducting a large-scale clinical trial of vitamin supplements by mail. The study population consisted of 151 women and 109 men with a median age of 64 y. At baseline, each participant completed a food-frequency questionnaire. At follow-up, fasting serum tHcy was measured. RESULTS: In multivariable linear regression and generalized linear models, there was an independent, inverse dose-response relation between dietary protein and ln tHcy ($P = 0.002$) and a positive, significant dose-response relation between coffee consumption and ln tHcy (P for trend = 0.01). Other significant predictors of ln tHcy were creatinine (positive; $P = 0.0001$) and prestudy use of supplemental B vitamins (inverse; $P = 0.03$). In stratified analyses restricted to persons receiving standard multivitamin therapy, the association of ln tHcy with dietary protein and coffee persisted. CONCLUSIONS: These results support the hypothesis that increased protein intake and decreased coffee consumption may reduce tHcy and potentially prevent atherosclerotic cardiovascular disease and other disease outcomes.

Am J Clin Nutr 1999 Mar;69(3):467-75

Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocyst(e)inemia in humans.

BACKGROUND: Moderate elevations in plasma homocysteine concentrations are associated with atherosclerosis and hypertension. We tested the hypothesis that experimental perturbation of homocysteine levels produces resistance and conduit

vessel endothelial dysfunction and that occurs through increased oxidant stress. METHODS AND RESULTS: Oral administration of L-methionine (100 mg/kg) was used to induce moderate hyperhomocysteinemia (approximately 25 micromol/L) in healthy human subjects. Endothelial function of forearm resistance vessels was assessed by use of forearm vasodilatation to brachial artery administration of the endothelium-dependent dilator acetylcholine. Conduit vessel endothelial function was assessed with flow-mediated dilatation of the brachial artery. Forearm resistance vessel dilatation to acetylcholine was significantly impaired 7 hours after methionine (methionine, 477+/-82%; placebo, 673+/-110%; P=0.016). Methionine did not alter vasodilatation to nitroprusside and verapamil. Flow-mediated dilatation was significantly impaired 8 hours after methionine loading (0.3+/-2.7%) compared with placebo (8.2+/-1.6%, P=0.01). Oral administration of the antioxidant ascorbic acid (2 g) prevented methionine-induced endothelial dysfunction in both conduit and resistance vessels (P=0.03). CONCLUSIONS: Experimentally increasing plasma homocysteine concentrations by methionine loading rapidly impairs both conduit and resistance vessel endothelial function in healthy humans. Endothelial dysfunction in conduit and resistance vessels may underlie the reported associations between homocysteine and atherosclerosis and hypertension. Increased oxidant stress appears to play a pathophysiological role in the deleterious endothelial effects of homocysteine.

Circulation 1999 Sep 14;100(11):1161-8

Homocysteine-dependent alterations in mitochondrial gene expression, function and structure. Homocysteine and H2O2 act synergistically to enhance mitochondrial damage.

Mitochondrial abnormalities have been identified in hepatocytes of patients with hyperhomocysteinemia and in endothelial cells from the aortas of rats with diet-induced hyperhomocysteinemia. However, the mechanism by which homocysteine affects mitochondria is unknown. In this report, homocysteine-induced expression of the mitochondrial electron transport chain gene, cytochrome c oxidase III/ATPase 6,8 (CO3/ATPase 6,8), was identified in a human megakaryocytic cell line DAMI using mRNA differential display. Steady-state mRNA levels of CO3/ATPase 6,8, as well as other mitochondrial transcripts, were increased in DAMI cells by homocysteine in a concentration- and time-dependent manner. Despite an increase in mitochondrial RNA levels and changes in mitochondrial ultrastructure, no effect on either cell growth or mitochondrial respiration rates was observed in DAMI cells exposed to homocysteine at concentrations up to 1 mM. In contrast, 1 mM homocysteine in the presence of Cu²⁺, which is known to generate H₂O₂, significantly decreased mitochondrial RNA levels, caused gross morphological changes in mitochondrial ultrastructure, and inhibited both cell growth and mitochondrial respiration rates. However, precursors of cellular glutathione and preexposure to heat shock blocked the decrease in mitochondrial RNA levels caused by homocysteine and Cu²⁺. The observations that (i) homocysteine and H₂O₂, but not H₂O₂ alone, caused a decrease in mitochondrial RNA levels, (ii) intracellular levels of H₂O₂ were significantly increased in the presence of homocysteine and Cu²⁺, and (iii) catalase, but not free radical scavengers, prevented a decrease in mitochondrial RNA levels, provide evidence that homocysteine and H₂O₂ act synergistically to cause mitochondrial damage. Furthermore, our findings suggest that intracellular glutathione and heat shock proteins play a role in protecting mitochondria against the adverse effects elicited by homocysteine and H₂O₂.

J Biol Chem 1998 Nov 13;273(46):30808-17

Homocysteine induces iron-catalyzed lipid peroxidation of low-density lipoprotein that is prevented by alpha-tocopherol.

Homocystinuria is an inborn error of methionine metabolism that is characterized by the premature development of arteriosclerosis. As one of the major factors in the pathogenesis of arteriosclerosis, modification of low-density lipoprotein (LDL) has received widespread attention by many investigators. In this study, to elucidate the relationship between elevated homocysteine levels and premature arteriosclerosis, we investigated the role of homocysteine in the iron-catalyzed oxidative modification of LDL. When LDL isolated from a healthy subject was incubated with homocysteine and ferric ion, a gradual decrease of polyunsaturated fatty acids (PUFA), formation of thiobarbituric acid-reactive substances (TBARS) and fluorescent substances, and the fragmentation of apoprotein B (apoB) were observed. The extent of oxidative modification was dependent on the concentration of homocysteine. Modification of LDL was suppressed until the remaining alpha-tocopherol concentration reached a critical level. When the alpha-tocopherol content of LDL was increased by 2.6-fold, both the formation of TBARS and the fragmentation of apoB were suppressed. These results suggest that homocysteine might promote iron-catalyzed oxidation of LDL and imply its role for the development of premature arteriosclerosis.

Free Radic Res 1994 Oct;21(5):267-76

Increased plasma homocysteine is an independent predictor of new coronary events in older persons.

A prospective study investigated the association of plasma homocysteine and other risk factors with the incidence of new coronary events at 31 +/- 9 month follow-up in 153 men and 347 women, mean age 81 +/- 9 years. The stepwise Cox regression model showed that significant independent predictors of new coronary events in older persons were age (risk ratio 1.041), plasma homocysteine (risk ratio 1.073), current cigarette smoking (risk ratio 2.524), hypertension (risk ratio 2.032), diabetes mellitus (risk ratio 2.022), serum total cholesterol (risk ratio 1.013), serum high-density lipoprotein cholesterol (risk ratio 0.925), and serum triglycerides (risk ratio 1.004).

Alpha Lipoic Acid

Oxidative stress in the aging rat heart is reversed by dietary supplementation with (R)-alpha lipoic acid.

Oxidative stress has been implicated as a causal factor in the aging process of the heart and other tissues. To determine the extent of age-related myocardial oxidative stress, oxidant production, antioxidant status, and oxidative DNA damage were measured in hearts of young (2 months) and old (28 months) male Fischer 344 rats. Cardiac myocytes isolated from old rats showed a nearly threefold increase in the rate of oxidant production compared to young rats, as measured by the rates of 2,7-dichlorofluorescein diacetate oxidation. Determination of myocardial antioxidant status revealed a significant twofold decline in the levels of ascorbic acid ($P = 0.03$), but not alpha-tocopherol. A significant age-related increase ($P = 0.05$) in steady-state levels of oxidative DNA damage was observed, as monitored by 8-oxo-2'-deoxyguanosine levels. To investigate whether dietary supplementation with (R)-alpha lipoic acid (LA) was effective at reducing oxidative stress, young and old rats were fed an AIN-93M diet with or without 0.2% (w/w) LA for 2 wk before death. Cardiac myocytes from old, LA-supplemented rats exhibited a markedly lower rate of oxidant production that was no longer significantly different from that in cells from unsupplemented, young rats. Lipoic acid supplementation also restored myocardial ascorbic acid levels and reduced oxidative DNA damage. Our data indicate that the aging rat heart is under increased mitochondrial-induced oxidative stress, which is significantly attenuated by lipoic acid supplementation.

FASEB J. 2001 Mar;15(3):700-6.

Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by micromolar concentrations of alpha lipoic acid.

In diabetic patients, alpha lipoic acid (LA) improves skeletal muscle glucose transport, resulting in increased glucose disposal; however, the molecular mechanism of action of LA is presently unknown. We studied the effects of LA on basal and insulin-stimulated glucose transport in cultured rat L6 muscle cells that overexpress GLUT4. When 2-deoxy-D-glucose uptake was measured in these cells, they were more sensitive and responsive to insulin than wild-type L6 cells. LA, at concentrations ≤ 1 mmol/l, had only small effects on glucose transport in cells not exposed to oxidative stress. When cells were exposed to glucose oxidase and glucose to generate H_2O_2 and cause oxidative stress, there was a marked decrease in insulin-stimulated glucose transport. Pretreatment with LA over the concentration range of 10-1,000 pmol/l protected the insulin effect from inhibition by H_2O_2 . Both the R and S isomers of LA were equally effective. In addition, oxidative stress caused a significant decrease (approximately 50%) in reduced glutathione concentration, along with the rapid activation of the stress-sensitive p38 mitogen-activated protein kinase. Pretreatment with LA prevented both of these events, coincident with protecting insulin action. These studies indicate that in muscle, the major site of insulin-stimulated glucose disposal, one important effect of LA on the insulin-signaling cascade is to protect cells from oxidative stress-induced insulin resistance.

Diabetes 2001 Feb;50(2):404-10

Cataract development in diabetic sand rats treated with alpha-lipoic acid and its gamma-linolenic acid conjugate.

BACKGROUND: Diabetes commonly leads to long-term complications such as cataract. This study investigated the effects of alpha-lipoic acid (LPA) and its gamma-linolenic acid (GLA) conjugate on cataract development in diabetic sand rats. **METHODS:** Two separate experiments were conducted. In Experiment 1, sand rats were fed a "high-energy" diet (70% starch), an acute model of Type 2 diabetes, and injected with LPA. In Experiment 2, the animals received a "medium-energy" diet (59% starch), a chronic diabetic model, and were intubated with LPA or its GLA conjugate. Throughout the experiments, blood glucose levels and cataract development were measured. At the termination of the experiments, lens aldose reductase (AR) activity and lenticular reduced glutathione (GSH) levels were analyzed. **RESULTS:** LPA injection significantly inhibited cataract development and reduced blood glucose levels in rats fed the 'high-energy' diet. Lens AR activity tended to be lower, while lenticular GSH levels increased. In sand rats fed a "medium-energy" diet (59% starch), LPA intubation had no effect on blood glucose levels and cataract development but GSH levels were increased. In contrast, sand rats intubated with GLA conjugate showed the highest blood glucose levels and accelerated cataract development. The conjugate treatment also decreased lenticular GSH content. **CONCLUSIONS:** The hypoglycemic effects of LPA are beneficial in the prevention of acute symptoms of Type 2 diabetes. It remains to be shown that the antioxidant activity of LPA is responsible for prevention or inhibition of cataract progression in sand rats.

Diabetes Metab Res Rev 2001 Jan-Feb;17(1):44-50

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