Vitamin E and its Effects on Endothelial Function in Healthy People, Diabetics and People with known Coronary Artery Disease: Who will benefit the most from this supplement?

Rebecca Press

A. Study Purpose and Rationale

There are about 1.5 million myocardial infarctions each year in the United States and 450,000 of these MIs result in death. There is also significant morbidity from coronary artery disease (CAD). Often CAD is first detected at a late stage of the disease when treatment options may be limited to invasive techniques including percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, both of which carry significant risks. Ideally, one would want to prevent or slow the progression of atherosclerosis at an early stage of the disease with an intervention that is easy to comply with and has few or no associated risks. Vitamin E has been under investigation for many years for its role in reducing the complications of ischernic heart disease. This study will attempt to clarify who may benefit the most from supplemental vitamin E.

The first step in the development of atherosclerosis is thought to be a process known as lipid peroxidation. The oxidation of low density lipoproteins (LDL) is due to free radicals which are formed from a variety of processes including smoking, radiation and oxygen metabolism. The oxidized lipoproteins are then taken up into macrophages via a scavenger receptor to form cholesterol-laden foam cells which are characteristic of a fatty streak, an early atherosclerotic lesion. Oxidized LDL also stimulates monocyte recruitment and differentiation to macrophages and is cytotoxic to vascular cells, which enhances the progression of atherosclerosis. Vitamin E is known as a chain breaking antioxidant that can prevent the propagation of free radical damage, thereby increasing the resistance of LDL to oxidation and subsequently decreasing the formation of atherosclerotic plaques. There are additional mechanisms that have been proposed as to how vitamin E may improve outcomes in patients with CAD. For example, vitamin E has been shown to reduce platelet aggregation and adhesion, to improve fasting and postprandial endothelial function, to reduce postprandial hyperglycernia and preserve nitric-oxide mediated vasodilation (1).

In studying the effects of vitamin E, one may ideally want to look at endpoints such as fatal/non-fatal MIs, angina or CAD assessed by cardiac catheterization. However, due to both the length of time needed for follow up and/or the risks associated with an invasive procedure, these endpoints are often impractical. Therefore, endothelial dysfunction of the brachial artery has been used as a surrogate for CAD. Anderson et al. (3) studied 50 patients who were referred to the cardiac catheterization laboratory. Acetylcholine was infused during the study and coronary vasomotor response was measured. Less than 24 hours later a second study was done on the same patients to measure the change in brachial artery diameter in response to reactive hyperemia. They found that patients with coronary artery endothelial dysfunction also had decreased brachial artery vasodilator response.

There have been many studies performed to assess the effectiveness of Vitamin E on endothelial function and/or coronary artery disease. Two prospective observational studies, the Nurses' Health Study (6) and the Health Professionals Follow-up Study (7), showed an association between supplemental intake of vitamin E (200 - 400 IU/day) and a lower risk of ischernic heart disease. The inverse relationship between vitamin E and coronary artery disease remained after adjusting for other CAD risk factors in both of the study groups. The Cholesterol Lowering Atherosclerosis Study (CLAS) used a 7-day dietary record and concluded that there is an association between supplementary vitamin E intake

and reduction of coronary artery disease progression (16). These epidemiological correlations, although statistically significant, do not prove a cause and effect relationship.

Two short-term prospective intervention studies showed positive effects of vitamin E supplementation. Kugiyama et al. (8) studied patients with hicrh levels of remnant lipoproteins vs. low lipoproteins. The patients received alpha-tocopherol or placebo for 4 weeks. They found that the patient with high lipoprotein levels had improved impairment of endothelium-dependent vasodilation. Neunteufl et al. (9) showed improved brachial artery vasodilation after 4 weeks of vitarnin E and simvastatin compared to simvastatin alone or no treatment.

There have also been several intervention studies in smaller groups that have had mixed results. Simons, et al (10), showed no difference between 10 weeks of placebo vs. vitamin E 1000 IU/day on the flow-mediated brachial artery dilation. One possible explanation for this is that it has been shown that vitamin E may have prooxidant effects at higher doses (5). In another study by Gilligan, et al (l 1), endothelial function was not changed after I month of the antioxidant vitarnin supplements, beta-carotene 30mg, ascorbic acid 1000mg, vitamin E 800 IU. This may be explained by the possible negative effects of a combination of antioxidants (5). The results from the ATBC Study (Alpha-Tocopherol Beta-Carotene Cancer Prevention) also failed to show a significant difference between placebo and vitamin E supplementation in male smokers with a history of previous MI (12). The low dose of 50 IU/day of vitamin E may in part explain the lack of benefit. Also, this finding indicates that Vitamin E's most powerful mechanism of action might be through increasing the resistance of LDL to oxidation and therefore would be best used to prevent progression of atherosclerosis . This finding was supported by Heitzer et al. (13) who found an association between vitamin E and improved endothelium-dependent relaxation in subjects who smoked and who had hypercholesterolemia but not in subjects who had hypercholesterolemia or who smoked. This again helps support the theory that vitamin E may exert its effects by increasing the resistance of LDL to oxidation. Since the hypercholesterolemic smokers may be more prone to LDL oxidation, they may show the most benefit from vitamin E. The CHAOS study (14) found that treatment with alpha-tocopherol in men and women with CAD reduced the risk of non-fatal MIs. There was however, a nonsignificant greater number of deaths in the alpha-tocopherol vs. the placebo group.

This study proposes that vitamin E may be more beneficial in patients with some baseline endothelial dysfunction due to a CAD risk factor than in healthy people or in patients with known CAD. A comparison will be made between patients with no known risk factors for CAD, patients with diabetes mellitus, a known risk factor for CAD, and patients with known CAD.

B. Study Design and Statistical Analysis

A prospective single-center intervention study will be performed.

Three groups of study patients will be recruited to participate. The three groups will be divided into normals, patients with diabetes mellitus and patients with known CAD. The age range will be from 50 to 80 years.

The three groups will have their endothelial function measured using a non-invasive test of high-resolution ultrasound. The ultrasound will be used to measure brachial artery diameter by a technique similar to the one described by Celermajer et al. (4). After an overnight fast of 12 hours the patients will be brought to the ultrasound laboratory in Presbyterian Hospital. The patients will be laying at rest for 10 minutes and the ultrasound transducer will be placed 2 to 3 cm. above the elbow and the artery will be scanned in the longitudinal direction. A blood pressure cuff will then be inflated to 200mmRg for 4 minutes and another brachial artery diameter will be measured 60 seconds after cuff deflation. This well be recorded as % change in diameter. The patients will then be given an oral fat load consisting of a McDonalds Big Mac and large French fries which has a total of 48gm of fat. The fat load will be used since this has been shown to produce endothelial dysfunction (5) and the brachial artery diameter will be measured 2 hours post fat load. This measurement will be recorded as % change of diameter. All study participants will then be given an oral vitamin E supplement of 400 IU/day for six

months. During the study period the participants will continue their baseline diet and lifestyle. At the end of the 6 months the brachial artery diameter measurements will again be done by the above technique, pre and post fat load.

A comparison between the groups will be done using an analysis of variance (ANOVA).

Each group will contain about 150 subjects in order to detect a 3% change with power of 80 % and alpha of 0.05.

The ultrasound readers used in this study will be blinded to which group the patient is in. The interobserver variability at Presbyterian Hospital of brachial artery diameter using the above technique has been shown to be 2.7% and the intraobserver variability, 1.3%.

C. Study Procedures

Brachial artery ultrasound will be used by the technique described above and carries no risk to the patient. The only risk is possible transient arm discomfort from inflation of the blood pressure cuff.

D. Study Drugs - Vitamin E

Vitamin E is a lipid-soluble antioxidant found in vegetable oils, cereal grains, seeds, nuts, egg yolk, liver and milk and the RDA is 15 IU/day. Most supplements are in the form of alphatocopherol and this is the most biologically active form of vitamin E. Animal studies of vitamin E safety have shown no evidence of mutagenesis, carcinogenesis or teratogenesis. Double-blind human studies with oral dosage up to 3.2 grams/day resulted in few side-effects. The side effects, such as diarrhea, fatigue, weakness and breast soreness, have been case reports that were not supported in larger studies. Vitamin E is contraindicated in people with vitamin K deficiency since vitamin E increases vitamin K requirement and may exacerbate a blood coagulation defect. Up to 1000 IU/day has now been accepted as safe (15). This study will use 400 IU/day of alphatocopherol.

E. Medical Devices

N/A

F. Study Questionnaires

none

G. Study Subjects

As stated above, the subjects will be divided into three groups, aged 50 to 80. The normals will have no hypertension, diabetes mellitus, hypercholesterolemia and no known history of CAD. The diabetics will have no hypertension, hypercholesterolernia and no history of angina or known CAD. The third group of patients will have known CAD either by coronary catheterization, an abnormal exercise stress test or history of MI. Patients on warfarin or with vitamin K deficiency will be excluded. Patients already on antioxidant supplements will also be excluded. Each group will have an equal number of men and women and will have equal numbers of Whites, Blacks and Hispanics.

H. Recruitment of Subjects

Study patients will be hospital employees and patients at the AIM j clinics at CPMC. Flyers will be posted both in the hospital and at AIM and residents will be asked to help recruit volunteers.

I. Confidentiality of Study Data

The patients' names will not be used and the record linking name to a code number will be secure with the principal investigator.

J. Potential Conflict of Interest

none

K. Location of the Study

CPMC

L. Potential Risks

As described above in sections C and D.

M. Potential Benefits

Patients will have the option of staying on vitamin E after the end of the study period and will continue to follow up with their PMD in AIM to receive advice on CAD prevention and treatment.

N. Alternative Therapies

none

O. Compensation to Subjects

none

P. Costs to Subjects

none

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

none

S. References

1. Vogel R. Antioxidants are Useful in Preventing Cardiovascular Disease: A Debate. Prooxidants. Can J. Cardiol. 1999:15(Supple B):23B - 25B.
2. Diaz, MN, et al. Antioxidants and Atherosclerotic Heart Disease. NEJM. 1997;337: 408-416.
3. Anderson, TJ, et al. Close Relation of Endothelial Function in the Human Coronary and Peripheral Circulations. J Am Coll Cardiol. 1995; 26: 1235-41.
4. Celermajer DS, et al. Non-invasive Detection of Endothelial Dysfunction in Children and Adults at Risk of Atherosclerosis. The Lancet. 1992; 340:1111-1115.

5. Vogel RA, et al. Effect of a Single High-Fat Meal on Endothelial Function in Healthy Subjects. Am J Cardiol. 1997; 79: 350-354.
6. Stampfer, MJ, et al. Vitamin E Consumption and the Risk of Coronary Disease in Women. NEJM. 1993; 328:1444-9.
7. Rimm, EB, et al. Vitamin E Consumption and the Risk of Coronary Heart Disease in Men. NEJM. 1993; 328: 1450-6.
8. Kugiyama K, et al. Improvement of Endothelial Vasomotor Dysfunction by Treatment with Alpha-Tocopherol in Patients with High Remnant Lipoprotein Levels. J Am Coll Cardiol. 1999;33: 1512-8.
9. Neunteufl T, et al. Additional Benefit of Vitamin E Supplementation to Simvastatin Therapy on Vasoreactivity of the Brachial Artery of Hypercholesterolemic Men. J Am Coll Cardiol. 1998; 32: 711-6.
10. Simons LA, et al. Vitamin E Ingestion does not Improve Arterial Endothelial Dysfunction in Older Adults. Atherosclerosis. 1999; 143: 193-199.
11. Gilligan et al. Effect of Antioxidant Vitamins on Low Density Lipoprotein Oxidation and Impaired Endothelium-Dependent Vasodilation in Patients with Hypercholesterolemia. J Am Coll Cardiol. 1994; 24:1611-7.
12. Rapola JM, et al. Randomized Trial of Alpha-Tocopherol and Beta-Carotene Supplements on Incidence of Major Coronary Events in Men with Previous Myocardial Infarction. The Lancet. 1997; 349: 1715-20.
13. Heitzer T, et al. Effect of Vitamin E on Endothelial Vasodilator Function in Patients with Hypercholesterolemia, Chronic Smoking of Both. J Am Coll Cardiol. 1999; 33: 499-505.
14. Stephens NG, et al. Randomized Controlled trial of Vitamin E in Patients with Coronary Disease: Cambridge Heart Antioxidant Study (CHAOS). The Lancet. 1996;347:781-86.
15. Diplock AT, et al. The Safety of Beta-Carotene and the Antioxidant Vitamins C and E. Antioxidants and Disease Prevention. 1997; CRC Press. 3-17.
16. Dodis HN, et al. Serial Coronary Angiographic Evidence that Antioxidant Vitamin Intake Reduces Progression of Coronary Artery Atherosclerosis. JAMA. 1995; 273: 1849-1854.
17. Plotnick GD, et al. Effect of Antioxidant Vitamins on the Transient Impairment of Endothelium-Dependent Brachial Artery Vasoactivity Following a Single High-Fat Meal. JAMA. 1997;278: 1682-1686.
18. Meyers DG, et al. Safety of Antioxidant Vitamins. Arch Inter Med. 1996; 156:925-935.
19. Rock CL, et al. Update on the Biological Characteristics of the Antioxidant Micronutrients: Vitamin C, Vitamin E and the Carotenoids. J. of the Am. Dietetic Assoc. 1996; 96:693-702.
20. Maxwell SR and Lip GY. Free Radicals and Antioxidants in Cardiovascular Disease. Br. J. Clin Pharmacol. 1997; 44:307-317.