BIBI I. HASNAIN, MD
Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, St. Louis University School of Medicine, St. Louis, MO

ARSHAG D. MOORADIAN, MD
Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, St. Louis University School of Medicine, St. Louis, MO

Recent trials of antioxidant therapy: What should we be telling our patients?

ABSTRACT

The current evidence does not support the indiscriminate use of vitamins A, C, or E or beta carotene to prevent or reduce cardiovascular disease. Despite a plausible theory that antioxidants can prevent diseases caused by oxidative damage, trials thus far have not proven this. In fact, some studies found antioxidants may be harmful in some people. We review important studies of the effects of four antioxidants (vitamins A, C, and E, and beta carotene) and analyze whether the current evidence supports or confirms or rejects the presumed protective role.

KEY POINTS

Evidence from observational studies suggests that taking antioxidant supplements can lower the risk of cardiovascular disease. But limitations of these studies mean that we should view the results only as preliminary observations of effects that need further study in randomized controlled trials.

Our decision to prescribe antioxidants should be based on an assessment of the patient's nutritional status. Supplementation may be more advisable in the elderly, strict vegetarians, or people on calorie-restricted diets. Supplement intake should not exceed the recommended daily allowances.

See related editorial, page 285

WE SHOULD ADVISE our patients not to indiscriminately use antioxidant supplements until the perplexing questions about their benefits are answered. Instead, we should use a patient's nutritional status to guide our counsel about supplement use.

Despite the plausible theory that oxidation is responsible for initiating and perpetuating many human diseases, and that the antioxidants vitamin A, vitamin C, vitamin E, and beta carotene can therefore prevent diseases due to oxidative damage, clinical trials thus far have been controversial and inconsistent. Nevertheless, patients are often enticed by claims of health benefits made by manufacturers of antioxidant vitamins and may take them regularly—with or without first asking their physician.

We must scrutinize the available data before counseling our patients on the use of antioxidants, especially since some studies indicate that high doses of antioxidants may be harmful to some. This article will review pivotal studies conducted to reveal the benefits of antioxidants, notably vitamins A, C, and E and beta carotene, and analyze whether the current evidence corroborates or rejects the presumed protective role of these antioxidants. This article will also address what we should recommend to our patients regarding the intake of antioxidants.

OXIDATION FACTS

Oxidation is defined as removal of electrons from a molecule.[1] Oxidation can instigate tissue damage by modifying a number of molecular species, such as lipids, proteins, and nucleic acid, leading to diseases such as atheroscle-

rosis and cancer.[2] Oxidants are substances that promote oxidation, and we are constantly exposed to them.

Antioxidants significantly delay or inhibit the oxidation of an oxidizable substrate.[3] Hence, a balance between oxidants and antioxidants is imperative. Certain antioxidants are endogenous (eg, ferritin, transferrin, urate) and others are acquired exogenously.[4]

The idea of consuming exogenous antioxidants such as vitamin E, vitamin A, and vitamin C to counteract oxidative damage is very intriguing and has prompted much research into the role of dietary and supplemental antioxidant vitamins in preventing human disease. Most of the current literature addresses the role of these three vitamins and beta carotene. In our discussion, then, we will use the term "antioxidants" to refer to this limited list of compounds.

OBSERVATIONAL STUDIES OF ANTIOXIDANTS

Oxidation is bad, so antioxidants are good? Not quite so easy

A number of observational studies suggest beneficial effects of consuming antioxidant supplements. However, observational studies are often inherently limited by a number of confounding variables that are difficult to weed out:

- They tend to rely on subjective data such as patients' 24-hour recall of dietary intake
- Those who enter such studies are often "health-conscious": ie, they exercise, limit their fat intake, and do not smoke
- Diets contain many substances, and it is difficult to know which specific nutrient in the diet or supplements is the one that led to a positive outcome.

Despite their potential flaws, however, some of the larger observational studies of antioxidants are worthy of recognition.

The Rotterdam study

The Rotterdam study[5] assessed the relationship between cardiovascular events and dietary intake of beta carotene, vitamin C, and vitamin E in 4,802 people ages 55 to 95 with no history of myocardial infarction. Intake of these vitamins was evaluated for 4 years using computerized food-frequency questionnaires administered at baseline and validated in 80 subjects with food diaries.

Results. The investigators concluded that a high intake of beta carotene protected against myocardial infarction and that this effect was more pronounced in current and former smokers. The study revealed no beneficial effect of vitamin C or vitamin E against myocardial infarction. However, this study, like other observational studies, did not have independent measurements to evaluate the micronutrient status of the enrollees or the biological efficacy of the vitamins consumed.

The Iowa Women's Health Study

The Iowa Women's Health Study[6] tested for an inverse relationship between mortality due to coronary artery disease and intake of antioxidant vitamins from food sources and supplements. It followed 34,486 postmenopausal women (ages 55–69) with no history of cardiovascular disease for 7 years. Intake of vitamins A, E, and C was estimated using food-frequency questionnaires administered at baseline and then validated in 44 women with five 24-hour dietary-recall interviews. The validity of the estimates of vitamin intake from food-frequency questionnaires was further examined in comparison with plasma levels of beta carotene ($r = 0.30$) and alpha tocopherol (vitamin E) ($r = 0.41$).

Results. A high intake of vitamin E seemed to protect against death from coronary artery disease. Vitamin A and C consumption did not affect coronary artery disease mortality.

Established Population for Epidemiologic Studies of the Elderly

The Established Population for Epidemiologic Studies of the Elderly (EPESE) followed 11,178 people ages 67 to 105 for 8 to 9 years[7] to see what effect their use of vitamin E and vitamin C supplements had on all-cause mortality and risk of death from coronary artery disease.

Results. Vitamin E use was associated with a decrease in all-cause mortality and, especially, with a reduction in mortality due to coronary artery disease. The beneficial effect

of vitamin E was enhanced when taken with vitamin C. Older people who take vitamin supplements tend to be more health-conscious and usually have a healthier lifestyle, a fact that should be considered when interpreting the results of this study.

Finnish study

Knekt et al studied 5,133 Finnish men and women aged 30 to 69 years who were free of heart disease at baseline and were followed for a mean of 14 years.[8] The aim of the study was to investigate the effect of dietary intake of carotene, vitamin C, and vitamin E on coronary mortality. Food consumption was estimated by recording dietary history.

Results. Vitamin E consumption was linked to a reduction in deaths from coronary artery disease in both men and women. Carotene and vitamin C appeared to impart coronary protection to women only.

Health Professionals Follow-up Study

To examine the effect of antioxidants on prevention of coronary artery disease, the Health Professionals Follow-up Study[9] measured the effects of dietary antioxidant intake over a 4-year period in 39,910 US male health professionals ages 40 to 75 with no diagnosed coronary artery disease. The presence or absence of coronary disease was determined by clinical history rather than by a specific screening procedure. Vitamin intake information was obtained through a dietary questionnaire, the validity of which was tested in a random sample of 127 men with two 1-week diet records spread 6 months apart.

Results. Increased intake of vitamin E was associated with a lower risk of coronary artery disease.

Nurses' Health Study

The Nurses' Health Study[10] was an 8-year study of 87,245 female nurses ages 34 to 59 with no diagnosed cardiovascular disease or cancer to measure any cardioprotective effects of dietary antioxidant intake. Antioxidant intake was assessed through food questionnaires.

Results. Those in the first quintile with respect to vitamin E intake for more than 2 years had a lower risk of coronary heart disease, especially if the antioxidant was taken in supplement form.

NHANES I

The first National Health and Nutrition Examination Survey (NHANES I)[11] of 11,348 noninstitutionalized US adults ages 25 to 74 studied the association of normal dietary intake and supplemental intake of vitamin C with all-cause mortality and cardiovascular disease.

Results. Dietary consumption and supplemental intake of vitamin C were inversely associated with all-cause mortality and cardiovascular disease in men, but not in women.[11]

The potential limitations in this study are similar to those of the Health Professionals Follow-up Study and the Nurses' Health Study: ie, lack of a uniform screening procedure to determine the presence or absence of coronary vascular disease in the population, and lack of an independent validation of vitamin intake (via biological assays).

Scottish Heart Health Study

A Scottish study[12] of 4,036 men and 3,833 women ages 40 to 59 with no history of heart disease tested the effects of dietary and supplemental intake of vitamin C, beta carotene, and vitamin E on coronary artery disease.

Results. Vitamin C and beta carotene reduced coronary artery disease events in men only.[12] Vitamin E ingestion did not seem to confer any significant protection against coronary heart disease in men or women. No antioxidant had any effect on all-cause mortality.

Observational studies suggest benefits, but randomized trials are needed

Conclusions from observational data

The evidence from these observational studies suggests that increased intake of antioxidants is associated with a reduced risk of cardiovascular disease. However, because of inconsistencies among the studies, difficulty accounting for confounding variables, a reliance on food questionnaires, and a lack of validation of historical data or vitamin intake with objective laboratory evaluations, we should view these studies as preliminary observations of effects that need to be further addressed in randomized controlled trials.

INTERVENTIONAL STUDIES THAT SHOWED NEITHER HARM NOR BENEFIT

Of the interventional clinical trials that have explored the benefits of antioxidants, a few have shown a protective effect of antioxidant vitamins, but most have not. The mixed results can be attributed to the different doses of antioxidants used in each trial and to differences in the baseline demographic characteristics of the participants. It is also plausible that taking an optimal dose of antioxidants at an early age and for a longer duration would reveal the protective advantages of the antioxidants. Some of the larger randomized trials that addressed the use of antioxidants for disease prevention are discussed briefly below.

Most interventional trials of antioxidants showed no protective effect

Heart Protection Study

In the Heart Protection Study,[13] 20,536 adults age 40 to 80 with coronary artery disease, other occlusive arterial disease, or diabetes were given vitamin E 600 mg daily, vitamin C 250 mg daily, and beta carotene 20 mg daily, or placebo.[13] Follow-up was for 5 years. The objective was to describe the relationship of antioxidant supplementation to major coronary events, fatal or nonfatal vascular events, cancer, and other major morbidity.

Results. Antioxidant supplementation was associated with neither harm nor benefit, even though plasma concentrations of alpha tocopherol increased approximately twofold, plasma ascorbate levels increased by one third, and plasma concentrations of beta-carotene quadrupled. (This information confirmed that the subjects randomized to antioxidant supplementation were actually consuming the prescribed agents.)

Primary Prevention Project

In the Primary Prevention Project,[14] 4,495 people with a mean age of 64 who had at least one risk factor for coronary artery disease were given low-dose aspirin (100 mg/day) or vitamin E (300 mg/day) to see if either protected against coronary events.

Results. The trial was stopped early, after 3.6 years, as other trials had meanwhile proven the beneficial effect of aspirin. Aspirin reduced cardiovascular mortality and cardiovascular events. Vitamin E supplementation was not associated with any benefit.

Heart Outcomes Prevention Evaluation study

Vitamin E supplementation was also not associated with any favorable effects in the Heart Outcomes Prevention Evaluation (HOPE) study.[15] In this trial, 2,545 women and 6,996 men age 55 or older with a history of coronary artery disease or diabetes in addition to one other risk factor for atherosclerosis were studied. Participants were randomly assigned to receive either 400 IU of vitamin E or placebo, and either an angiotensin-converting enzyme inhibitor or placebo. The primary outcomes were myocardial infarction, stroke, or death from cardiovascular causes.

Results. At 4.5 years, vitamin E intake had no apparent effect on cardiovascular outcome.

GISSI

In the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico* (GISSI) study,[16] 11,324 patients who had survived a myocardial infarction within the previous 3 months were randomized to receive omega-3 polyunsaturated fatty acid 1 g daily, vitamin E 300 mg daily, both, or neither. The participants were followed for 3 to 5 years.

Results. Vitamin E supplementation showed no benefit, whereas omega-3 polyunsaturated fatty acid supplementation seemed beneficial.

Women's Health Study

The Women's Health Study monitored 39,876 women age 45 or older[17] to study the effect of aspirin (100 mg), vitamin E (600 IU), and beta carotene (50 mg on alternate days) either alone or in different combinations of the three agents in the prevention of cancer and cardiovascular disease.

Results. The arm that received beta carotene vs placebo was prematurely terminated after 2.1 years because of concerns of harmful effects of beta carotene in people at high risk of developing lung cancer, as indicated by results of other trials.[18,19] Patients in the beta-carotine arm were followed for an additional 2 years after this arm was terminated, and use of beta-carotine was associated with neither harm nor benefit.

Physicians' Health Study

The Physicians' Health Study[20] of 22,071 male physicians age 40 to 84 examined the effects of beta carotene supplementation in the primary prevention of cardiovascular disease and cancer.

Results. Beta carotene 50 mg taken on alternate days was associated with neither harm nor benefit.

INTERVENTIONAL STUDIES THAT SHOWED POSSIBLE DELETERIOUS EFFECTS

Two large interventional studies raised the specter that some antioxidants may have deleterious health effects.

Beta Carotene and Retinal Efficacy Trial

The Beta Carotene and Retinal Efficacy Trial (CARET) studied 18,314 men and women at high risk of lung cancer.[18] Participants received either a combination of 30 mg of beta carotene and 25,000 IU of vitamin A daily or placebo.

Results. The group taking a supplement had a statistically significant 28% higher incidence of lung cancer and 17% more deaths than the placebo group.

Alpha Tocopherol Beta Carotene Cancer Prevention Study

Similar concerns were raised in the Alpha-Tocopherol Beta Carotene Cancer Prevention study (ATBC).[19] In this study, 29,133 male smokers age 50 to 69 were assigned to treatment with alpha tocopherol 50 mg daily or beta carotene 20 mg daily or a combination of both vitamins or placebo.

Results. The total mortality rate was 8% higher (a statistically significant difference) in the group taking beta carotene compared with those who did not receive beta carotene, primarily due to more deaths from lung cancer.

HDL Atherosclerosis Treatment Study

A small randomized trial of importance is the High-density Lipoprotein (HDL) Atherosclerosis Treatment Study (HATS),[21] in which 160 men under age 63 and women under age 70 with established coronary artery disease were studied. All participants had low HDL cholesterol levels, low-density lipoprotein cholesterol levels below 145 mg/dL, and triglyceride levels below 400 mg/dL. Participants were assigned to receive one of several regimens:

- Simvastatin plus niacin
- Antioxidants (vitamin E 800 IU, vitamin C 1,000 mg, beta carotene 25 mg, and selenium 100 μg)
- Simvastatin plus niacin plus antioxidants
- Placebo.

Follow-up was for 3 years. The objective was to study the effect of each regimen on cardiovascular protection in patients with coronary disease and low HDL cholesterol.

Results. Simvastatin plus niacin led to a statistically significant clinical, angiographically measurable benefit. Antioxidants failed to show any substantial benefit.

Of concern was the observation that antioxidants seemed to diminish the beneficial effect of simvastatin plus niacin. Specifically, the niacin-induced elevation of HDL_2 was blunted by antioxidants.

INTERVENTIONAL STUDIES THAT SHOWED POSSIBLE BENEFIT

The Cambridge Heart Antioxidant Study

The Cambridge Heart Antioxidant Study (CHAOS)[22] examined 2,002 patients with angiographically proven coronary artery disease. Subjects received 800 IU or 400 IU of alpha tocopherol daily or placebo. The primary end point of the trial was the combination of cardiovascular death and nonfatal myocardial infarction or nonfatal myocardial infarction alone. Mean follow-up was about 1.4 years.

In one study, antioxidants seemed to diminish the effect of simvastatin plus niacin

Results. While there were fewer nonfatal myocardial infarctions in those taking alpha tocopherol, the number of cardiovascular deaths was not reduced.

One shortcoming of the CHAOS trial was that the randomization was not ideal, which might have affected the results. There was no attempt at randomization between the two doses of vitamin E. The first 546 patients were given 800 IU per day, and when the measurements of plasma levels suggested that lower doses would exceed physiologic levels, the newly recruited subjects were given 400 IU per day. Also, the 800-IU dose of alpha

tocopherol was discontinued early because of safety concerns.

Antioxidant Supplementation in Atherosclerosis Prevention study

The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study[23] was a relatively small study of 520 men and postmenopausal women age 45 to 69. The objective of this study was to evaluate the effect of twice-daily consumption of 136 IU of d-alpha-tocopherol or 250 mg of slow-release vitamin C or a combination of the two on the progression of carotid atherosclerosis over 3 years.

Results. The progression of carotid atherosclerosis was reduced only in men who were smokers and who took both vitamin E and vitamin C. It is likely that smokers are under greater oxidative stress and, hence, benefitted the most from the use of antioxidants. Another possible deduction from this study is that the combination of vitamins E and C has a synergistic or additive effect due to the discrete antioxidant properties of each.

It is noteworthy that this study used somewhat smaller doses of vitamin E and vitamin C compared with other interventional trials. The antioxidant effect of these doses was not demonstrated in this population, although plasma concentrations of ascorbate, dehydroascorbate, and alpha tocopherol were measured. The validity of the randomization and consumption of the vitamin supplements in each group was confirmed. The plasma levels of alpha tocopherol and ascorbate were increased by 50% to 90% in those taking the vitamin supplements.

Too much vitamin A may promote osteoporosis and teratogenicity

Chinese nutrition intervention trials

Also showing potential benefits of antioxidants were the nutrition intervention trials in Linxian, China.[24] In all, 29,548 participants age 40 to 69 were studied. Participants were assigned to intervention with one of following combinations:

- Retinol 5,000 IU + zinc 22.5 mg
- Riboflavin 3.2 mg + niacin 40 mg
- Ascorbic acid 120 mg + molybdenum 30 µg
- Beta carotene 15 mg + selenium 50 µg + alpha tocopherol 30 mg.

Results. Total mortality was significantly lower in those receiving beta carotene, vitamin E, and selenium. The reduction was mainly due to lower rates of cancer, especially stomach cancer, with the reduced risk beginning to arise about 1 to 2 years after the start of supplementation.

However, the people in this study were not screened for nutritional deficiencies at baseline. It is possible that the results of this trial cannot be applied to people who consume a well-balanced diet. Furthermore, it is hard to tell which constituent was responsible for the beneficial effect. It is also possible that the three antioxidants given together had a synergistic effect.

WHAT SHOULD WE TELL OUR PATIENTS?

After reviewing the results of the above trials, it is apparent that most did not prove beneficial effects of taking antioxidants. Of even greater concern is that antioxidants may not be as harmless as once thought.

The ATBC trial, for example, showed greater mortality in the group that received beta carotene,[19] and this concern was reinforced by the CARET trial, which showed an increased incidence of lung cancer and mortality in those treated with vitamin A.[18] We should recognize that an increase in cancer incidence and mortality was mainly seen in subjects at high risk of developing lung cancer based on their history of smoking or exposure to asbestos.

In addition, the HATS trial raised the intriguing possibility that the beneficial cardiovascular effect of simvastatin or niacin could be attenuated with the concurrent use of antioxidants.[21] These observations warrant further investigation.

Concern about overuse of antioxidants

High intake of vitamin C can lead to bloating and diarrhea and can cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[25] Vitamin C use may also cause serious cardiac arrhythmias in people with iron overload.[26]

Excessive use of vitamin A may promote osteoporosis[27] and teratogenicity,[28] in addition to other toxicities related to overdose.[25]

Furthermore, vitamin E use can allegedly worsen retinitis pigmentosa[29] and may

increase the risk of hemorrhagic stroke.[30]

What meta-analysis showed

In a recent meta-analysis of seven randomized trials of vitamin E treatment and, separately, of eight trials of beta carotene treatment, vitamin E and beta carotene had no beneficial effect on cardiovascular mortality and morbidity in the long term.[31]

The dose range for vitamin E was 50 to 800 IU, and for beta carotene 15 to 50 mg. Follow-up ranged from 1.4 to 12.0 years. The vitamin E trials involved a total of 81,788 patients in the all-cause mortality analyses, and the beta carotene trials included 138,113. (Each trial had at least 1,000 subjects.)

Taking beta carotene led to a small but significant increase in all-cause mortality (7.4% vs 7.0%, $P = .003$) and a slight increase in cardiovascular deaths (3.4 vs 3.1%, $P = .003$). This further raises the possibility that some antioxidant vitamins, notably beta carotene, may be harmful.

All the trials we have discussed have shortcomings worth noting:

- Most were done in people with symptoms, and it may be easier to prevent the onset of the disease than to reverse an established atherosclerotic lesion.
- Clinical trials generally do not include measures of oxidation; thus, vitamin E or C may have effectively inhibited lipid peroxidation without altering cardiovascular end points. For the same reason, it is not clear that sufficient amounts of the prescribed antioxidants were absorbed or were biologically active.
- The failure of vitamin E or beta carotene to reduce the incidence of cardiovascular end points does not necessarily mean that other antioxidants yet to be tried would not be successful as therapeutic agents. Since oxidation of compounds can occur via alternate pathways that are not inhibited by vitamin E or beta carotene, it is possible that if we use more potent or alternative forms of antioxidants, we may be able to achieve reduction in cardiovascular risk.

We should therefore advise our patients to avoid the indiscriminate use of antioxidant supplements until the perplexing questions about their benefits are answered. In addition, we should base our decision to prescribe antioxidants on an assessment of the patient's nutritional status. Vitamin supplementation may be more advisable in the elderly, strict vegetarians, or people on calorie-restricted diets, but supplement intake should not exceed the recommended daily allowances. We should always promote healthy balanced diets to ensure intake of micronutrients from dietary sources.

We should always promote healthy, balanced diets

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ADDRESS: *Arshag D. Mooradian, MD, Division of Endocrinology, Saint Louis University, 1402 South Grand Boulevard, St. Louis, MO 63104; e-mail mooradad@slu.edu.*