The Role of Vitamin E in the Prevention of Heart Disease

David H. Emmert, MD; Jeffrey T. Kirchner, DO

Data from the 1970s first suggested that vitamin E may be effective in decreasing mortality from cardiovascular disease. As the understanding of the antioxidant effect of this vitamin evolved, researchers began to further study the biologic effects of vitamin E. In vitro studies have shown vitamin E to have several potentially cardioprotective effects, including antagonizing the oxidation of low-density lipoproteins, inhibiting platelet aggregation and adhesion, preventing smooth muscle proliferation, and preserving normal coronary dilation. Several prospective studies, including the US Nurses’ Health Study and the US Health Professionals’ Follow-up Study, found a 34% and 39% reduction, respectively, in the risk of having a cardiac event for those taking vitamin E supplements. The Iowa Women’s Health Study found a 47% reduction in cardiac mortality. Results of randomized, controlled clinical trials have not found consistent benefit, however. The best known of these trials, the Cambridge Heart Antioxidant Study, found a 47% reduction in fatal and nonfatal myocardial infarction in patients with proven coronary atherosclerosis who were given 400 or 800 IU of vitamin E daily. There was, however, no effect on mortality. While emerging and promising data suggest the potential benefit of vitamin E for high-risk cardiac patients, physicians should be alert to the results of randomized, controlled clinical trials already in progress.

Vitamin supplement use is becoming increasingly common: 46% of Americans occasionally use some sort of supplement, and 24% report daily use. Once known only for correcting deficiencies, some vitamins are being investigated for benefits derived from their antioxidant abilities. Epidemiologic studies beginning in the 1970s suggested an association between higher dietary and supplemental intake of vitamin E and lower mortality from cardiovascular disease. There is now evidence that oxidation plays an important role in the pathogenesis of atherosclerosis and subsequent cardiac deaths. The issue is whether vitamin E, the antioxidant most frequently studied, should find a place in routine preventive strategies for patients with risk factors for coronary disease.

OXIDATION AND DISEASE: THE ANTIOXIDANT HYPOTHESIS

Free radicals, also known as reactive oxygen species, are chemical compounds that have one or more unpaired electrons, allowing them to react quickly and unpredictably with nearly any nearby protein, fat, carbohydrate, or nucleic acid in a chemical reaction called oxidation. Sources of free radicals are endogenous (oxygen metabolism, phagocytosis, chemotaxis, apoptosis, or coagulation) and exogenous (cigarette smoke, drugs, diet, pesticides, radon, ozone, nitrogen oxides, sul-

Editor’s Note: During my residency (1976-1979), one of my clinical faculty members routinely told patients to take vitamin E to prevent heart disease. Some physicians felt this was inappropriate because there was insufficient evidence of efficacy. More than 20 years later, has he been vindicated yet? How much evidence of what amount do we need to decide value?

Marjorie A. Bowman, MD, MPA

From the Department of Family and Community Medicine, Lancaster General Hospital, Lancaster, Pa.
fur dioxide, car exhaust, x-rays, and UV light. Notable free radicals in humans may include the hydroxyl radical, the superoxide anion radical, hydrogen peroxide, and the singlet molecular oxygen.

Oxidation can alter a target’s structure and, therefore, function. These changes accumulate eventually, perhaps leading to anatomical and physiological derangements such as malignancy and cardiovascular disease, as well as a variety of degenerative conditions, including aging itself. It has been estimated that the DNA in every human cell receives an estimated 10,000 oxidative “hits” each day, indicating that oxidative stress is ubiquitous. Fortuitously, the antioxidant mechanisms of the human defense system are excellent, involving strategies such as prevention (accomplished by extracellular proteins), repair (by enzymes such as superoxide dismutase), and interception, which is how so-called antioxidants are theorized to exert their protective effects. These endogenous antioxidants include vitamins C and E, as well as the carotenoids, glutathione, urate, and bilirubin.

There is, ideally, a perfect balance between the oxidants and the antioxidants, but external toxins, uncorrected DNA mutations, and oxidized membrane lipids eventually build up, and this accumulation is thought to result in disease and aging. Interest in improving the body’s ability to fight oxidation has grown. Of all the compounds subjected to scientific review, vitamin E has the most consistent data supporting a benefit. The setting in which vitamin E benefit has been best demonstrated is in the prevention and treatment of cardiovascular disease.

VITAMIN E

Vitamin E refers to a group of 8 naturally occurring tocopherols. α-Tocopherol is the most prevalent of these, composing more than 90% of the tocopherols in animal tissues and displaying the most activity in vitro. While most of its functions have been thought to be related to antioxidation in the patient, new research has identified the hormonal effects of vitamin E. Homologues of α-tocopherol, for example, suppress arachidonic acid metabolism, and conjugates of vitamin E can affect cell signaling functions. Perhaps most importantly, α-tocopherol has been found to inhibit smooth muscle proliferation by a kind of tocopherol receptor (not yet identified) on smooth muscle cell walls.

α-Tocopherol from plants is found exclusively in the all-dextro stereoisomer (RRR) (d-α-tocopheryl acetate), although the synthetic, cheaper form more commonly available to consumers is racemic (dl-α-tocopheryl acetate). There are several studies indicating that neither form is more effective in preventing atherosclerosis, although debate still exists. The conversion between milligrams and international units depends on the formulation of vitamin E, since various forms have different potencies: 1.00 IU equals the activity of dl-α-tocopheryl acetate, or racemic vitamin E, the most commonly available form. Equivalent doses of other formulations are given in Table 1.

Absorption in the intestine is inefficient but is facilitated by the presence of dietary fat. Most vitamin E is excreted unmethylated in feces; some recycling or regeneration is thought to occur. Deficiency of vitamin E is most commonly due to intestinal malabsorption. A lack of this vitamin appears to have multisystem effects, leading to neurological and myopathic symptoms, as well as causing anemia, irreversible sterility in men, and recurrent spontaneous abortion in women. Deficiency takes months to develop and is rare. The recommended dietary allowance is 10 mg/d, which is easily met by dietary sources. Good dietary sources include avocados, dark green leafy vegetables, eggs, nuts, peanut butter, and ready-to-eat or whole-grain breakfast cereals. Cooking oils are the largest source of vitamin E in the American diet; those such as olive, canola, safflower, and sunflower oil contain primarily α-tocopherol, but corn and soybean oil have proportionally more γ-tocopherol. Diet probably cannot supply vitamin E in amounts sufficient to prevent chronic disease.

The toxic effects of vitamin E are very low. Even after years of high doses it has proven to be nonmutagenic and nonteratogenic. Reports in the 1980s of higher rates of necrotizing enterocolitis and sepsis owing to supplemental vitamin E in low-weight premature infants were later contradicted. An intravenous vitamin E preparation was associated with a vasculopathic hepatoxic effect in premature infants, but there has not been a recurrence since its withdrawal.

There is an important interaction of vitamin E with warfarin sodium, as large doses of vitamin E appear to increase the vitamin K requirement several-fold. Healthy patients not receiving warfarin and without a vitamin K deficiency are not affected. However, since anticoagulation is potentiated when warfarin and vitamin E are used together, their use together is contraindicated. Patients wishing to take both drugs should do so only after informed consent has been obtained.

Vitamin E is the major lipidsoluble antioxidant in humans, and thus plays the largest role in protecting cell membranes. Vitamin E is also the most abundant antioxidant in low-density lipoproteins (LDLs), present at a level of 6 to 8 molecules per LDL molecule, while other antioxidant compounds are present at ratios less than 1 per molecule. Vitamin E breaks the chain of free radical LDL oxidation and prevents cell wall damage. As long as vitamin E is present, oxidant damage does not occur. However, oxidation does occur after vitamin E has been consumed.

CARDIOVASCULAR DISEASE

A simple but coherent model of the development of atherosclerosis, called the oxidative-modification hy-
foam cells. Foam cells are the hallmark of the atherosclerotic fatty streak, the first stage in the development of cardiovascular disease. Oxidized LDLs are also directly toxic to the vascular and smooth muscle cells, causing the release of oxidative lysosomal enzymes into the intimal space. This enhances the progression of atherosclerotic lesions. Next, smooth muscle proliferation and fibrous connective tissue secretion occurs, producing lesions that protrude into the vessel lumen. As mentioned above, this step can apparently be prevented in vitro by vitamin E.

In the absence of vitamin E, endothelial damage continues, and part of this process may be mediated by the body’s own immune system reacting against oxidized LDL. Indeed, antibodies against oxidized LDL have been isolated, and high levels are significant independent risk factors for myocardial infarction (MI).

The final phenomenon is platelet adhesion and aggregation, causing thrombosis, and, clinically, infarction. Researchers have demonstrated in vitro reduction in platelet adhesion and aggregation attributable to vitamin E. The mechanism is different than that of aspirin: vitamin E reduces the development of long, thin pseudopodia that occurs when platelets adhere to a surface. Platelets enriched in vitamin E produce only short, stubby pseudopodia that appear to anchor the platelets poorly to the adhesive surface.

Oxidized LDL exacerbates the atherosclerotic progression by inhibiting the normal compensatory vasodilation of coronary vessels. There is evidence that vitamins E and C can preserve arterial vasodilation in the presence of oxidative stress, and inhibiting the normal compensatory vasodilation by vitamin E and C can preserve arterial vasodilation in the presence of oxidative stress. At the same time, in vitro studies and animal models have shown convincing evidence that tocopherol is effective in the protection of LDL from oxidative stress.

### Table 2: Prospective Observational Studies of the Effect of Vitamin E on Heart Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study</th>
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<tbody>
<tr>
<td>Study</td>
<td>NHS</td>
</tr>
<tr>
<td>Population</td>
<td>87 245 Female nurses without heart disease</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>8</td>
</tr>
<tr>
<td>Variable measured</td>
<td>Diet and supplement use</td>
</tr>
<tr>
<td>Outcome measured</td>
<td>Nonfatal and fatal MI</td>
</tr>
<tr>
<td>Risk reduction, %</td>
<td>41</td>
</tr>
<tr>
<td>Notes</td>
<td>Reduction highest in those receiving supplements &gt;100 IU/d for &gt;2 y</td>
</tr>
</tbody>
</table>

*NHS indicates Nurses’ Health Study; HPS, Health Professionals’ Follow-up Study; EPESE, Established Populations for Epidemiologic Studies of the Elderly; IWHS, Iowa Women’s Health Study; MI, myocardial infarction; and ellipses, none.

Evidence for a link between vitamin E intake and the risk of cardiovascular disease began with epidemiologic observations. For example, in a cross-cultural study of men from 16 different European cultures, serum levels of vitamin E were powerful predictors of ischemic heart disease, accounting for 53% of the differences between populations.

At the same time, in vitro studies and animal models have shown convincing evidence that tocopherol is effective in the protection of LDL from oxidative stress.

Several prospective cohort studies have observed a relationship between vitamin E intake and subsequent cardiovascular endpoints (Table 2). The US Nurses’ Health Study found that, over 8 years, nurses taking vitamin E supplements had a 34% reduction in the risk of having a cardiac event. The risk reduction was only seen with vitamin E supplementation of more than 100 IU/d, and only supplement use for longer than 2 years was associated with significantly lower risk in these women. Clinical trials of lowering cholesterol to reduce atherosclerosis demonstrate that it takes 2 years of intervention before differences in clinical events begin to emerge. If vitamin E reduces atherosclerosis, clinical benefit from this action...
The first major trial to address the issue of vitamin E in heart disease was the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study. In this study, smokers were given α-tocopherol alone (50 mg/d), beta carotene alone (20 mg/d), both together, or placebo. Follow-up continued for 5 to 8 years, and there were no significant benefits as documented by the frequency of major cardiac events for either vitamin E or beta carotene in the population as a whole. However, a subgroup of men with diabetes did appear to benefit from even this minimal amount of vitamin E. For this group, the relative risk of major cardiac disease was 0.69 (P = .04).

The validity and relevance of this study to the average American patient have been questioned. The Alpha-Tocopherol, Beta Carotene study was not designed to assess cardiovascular end points, having been conceived as a cancer prevention trial. In addition, the dose of vitamin E supplements was small, and serum levels were documented to rise only modestly during the course of the trial.

In contrast, the Cambridge Heart Antioxidant Study (CHAOS) randomly assigned patients with angiographically proven coronary atherosclerosis to a treatment group receiving either 400 to 800 IU of vitamin E daily or to a control group receiving placebo. Patients were followed up for an average of 510 days for either cardiovascular death or nonfatal MI. There was a 47% reduction in total MI, both fatal and nonfatal, in those who took either 400 IU or 800 IU of vitamin E daily. The difference began to be statistically significant after only 200 days, and was largely attributable to a 77% reduction in the number of nonfatal MIs. There was no effect on mortality; indeed, there was an insignificant increase in mortality in the vitamin E group, confined to early events (before 200 days). The authors found this early mortality increase difficult to explain.

The CHAOS trial suggests that patients with existing coronary artery disease appear to benefit from the use of vitamin E. However, CHAOS failed to demonstrate any mortality benefit to vitamin E. An ar-

### Table 3. Randomized, Controlled Trials of the Effect of Vitamin E on Heart Disease*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ATBC</th>
<th>CHAOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>27,711 Male Finnish smokers</td>
<td>2002 British men and women with proven CAD</td>
</tr>
<tr>
<td>Type of prevention</td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Formulation, IU/d</td>
<td>Racemic</td>
<td>Racemic</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>5-8</td>
<td>5-8</td>
</tr>
<tr>
<td>Outcome measured</td>
<td>Fatal and nonfatal MI</td>
<td>Fatal and nonfatal MI</td>
</tr>
<tr>
<td>Findings</td>
<td>Non-significant (P = .75) 8% decrease in fatal MI</td>
<td>77% Decrease in nonfatal MI (P = .05), no difference in fatal MI</td>
</tr>
</tbody>
</table>

*ATBC indicates Alpha-Tocopherol, Beta Carotene Cancer Prevention Study; CHAOS, Cambridge Heart Antioxidant Study; CAD, coronary artery disease; RRR, all-dextro stereoisomer; and MI, myocardial infarction.

†Effect on decreasing total number (nonfatal, fatal) of coronary events significant among men with type 2 diabetes mellitus (0.69 vs 0.98, P = .04).
agement could be made that the trial length may not have been long enough to allow this effect to surface; after all, one might expect a cumulative benefit from avoiding repetitive nonfatal cardiac damage. Interestingly, the CHAOS trial is the first to suggest that a protective mechanism besides the regression of atherosclerosis may play a role in preventing cardiac events as the benefit of vitamin E appeared before 2 years of use.

There are several large, randomized, controlled trials that are intended to answer questions about the role of therapeutic antioxidants in heart disease. The Women’s Health Study has randomized 40,000 apparently healthy women to receive beta carotene, vitamin E (600 IU on alternate days), or low-dose aspirin. The Heart Outcomes Protection Study has assigned 3600 subjects with diabetes and 6000 subjects without to receive either ramipril (or placebo) and vitamin E (or placebo) to assess the development of microalbuminuria, cardiovascular disease, and stroke. Carotid disease progression is the subject of a substudy called the Study to Evaluate progression is the subject of a progression, and stroke. Carotid disease progression is the subject of a substudy of the Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E. Although the effects of vitamin E on peripheral vascular disease, cerebrovascular disease, and operative coronary events have been investigated, these topics are beyond the scope of this study.

OTHER ISSUES

The cost-effectiveness of vitamin E therapy was examined recently using CHAOS data and the cost of hospital admissions for nonfatal infarction as variables. It was suggested that $578 per person could be saved by giving vitamin E for secondary prevention in the appropriate patients. The annual cost of a generic brand of racemic tocopherol is less than $2; “natural” RRR formulations are more expensive.

It is unclear whether the formulation of vitamin E could influence the degree of benefit possible from supplementation. As mentioned earlier, some studies indicate that both forms confer similar benefits in preventing atherosclerosis. The only major trial to demonstrate benefit, the CHAOS trial, used the RRR formulation. The optimal dosage of supplementation is likewise unknown. The most commonly researched doses are 200 IU and 400 IU daily, and there is no literature yet from trials to support the use of one dose over another. There is some indication from in vitro and in vivo studies that at least 400 IU daily is required to prevent LDL oxidation, and there seems to be a dose-response curve in preventing LDL oxidation up to at least 1200 IU daily.

There is at least one published objection to recommending that all patients at risk for heart disease use vitamin E supplementation. The full complexity of the body’s antioxidant system is not fully understood. There is a theoretical concern, forwarded by a vocal minority of researchers, that overwhelming our natural system with one constituent could damage the system as a whole, with unforeseen, harmful consequences in the long term. Specifically, the role of γ-tocopherol, a form of vitamin E that is found abundantly in plants but in low concentrations in human plasma, has yet to be determined. γ-Tocopherol is a less potent antioxidant than α-tocopherol but has been found to have some potentially important functions in in vitro experiments. Supplementing solely with α-tocopherol reduced the efficacy of γ-tocopherol in this artificial environment. So far, no human data exists to support this concern, and there is a wealth of safety data opposing it.

CONCLUSIONS

The theory relating oxidative damage to human disease is potentially quite powerful, and the work of delineating the therapeutic role of antioxidants is only beginning. The evidence for the efficacy of vitamin E supplementation in cardiovascular disease is beginning to mount but is still somewhat contradictory. Based on prospective studies and the CHAOS trial, α-tocopherol, by itself or in conjunction with other antioxidants, may significantly influence cardiovascular disease, both in its initial stages and in severe disease. Ongoing studies may resolve the inconsistencies between the CHAOS and Alpha-Tocopherol, Beta Carotene trials.

Supplementation is the only feasible way to provide large doses of vitamin E, since dietary sources do not lend themselves to this purpose. For example, it would take 1000 almonds, containing 33 472 J and 658 g of fat, to provide 400 IU. Contraindications are few and adverse reactions are extremely rare, making vitamin E one of the safest “drugs” available. However, the use of vitamin E must be restricted to those patients not currently receiving warfarin because of its potential interaction with vitamin K inhibition.

The major drawback to promoting the use of vitamin E is that patients interested in a “quick fix” may choose to take their chances with vitamin E supplementation rather than quitting smoking or exercising more conscientiously. These lifestyle modifications, along with careful attention to diet, have proven beyond a doubt to be extremely powerful tools in the prevention of heart disease. To ignore them in favor of a treatment for which there is suggestive, but not conclusive, support would be premature. Currently, the most prudent niche for vitamin E is as an adjunct to lifestyle modification.

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Corresponding author: David H. Emmert, MD, Manor Family Health Center, 16A Manor Ave, Millersville, PA 17551 (e-mail: emmert@lancnews.infi.net).

REFERENCES

Among healthy women trying to conceive, nearly all pregnancies can be attributed to intercourse during a 6-day period ending on the day of ovulation. (N Engl J Med. 1995;333:1517-1521.)