



Human Nutrition Research Monthly Update

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TABLE OF CONTENTS

Antioxidants

Pharmacological Doses of Vitamin E Improve Cardiac Autonomic Nervous System in Type 2 Diabetics*	2
Protection by Vitamin C Against Aspirin-Induced Gastric Damage*	3

Eye Health

High Dose Vitamin A and Vitamin E Supplementation After Photorefractive Keratectomy*	4
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Lycopene

Serum Carotenoids and Breast Cancer*	5
--------------------------------------------	---

Folic Acid

Low dietary Folate Intake Is Associated with an Excess Incidence of Acute Coronary Events*	6
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Pharmacological Doses of Vitamin E Improve Cardiac Autonomic Nervous System in Type 2 Diabetics

Article Title:

Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes.

Article Commentary:

It is well known that type 2 diabetes is associated with elevated oxidative stress, which in turn is associated with an imbalance of the cardiac autonomic nervous system (involuntary nervous system of the heart). Thus, it is possible that antioxidants may have beneficial effects on the cardiac autonomic nervous system, particularly in type 2 diabetics. In this study, the effect of chronic administration of vitamin E (600 mg/day) or a placebo on the cardiac autonomic nervous system was investigated over a period of 4 months in 50 type 2 diabetic patients with cardiac autonomic neuropathy (nerve disease). Vitamin E significantly improved measures of diabetes (decreased glycated hemoglobin, plasma insulin) and oxidative stress (biomarkers of oxidation and indexes of oxidative stress). Vitamin E also significantly improved measures of cardiac autonomic nervous system balance (increased R-R interval, total power and decreased LF and the LF-HF ratio). Thus, this study showed that chronic vitamin E administration improved oxidative stress in type 2 diabetics, decreased plasma catecholamine concentration and improved the ratio of cardiac sympathetic to parasympathetic tone. Additional research is needed to determine the mechanism of action.

(JG Elliott)

Article Abstract:

Background: Type 2 diabetes is associated with elevated oxidative stress and declines in antioxidant defense. The disease is also characterized by an imbalance in the ratio of cardiac sympathetic to parasympathetic tone. Antioxidants, vitamin E in particular, may have beneficial effects on the cardiac autonomic nervous system through a decline in oxidative stress.

Objective: We investigated the possible effects of vitamin E on the cardiac autonomic nervous system, as assessed by analysis of heart rate variability, in patients with type 2 diabetes and cardiac autonomic neuropathy.

Design: In a double-blind randomized controlled trial, 50 patients with type 2 diabetes were assigned to treatment with vitamin E (600 mg/d) or placebo for 4 mo.

Results: The anthropometric characteristics of the patients remained unchanged throughout the study. Chronic vitamin E administration was associated with decreases in concentrations of glycosylated hemoglobin ($P < 0.05$), plasma insulin ($P < 0.05$), norepinephrine ($P < 0.03$), and epinephrine ($P < 0.02$); a lower homeostasis model assessment index ($P < 0.05$); and improved indexes of oxidative stress. Furthermore, vitamin E administration was associated with increases in the R-R interval ($P < 0.05$), total power ($P < 0.05$), and the high-frequency component of heart rate variability (HF; $P < 0.05$) and decreases in the low-frequency component (LF; $P < 0.05$) and the ratio of LF to HF ($P < 0.05$). Finally, change in the plasma vitamin E concentration was correlated with change in the LF-HF ratio ($r = -0.43$, $P < 0.04$) independently of changes in the homeostasis model assessment index and plasma catecholamines concentrations.

Conclusions: Chronic vitamin E administration improves the ratio of cardiac sympathetic to parasympathetic tone in patients with type 2 diabetes. Such an effect might be mediated by a decline in oxidative stress.

Full Citation:

Manzella D, Barbieri M, Ragno E, Paolisso G. Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes *Am J Clin Nutr* 2001; 73:1052-1057.

Protection by Vitamin C Against Aspirin-Induced Gastric Damage

Article Title:

Role of reactive oxygen metabolites in aspirin-induced gastric damage in humans: gastroprotection by vitamin C.

Article Commentary:

It is well established that therapy with non-steroidal anti-inflammatory drugs such as aspirin can produce gastric bleeding, gastrointestinal ulcers and erosions. It is also known that aspirin damages the gastric mucosa due to inhibition of protective prostaglandins and by direct action on this mucosa. Other evidence shows that aspirin causes release of reactive oxygen species and enhances lipid peroxidation through the release of activated neutrophils. In this study, 10 healthy males and 10 healthy females were given aspirin alone (400 mg twice daily) or aspirin (400 mg twice daily) plus vitamin C (480 mg twice daily) for 3 days and tested for measures of gastric injury and lipid peroxidation. The addition of vitamin C significantly reduced the gastric damage (micro-bleeding) induced by the aspirin and reversed the negative effects of aspirin including erosions, reactive oxygen release, lipid peroxidation, myeloperoxidase (measure of activated neutrophils), reduced gastric blood flow and reduced activity of the antioxidant enzymes, superoxide dismutase and glutathione peroxidase. Vitamin C also restored the levels of superoxide dismutase and glutathione peroxidase mRNAs to their regular levels. However, the gastric mucosal superoxide dismutase activity did not return to levels observed before aspirin administration. These results suggest that vitamin C protects against the gastric damage of aspirin due to its antioxidant activity.

(JG Elliott)

Article Abstract:

Background: The roles of active oxygen metabolites and anti-oxidative defenses in aspirin (ASA)-induced gastric damage have been little studied.

Aim: We determined the effects of aspirin (400 mg b.d.) with or without vitamin C (480 mg b.d.) for 3 days on gastric mucosa in human volunteers.

Methods: Gastric injury was assessed endoscopically; gastric blood flow, reactive oxygen release (quantified by chemiluminescence), lipid peroxidation, myeloperoxidase, superoxide dismutase and

glutathione peroxidase activity and intragastric vitamin C content were measured. Expression of superoxide dismutase and glutathione peroxidase mRNAs was assayed semi-quantitatively.

Results: ASA produced erosions, a marked increase in chemiluminescence, lipid peroxidation, and myeloperoxidase activity. It also resulted in a suppression of gastric blood flow, intragastric vitamin C levels, superoxide dismutase and glutathione peroxidase activities. The addition of vitamin C significantly attenuated gastric damage and reversed the effects of ASA on these parameters. Superoxide dismutase and glutathione peroxidase mRNAs were decreased in ASA-treated subjects; the addition of vitamin C restored their regular levels.

Conclusions: (i) free radical-induced lipid peroxidation and suppression of antioxidizing enzymes play an important role in gastric damage induced by aspirin; (ii) increased myeloperoxidase activity suggests activated neutrophils to be the major source of these radicals; (iii) vitamin C protects against ASA-induced damage due to its anti-oxidizing activity.

Full Citation:

Pohle T, Brzozowski T, Becker JC, Van Der Voort IR, Markmann A, Konturek SJ, Moniczewski A, Domschke W, Konturek JW. Role of reactive oxygen metabolites in aspirin-induced gastric damage in humans: gastroprotection by vitamin C. *Aliment Pharmacol Ther* 2001;15:677-687

High Dose Vitamin A and Vitamin E Supplementation After Photorefractive Keratectomy

Article Title:

A randomised, double masked, clinical trial of high dose vitamin A and vitamin E supplementation after photorefractive keratectomy.

Article Commentary:

In humans suffering from myopia (defective vision of distant objects), the surgical procedure for correction is an excimer laser surgery procedure called photorefractive keratectomy. Following surgery, the cornea must heal without complications to restore normal vision. It is thought that keratocytes and epithelial cells are mainly involved in the healing process. Corneal haze and myopic regression are the main complications after excimer laser surgery. It has been suggested that the disappearance of anterior stromal keratocytes after laser surgery is the initiating factor. The death of these cells may be due to the production of hydroxyl radicals formed by the excimer laser. An excimer laser uses a noble gas halide to generate radiation usually in the ultraviolet region of the spectrum and this radiation may produce free radicals. This study in Italy evaluated the effect of a high dose vitamin A (25,000 IU) and vitamin E (230 mg) supplementation or placebo on corneal re-epithelialization time (healing time), visual acuity and haze using two groups of 20 patients who underwent photorefractive keratectomy. The clinical outcomes from treatment were followed for up to 360 days. In the vitamin treated group compared to the placebo group, re-epithelialization time was faster ($p < 0.029$), haze incidence was reduced ($p < 0.035$) and uncorrected visual acuity was improved ($p < 0.043$). These results are encouraging and suggest that high dose vitamin A and E oral supplementation may accelerate the healing process and reduce corneal haze formation following photorefractive keratectomy surgery. **(JG Elliott)**

Article Abstract:

AIM: To evaluate the effect of a high dose vitamin A and E supplementation on corneal re-epithelialisation time, visual acuity and haze following photorefractive keratectomy (PRK).

METHODS: Two groups of 20 patients who underwent myopic PRK were supplemented with either 25 000 IU retinol palmitate and 230 mg [alpha] tocopheryl nicotinate or a placebo. Clinical outcomes were evaluated up to 360 days.

RESULTS: In the vitamin treated group, re-epithelialisation time was significantly faster ($p=0.029$) and haze incidence was reduced ($p=0.035$), especially for high myopic corrections ($p=0.043$). This group also reported a significantly better uncorrected visual acuity ($p=0.043$).

CONCLUSIONS: High dose vitamin A and E oral supplementation may accelerate re-epithelialisation time and may reduce corneal haze formation after PRK.

Full Citation:

Vertugno M, Maino A, Cardia G, Quaranta GM, Cardia L. A randomised, double masked, clinical trial of high dose vitamin A and vitamin E supplementation after photorefractive keratectomy. Br J Ophthalmol. 2001; 85:537-539.

Serum Carotenoids and Breast Cancer

Article Title:

Serum carotenoids and breast cancer.

Article Commentary:

Previously, ten epidemiological studies have been reported which examined the role of lycopene and breast cancer. Five of these studies based on dietary lycopene showed no association. The remaining studies based on serum lycopene or adipose lycopene showed an inverse association but only three studies had risk reductions which were statistically significant. This latest study performed a case-control analysis (270 cases and 270 controls) nested within a prospective cohort of 14, 275 women in New York (New York University Women's Health Study) during 1985-1994. For total carotenoids, the risk of breast cancer at the lowest quartile of serum carotenoids increased by 131% ($p < 0.0008$). For individual carotenoids, the risk of breast cancer at the lowest quartile of serum levels increased by 121% for β -carotene ($p < 0.006$), 108% for lutein ($p < 0.01$), 99% for α -carotene ($p < 0.0006$), 68% for β -cryptoxanthin ($p < 0.05$), 50% for lycopene ($p < 0.15$), and 12% for zeaxanthin ($p < 0.54$). Only lycopene and zeaxanthin had risk reductions that were not statistically significant. These results were strongest for total carotenoids and suggest that low intakes of carotenoids are associated with an increased risk of breast cancer.

(JG Elliott)

Article Abstract:

The consumption of vegetables and fruit may protect against many types of cancer, but research evidence is not compelling for breast cancer. Carotenoids are pigments that are present in most plants and have known antioxidant properties. Blood concentrations of carotenoids have been proposed as integrated biochemical markers of vegetable, fruit, and synthetic supplements consumed. In a case-control study (270 cases, 270 controls) nested within a cohort in New York during 1985–1994, the carotenoids lutein, zeaxanthin, β -cryptoxanthin, lycopene, α -carotene, and β -carotene were measured in archived serum samples using liquid chromatography. There was an evident increase in the risk of breast cancer for decreasing β -carotene, lutein, α -carotene, and β -cryptoxanthin. The risk of breast cancer approximately doubled among subjects with blood levels of β -carotene at the lowest quartile, as compared with those at the highest quartile (odds ratio = 2.21; 95% confidence interval (CI): 1.29, 3.79). The risk associated with the other carotenoids was similar, varying between 2.08 (95% CI: 1.11, 3.90) for lutein and 1.68 (95% CI: 0.99, 2.86) for β -cryptoxanthin. The odds ratio for the lower quartile of total carotenoids was 2.31 (95% CI: 1.35, 3.96). These observations offer evidence that a low intake of carotenoids, through poor diet and/or

lack of vitamin supplementation, may be associated with increased risk of breast cancer and may have public health relevance for people with markedly low intakes.

Full Citation:

Toniolo P, Van Kappel AL, Akhmedkhanov A, Ferrari P, Kato I, Shore RE, Rifoli E. Serum carotenoids and breast cancer. *Am J Epidemiol* 2001;153:1142-1147.

Low dietary Folate Intake Is Associated with an Excess Incidence of Acute Coronary Events

Article Title:

Low dietary folate intake is associated with an excess incidence of acute coronary events : the kuopio ischemic heart disease risk factor study.

Article Commentary:

Previous studies have reported a higher concentration of plasma homocysteine in patients with cardiovascular disease than in healthy controls. Also, in a number of cross-sectional studies, an inverse association has been observed between folate intake or serum folate and risk of cardiovascular disease. However, the results are inconsistent. The purpose of the Kuopio Ischemic Heart Disease Risk Factor Study was to test the hypothesis that high folate intake levels are associated with a decreased risk of acute coronary events in middle-age Finnish men free of prior CHD at the beginning of the study. During an average 10 year follow up, 199 acute coronary events occurred. All men in the highest quintile of folate intake (mean >297 µg/day) had a 55% reduction in risk of acute coronary events compared to men in the lowest quintile ($p < 0.008$). The association was stronger among non-smokers (64% reduction) than smokers (31% reduction) and in low alcohol users (73% reduction) than in moderate or heavy alcohol users (28% reduction). Vitamin B₆ showed no significant association and vitamin B₁₂ had only a weak association. **(JG Elliott)**

Article Abstract:

Background: Although several prospective studies have shown that low folate intake and low circulating folate are associated with increased risk of coronary heart disease (CHD), the findings are inconsistent.

Methods and Results: We studied the associations of dietary intake of folate, vitamin B₆, and vitamin B₁₂ with the risk of acute coronary events in a prospective cohort study of 1980 Finnish men 42 to 60 years old examined in 1984 to 1989 in the Kuopio Ischemic Heart Disease Risk Factor Study. Nutrient intakes were assessed by 4-day food record. During an average follow-up time of 10 years, 199 acute coronary events occurred. In a Cox proportional hazards model adjusted for 21 conventional and nutritional CHD risk factors, men in the highest fifth of folate intake had a relative risk of acute coronary events of 0.45 (95% CI 0.25 to 0.81, $P = 0.008$) compared with men in the lowest fifth. This association was stronger in nonsmokers and light alcohol users than in smokers and alcohol users. A high dietary intake of

vitamin B6 had no significant association and that of vitamin B12 a weak association with a reduced risk of acute coronary events.

Conclusions: The present work in CHD-free middle-aged men is the first prospective cohort study to observe a significant inverse association between quantitatively assessed moderate-to-high folate intakes and incidence of acute coronary events in men. Our findings provide further support in favor of a role of folate in the promotion of good cardiovascular health.

Full Citation:

Voutilainen S, Rissanen TH, Virtanen J, Lakka TA, Salonen JT. Low dietary folate intake is associated with an excess incidence of acute coronary events : the kuopio ischemic heart disease risk factor study. *Circulation* 2001; 103:2674-2680.