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311. Probl Endokrinol (Mosk) 1994 May-Jun;40(3):10-2

[Effect of high doses of tocopherol on the processes of lipid peroxidation and insulin secretion in patients with non-insulin-dependent diabetes mellitus].

[Article in Russian]

Balabolkin MI, Mikhailova EV, Kniazeva AP, Pankova SS

Forty-one patients with type II diabetes mellitus were examined, divided into four groups administered various types of treatment: (1) diets, (2) predian, (3) glibenclamide, and (4) sugar-reducing drugs and insulin. All the patients were prescribed vitamin E in daily doses 600 and 1200 mg. The results indicate that vitamin E in high doses stimulates pancreatic insulin-producing function and is conducive to normalization of lipid peroxidation no matter what kind of therapy is administered.

312. Vitamin E and Immunity

Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, Thompson C, Pedrosa MC, Diamond RD, Stollar BD JAMA (1997 May 7) 277(17):1380-6

OBJECTIVE: To determine whether long-term supplementation with vitamin E enhances in vivo, clinically relevant measures of cell-mediated immunity in healthy elderly subjects. **DESIGN:** Randomized, double-blind, placebo-controlled intervention study. **SETTING AND PARTICIPANTS:** A total of 88 free-living, healthy subjects at least 65 years of age. **INTERVENTION:** Subjects were randomly assigned to a placebo group or to groups consuming 60, 200, or 800 mg/d of vitamin E for 235 days. **MAIN OUTCOME MEASURES:** Delayed-type hypersensitivity skin response (DTH); antibody response to hepatitis B, tetanus and diphtheria, and pneumococcal vaccines; and autoantibodies to DNA and thyroglobulin were assessed before and after supplementation. **RESULTS:** Supplementation with vitamin E for 4 months improved certain clinically relevant indexes of cell-mediated immunity in healthy elderly. Subjects consuming 200 mg/d of vitamin E had a 65% increase in DTH and a 6-fold increase in antibody titer to hepatitis B compared with placebo (17% and 3-fold, respectively), 60-mg/d (41% and 3-fold, respectively), and 800-mg/d (49% and 2.5-fold, respectively) groups. The 200-mg/d group also had a significant increase in antibody titer to tetanus vaccine. Subjects in the upper tertile of serum alpha-tocopherol (vitamin E) concentration (>48.4 micromol/L [2.08 mg/dL]) after supplementation had higher antibody response to hepatitis B and DTH. Vitamin E supplementation had no effect on antibody titer to diphtheria and did not affect immunoglobulin levels or levels of T and B cells. No significant effect of vitamin E supplementation on autoantibody levels was observed. **CONCLUSIONS:** Our results indicate that a level of vitamin E greater than currently recommended enhances certain clinically relevant in vivo indexes of T-cell-mediated function in healthy elderly persons. No adverse effects were observed with vitamin E supplementation.

313. Ann N Y Acad Sci 1998 Nov 20;854:352-60

The effect of long-term dietary supplementation with antioxidants.

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The impact of diet and specific food groups on aging and age-associated degenerative diseases has been widely recognized in recent years. The modern concept of the free radical theory of aging takes as its basis a shift in the antioxidant/prooxidant balance that leads to increased oxidative stress, dysregulation of cellular function, and aging. In the context of this theory, antioxidants can influence the primary "intrinsic" aging process as well as several secondary age-associated pathological processes. For the latter, several epidemiological and clinical studies have revealed potential roles for dietary antioxidants in the age-associated decline of immune function and the reduction of risk of morbidity and mortality from cancer and heart disease. We reported that long-term

supplementation with vitamin E enhances immune function in aged animals and elderly subjects. We have also found that the beneficial effect of vitamin E in the reduction of risk of atherosclerosis is, in part, associated with molecular modulation of the interaction of immune and endothelial cells. Even though the effects of dietary antioxidants on aging have been mostly observed in relation to age-associated diseases, the effects cannot be totally separated from those related to the intrinsic aging process. For modulation of the aging process by antioxidants, earlier reports have indicated that antioxidant feeding increased the median life span of mice to some extent. To further delineate the effect of dietary antioxidants on aging and longevity, middle-aged (18 mo) C57BL/6NIA male mice were fed ad libitum semisynthetic AIN-76 diets supplemented with different antioxidants (vitamin E, glutathione, melatonin, and strawberry extract). We found that dietary antioxidants had no effect on the pathological outcome or on mean and maximum life span of the mice, which was observed despite the reduced level of lipid peroxidation products, 4-hydroxynonenol, in the liver of animals supplemented with vitamin E and strawberry extract (1.34 0.4 and 1.6 0.5 nmol/g, respectively) compared to animals fed the control diet (2.35 1.4 nmol/g). However, vitamin E-supplemented mice had significantly lower lung viral levels following influenza infection, a viral challenge associated with oxidative stress. These and other observations indicate that, at present, the effects of dietary antioxidants are mainly demonstrated in connection with age-associated diseases in which oxidative stress appears to be intimately involved. Further studies are needed to determine the effect of antioxidant supplementation on longevity in the context of moderate caloric restriction.

314. *Biofactors* 1998;7(1-2):113-74

Vitamins E plus C and interacting nutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer.

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Antioxidants are crucial components of fruit/vegetable rich diets preventing cardiovascular disease (CVD) and cancer: plasma vitamins C, E, carotenoids from diet correlate prevalence of CVD and cancer inversely, low levels predict an increased risk of individuals which is potentiated by combined inadequacy (e.g., vitamins C + E, C + carotene, A + carotene); self-prescribed rectification of vitamins C and E at adequacy of other micronutrients reduce forthcoming CVD, of vitamins A, C, E, carotene and nutrients also cancer; randomized exclusive supplementation of beta-carotene +/- vitamin A or E lack benefits except prostate cancer reduction by vitamin E, and overall cancer reduction by selenium; randomized intervention with synchronous rectification of vitamins A + C + E + B + minerals reduces CVD and counteracts precancerous lesions; high vitamin E supplements reveal potentials in secondary CVD prevention. Plasma values desirable for primary prevention: > or = 30 $\mu\text{mol/l}$ lipid-standardized vitamin E (alpha-tocopherol/cholesterol > or = 5.0 $\mu\text{mol/mmol}$); > or = 50 $\mu\text{mol/l}$ vitamin C aiming at vitamin C/vitamin E ratio > 1.3-1.5; > or = 0.4 $\mu\text{mol/l}$ beta- (> or = 0.5 $\mu\text{mol/l}$ alpha+ beta-) carotene. CONCLUSIONS: In CVD vitamin E acts as first risk discriminator, vitamin C as second one; optimal health requires synchronously optimized vitamins C + E, A, carotenoids and vegetable nutrients.

315. *Leukemia* 1997 Sep;11(9):1546-53

Induction of the differentiation of HL-60 promyelocytic leukemia cells by vitamin E and other antioxidants in combination with low levels of vitamin D3: possible relationship to NF-kappaB.

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Epidemiological studies have provided evidence that diets rich in antioxidant nutrients may reduce the risk of cancer. To evaluate the possibility that dietary phytochemicals with antioxidant potential would create an environment capable of affecting the differentiation of HL-60 leukemia cells, we measured the effects of vitamin E and other dietary antioxidants on the differentiation produced by low levels of vitamin D3 and analogs thereof. Vitamin E succinate and other antioxidant compounds (ie butylated hydroxyanisole, beta-carotene and lipoic acid) used alone had no significant effect on the differentiation of

HL-60 cells; however, these agents markedly increased the differentiation produced by vitamin D3. Previous studies from this laboratory have shown that a sequence-specific antisense phosphorothioate oligonucleotide to the Rel A subunit of NF-kappaB enhanced the differentiation of HL-60 cells produced by several inducing agents. Consistent with these observations, vitamin E succinate caused a marked reduction in the nuclear content of NF-kappaB both in the presence and absence of vitamin D3. These findings suggest that NF-kappaB may be a factor in regulating the differentiation of myeloid leukemia cells. The results also indicate that combinations of vitamin D3 and analogs thereof with dietary antioxidants may be useful in overcoming the differentiation block present in acute promyelocytic leukemia cells.

316. *Altern Med Rev* 1999 Dec;4(6):414-23

Therapeutic uses of vitamin E in prevention of atherosclerosis.

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The purpose of this review is to present the evidence-based pharmacotherapeutic properties of vitamin E and provide clinical recommendations for use in the arena of atherosclerosis. **Methods:** A literature search was conducted from 1966 through March 1999. All usable papers were retrieved, with large, randomized, double-blinded, clinical trials and epidemiological trials receiving emphasis. **Results:** Vitamin E, a lipid soluble vitamin, is a potent antioxidant. Several epidemiological studies have demonstrated positive relationships between vitamin E intake and the prevention of atherosclerotic heart disease; however, only one, large randomized clinical trial (The CHAOS Trial) has been conducted using more than 400 IU per day of vitamin E. Positive outcomes included a 77-percent reduction in nonfatal myocardial infarction (MI), but no corresponding reduction in mortality. Several large clinical trials are ongoing, investigating vitamin E for the prevention of atherosclerosis. Much less work has been undertaken studying vitamin E for prevention of cerebro- and peripheral vascular disease, but there appears to be promise in these areas as well. **Conclusions:** On the basis of the literature search, the authors recommend 400 IU or more per day of vitamin E to patients at high risk or already diagnosed with coronary artery disease. Vitamin E supplementation may also be beneficial in the prevention of cerebro- and peripheral vascular diseases.

317. *Atherosclerosis* 1999 Dec;147(2):297-307

Effect of vitamin E on human aortic endothelial cell production of chemokines and adhesion to monocytes.

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Epidemiological and clinical studies indicate that vitamin E may reduce the risk of cardiovascular disease (CVD). Modulation of adhesion molecule expression and chemokine production by vitamin E may contribute to its beneficial effect. In this study we found that the enrichment of confluent human aortic endothelial cells (HAEC) or U937 monocytic cells with increasing doses of vitamin E (d-alpha-tocopherol, 20, 40, and 60 micromol/l for 20 h) inhibited their adhesion when either or both cell types were stimulated with interleukin (IL)-1beta. Enrichment of HAEC with the same doses of vitamin E suppressed IL-1beta-stimulated expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin). Supplementation with increasing doses of vitamin E up to 60 micromol/l was not effective in preventing spontaneous production of monocyte chemoattractant protein-1 (MCP-1), but supplementation with vitamin E at 60 micromol/l reduced IL-8 production significantly. However, IL-1beta-induced productions of both MCP-1 and IL-8 were dose-dependently suppressed by enrichment of cells with vitamin E. Vitamin E, at the doses used, did not significantly change the spontaneous production but dose-dependently inhibited the IL-1beta-induced production of inflammatory cytokine IL-6. We concluded that vitamin E could inhibit production of chemokines and inflammatory cytokines, in addition to inhibiting adhesion of HAEC to monocytes by reducing expression of adhesion molecules when cells were activated with an inflammatory cytokine. These mediators are actively involved in the pathogenesis of atherosclerosis. Therefore, their inhibition by vitamin E may contribute to vitamin E's reported reduction in risk of CVD.

318. *Am J Cardiol* 1998 Aug 15;82(4):414-7

Cost-effectiveness of vitamin E therapy in the treatment of patients with

angiographically proven coronary narrowing (CHAOS trial). Cambridge Heart Antioxidant Study.
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Epidemiologic studies have suggested that vitamin E (alpha-tocopherol) may play a preventive role in reducing the incidence of atherosclerosis. The aim of this paper was to conduct a cost-effectiveness analysis of vitamin E supplementation in patients with coronary artery disease using data from the Cambridge Heart Antioxidant Study (CHAOS). The study compared cost-effectiveness in the context of Australian and United States (US) health care utilization. The main clinical outcome used in the economic evaluation was the incidence of acute myocardial infarction (AMI) which was nonfatal. Utilization of health care resources was estimated by conducting a survey of Australian clinicians and published Australian and US cost data. Cost savings of \$127 (A\$181) and \$578/patient randomized to vitamin E therapy compared with patients receiving placebo were found for Australian and US settings, respectively. Savings in the vitamin E group were due primarily to reduction in hospital admissions for AMI. This occurred because the vitamin E group had a 4.4% lower absolute risk of AMI than did the placebo group. Less than 10% of health care costs in the Australian evaluation was due to vitamin E (\$150 [A\$214/patient]). Our economic evaluation indicates that vitamin E therapy in patients with angiographically proven atherosclerosis is cost-effective in the Australian and US settings.

319. Can J Cardiol 1997 May;13(5):533-5
Acetylsalicylic acid and vitamin E in prevention of arterial thrombosis.
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Both acetylsalicylic acid and vitamin E have been shown to be beneficial in the prevention of stroke and heart attacks. It is implied that their combination in the treatment of thrombotic complications of atherosclerosis may have added benefits. It is suggested that vitamin E may work as a platelet lysosome stabilizing agent.

320. Cleve Clin J Med 2000 Apr;67(4):287-93
The HOPE study. Ramipril lowered cardiovascular risk, but vitamin E did not.
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The Heart Outcomes Prevention Evaluation (HOPE) study found that the ACE inhibitor ramipril can lower the risk of atherosclerotic disease events and death in patients without heart failure but with known atherosclerosis or with diabetes plus at least one cardiovascular risk factor. This benefit was independent of ramipril's effect on blood pressure. Additional benefits were a reduced risk of diabetic nephropathy in diabetic patients, and a lower likelihood of newly diagnosed diabetes. On the other hand, vitamin E in the doses and duration studied (400 IU/day for 4.5 years) did not lower risk significantly.