Antioxidants and Heart Disease

Antioxidants help protect every cell and membrane in the body against the ravages of everyday living, and thus may help prevent diseases that result from accumulated damage due to oxidation.

Oxidation is not necessarily a bad thing. Many cycles in the body depend on an interlocking chain of reactions involving both oxidation—in which an electron is lost—and reduction—in which an electron is gained. Electrons are passed back and forth continually in countless metabolic reactions without generating "oxidative damage." However, the oxidation of some compounds (such as lipids) can be damaging and some oxidative reactions can produce "free radicals," which are dangerous because they set up a chain reaction that can rapidly damage a large number of molecules. One way to prevent oxidative damage is to surround the sensitive compound with "antioxidants" that can be offered up as targets of oxidation *instead of* the sensitive compound. Antioxidants are molecules that can easily and harmlessly give up or accept electrons. That is, antioxidants are *substances that are themselves easily oxidized and that are benign* in their oxidized form. Once oxidized, they are also readily reduced back to their active form, making them available for another round of protection.

In the antioxidant cycle, one antioxidant often hands off electrons to another. Antioxidants thus operate as a team, passing electrons back and forth as necessary in order to prevent unwanted oxidation of sensitive compounds. The antioxidant team includes vitamin E and vitamin C. Some minerals, such as selenium, are integral components of antioxidant enzymes and thus are recognized to serve an antioxidant function. Other food components have also been shown to be protective. These include carotenoids (such as beta-carotene, lutein, and lycopene), flavonoids, and polyphenols.

Vitamin E is the primary fat-soluble antioxidant in the body, and has been shown to protect lipids from peroxidation. This is particularly relevant to heart disease risk, since it is believed that the initiating factor that ultimately leads to atherosclerosis is the oxidation of LDL cholesterol and its incorporation into foam cells or fatty streaks deposited inside blood vessels.

Two studies published in 1993 created widespread excitement about the possibility that vitamin E supplementation could dramatically reduce the risk of heart disease. One was based on data from the Nurses' Health Study, involving more than 87,000 women. Dr. Meir Stampfer and colleagues at Harvard Medical School and the Harvard School of Public Health reported a 41 percent reduction in risk of heart disease among nurses who had taken vitamin E for more than two years. The average vitamin E intake in the lowest-risk group was 200 IU. The researchers noted that a beneficial effect of vitamin E on heart disease "is plau-

sible because of the substantial evidence indicating the importance of oxidation of LDL in atherosclerosis." (Stampfer, Hennekens, et al., 1993)

The second study was based on data from the Health Professionals Follow-up Study involving almost 40,000 men. Dr. Eric Rimm and colleagues at the Harvard School of Public Health and Harvard Medical School found that men who had taken vitamin E for more than two years had a 37 percent lower risk of heart disease, compared to men who had not taken supplements of vitamin E. The average level of vitamin E intake in the lowest-risk group was 400 IU. (Rimm, Stampfer, et al., 1993)

These studies, together with an abundance of other evidence, spurred a large number of clinical trials on vitamin E and heart disease. Two of these showed positive benefits from vitamin E, and these happen to be the two studies that used 800 IU for all or part of the study, a higher level than used in other trials. The most striking is the Cambridge Heart Anti-Oxidant Study (CHAOS), a randomized controlled trial that found that vitamin E supplementation was dramatically effective in reducing the incidence of heart attacks in patients who already had confirmed evidence of coronary disease. In this study, 1,000 men with heart problems were given 800 IU of vitamin E early in the study, lowered to 400 IU of vitamin E later in the study. Another 1,000 men were given a placebo. After 18 months, the number of heart attacks in the vitamin E group was only one quarter of the number in the placebo group. In other words, vitamin E reduced the risk of heart attack by 75 percent. (Stephens, Parsons, et al., 1996)

The WHS found a 24 percent reduction in cardiovascular death and a 26 percent decreased risk of major cardiovascular events in women over 65 with 600 IU every other day of vitamin E.

Another positive study is a study of patients with endstage renal disease requiring chronic hemodialysis. According to the authors of the study, "The cardiovascular-disease mortality rate in this patient group is estimated to be five to 20 times that of the general population," and the increased mortality is considered to be due in part to a high level of oxidative stress. In the SPACE trial (Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease), researchers tested the effect of 800 IU per day of vitamin E supplementation on cardiovascular disease in almost 200 patients over a period of two years. The authors concluded that vitamin E treatment has a significant protective effect against cardiovascular death and non-fatal myocardial infarction (MI). (Boaz, Smetana, et al., 2000)

In the Women's Health Study (WHS), natural source vitamin E (600 IU every other day) or a placebo was given to almost 40,000 apparently healthy women over a period of 10 years. *The study found a significant 24 percent reduction in cardiovascular death, and a 26 percent decreased risk of major cardiovascular events in women over 65.* The significant reduction in cardiovascular events in women over 65 was made up of a 34 percent reduction in MI and a 49 percent reduction in cardiovascular death. These meaningful benefits were minimized by the authors because these were considered to be subgroup analyses, and there was no overall protective effect in the primary *combined* endpoint of MI, stroke, and cancer risk. (Lee, Cook, et al., 2005)

Further analysis of the Women's Health Study also showed a benefit of vitamin E in decreasing the risk of venous thromboembolism (clot formation in a vein) by 21 percent. (Glynn, Ridker, et al., 2007)

However, most of the major clinical trials on vitamin E and heart disease have failed to identify beneficial effects, and there is intense debate over the reasons for these disappointing findings. Has the potential effect of vitamin E on heart disease risk been disproven, or is it yet to be properly tested?

TRIALS OF VITAMIN E AND HEART DISEASE MAY BE FATALLY FLAWED

In a 2007 commentary, Drs. Jeffrey Blumberg and Balz Frei suggested that the "clinical trials on vitamin E and cardiovascular diseases may be fatally flawed." They indicated that few investigators have confirmed the bioavailability and the effects on biomarkers of oxidative stress of the vitamin E doses and formulations used in the trials. "Further, no randomized controlled trials have employed cut-off values of vitamin E intake or status as inclusion criteria for enrollment eligibility.... Absent evidence of significant changes in vitamin E and oxidative stress status, the antioxidant hypothesis is not being tested!" (Blumberg & Frei, 2007)

Plasma C-reactive protein (CRP) may be a candidate to serve as a marker of risk. CRP is an inflammatory biomarker that predicts cardiovascular disease, and lowering elevated CRP with statins has been shown to reduce the risk of heart disease. Block and coworkers recently found that vitamin C reduced CRP levels in people whose CRP was 1.0 mg/L or more to an extent comparable to the lowering observed with statins. They suggest that "research on clinical benefits of antioxidants should limit participants to persons with elevations in the target biomarkers." (Block, Jensen, et al., 2009)

GOALS FOR FUTURE RESEARCH: DR. STEINBERG

Dr. Daniel Steinberg of the University of California at San Diego, a leading researcher in the area of antioxidants and heart disease, posed the question, "Is there a potential therapeutic role for vitamin E or other antioxidants in atherosclerosis?" His answer was, "Probably, but it is too soon to say." (Steinberg, 2000) Following are some of the points he emphasized.

"A large body of evidence supports the hypothesis that oxidation of low-density lipoprotein (LDL) plays an important causative role in the atherosclerosis of several different animal models." Also, many studies demonstrate that supplementation of humans with vitamin E has effects on "markers" for cardiovascular disease. However, clinical trials of vitamin E in patients with pre-existing heart disease have been disappointing. Dr. Steinberg says it is "most unlikely that further studies in similar patient populations will change the conclusion that was reached, namely, that these doses of vitamin E in patients like these (i.e., with established severe coronary disease) will be ineffective, at least within a 3-5 year period." (Steinberg, 2000) Dr. Steinberg suggests "we may not be doing the right kind of clinical trial," and offers three possible explanations for the negative results of several clinical trials:

1. Vitamin E may inhibit the early stages of atherosclerosis but have little or no effect on advanced lesions. The animal data show a benefit of antioxidants given at very early stages of atherosclerosis, not at late stages. Dr. Steinberg suggests intervention trials that focus on detecting and quantifying the development of new lesions. "The epidemiologic data showing decreased CHD risk in patients with higher intakes or higher plasma levels of vitamin E reflect lifetime exposure to diets associated with higher intakes of vitamin E (or long-term use of supplements).

There is no reason to expect that a 3-5-year treatment with supplemental vitamin E can duplicate the protective effect of a lifetime of exposure to, for example, a Mediterranean diet."

2. Vitamin E may not be the most potent antioxidant for this purpose. Other antioxidant compounds, including synthetics, need further study. "More basic research is needed on the issues of where antioxidant activities are needed *in vivo* and how antioxidants can best be transported to those sites. At the moment, most investigators assume that oxidation in the wall of the artery itself is the most relevant but this has never been firmly established."

3. There could be a true species difference such that antioxidants shown to be effective in animal models "will simply never have an effect on atherogenesis in humans." This is a possibility that should not be accepted until the first two explanations are thoroughly explored, but it cannot be ruled out.

Dr. Steinberg concluded that the disappointing results of several clinical trials "lead us to re-examine the question of what might be the appropriate nature of trials in humans, but they do not invalidate the large body of experimental evidence supporting the role for oxidative modification of LDL in atherogenesis." (Steinberg, 2000)

HOW MUCH VITAMIN E? JUST ENOUGH!

Do the disappointing results of some clinical trials mean that vitamin E status is not an important determinant of health and disease? Not at all. Back in 1994, the ATBC trial found no effect of supplemental vitamin E on lung cancer risk. (ATBC Study Group, 1994) However, a recent analysis of 19 years of follow-up reported that *the men who had higher vitamin E blood levels at baseline had a lower subsequent risk of cancer and of other diseases including heart disease over the next couple of decades.* (Wright, Lawson, et al., 2006) During 19 years of follow-up of more than 29,000 men included in the ATBC trial, more than 13,000 of the subjects have died, and extensive data is now available on baseline serum vitamin E levels related to overall mortality and to mortality from specific causes. It turns out that men in the higher quintiles of *baseline vitamin E* levels had about a 20 percent lower total mortality, cancer mortality, and cardiovascular mortality, as compared to men in the bottom quintile of serum vitamin E. Within the categories of cancer and cardiovascular disease, they had significantly lower mortality for lung cancer, prostate cancer, ischemic stroke, hemorrhagic stroke, and respiratory disease. These are exactly the kind of protective effects that would have been predicted from the observational studies. Data such as these will keep investigators searching for improved research designs that hopefully will permit a new generation of RCTs (or their equivalent) to more effectively explore nutrient/disease relationships and to produce results that better capture the whole picture.

In an editorial accompanying the report mentioned above, Dr. Maret Traber asked and answered the question, "How much vitamin E? . . . Just enough!" The Wright study found that disease risk was decreased as serum vitamin E levels increased from nine to 13 mg/L. However, "estimates of the vitamin E intake

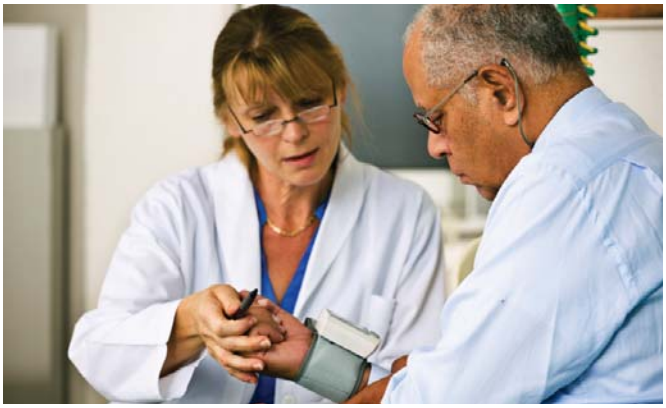
necessary to achieve a certain serum concentration of alpha-tocopherol have varied widely." In the ATBC baseline study, a dietary intake of about 12 mg was associated with serum levels of 11 to 12 mg/L. Traber observes, however, that "12 mg vitamin E is an amount that is greater than that estimated to be consumed by 93 percent of men and 96 percent of women in the United States." She suggests that "the vitamin E recommended dietary allowance of 15 mg/d may yield optimal serum concentrations to achieve significant reductions in chronic disease mortality. However, 15 mg/d may be a vitamin E intake that is achieved only with supplements, given the dietary habits of most Americans." (Traber, 2006)

KEY CLINICAL TRIALS

Following is a summary of numerous clinical trials on vitamin E and heart disease, in the U.S. and elsewhere.

In the GISSI (Gruppo Italiano per lo Studio della Sopravivenza nel'Infarto miocardico) trial in Italy, researchers gave 300 mg of vitamin E and/or one gram of omega-3 fatty acids or no supplement to over 11,000 patients who had survived an MI within the previous three months. The supplements were continued for an average of 3.5 years. The omega-3 fatty acid treatment reduced the risk of death, nonfatal heart attack, and stroke, but the vitamin E did not have a significant protective effect. The authors conclude that "the dose of vitamin E that is most effective and safe, as well as the minimum duration of treatment that is required to produce the postulated protective effects of vitamin E are still unknown." (GISSI, 1999)

The Alpha-Tocopherol Beta-Carotene Study (ATBC) was designed to test whether vitamin E and/or beta-carotene supplementation would reduce the risk of lung cancer in almost 30,000 smokers in Finland, but effects on coronary artery disease were also evaluated. In that study, neither supplement was found to protect against lung cancer or heart disease. Vitamin E appeared to have a protective effect against prostate cancer, colorectal cancer, and ischemic stroke, but increased the risk of hemorrhagic stroke. (ATBC Study Group, 1994) The Food and Nutrition Board of the Institute of Medicine in its report on Dietary Reference Intakes for antioxidant nutrients, noting that several other major trials using higher levels of vitamin E have not reported any increased risk of stroke, commented: "The unexpected finding of an increase in hemorrhagic stroke in the ATBC study was considered preliminary and provocative, but not convincing until it can be corroborated or refuted in further large-scale clinical trials." (Institute of Medicine, 2000)



In the Primary Prevention Project (PPP) in Italy, almost 4,500 people with at least one major risk factor for heart disease were given low-dose aspirin (100 mg) or vitamin E (300 mg) or both for three to six years. Aspirin lowered the frequency of cardiovascular events and cardiovascular deaths, but vitamin E did not. (PPP, 2001)

In the Heart Outcomes Prevention Evaluation study (HOPE), researchers enrolled more than 2,500 women and almost 7,000 men over 55 years of age who had existing heart disease or diabetes plus one additional risk factor for heart disease. They were given 400 IU of natural vitamin E (or a placebo) daily for a period of four to six years. Among the vitamin E group at

baseline, 53 percent had already had an MI and 26 percent had already undergone bypass surgery. There were no significant effects of vitamin E on the risk of later heart attacks, stroke, or death. This dose of the vitamin was "well tolerated, with no significant adverse events as compared with placebo." (Yusuf, Dagenais, et al., 2000)

The HOPE study was continued for another four years to further examine effects of vitamin E on heart disease and cancer risk. The results of the continued study, labeled HOPE-TOO, were published in 2005 and showed no benefit for cardiovascular or cancer risk, but some increase in risk of heart failure. During this extended study, ACE inhibitors were being recommended for all participants, based on the favorable outcome of the ACE inhibitor portion of the initial HOPE study. (Lonn, Bosch, et al., 2005)

In the Women's Antioxidant Cardiovascular Study (WACS), more than 8,000 female health professionals with a history of cardiovascular disease or with three or more risk factors were given 600 IU of vitamin E every other day, 500 mg vitamin C every day, 50 mg beta-carotene every day, or a placebo. There were no significant effects on cardiovascular events. (Cook, Albert, et al., 2007)

In the Physicians Health Study II, involving over 14,000 healthy men, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events (death, nonfatal MI, or stroke). This trial went on for eight years, but the authors point out that this may not have been long enough to encompass the "etiologic window" for heart disease. It is also important to note that the physicians in this trial were already 64 years old, on average, at the beginning of the study—perhaps past the age when true prevention would be operative, since it is believed that the process of atherosclerosis begins in youth. (Sesso, Buring, et al., 2008)

Bottom Line

Vitamin E, vitamin C, and other antioxidants have been linked in numerous observational studies to a decreased risk of various diseases, including heart disease. Some clinical trials have shown a benefit of vitamin E, at least in some subgroups, but most have not. Long-term follow-up of the men who participated in the ATBC trial showed a lower risk of cancer and heart disease over a period of 19 years in those who had higher serum vitamin E levels at baseline. It has been suggested that future studies should screen participants based on their initial antioxidant status and the presence of markers of oxidative or inflammatory risk, and researchers should confirm whether markers of oxidative risk are lowered, in addition to monitoring direct disease outcomes.

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