EDITORIAL COMMENT

Do Antioxidant Vitamins Protect Against Atherosclerosis?
The Proof Is Still Lacking*

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Cardiovascular diseases (CVD) are the major cause of mortality and morbidity worldwide, despite significant advances in our understanding of the underlying atherosclerotic process, its prevention and its treatment. Simple, accessible and cost-effective preventive therapies aimed at reducing the burden of CVD could be of great public health benefit. Therefore, substantial interest has focused on the potential benefits of antioxidant vitamins in cardiovascular prevention.

The potential role of antioxidant vitamins in CVD prevention is based on the biological rationale rendered by the “oxidative modification hypothesis,” which proposes an essential role for the oxidation of lipoproteins in the genesis and progression of atherosclerotic lesions, and by observational epidemiologic studies, that have shown associations between the dietary and supplemental intake of antioxidants and lower risk of coronary heart disease (CHD) and stroke.

The hypothesis that oxidative modification of lipoproteins, particularly of low density lipoprotein (LDL) cholesterol, may play an important causative role in atherosclerosis was advanced by Steinberg et al. (1) and is supported by an impressive body of in vitro findings and by rather persuasive findings in animal models of atherosclerosis. It was suggested that oxidation of LDL was particularly involved in the formation of foam cells and thus in the genesis of early atherosclerotic lesions. The relevance of LDL oxidation in human atherosclerosis, although widely accepted, has not been, however, conclusively proven, as there is no clinical evidence to date to clearly demonstrate that antioxidants can affect either the behavior of atherosclerotic lesions or prevent ischemic events.

A large number of observational epidemiologic studies have evaluated potential relationships between antioxidants and CVD. Such studies range from retrospective observations to broad cross-sectional geographic correlations between population-based antioxidant intake and rates of CHD, to large prospective cohort studies conducted in different parts of the world, characterized by a variety of dietary patterns and involving tens of thousands of men and women followed for prolonged periods of time. These studies suggested that: 1) persons with a high intake of fruits and vegetables have a lower incidence of ischemic heart disease events and strokes compared with those with low intake of these nutrients (2,3); and 2) increased intake of antioxidants through diet or supplements, particularly vitamins E (alpha-tocopherol) and C and beta-carotene, is associated with a lower risk of CHD and death (4).

Although the data on “healthy” diets that contain large amounts of fruits and vegetables are generally consistent, it is obviously very difficult to isolate which components of such diets indeed account for protection against atherosclerotic diseases.

The observational data on specific antioxidants and cardiovascular risk are, however, less consistent. For example, inverse associations between dietary or supplemental intake of beta-carotene and the risk of fatal and nonfatal CHD were shown primarily in men (5,6), whereas the larger studies in women documented neutral effects (7,8). Vitamin C appeared to be cardioprotective on crude analysis in some studies (7), but after adjustment for vitamin E intake this association lost statistical significance in most investigations; overall, seven studies done in the U.S. and in Europe, involving a total of 183,662 men and women ages 16 to 105 years, failed to show lower CVD rates with vitamin C, after adjustment for different variables including vitamin E intake (9). The epidemiologic data on vitamin E and reduced cardiovascular risk is more robust, although some questions remain. Thus, the Nurses’ Health Study and the Health Professionals Follow-up Study clearly identify the use of vitamin E in the form of supplements—that is, in higher doses than generally provided by balanced diets—to be beneficial and suggested that the observed benefit was associated only with relatively high intake of vitamin E supplements of at least 100 IU/day (5,7). By contrast, a large epidemiologic study in postmenopausal women conducted in the U.S. and a large cohort study from Finland identified vitamin E from food sources to be potentially cardioprotective, with no benefits from vitamin E in the form of supplements in the North American study (8,10).

Furthermore, the interpretation of any observational data needs to be very cautious, recognizing that such studies cannot provide proof of causality. Although many observational studies have attempted to adjust for other factors that could affect cardiovascular risk, such adjustments are difficult and often inadequate, and ultimately the use of diets rich in antioxidants and/or the use of vitamin supplements may be just markers that identify populations and subsets of individuals with higher health awareness and with various healthy lifestyle attributes, possibly entirely independent of antioxidant intake.

Randomized prospective morbidity and mortality trials

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are therefore considered to be quintessential in demonstrating the efficacy and the safety of any therapeutic intervention. Such trials were deemed necessary prior to making wide-ranging recommendations regarding the use of antioxidant supplements. Unfortunately, the overwhelming majority of large, randomized and prospective trials of antioxidant supplements in CVD have yielded disappointing results (9,11–16). The randomized clinical trials completed to date have tested primarily vitamin E and beta-carotene, with only limited data for vitamin C, and they have been conducted in men and in women in primary and in secondary prevention settings. The only two positive studies have both used vitamin E supplements, one in CHD and the secondary prevention settings. The only two positive studies have both used vitamin E supplements, one in CHD and the other in end-stage renal-disease patients (17,18). These studies were relatively small and found benefits on nonfatal myocardial infarction, but not on cardiovascular death.

These large prospective, randomized clinical trials have been, however, criticized as well. It was suggested that the study patients comprised primarily men and women with advanced atherosclerosis and that the failure of antioxidant vitamins to demonstrate benefit may be related to the fact that micronutrients and nutriceuticals could be expected to have an effect only on the very early stages of atherosclerosis and not on terminal events such as plaque rupture and thrombosis. It has also been suggested that studies of four to six years’ duration are too short to show a treatment effect, considering again that the hypothesized benefit would be primarily on the initiation of atherosclerotic lesions. Some investigators have suggested that it may be more relevant to study combinations of antioxidants, as the use of isolated single agents may actually result in pro-oxidative actions. Finally, it has recently been suggested that the average Western diet may provide adequate supplies of vitamin E, at least in a large proportion of individuals, and it may be difficult to observe benefits in this population with additional supplemental vitamin E intake and that clinical trials, therefore, should select subjects with vitamin-deficient states (19).

Because of these perceived limitations of large prospective trials with clinical end points Steinberg et al. (1) suggested that an additional strategy to evaluate antioxidants may be to study associations and treatment effects on atherosclerotic lesions. A number of investigations have evaluated associations between dietary and supplemental vitamin intake and carotid atherosclerosis, and there are also a few randomized controlled trials of antioxidant supplementation using as surrogates outcome changes in carotid intimal-medial thickness (IMT). Such randomized trials have been negative (20), with the exception of a subgroup analysis of the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study, which found benefit in hypercholesterolemic men who smoked and received combined supplementation of vitamins E and C (21).

In this issue of the Journal, McQuillan et al. (22) report an elegant observational study that examined relationships between dietary intake and plasma levels of antioxidant vitamins and carotid IMT. The study is well designed and enrolls over 1,000 men and women from Western Australia. Study participants have a mean age of 52 years for men and 53 years for women and an average prevalence of other risk factors for atherosclerosis, typical for relatively healthy individuals in Western societies. Subjects with known CVD are appropriately excluded from the analysis, as these individuals may be more motivated to have higher antioxidant vitamin intake.

The methodology used for the dietary assessment, the measurements of plasma levels of different antioxidants and the assessment of atherosclerosis are adequate. As indicated by the investigators, such measurements of carotid arterial wall thickness have been clearly shown to independently predict the risk of myocardial infarction and stroke in populations.

Unfortunately, I find the study results disappointing overall and a bit confusing. Dietary vitamin E intake is found to have an inverse relationship with carotid IMT in men; however, this relationship is very weak and explains only 1% of the variance in measured IMT in men. Furthermore, the relationship is not confirmed in women. There would be little biological rationale to support a differential effect of antioxidant vitamin E intake on the carotid arterial wall in men as compared to women. No relationships are found between dietary intake of other antioxidants such as vitamin C, beta-carotene and other naturally derived carotenoids and carotid IMT.

The large number of associations examined also raises the question as to whether the statistically significant association between vitamin E intake in men and carotid atherosclerosis may be a chance finding. The investigators (22) found also no independent association between the intake of vitamin supplements, including vitamin E, and carotid IMT and between dietary intake or plasma antioxidant vitamin levels and the risk of developing discrete carotid plaques. A weak relationship between plasma lycopene levels and carotid IMT is reported in women although no such correlation is found in men. Thus, overall, I believe that the study by McQuillan et al. (22) provides very little support for an association between antioxidant intake and/or plasma levels and early carotid atherosclerosis. The investigators honestly and appropriately outline the many neutral findings of their study and conclude that any association between individual antioxidant vitamins and early atherosclerosis, if present, is likely to be modest.

Although the investigators are thoughtful and cautious, I find their conclusion too optimistic, in that they ultimately do suggest that the study provides limited support for the hypothesis that dietary consumption of vitamin E may reduce the development of early atherosclerosis. As outlined in the Discussion section of their study, previous observational reports of subclinical atherosclerosis evaluated by carotid IMT and antioxidant vitamins have also generally yielded quite confusing and often conflicting results. Although some differences between the results of different
reports may be explained by differences in dietary habits of the populations studied, there are major inconsistencies even within individual studies. For example, a report from the Atherosclerosis Risk In Communities (ARIC) group found individuals with the highest carotid IMT to have lower levels of plasma carotenoids but higher alpha-tocopherol and retinol levels compared to controls (23). Thus, the current study (22) and the previous observational evaluations of carotid atherosclerosis and antioxidants fail in general to fulfill the expectation, that use of this technique, which allows the identification of early atherosclerosis, may lead to a more consistent demonstration of a relationship between dietary antioxidants and atherosclerotic disease.

Similar to many previous studies, the current report by McQuillan et al. (22) demonstrates again that our ability to evaluate micronutrients from dietary questionnaires is modest at best. Though plasma antioxidant levels did correlate with dietary intake assessments, these correlations were relatively weak. This observation combined with similar results from a multitude of other studies points out significant limitations of our current tools to assess dietary intake of micronutrients and may therefore explain some of the confusing results when using such tools in the study of associations between micronutrients and cardiovascular risk.

To date we do not have clear evidence that antioxidants provided by dietary intake or the addition of antioxidants in the form of vitamin supplements can reduce the risk of atherosclerosis. A number of studies are currently ongoing and will evaluate combinations of antioxidants and longer-term use in different populations, including those more susceptible to have early vascular damage. This research is necessary and should be encouraged. Until clear results emerge, however, neither individual persons nor physicians should focus their efforts in preventing heart disease and stroke on intake of such vitamin supplements or other alternative medicines. Prevention has been clearly and conclusively demonstrated to be the most efficacious strategy in fighting atherosclerotic diseases. Effective interventions are available and include smoking cessation, exercise, cholesterol lowering, blood pressure lowering and in high-risk individuals with established CVD the use of pharmacologic interventions such as aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors. Clear and rational guidelines for the management of the major cardiovascular risk factors have been outlined, and there is an urgent need to find more effective strategies to fight obesity, physical inactivity, smoking and diabetes.

We need to focus on the use of such preventive strategies with proven efficacy. Their implementation requires effort, patience and perseverance. The hope that other alternative interventions may be useful can detract from the focus required to implement these proven preventive strategies. Whereas further research is mandatory and should be encouraged, until we do have conclusive proof that other preventive measures, such as antioxidant vitamins, are beneficial, these should not be part of our main therapeutic regimen in CVD prevention.

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REFERENCES