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Vitamin E in Cardiovascular Disease

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Vitamin E was first introduced in 1946 as a therapeutic agent for angina.At that time, it was felt to significantly reduce angina in over 90% of patients studied.[1] However, three further controlled trials[2,3,4] showed no benefit over placebo in short-term treatment of angina. The use of vitamin E was abandoned in 1950, and it was not reconsidered until 1973 when a trial of 22 patients again heralded a statistically significant advantage of vitamin E over placebo in anginal therapy.[5] Further randomized trials using doses of vitamin E up to 3200 IU daily[6,7] showed no benefit, and again therapeutic use of vitamin E was discontinued. As techniques in molecular biology improve, the mechanisms of atherosclerosis have been elucidated, and vitamin E has re-emerged as possibly conferring benefit to patients suffering from coronary disease.

Postulated Mechanisms

Vitamin E is an antioxidant agent that may play a role in the pathophysiology of cardiovascular disease by either (i) attenuating levels of harmful oxygen free radicals which may damage myocardium, or (ii) reducing oxidation of molecules which may secondarily play a role in disease development.There is evidence that oxygen free radicals generated during reperfusion of ischemic myocardium contribute to myocardial cell injury.[8,9] Transient release of lipid peroxides occurs after percutaneous transluminal coronary angioplasty (PTCA),[10] and during coronary artery bypass grafting (CABG).[11] Coronary artery endothelial dysfunction worsens with increased susceptibility to oxidation, as measured by a vasoconstrictor response to acetylcholine in hypercholesterolemic patients treated with cholesterol-lowering agents.[12] One key player in the development of atherosclerosis is the foam cell – a macrophage laden with low-density lipoprotein (LDL) – which is responsible

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for endothelial damage and plaque formation. Macrophages have a very low affinity for circulating LDL, yet oxidation of the LDL molecule allows it to interact with a specific receptor on the macrophage, permitting rapid uptake. Vitamin E can attenuate the oxidation of LDL[13,14] and thus theoretically reduce the rate of atherosclerosis. Vitamin E may also have a beneficial effect on the vascular endothelium via reduced platelet adhesion to exposed collagen[15] and inhibition of smooth muscle cell proliferation.[16] Vitamin E has been shown in vivo to have a dose related effect on the oxidation of LDL. A statistically significant reduction in oxidation does not occur until doses of 400 IU per day.[17] However, little further reduction in LDL oxidation and production of conjugated dienes occurs with doses greater than 800 IU daily.

Epidemiologic Data

There appears to be no relation between serum vitamin E level and the prevalence of cardiovascular disease.[18,19,20] However, this data is based on retrospective analysis, and among two of the largest trials, vitamin E levels were calculated from samples of venous blood that had been stored at -20 degrees Celsius for up to seven years.[21,22] Two large prospective case-control studies on female nurses[23] and male health professionals[24] examined the relationship between intake of vitamin E and the risk of coronary events including fatal and non-fatal myocardial infarction (MI), PTCA and CABG. Both studies found a significant risk reduction in persons who were in the highest quintiles of median daily intake (208 IU[23] and 419 IU[24]). It is noteworthy that patients in higher quintiles of vitamin E intake also had better overall health profiles: better diet, more regular exercise, and increased use of Aspirin. A third study of 5133 Finnish men and women showed only a trend towards lower coronary heart disease events in those with higher intake of vitamin E.[25] However, this population had a very low vitamin E intake even in the highest tertile, with very few patients on vitamin E supplementation. Overall, there appears to be some possible benefit of vitamin E supplementation based on epidemiological evidence.

Clinical Trials

As mentioned previously, early clinical trials evaluating the efficacy of vitamin E focused on the treatment of angina pectoris. Most of these trials failed to show a benefit of vitamin E as an anti-anginal medication.[6,7] It was not until the early 1990's that clinical trials focused on cardiovascular morbidity and mortality in the investigation of vitamin E efficacy. One of the largest trials that indirectly looked at the effect of vitamin E on IHD randomized 29,133 male smokers between the ages of 50-69 years to either 50 IU daily of vitamin E alone, 20 mg of beta carotene alone, both, or placebo.[26] The primary endpoint was development of lung cancer; however, post hoc analysis showed a reduction in mortality from ischemic heart disease from 75 to 71 deaths per 10,000 patient years. While the statistical significance of this reduction is uncertain, the data suggests that one would need to treat 250 patients over 10 years to prevent one death from IHD. Further post-hoc analysis of the data from this trial revealed no reduction

in angina between groups of patients who were or were not treated with vitamin E.[27] Of note, this trial used only 50 IU of vitamin E, and cardiovascular morbidity and mortality was not examined as a primary endpoint.

A recent study examined the effect of 1200 IU of daily vitamin E versus placebo on the incidence of restenosis of coronary arteries 4 months after PTCA.[28] Patients who developed symptoms of restenosis prior to 4 months of therapy were withdrawn from the study, possibly introducing selection bias. Angiographic data suggested no benefit of vitamin E in reducing progression of restenosis.

A recent double blind, randomized, placebo-controlled trial assessed the effect of 400 IU and 800 IU of vitamin E on the incidence of cardiovascular death and non-fatal MI.[29] Two thousand and two patients were enrolled in the study with a median follow-up of 510 days. Initially, patients were recruited to receive 800 IU of vitamin E (546 patients), but later recruits were given 400 IU (489 patients) because of data suggesting this dose would be adequate. Overall, patients in the vitamin E arm had a relative risk of 0.53 (95% CI 0.34-0.83, p=0.005) for combined cardiovascular death and non-fatal MI. The relative risk for non-fatal MI alone was 0.23 (0.11-0.47), yet the relative risk for cardiovascular death was 1.18 (0.62-2.27), with slightly higher overall mortality in the vitamin E group (3.5% versus 2.7%, p=0.31).

Although the above data is encouraging, there are several concerning issues. If vitamin E works by reducing atherosclerosis, a median follow-up of only 510 days makes the biological plausibility of this effect seem unlikely. There is no evidence in the literature to suggest that vitamin E may regress atherosclerosis or reduce the incidence of plaque rupture. Since only patients with angiographically proven coronary artery disease were entered into the study, the mechanism by which vitamin E may act in such a short time is poorly understood. Patients were enrolled into the study immediately after coronary angiography, with plans to have PTCA or CABG. However, there is no mention of which patients underwent either intervention. Conceivably, if more patients in the vitamin E arm underwent PTCA or CABG, the results of the study would be biased.

Furthermore, complications of either intervention which could affect total event rate were not mentioned. Given the lack of identifiable adverse effects of vitamin E, explaining the increased overall mortality in the vitamin E group is difficult. Interestingly, this study also quotes a relative risk of 2.14 for cardiovascular death or non-fatal MI in patients treated with beta-blockers (compared to those not receiving such treatment), which suggests either a bias in patient selection or a detection of a harmful effect of beta-blocker therapy not previously recognized. Although this study does provide encouraging results suggesting reduction in non-fatal MI in patients treated with vitamin E, the above issues should be considered before accepting this data.

Conclusions

Basic research and epidemiological data suggest a benefit of vitamin E in prevention of coronary heart disease. It has been suggested that a dose of 400 IU of

vitamin E has significant in vivo effects on oxidation of LDL which may reduce the development of atherosclerosis. Although serum levels of vitamin E do not correlate with incidence of cardiac disease, patients in higher quintiles of vitamin E intake have a reduced risk of CHD based on evidence from case-control studies. Randomized placebo-controlled trials of vitamin E use suggest a reduction in non-fatal MI in patients taking vitamin E supplementation of at least 400 IU daily. However, post-hoc analysis, short-term follow-up, and biological implausibility of these studies make their interpretation difficult.

Several ongoing studies may improve the current understanding of the role of antioxidants in cardiovascular medicine. The Heart Outcomes Protection Evaluation study will assess the use of vitamin E in over 9000 patients with established cardiovascular disease.[30] The St. Michael's Hospital Division of Cardiology is studying the effect of vitamin E on coronary regression in type II diabetic patients. Another study by the collaborative group of the Primary Prevention Project[31] will evaluate the effect of vitamin E and Aspirin on over 2500 patients without cardiovascular disease, but with one or more cardiovascular risk factor. Over 35% of this patient population is diabetic, and over 50% have two or more risk factors.

In summary, a clear recommendation regarding routine vitamin E use cannot be made. It is possible that patients who already have coronary artery disease benefit from vitamin E in many ways: reduced platelet adhesion, reduced smooth muscle proliferation, attenuation of oxygen free radicals during ischemia, and reduced coronary vasoconstriction in response to acetylcholine. Furthermore, patients without evidence, but at risk for coronary artery disease, may benefit from vitamin E through prevention of atherosclerosis mediated by a reduction in LDL oxidation. Further studies need to be done to confirm this effect and to identify the patients who might benefit from such an intervention.

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Upcoming Scientific Meetings

4-7 August 96
44th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand
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25-29 August 96
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Birmingham, United Kingdom
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25-29 September 96
The Royal College of Physicians and Surgeons of Canada 65th Annual Meeting
Halifax, Nova Scotia
(Royal College of Physicians and Surgeons of Canada)
Tel.: 613-730-8177

3-5 October 96
New Aspects of Drug Therapy in Cardiovascular Disease
Sophia Antipolis, France
(European Congress Organization)
Tel.: 33 92 94 76 00

19-22 October 96
1st European Research Conference on Blood Pressure and Cardiovascular Disease
Noordwijkerhout, The Netherlands
(Leeuwenhorst Congress Center)
Tel.: 31 2523 78888

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Canadian Cardiovascular Society 1996 Annual Meeting
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(Canadian Cardiovascular Society)
Tel.: 604-681-5226

10-13 November 96
69th Scientific Sessions of the American Heart Association
New Orleans, Louisiana, USA
(American Heart Association)
Tel.: 214-706-1511

Abstracts of Interest

Antioxidant Supplementation Reduces the Susceptibility of Low Density Lipoprotein (LDL) to Oxidation in Patients with Coronary Artery Disease

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We studied the effect of a combination of vitamin E, vitamin C, and beta-carotene on the susceptibility of LDL, to oxidation, as determined by lag phase (minutes), in a 12 week clinical trial of 45 patients with coronary artery disease (CAD), mean age 60.6+ 8.6 years. Subjects were randomized to one of the following interventions (15 each): 1) placebo; 2) vitamin E 400 IU, vitamin C 500 mg, beta-carotene 12 mg (mid dose); or 3) vitamin E 800 IU, vitamin C 1000 mg, beta-carotene 24 mg (high dose). Two baseline, one 6 week and two 12 week measurements of standard lipoproteins and lag phase (Lag) were obtained. Compared to baseline, 12 week plasma concentrations of alpha-tocopherol increased 2 and 3 fold; vitamin C increased 1.5 and 2 fold; and beta-carotene increased 6 and 10 fold in the mid and high dose groups respectively with no change in the placebo group. Lag significantly increased from baseline (190.1+63.8) to 12 weeks (391.1+153.0) in the high dose group ($p<0.01$). No significant within group change for Lag was observed for the placebo or mid dose group at 12 weeks. A significant between group difference in Lag was observed at 12 weeks, attributable to high dose vs. placebo ($p<0.05$). Results were not altered by adjusting for age, sex or other significant clinical predictors of lag phase. We conclude supplementation with a combination of antioxidant vitamins reduces the susceptibility of LDL to oxidation in patients with CAD. These results may be significant for the secondary prevention of CAD.

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A randomised controlled trial of vitamin E in patients with coronary disease: The Cambridge heart antioxidant study (Chaos)

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Vitamin E is thought to play an important endogenous role in prevention of atherosclerosis, through inhibition of oxidation of low density lipoprotein. Some epidemiological data show an association between high dietary intake or high serum levels of a-tocopherol and reduced risk of ischaemic heart disease. We designed the CHAOS trial to test the hypothesis that treatment with a high dose of a-tocopherol (400 or 800IU/d) will reduce the subsequent risk of cardiovascular death and nonfatal myocardial infarction (MI) in patients with ischaemic heart disease. The study was double blind, placebo-controlled with stratified randomisation. 2002 patients with angiographically-proven coronary atherosclerosis were enrolled and followed up for a median of 510 days (3 -978). Treatment raised serum a-tocopherol levels from mean 34.2 µM/L to 51.1 µM/L with 400IU/d and 64.5 µM/L with 800 IU/d ($p < 0.001$). Vitamin E reduced the risk of cardiovascular death and non-fatal MI (OR 0.57 (0.36-0.89); P=0.014) and reduced the risk of non-fatal MI alone (OR 0.23 (0.11-0.47); P<0.001). Patients with a higher treatment level of lipid-adjusted serum a-tocopherol had a lower risk of events (OR 0.23 (0.06 - 0.84); P=0.026). Kaplan Meier survival curves for nonfatal MI are shown (broken line = placebo, survival time in days).

We conclude that Vitamin E therapy is effective in reducing the incidence of major cardiovascular events in patients with coronary disease, with beneficial effects apparent after one year of treatment.

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