

**ABSTRACTS FOR THE VITAMIN C CONTROVERSY**

71. Increased adhesiveness of isolated monocytes to endothelium is prevented by VITAMIN C intake in smokers.

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**BACKGROUND:** To explore pathophysiological mechanisms of cigarette smoking involved in atherogenesis, we compared adhesiveness of isolated blood monocytes with endothelium and plasma levels of the aqueous phase antioxidant VITAMIN C in nonsmokers and smokers before and after supplementation, using a novel monocyte adhesion assay with fixed human endothelial cells. **METHODS AND RESULTS:** Monocyte adhesion to unstimulated human umbilical vein endothelial cells ranged from 0.17% to 0.51% in the nonsmoker group (0.37±0.09%, mean ±SD, n=13). In smokers with a 1 to 2 packs per day consumption, monocyte adhesion was increased to 0.71±0.17% (mean ±SD, n=10, P<.001), ranging from 0.46% to 0.99%. Increased adhesiveness was mediated by the integrin CD11b/CD18, as shown by inhibition with a monoclonal antibody to CD11b but not associated with altered CD11b surface expression. Plasma VITAMIN C levels were reduced in smokers (48.2±14.1 micromol/L) versus nonsmokers (67.7±17.6 micromol/L; P<.025), while no significant differences were found in retinol, vitamin E, or beta-carotene levels. This confirms that the radical scavenger VITAMIN C reacts sensitively to oxidative stress induced by cigarette smoke in human plasma. Consistently, dietary supplementation with VITAMIN C (2 g per day) for 10 days raised plasma levels to 82.6±11.0 micromol/L (n=10, P<.001) in smokers and decreased monocyte adhesion to values found in nonsmokers (0.38±0.18%, P<.001). In contrast, VITAMIN C intake did not affect monocyte adhesiveness in nonsmokers (0.37±0.14%, n=6) despite increasing plasma levels to 82.9±11.8 micromol/L. **CONCLUSIONS:** Our data show that cigarette smoking increases CD11b-dependent monocyte adhesiveness in humans. Restoring reduced plasma VITAMIN C concentrations in smokers by oral supplementation decreased monocyte adhesion to values found in nonsmokers.

72. Ascorbic acid induces a favorable lipoprotein profile in women.

J Am Coll Nutr 1996 Apr;15(2):154-8

Gatto LM, Hallen GK, Brown AJ, Samman S Department of Biochemistry, University of Sydney, NSW, Australia.

**OBJECTIVES:** The aim of this study was to determine the effect of Ascorbic acid (AA) supplements on plasma lipids and lipoproteins in healthy, young women. **METHODS:** Ten women were recruited to participate in a randomized double-blind cross-over trial and supplemented with 1000 mg AA daily for 4 weeks, followed by placebo, and vice versa. **RESULTS:** Plasma AA concentrations were significantly higher at 2 weeks (p < 0.0001) and at 4 weeks (p < 0.001), compared with baseline. Plasma AA levels appeared to peak after 2 weeks of supplementation. Plasma concentrations of LDL-C were found to be 16% lower at 4 weeks compared with baseline (p < 0.05) and although HDL-C levels did not change significantly with AA supplementation, the change in HDL-C was positively associated with the change in plasma AA (p < 0.05). Significant decreases were observed in the total cholesterol (TC) to HDL-C at 2 weeks and LDL-C to HDL-C ratios at 2 and 4 weeks supplementation (p < 0.05). **CONCLUSIONS:** Our findings agree with those from epidemiological studies and suggest that increases in AA intake may favorably alter the lipoprotein profile in young women.

73. Usefulness of antioxidant vitamins in suspected acute myocardial infarction (the Indian experiment of infarct survival-3).

Am J Cardiol 1996 Feb 1;77(4):232-6

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In a randomized, double-blind, placebo-controlled trial, the effects of combined treatment with the antioxidant vitamins A (50,000

IU/day), VITAMIN C (1,000 mg/day), vitamin E (400 mg/day), and beta-carotene (25 mg/day) were compared for 28 days in 63 (intervention group) and 62 (placebo group) patients with suspected acute myocardial infarction. After treatment with antioxidants, the mean infarct size (creatin kinase and creatine kinase-MB gram equivalents) was significantly less in the antioxidant group than in the placebo group. Serum glutamic-oxaloacetic transaminase decreased by 45.6 IU/dl in the antioxidant group versus 25.8 IU/dl in the placebo group ( $p < 0.02$ ). Cardiac enzyme lactate dehydrogenase increased slightly (88.6 IU/dl) in the antioxidant group compared with that in the placebo group (166.5 IU/dl) ( $p < 0.01$ ). QRS score in the electrocardiogram was significantly less in the antioxidant than in the placebo group. The following levels increased in the antioxidant group versus the placebo group, respectively: plasma levels of vitamin E increased by 8.8 and 2.2  $\mu\text{mol/L}$  ( $p < 0.01$ ), VITAMIN C increased by 12.6 and 4.2  $\mu\text{mol/L}$  ( $p < 0.01$ ), beta-carotene increased by 0.28 and 0.06  $\mu\text{mol/L}$  ( $p < 0.01$ ), and vitamin A increased by 0.36 and 0.12  $\mu\text{mol/L}$  ( $p < 0.01$ ). Serum lipid peroxides decreased by 1.22  $\text{pmol/ml}$  in antioxidant versus 0.22  $\text{pmol/ml}$  in the placebo group ( $p < 0.01$ ). Angina pectoris, total arrhythmias, and poor left ventricular function occurred less often in the antioxidant group. Cardiac end points were significantly less in the antioxidant group (20.6% vs 30.6%, respectively). These results suggest that combined treatment with antioxidant vitamins A, E, C, and beta-carotene in patients with recent acute myocardial infarction may be protective against cardiac necrosis and oxidative stress, and could be beneficial in preventing complications and cardiac event rate in such patients.

#### 74. Effect of VITAMIN C on lipoproteins in healthy adults.

Ann Med Interne (Paris) 1994;145(1):13-9

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**BACKGROUND:** It has been suggested that VITAMIN C can modify the composition of lipoproteins in healthy subjects. **OBJECTIVE:** To determine the possible modification of lipid levels in the presence of VITAMIN C, and the effect of various doses on lipid levels. **DESIGN:** This is a sequential open clinical trial, where the same individuals are used as their own controls, and where the same observer at random administers 1 or 2 g of oral VITAMIN C during a month, followed by a further month without treatment. **PATIENTS:** 124 healthy volunteers of both sexes, between 17 and 74 years of age, whose lifestyle was not modified during the study. **MEASUREMENT:** At the beginning of the study a determination was made of lipid levels, risk factors such as age, physical activity, tobacco and alcohol use, weight and arterial pressure; at the end of the first month during VITAMIN C therapy, and again at the end of the second month without therapy, lipid levels were determined, namely, TG, TC, HDL-C, HDL2-C, HDL3-C, LDL-C, ApoA1, ApoB and Lp(a). **RESULTS:** After one month of treatment with 2 grams of VITAMIN C, a significant decrease of ApoB was observed, namely, 5.5% in females and 8% in males ( $p = 0.019$ ). VITAMIN C treatment shows the following differential data: a negative correlation of Lp(a) with HDL3-C, in both sexes; in males, the positive correlation of age with LDL-C and the negative correlation of tobacco with HDL-C disappear, positive correlations appear between physical activity and HDL-C, between tobacco and LDL-C, between weight and ApoB, between SBP and TG, and between DBP and ApoB; in females, the positive correlation between weight and TG, and the negative correlation between weight and HDL-C both disappear, negative correlations appear between physical activity and both TC and ApoB, between weight and HDL3-C, a positive correlation appears between DBP and HDL2-C. Compared to non-drinkers, in males who consume less than 50 grams of alcohol daily, VITAMIN C produces a significant decrease in HDL3-C, while the significant increase in Lp(a) disappears. **CONCLUSIONS:** From the results in the follow-up of this group of healthy individuals, it can be deduced that VITAMIN C produces a decrease in ApoB in both sexes where 2 g are administered daily. When the risk factors are correlated, the results vary substantially, particularly with reference to the sex of the individuals. Women benefit much more than men from VITAMIN C therapy, especially when physical activity, weight and diastolic blood pressure are considered. Compared to non-drinkers, male drinkers demonstrate a decrease in HDL3-C, and the significant increase in Lp(a) disappears.

#### 75. Possible prevention of postangioplasty restenosis by Ascorbic acid.

Am J Cardiol 1996 Dec 1;78(11):1284-6

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In this preliminary study to assess the possibility of using Ascorbic acid to prevent post-percutaneous transluminal coronary angiography (PTCA) restenosis, the incidence of restenosis was significantly less in 50 patients receiving 500 mg/day of oral Ascorbic acid than in 51 control patients. Thus, Ascorbic acid, a potent natural antioxidant, appeared to be possibly effective in attenuating post-PTCA restenosis.

#### 76. Mortality and clinical course of patients with acute myocardial infarction treated with streptokinase and antioxidants: mannitol and Ascorbic acid.

Int J Cardiol 1995 Mar 3;48(3):235-7

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There is increasing evidence that free radical scavengers limit reperfusion injury in animal experiments. We randomly administered 250 ml 20% mannitol infusion and 10.0 g Ascorbic acid infusion, potent free radical scavengers to 42 patients with acute myocardial infarction receiving streptokinase. A control group of 42 patients received only standard fibrinolytic therapy. We found that additional antioxidant treatment with Ascorbic acid and mannitol decreased the number of some complications of acute myocardial infarction.

#### 77. Magnesium and Ascorbic acid supplementation in diabetes mellitus.

Ann Nutr Metab 1995;39(4):217-23

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The effect of magnesium (Mg) and Ascorbic acid (AA) supplementation on metabolic control was assessed in 56 outpatient diabetics. A 90-day run-in period was followed by two 90-day treatment periods, during which Mg (600 mg/day) and AA (2 g/day) were administered in a randomized double-blind cross-over fashion. A decrease in systolic and diastolic blood pressure (132 +/- 3 vs. 138 +/- 4 and 77 +/- 2 vs. 82 +/- 2 mm Hg;  $p < 0.05$ ) was observed in insulin-dependent diabetes mellitus subjects during Mg supplementation. No beneficial effect of Mg supplementation was observed on glycemic control, lipids or blood pressure in non-insulin-dependent diabetes mellitus (NIDDM) subjects. AA supplementation improved glycemic control among NIDDM subjects and both fasting blood glucose (9.1 +/- 0.5 vs. 10.1 +/- 0.6 mmol/l;  $p < 0.05$ ) and HbA1c (8.5 +/- 0.3 vs. 9.3 +/- 0.3%;  $p < 0.05$ ) improved. Beneficial effects of AA supplementation on cholesterol (5.9 +/- 0.2 vs. 6.2 +/- 0.2 mmol/l;  $p < 0.05$ ) and triglycerides (2.2 +/- 0.2 vs. 2.5 +/- 0.2;  $p < 0.05$ ) were also observed in NIDDM subjects. The results suggest that high-dose AA supplementation may have a beneficial effect in NIDDM subjects on both glycemic control and blood lipids.

#### 78. Effect of antioxidant vitamins on low density lipoprotein oxidation and impaired endothelium-dependent vasodilation in patients with hypercholesterolemia.

J Am Coll Cardiol 1994 Dec;24(7):1611-7

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**OBJECTIVES.** The aims of this study were to determine whether antioxidant vitamins could reduce the susceptibility of low density lipoprotein (LDL) to oxidation and improve endothelium-dependent vasodilator responsiveness in patients with hypercholesterolemia. **BACKGROUND.** Animals and humans with hypercholesterolemia have exhibited impaired endothelium-dependent vasodilation. In vitro studies suggest that oxidatively modified LDL can impair nitric oxide production. **METHODS.** Forearm blood flow was measured with strain gauge plethysmography and brachial artery drug infusions in 19 patients, aged 52 +/- 9 years, with hypercholesterolemia (mean +/- SD total cholesterol 283 +/- 22 mg/dl, LDL 197 +/- 31 mg/dl) and in 14 subjects, aged 48 +/- 8 years, with normal cholesterol levels (total cholesterol 169 +/- 20 mg/dl, LDL 102 +/- 25 mg/dl). Acetylcholine (7.5, 15 and 30 micrograms/min) was utilized as an endothelium-dependent vasodilator, and sodium nitroprusside (0.8, 1.6 and 3.2 micrograms/min) was used to test endothelium-independent vasodilation. Oxidative susceptibility of LDL was measured by a spectrophotometric assay of conjugated diene production after the addition of copper chloride. Hypercholesterolemic patients then received daily antioxidant vitamin supplements (beta-carotene [30 mg], Ascorbic acid [VITAMIN C] [1,000 mg], vitamin E [800 IU]) for 1 month, with repeat measurement of both forearm blood flow responsiveness to the same agonists and LDL oxidizability. **RESULTS.** The maximal flow in response to acetylcholine was impaired in patients compared with that in normal subjects (9.8 +/- 7.8 vs. 15.9 +/- 8.1 ml/min per 100 ml,  $p = 0.03$ ), with similar maximal flow responses to sodium nitroprusside (9.5 +/- 4.2 vs. 9.0 +/- 2.8 ml/min per 100 ml,  $p = 0.72$ ). After 1 month of vitamin therapy, the onset of LDL oxidation was prolonged over baseline measurements by 71 +/- 67%, and the maximal rate of oxidation was decreased by 26 +/- 25% (both  $p < 0.001$ ). However, the maximal forearm blood flow response to acetylcholine remained unchanged from baseline values (maximal flow after acetylcholine 9.0 +/- 6.2 vs. 9.8 +/- 7.8 ml/min per 100 ml,  $p = 0.57$ ). This study had 80% power ( $\alpha = 0.05$ ) to exclude a 45% increase over baseline value in acetylcholine-stimulated flow during vitamin therapy. **CONCLUSIONS.** Although 1 month of administration of antioxidant vitamin supplements in hypercholesterolemic patients reduced the susceptibility of LDL to oxidation, impairment in endothelial function remained unaltered. The use of nonvitamin antioxidants or concomitant reduction in LDL levels, as well as more sensitive techniques for measuring vascular responsiveness, may be required to show a beneficial effect on endothelial vasodilator function.

#### 79. Plasma lipids, lipoproteins and atherogenic index in men and women administered vitamin C.

Cor Vasa 1992;34(3):246-54

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The aim of the study was to establish whether it is possible, in a group of deliberately selected subjects with hyperlipidaemia, to modulate cholesterol levels by ascorbic acid administered at a dose of 500 mg/day. The authors assessed the levels of vitamin c, total and HDL cholesterol, triacylglycerols in the blood serum of 140 probands assigned to an 83-member experimental group, and to a 57-member control group. The experimental group was provided Celaskon effervescens Spofa at a dose of 500 mg/day/person. The experiment lasted for 18 months. Blood collections were made in the whole cohort at six-month intervals. Administration of L-ascorbic acid led to a highly significant decrease in the levels of total and LDL cholesterol. After 12 months of study, a highly significant decrease in atherogenic index and an increase in HDL cholesterol levels were found persisting until the end of the experiment.

80. Protective effect of alpha-tocopherol and L-ascorbic acid against the ischemic-reperfusion injury in patients during open-heart surgery.

Bratisl Lek Listy 1991 Mar-Apr;92(3-4):174-83

Barta E, Pechan I, Cornak V, Luknarova O, Rendekova V, Verchovodko P

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The purpose of the investigation was: 1. to examine the effect of cardiopulmonary bypass (CPB) on the generation of cytotoxic oxygen-derived radicals and 2. to determine if the pretreatment of patients with vitamins E and C will combat generation of such radicals. Twenty patients undergoing CPB for treatment of cardiac disease were entered into the study and randomized to one of two groups. Group 1 (n = 9) served as control. Group 2 (n = 11) consisted of patients pretreated with 2000 IU of vitamin E 12 h prior to surgical intervention and 2 g of vitamin c given in the morning on the day of operation. Blood samples from arterial and mixed venous blood for analysis were obtained at the following intervals: 1. before anesthesia, 2. before sternotomy, 3. at the start of CPB, 4. at the end of CPB, 5. at the time of skin closure, 6. in the morning of the following day. Blood specimens from the coronary sinus were withdrawn A--before aortic cross-clamping, B--immediately after aortic declamping, C--in the 5th min, and D--in the 15th min of reperfusion. The concentration of inorganic phosphate as well as of uric acid was significantly higher in the control group what might indicate that vitamins E and C attenuate the degradation of adenine nucleotides. The most important difference between treated and control groups was observed in plasma concentration of malondialdehyde--a marker of lipid peroxidation--which was significantly lower in pretreated patients. A similar pattern of changes was found in the level of the lysosomal enzyme N-acetyl-glucosaminidase. Finally, pretreatment with vitamins E and C inhibited the decrease of catalase, observed in controls.

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