

ABSTRACTS FOR THE VITAMIN C CONTROVERSY

81. Effects of antioxidant supplementation on platelet function: a randomized pair-matched, placebo-controlled, double-blind trial in men with low antioxidant status.

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Salonen JT, Salonen R, Seppanen K, Rinta-Kiikka S, Kuukka M, Korpela H, Alfthan G, Kantola M, Schalch W Department of Community Health and General Practice, University of Kuopio, Finland.

We investigated the effect on platelet function of supplementing men with low antioxidant status with 600 mg Ascorbic acid, 300 mg alpha-tocopherol, 27 mg beta-carotene, and 75 micrograms selenium in yeast daily. Eighty men were randomly assigned in pairs (matched for smoking, baseline antioxidant status, and time and day of entry) by use of a double-blind design to receive supplement or placebo for 5 mo. Compared with 39 control subjects, 39 antioxidant-supplemented men experienced the following net reductions during the double-blind period: 20% ($P = 0.012$) in serum lipid peroxides, 24% ($P = 0.035$) in ADP-induced platelet aggregation, 42% ($P = 0.040$) in the rate of ATP release during aggregation, 51% ($P = 0.018$) in serum (platelet-produced) thromboxane B₂, and 29% ($P = 0.024$) in plasma beta-thromboglobulin concentration. The data support our hypothesis that antioxidant supplementation of men with low antioxidant status and high fat intake reduces lipid peroxidation, the capacity of platelets to aggregate and to produce thromboxane A₂, and in vivo platelet activation.

82. Vitamin c improves endothelial function of conduit arteries in patients with chronic heart failure.

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BACKGROUND: Chronic heart failure (CHF) is associated with endothelial dysfunction including impaired endothelium-mediated, flow-dependent dilation (FDD). There is evidence for increased radical formation in CHF, raising the possibility that nitric oxide is inactivated by radicals, thereby impairing endothelial function. To test this hypothesis, we determined the effect of the antioxidant vitamin c on FDD in patients with CHF. **METHODS AND RESULTS:** High-resolution ultrasound and Doppler was used to measure radial artery diameter and blood flow in 15 patients with CHF and 8 healthy volunteers. Vascular effects of vitamin c (25 mg/min IA) and placebo were determined at rest and during reactive hyperemia (causing endothelium-mediated dilation) before and after intra-arterial infusion of N-monomethyl-L-arginine (L-NMMA) to inhibit endothelial synthesis of nitric oxide. Vitamin c restored FDD in patients with heart failure after acute intra-arterial administration ($13.2 \pm 1.7\%$ versus $8.2 \pm 1.0\%$; $P < .01$) and after 4 weeks of oral therapy ($11.9 \pm 0.9\%$ versus $8.2 \pm 1.0\%$; $P < .05$). In particular, the portion of FDD mediated by nitric oxide (ie, inhibited by L-NMMA) was increased after acute as well as after chronic treatment (CHF baseline: $4.2 \pm 0.7\%$; acute: $9.1 \pm 1.3\%$; chronic: $7.3 \pm 1.2\%$; normal subjects: $8.9 \pm 0.8\%$; $P < .01$). **CONCLUSIONS:** Vitamin c improves FDD in patients with CHF as the result of increased availability of nitric oxide. This observation supports the concept that endothelial dysfunction in patients with CHF is, at least in part, due to accelerated degradation of nitric oxide by radicals.

83. Antioxidant vitamin c improves endothelial dysfunction in chronic smokers.

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BACKGROUND: Chronic smoking is associated with endothelial dysfunction, an early stage of atherosclerosis. It has been suggested that endothelial dysfunction may be a consequence of enhanced degradation of nitric oxide secondary to formation of oxygen-derived free radicals. To test this hypothesis, we investigated the effects of the antioxidant vitamin c on endothelium-dependent responses in chronic smokers. **METHODS AND RESULTS:** Forearm blood flow responses to the endothelium-dependent vasodilator acetylcholine (7.5, 15, 30, and 60 micrograms/min) and the endothelium-independent vasodilator sodium nitroprusside (1, 3, and 10 micrograms/min) were measured by venous occlusion plethysmography in 10 control subjects and 10 chronic smokers. Drugs were infused into the brachial artery, and forearm blood flow was measured for each drug before and during concomitant intra-arterial infusion of the antioxidant vitamin c (18 mg/min). In control subjects, vitamin c had no effect on forearm blood flow in response to acetylcholine and sodium nitroprusside. In contrast, in chronic smokers the attenuated forearm blood flow responses to acetylcholine were markedly improved by concomitant administration of vitamin c, whereas the vasodilator responses to sodium nitroprusside were not affected. **CONCLUSIONS:** The present studies demonstrate that the antioxidant vitamin c markedly improves endothelium-dependent responses in chronic smokers. This observation supports the concept that endothelial dysfunction in chronic smokers is at least in part mediated by enhanced formation of oxygen-derived free radicals.

84. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering.

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BACKGROUND: There is accumulating experimental, epidemiological, and clinical evidence of an association between anti-oxidant vitamin intake and reduced risk of coronary heart disease. Using data from the Cholesterol Lowering Atherosclerosis Study (CLAS), we explored the association of self-selected supplementary antioxidant vitamin intake on the rate of progression of early preinvasive atherosclerosis. **METHODS AND RESULTS:** CLAS was an arterial imaging trial in which nonsmoking 40- to 59-year-old men with previous coronary artery bypass graft surgery were randomized to colestipol/niacin plus diet or placebo plus diet. The rate of progression of early preinvasive atherosclerosis was determined in 146 subjects using high-resolution B-mode ultrasound quantification of the distal common carotid artery far wall intima-media thickness (IMT). From the nutritional supplement database, 22 subjects had an on-trial average supplementary vitamin E intake of ≥ 100 IU per day (high users) and 29 subjects had an average on-trial supplementary VITAMIN C intake of ≥ 250 mg per day (high users). Within the placebo group, less carotid IMT progression was found for high supplementary vitamin E users when compared with low vitamin E users (0.008 versus 0.023 mm/y, $P = .03$). No effect of vitamin E within the drug group was found. No effect of VITAMIN C within the drug or placebo group was found. **CONCLUSIONS:** Supplementary vitamin E intake appears to be effective in reducing the progression of atherosclerosis in subjects not treated with lipid-lowering drugs while the process is still confined to the arterial wall (early preinvasive atherosclerosis). Publication Types: Clinical trial Randomized controlled trial PMID: 8921775, UI: 97080430

85. Vitamin c intake and cardiovascular disease risk factors in persons with non-insulin-dependent diabetes mellitus. From the Insulin Resistance Atherosclerosis Study and the San Luis Valley Diabetes Study.

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BACKGROUND: Persons with non-insulin-dependent diabetes mellitus (NIDDM) are at increased risk for cardiovascular disease, partly due to concomitant worsening of traditional risk factors including dyslipidemia and hypertension. Based on evidence from small, controlled clinical trials, we hypothesized that increased intake of vitamin c would be associated with improved cardiovascular disease (CVD) risk factor status among community-dwelling persons with NIDDM. **METHODS:** In separate but parallel statistical analyses, hypotheses were evaluated among persons with NIDDM confirmed by WHO criteria from the Insulin Resistance Atherosclerosis Study (IRAS, $n = 520$) and from the San Luis Valley Diabetes Study (SLVDS, $n = 422$). For IRAS, diet and vitamin supplement use was assessed by food frequency interview and for SLVDS, by 24-hr dietary recall interview. **RESULTS:** Mean vitamin c intake (mg/day) was 275 for IRAS and 133 for SLVDS, including supplements. In cross-sectional regression models from each data set, vitamin c intake was not associated with systolic or diastolic blood pressure nor with HDL-C, LDL-C, or triglycerides (P values > 0.10 ; adjusted for calories, demographic and lifestyle variables, obesity, diabetes duration, and medications). In prospective analyses including 285 SLVDS participants, baseline vitamin c intake was not related to any of these CVD risk factors measured an average of 4 years later nor to change in CVD risk factor status during the follow-up period. **CONCLUSIONS:** We conclude that, across a wide range of intake, vitamin c does not appear to be associated with improved CVD risk factor status among community-dwelling persons with diabetes.

86. The influence of antioxidant nutrients on platelet function in healthy volunteers.

Atherosclerosis 1997 Jan 3;128(1):97-105

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There is mounting evidence that antioxidants may help to prevent coronary heart disease and modulate some thrombotic events such as platelet adhesion. However, the effects of antioxidant supplementation on platelet function in vivo are controversial. A double-blind, randomised, placebo-controlled study was performed on 40 healthy volunteers (20-50 years) supplemented daily with vitamin E (300 mg), vitamin C (250 mg) or beta-carotene (15 mg) for 8 weeks. Platelet function was assessed by platelet aggregation induced by ADP, arachidonic acid or collagen, platelet responsiveness to the inhibitor PGE₁, beta-thromboglobulin release and ATP secretion. Supplementation with vitamin E resulted in a significant increase in platelet alpha-tocopherol level (+68%) reflecting closely the increase in plasma alpha-tocopherol level (+69%). Platelet function was significantly decreased by vitamin E as revealed by the decreased platelet aggregation in response to ADP and arachidonic acid, the increased sensitivity to inhibition by PGE₁, the decreased plasma beta-thromboglobulin concentration and the decreased ATP secretion. Supplementation with vitamin C did not affect platelet function significantly although a trend towards a decreased platelet aggregability and an increased sensitivity to the inhibitor PGE₁ were observed. No significant changes in platelet function occurred after supplementation with beta-carotene. In conclusion, supplementation of healthy volunteers with vitamin E decreased platelet function whereas supplementation with vitamin C or beta-carotene had no significant effects.

87. The effect of high-dose ascorbate supplementation on plasma lipoprotein(a) levels in patients with premature coronary heart disease.

Pharmacotherapy 1995 Jul-Aug;15(4):458-64

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STUDY OBJECTIVE. To determine the efficacy of high-dose ascorbate supplementation in lowering lipoprotein(a) [Lp(a)] levels in patients with premature coronary heart disease (CHD). **DESIGN.** Randomized, double-blind, placebo-controlled trial. **SETTING.** Outpatient clinic. **PATIENTS.** Forty-four patients with documented premature CHD, defined as confirmed myocardial infarction and/or angiographically determined stenosis of 50% or greater in at least one major coronary artery before age 60 years. **INTERVENTIONS.** Patients were block randomized on the basis of age, gender, and screening Lp(a) concentrations to receive ascorbate 4.5 g/day or placebo for 12 weeks. **MEASUREMENTS AND MAIN RESULTS.** High-dose ascorbate was well tolerated and produced a marked elevation in mean plasma ascorbate levels (+1.2 mg/dl; $p < 0.001$). Multiple linear regression analysis revealed no significant effect of supplementation on postintervention Lp(a) levels ($p = 0.39$) in a model that included treatment group assignment, and baseline Lp(a) levels. **CONCLUSIONS.** Our findings do not support a clinically important lowering effect of high-dose ascorbate on plasma Lp(a) in patients with premature CHD.

88. Effect of VITAMIN C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations.

Ann Epidemiol 1995 Jan;5(1):52-9

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Plasma Ascorbic acid (AA) frequently is positively correlated with high-density-lipoprotein (HDL) cholesterol and inversely related to total cholesterol concentration. To determine if VITAMIN C intake can alter cholesterol concentration, we examined the effect of VITAMIN C supplementation (1 g/d) on lipoprotein cholesterol and triglyceride levels in 138 subjects, aged 20 to 65 years, who completed an 8-month randomized, double-blinded, placebo-controlled trial. Individuals with higher levels of plasma AA (> 80 $\mu\text{mol/L}$ for men and > 90 $\mu\text{mol/L}$ for women), HDL cholesterol (> 1.4 mmol/L for men and > 1.7 mmol/L for women), and total cholesterol (> 6.7 mmol/L) were excluded from this trial. We observed no overall effect of supplementation on plasma concentrations of HDL, LDL, or total cholesterol, apolipoprotein (apo) B, or triglyceride. We did observe a marginally significant ($P < 0.10$) increase of 1.9 $\mu\text{mol/L}$ (5.3 mg/dL) in apo A-I concentration with supplementation and a significant ($P < 0.05$) difference of 0.10 mmol/L (3.8 mg/dL) in HDL cholesterol concentration between VITAMIN C and placebo treatment in a nonrandomized subgroup of individuals ($n = 43$) and a baseline plasma AA level less than 55 $\mu\text{mol/L}$. Although the apo A-I concentration increase was only marginally significant with supplementation, change in plasma AA concentration was significantly ($P < 0.05$) correlated with change in apo A-I concentration in the entire sample. The overall results of this trial were negative, but our data do not allow us

to rule out the possibility that VITAMIN C supplementation might increase HDL cholesterol or apo A-I concentrations among individuals with lower plasma AA levels.

89. Response patterns and cardiovascular effects during response sequence acquisition by humans.

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The effects of temporal delays imposed between successive responses and of vitamin c administration were examined on the acquisition of response sequences and on cardiovascular reactivity during sequence acquisition. Thirteen adult subjects (6 female, 7 male), in good health, gave written consent prior to participating in 12 weekly 45-min sessions. Points, exchanged for money after each session, were resented when subjects completed 15-response sequences on a touch-sensitive three-response keypad. A position counter increased from 0 to 14 as subjects emitted correct responses in the sequence. Four novel 15-response sequences were presented each session. No delays were imposed between successive responses during the acquisition of one sequence; delays were imposed immediately following each response during the acquisition of a second sequence, thereby delaying response feedback; delays were imposed following feedback during acquisition of a third sequence, resulting in the removal of the stimulus correlated with sequence position; and, as a control condition, delays were imposed following feedback, but stimuli correlated with sequence position were reinstated prior to the next response during acquisition of a fourth sequence. Subjects were exposed to one of two delay durations (0.2 and 0.5 or 0.5 and 1.0 s) each session, and delay durations alternated every session. During Weeks 5 to 8, subjects received 3 grams of vitamin c per day, whereas during Weeks 1 to 4 and 9 to 12, subjects received placebo under single-blind conditions. All subjects acquired the sequences, as evidenced by decreasing percentages of incorrect responses across trials. When temporal delays were imposed between successive responses during sequence acquisition, acquisition efficiency was enhanced. Examination of response latencies suggested that the status of preceding responses (i.e., correct or incorrect) rather than the status of the position counter influenced subsequent responding. Cardiovascular effects were inversely related to the length of the temporal delay. Neither cardiovascular reactivity or sequence acquisition were related to vitamin c administration.

90. Effect of preoperative supplementation with alpha-tocopherol and ascorbic acid on myocardial injury in patients undergoing cardiac operations.

J Thorac Cardiovasc Surg 1997 May;113(5):942-8

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Augmentation of antioxidant defenses may help protect tissues against ischemia-reperfusion injury associated with operations involving cardiopulmonary bypass. In this study we examined the effect of pretreating patients with alpha-tocopherol (vitamin E) and ascorbic acid (vitamin c) or placebo on injury to the myocardium. Seventy-six subjects undergoing elective coronary artery bypass grafting participated in a prospective, double-blind, placebo-controlled randomized trial, receiving either placebo or both 750 IU dl-alpha-tocopherol per day for 7 to 10 days and 1 gm ascorbic acid 12 hours before the operation. Plasma alpha-tocopherol concentrations, raised fourfold by supplementation, fell by 70% after the operation in the supplemented group and to negligible levels in the placebo group. There were no significant differences between the groups with respect to release of creatine kinase MB isoenzyme over 72 hours, nor in the reduction of the myocardial perfusion defect determined by thallium 201 uptake. Electrocardiography provided no evidence of a benefit from antioxidant supplementation. Thus the supplementation regimen prevented the depletion of the primary lipid soluble antioxidant in plasma, but provided no measurable reduction in myocardial injury after the operation

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