Agency for Healthcare Research and Quality

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Number 83

Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease

Summary

Overview

The purpose of this study was to conduct a systematic review of the scientific literature to identify and assess the evidence for the efficacy of three antioxidants, vitamin E, vitamin C, and coenzyme Q10, for the prevention and treatment of cardiovascular disease (CVD) or modification of known risk factors for CVD. A broad search found sufficient literature to perform a detailed review of the use of these antioxidants for CVD.

CVD, defined as coronary artery disease, hypertensive heart disease, congestive heart failure, peripheral vascular disease, and atherosclerosis, including cerebral artery disease and strokes, is the leading cause of death in the United States. Modification of the major risk factors for CVD (diabetes mellitus, hypertension, hypercholesterolemia, and smoking) has been associated with a decreased risk of CVD. Thus, identification of interventions that treat CVD or modify the underlying risk factors would be of great interest.

Observational data suggest that fruit and vegetable consumption lowered the risk of developing CVD. It has been postulated that the antioxidant component of fruits and vegetables accounted for the observed protection. Decreased risk of cardiovascular death has been associated with higher blood levels of vitamin C and coenzyme Q10. In addition, vitamin C, vitamin E, and coenzyme Q10 have demonstrated antioxidant effects, including beneficial effects on oxidation of low-density lipoprotein. There is evidence that these vitamins affect other risk factors for CVD such as hypertension. Vitamin E may also reduce coronary artery blockage by decreasing blood platelet aggregation. Thus, it was reasonable to expect that supplementation with these antioxidants would decrease the risk of developing CVD. Large numbers of people are taking antioxidants with the expectation that they will prevent disease.

Methodology

Search Strategy

A comprehensive search for citations in English and other languages was conducted using 15 databases. We used the search terms antioxidant, vitamin E, vitamin C, coenzyme Q10, and all pharmacologic synonyms in combination with the MeSH term cardiovascular disease. We also identified appropriate literature by searching the bibliographies of review articles and asking our experts for articles.

Selection Criteria

The literature search was confined to the three antioxidants—vitamin E, vitamin C, and coenzyme Q10—and cardiovascular disease. Reports were included in the synthesis of evidence, if they focused on one of the identified antioxidants, alone or in combination, for the selected disease state of CVD. CVD included coronary artery disease and its sequelae, as well as stroke, heart failure, and peripheral vascular disease. Studies were also included if they affected known risk factors for CVD such as blood lipids or hypertension. Language of publication was not a barrier to inclusion.

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Data Collection and Analysis

Information was collected about trial design and quality, number and characteristics of patients, details on the intervention, and time between intervention and outcome measurement. Two physicians independently reviewed each article, abstracted data, and resolved differences by consensus. After abstraction of data, all studies were considered for inclusion in the pooled analysis based on similarity of patients studied, interventions given, and outcomes measured. The only studies sufficiently similar for pooling were those on the effects of vitamin E alone and in combination regarding risk of death, myocardial infarction (MI), and blood lipid levels. We judged the studies on vitamin C and coenzyme Q10 to be insufficiently similar to justify pooling. Our synthesis of these studies is qualitative and restricted to placebo-controlled randomized trials that enrolled at least 60 patients, reported clinical outcomes, and were at least 6 months' duration of treatment.

Findings

Our literature search identified 1,339 articles that met our search criteria, of which we were able to find 1,127. Based on an independent review by two physicians, 528 were selected for screening. They included clinical trials, review articles, and reports that contained supplemental information. Of these, we identified 156 articles that represented results from 159 reports on 144 unique trials (i.e., those reporting data not duplicated in another publication). Of the 159 reports referred for further analysis, one-third was judged to be of high quality using the Jadad method.

Studies reporting on outcomes of death, MI, and/or blood lipid levels were selected for further analysis. For the interventions of vitamin E alone and in combination with other antioxidants, sufficient numbers of heterogeneous populations existed to perform pooled analysis.

The available evidence did not generally support the assertion that there was any positive benefit associated with the use of vitamin E either alone or in the combinations tested for the prevention of all-cause death or cardiovascular death. Neither was there any evidence of significant harm from the same interventions. An effect of vitamin E on overall mortality and on cardiovascular mortality reported in the GISSI trial was only observed in the "four way" analysis (that is, comparing each arm of the 2x2 factorial study separately), and not seen in the "two way" analysis (comparing all subjects who received vitamin E to all those who did not). The GISSI investigators themselves noted that the results in the "four way" analysis are probably due to chance, and concluded that vitamin E supplementation conferred no benefit. Reduction in all-cause mortality (9percent) reported in the Linxian study was primarily due to a decrease in cancer deaths, not cardiovascular deaths. Therefore, there is little evidence that vitamin E supplementation results in a reduction in cardiovascular mortality.

For the risk of MI, fatal and nonfatal, the evidence regarding results of supplementation with vitamin E alone or in combination is mixed. No pooled analysis yielded a beneficial or adverse effect for vitamin E supplementation, either alone or in combination. However, individual studies did report significant effects. The GISSI study reported a benefit on fatal MI but a nonsignificant adverse effect on nonfatal MI. Furthermore, the beneficial effects in GISSI were seen only in the "four way" analysis and not in the larger "two way" analysis. The Alpha-Tocopherol Beta Carotene (ATBC) trials reported just the opposite of the GISSI "four way" results: a significant adverse effect of vitamin E on fatal MI but a nearly significant beneficial effect of vitamin E on nonfatal MI. While there were distinct differences in the two trials (ATBC assessed 50 mg of vitamin E, while GISSI assessed 300 mg; but the baseline risk of both fatal and nonfatal MI was approximately equivalent in the two studies), such disparities in results cast doubt on the observed effects being due to a causal relationship, since consistency of effect and a dose response effect are two important constituents of causality.

Supplementation with vitamin E alone and in combinations in doses ranging from 100 IU to 1,200 IU did not demonstrate a statistically significant effect on serum lipids after at least 8 weeks and no more than 24 weeks of treatment. Two large primary prevention trials reported clinically insignificant (but statistically significant) changes in these outcomes. Thus, there is no evidence that vitamin E alone or in combination has a clinically and statistically significant favorable or unfavorable effect on lipids.

There have been few studies of the use of coenzyme Q10 that have enrolled at least 60 patients and completed at least 6 months' duration of treatment and measured clinical outcomes. A meta-analysis of the effect of coenzyme Q10 on indices of cardiac function concluded that its use was associated with a substantial improvement. This conclusion was not confirmed by two subsequent randomized trials. The studies reporting clinical outcomes yielded mixed results. Two studies reported distinctly favorable clinical outcomes for coenzyme Q10 treated patients. However, one study probably had a serious potential flaw in design and execution in that it is not reported to be placebo controlled or blinded with respect to outcome measurement. The second study is reported in insufficient detail to allow an adequate assessment of the enrolled population or the results. Four subsequent studies reported either no or clinically small improvements. Therefore, the value of coenzyme Q10 supplementation in patients with CVD is still an open question, with neither convincing evidence supporting nor refuting evidence of benefit or harm.

Four studies assessing vitamin C (mostly in combination with vitamin E) provide scant evidence that these combinations of antioxidant supplements have any cardiovascular health benefits. The only reported benefit was in the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study and that was in an intermediate outcome only, and then only in the subpopulation of male smokers. The Heart Protection Study, in particular, due to its size and follow-up provides good evidence that these antioxidant supplements in these doses are unlikely to have any substantial effects on coronary vascular disease outcomes.

Future Research

One outcome of this analysis is the discordant results between the observational data, which suggest that foods high in the selected antioxidants are beneficial, and the majority of the research presented here on supplemental antioxidants. These discordant results could occur for at least two reasons:

1. The tested antioxidant supplements do not contain the agents responsible for the benefit reported in observational studies.
2. The observational studies of food consumption are confounded by some other factor that is responsible for the effect. The recent failure of hormone replacement therapy to achieve in a randomized controlled trial (RCT) the cardiovascular benefit reported in observational studies has been attributed to confounding in the observational studies, demonstrating that no matter how well designed and how often replicated, confounding must always be considered a possibility.

Therefore, the thrust of new research into antioxidants and CVD should be randomized trials. These RCTs should consider the following:

- Use supplements that are standardized in terms of dose, source, and stereoisomers.
- Measure clinical outcomes (that include death, MI, hospitalization, quality of life, exercise tolerance, and so on) in addition to intermediate outcomes (levels of antioxidants, blood lipid levels, and so on).
- Be conducted over a sufficiently long period of time, e.g., years, to see an effect.
- Enroll heterogeneous populations so that the results may be extrapolated to the U.S. population. (Most existing studies have enrolled only or predominantly Caucasian participants.)

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California–RAND Evidence-based Practice Center, under Contract No. 290-97-0001. It is expected to be available in June 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 83, *Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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