Nutrient supplements and cardiovascular disease: a heartbreaking story

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Abstract   Observational data have identified associations between carotenoids, folic acid, and vitamin E, or metabolites altered by these nutrients, and cardiovascular disease (CVD) risk. Despite biological plausibility, for the most part, data derived from nutrient supplement trials using moderate to high doses of single nutrients or nutrient combinations (exceeding amounts to avoid nutrient deficiency) have been disappointing. The data for vitamin D is not yet adequate to evaluate; observational data suggest were a relationship to exist it would be related to nutrient insufficiency. There is some evidence that use of nutrient supplements intended to decrease CVD risk has resulted in unanticipated adverse consequences. Potential discrepancies between observational and interventional data include concerns of residual confounding by diet and lifestyle patterns, publication bias against studies with null or negative outcomes, reliance on secondary rather than primary prevention trials, and unaccounted for contribution of genotypic variations. At this time there are insufficient data to recommend the routine use of nutrient supplements to prevent or treat CVD. In the recent past we have learned a great deal about anticipated and unanticipated consequences of nutrient supplementation and cardiovascular outcomes. As a result, we are in a better position to adjudicate new potential relationships as data emerge.**—Lichtenstein, A. H. Nutrient supplements and cardiovascular disease: a heartbreaking story. *J. Lipid Res.* 2009. **50:** S429–S433.

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Hope springs eternal that a single or combination nutrient supplement will be identified to dramatically reduce cardiovascular disease (CVD) risk and will require no more dietary restraint or physical exertion than the quick sideward twist of the wrist (open container) and front hand bend (insert pill in mouth). The evidence to date, however, has yet to identify a nutrient supplement meeting these criteria and, in some cases, raises concern regarding unintended adverse consequences. This mini-review provides a short synopsis of the topic. It is limited to essential nutrients. The order of presentation is arranged alphabetically.

CAROTENOIDS

A number of retrospective and prospective longitudinal studies have identified an inverse association between carotenoid intake or plasma/serum concentrations and CVD risk (as reviewed in Ref. 1). The biological mechanism for these associations has been attributed to the antioxidant potential of carotenoids (2).

Results from a series of intervention trials using β-carotene supplements, the major dietary carotenoid, have not supported the hypothesis that β-carotene reduces CVD risk (as reviewed in Refs. 1, 3). It is not clear why there is a discrepancy between the observational and interventional data; nor is it possible to determine whether the putative factor(s) in the observational studies was the β-carotene, other carotenoids, or phytochemicals occurring in the same foods as carotenoids (fruits and vegetables), or dietary patterns characterized by high intakes of carotenoids. Summarized are the major carotenoids-cardiovascular intervention studies.

The Alpha-Tocopherol-Beta-Carotene Prevention Study (4) was designed to assess the effect of β-carotene and/or vitamin E supplements in individuals at high risk of developing lung cancer. After a 5–8 year follow-up period, no significant benefit of supplementation with either nutrient was reported. In those individuals who received β-carotene supplements, there was an increased incidence of lung cancer, and more deaths from hemorrhagic stroke and ischemic heart disease. The 6-year posttrial assessment data suggested that those individuals who had received β-carotene were at increased risk of first-time nonfatal myocardial infarction (5). The Carotene and Retinol Efficiency Trial also focused on individuals at high risk of developing lung cancer (6). After a mean follow-up period of 4 years, those

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individuals receiving the β-carotene and vitamin A were at increased risk for cardiovascular mortality and lung cancer, and more likely to be diagnosed with lung cancer.

Around that same time, data from the Physician's Health Study, in which only a small percentage of subjects were at high risk of lung cancer, showed that, after 12 years of supplementation with β-carotene, there was no significant effect on CVD or lung cancer (7). Likewise, individuals at high risk of developing nonmelanoma skin cancer were supplemented with β-carotene for 4.3 years and then followed for an additional 3 years. No significant effect of β-carotene on CVD or total mortality was reported (8).

At this time, the data do not support the use of β-carotene supplements to reduce CVD risk and some data to indicate that in individuals at high risk of lung cancer b-carotene supplements should be avoided.

FOLIC ACID (AND OTHER B VITAMINS)

Almost 40 years ago, McCully (9) concluded that homocysteine was associated with progressive arterial disease based on evidence from two case studies which had different etiologies but a common outcome: hyperhomocysteinemia. Subsequent data from studies in animals (10, 11) and case-controlled and retrospective studies in humans supported the relationship (as reviewed in Ref. 12). In contrast, data from prospective studies focused on the relationship between homocysteine and CVD risk were equivocal, ranging from a positive significant association (13), weak nonsignificant association (14) to no significant association (15).

A number of factors have been identified as associated with elevated homocysteine concentrations. These include inadequate dietary intake of folic acid, vitamin B6 and/or vitamin B12, pre-existing atherosclerotic disease, coffee consumption, smoking, alcohol consumption, diabetes, use of antiepileptic drugs or methotrexate, renal failure, cancer, rheumatoid arthritis, hypothyroidism, and mutations in cystathione-β-synthase and methylenetetrahydrofolate reducatase (12, 16). Elevated homocysteine concentrations have been related to increased oxidant stress, impaired endothelial function, and increased thrombogenicity (12, 16). A common phenotype of hyperhomocysteinemia in animal models is endothelial dysfunction accompanied by decreased bioavailability of endothelium-derived nitric oxide, increased susceptibility to arterial thrombosis, and accelerated development of atherosclerotic lesions (17).

Despite observational data and biological plausibility suggesting an association between elevated homocysteine concentrations and increased CVD risk, a series of findings from well-controlled intervention trials using either folic acid or a combination of folic acid and vitamins B6 and B12 at doses sufficient to lower plasma homocysteine concentrations reported no significant effect on cardiovascular events or all cause mortality [see meta-analyses (18, 19)]. Potential adverse effects of the folic acid plus B vitamin supplementations were noted.

In the Vitamin Intervention for Stroke Prevention trial, a cocktail of folic acid and vitamins B6 and B12 was given to patients who had a nondisabling cerebral infarction. After 2 years of follow-up, the treatment was successful in lowering homocysteine concentrations but had no significant effect on vascular outcomes (20). Patients recovering from successful coronary stenting procedures were given an intravenous dose, followed by oral daily dose of folic acid and vitamins B6 and B12 for 6 months (21). The treatment group exhibited higher, rather than lower, in-stent restenosis and need for target-vessel revascularization. In the only randomized-controlled trial to report a positive effect of B-vitamin supplementation, patients who underwent percutaneous coronary intervention and were given a cocktail of folic acid and vitamins B6 and B12 were reported to have significantly lower homocysteine concentrations and lower rate of target lesion revascularization after 1 year (22). No significant effect was reported for deaths and nonfatal myocardial infarctions in these patients.

Patients with end-stage renal disease have impaired homocysteine excretion rates, hence, elevated plasma concentrations. Supplementation with folic acid for 2 years lowered homocysteine concentrations yet had no significant effect on cardiovascular events (23). These findings were confirmed in two subsequent studies focusing on a similar patient population (24, 25).

After 1 year of combined folic acid and statin therapy in hypercholesterolemic postmyocardial infarct patients, despite a decrease in homocysteine concentrations, there was no significant additive effect of folic acid on cardiovascular mortality or morbidity (26). Folic acid treatment for 1 year in heart transplant recipients resulted in a decrease in homocysteine concentration but had no significant effect on the progression of coronary intimal area (27). In the Norwegian Vitamin (NORVIT) trial, patients identified with acute myocardial infarction were treated within 7 days with folic acid with or without vitamins B6 and B12 (28). After 3 years there was no significant effect of treatment on recurrent CVD. A trend toward increased risk was reported in the group receiving the three-vitamin combination therapy, in addition to a nonsignificant increase in cancer risk.

At about the same time, the Heart Outcomes Prevention Evaluation 2 study reported that treating patients with either vascular disease or diabetes with folic acid and vitamins B6 and B12 for an average of 5 years had no significant effect on death from cardiovascular causes or myocardial infarction, or secondary outcomes (29). Of note, fewer patients in the treatment group had a stroke, but more patients in the treatment group were hospitalized for unstable angina. Focusing on high-risk women, with and without CVD, folic acid and vitamins B6 and B12 supplementation for a mean of 7.3 years resulted in similar risk for the composite cardiovascular primary endpoint as well as secondary outcomes (30).

The Western Norway B Vitamin Intervention Trial was designed to assess the effect of folic acid and vitamins B6 and B12, folic acid and B12, vitamin B6, or placebo in patients undergoing coronary angiography (31). Due to the media attention given to the NORVIT study results, lack of benefit of B vitamins and potential increased cancer risk, this trial was terminated early because of concern that pa-

tient adherence would be adversely effected. After a mean follow-up time of 3 years, no significant effect of treatment was observed on total mortality or cardiovascular events, and a nonsignificant increase in cancer risk was noted in the groups receiving folic acid.

At this time the data do not support the use of folic acid alone or combined with other B vitamins to reduce CVD risk (18).

VITAMIN D

A newly emerging area is the potential association between vitamin D and CVD risk. In contrast to the other nutrients discussed in this review where the focus was on the benefits of nutrient supplementation beyond that traditionally thought to meet nutrient requirements, the focus of this relationship is on low vitamin D status.

Evidence for an association between vitamin D and CVD hails from different sources: higher incidence of CVD during winter months and in individuals residing in higher geographic latitudes, in both cases when circulating 25(OH) vitamin D concentrations (indicator of vitamin D status) are lowest. Low circulating 25(OH) vitamin D concentrations have been associated with metabolic states such as hypertension, obesity, diabetes mellitus, and metabolic syndrome (32, 33). Potential biological mechanisms for a relationship between vitamin D status and cardiovascular outcomes include inhibition of vascular smooth muscle cell proliferation, suppression of vascular calcification, down-regulation of proinflammatory cytokines, up-regulation of anti-inflammatory cytokines, and negative endocrine regulator of the renin-angiotensin system (34).

Early work centered on concern that high plasma vitamin D concentrations were associated with increased risk of CVD by favoring arterial calcification (as reviewed in Ref. 35). The data on this topic were inconsistent (35–37). Attention has now shifted to an inverse relationship between plasma vitamin D concentrations and CVD risk.

Low serum 25(OH) vitamin D concentrations have been associated with a higher prevalence of peripheral arterial disease in the National Health and Nutrition Examination Survey cohort (38) and myocardial infarction in the Heath Professionals Follow-up Study (39). Vitamin D deficiency has been associated with incident CVD in the Framingham Offspring Study (40), and low plasma 25(OH) vitamin D and $1,25(OH)_2$ (the bioactive form of vitamin D) concentrations in the Ludwigshafen Risk and Cardiovascular Health study (41).

The only intervention data to date for vitamin D supplementation and CVD outcomes is the Women's Health Initiative (42). Women were randomized to receive either calcium and vitamin D, or placebo. CVD was a secondary outcome. After 7 years there was no significant effect, either positive or negative, on coronary or cerebrovascular risk. Of note, women in the Women's Health Initiative were not specifically selected on the basis of vitamin D nurture.

Vitamin D toxicity resulting from high chronic intakes is well documented (43). For this reason it is important not to make premature statements about the potential benefits of supplemental vitamin D and CVD until randomized controlled intervention trial data are available in cohorts well characterized for vitamin D status prior to the intervention.

VITAMIN E

Initial interest in the potential benefit of vitamin E with regard to CVD risk was related to its antioxidant capacity. Oxidized LDL is avidly taken up by macrophage scavenger receptors, bypassing the regulatory controls governed by receptor mediated uptake (44). In humans, supplemental vitamin E was shown to decrease the susceptibility of LDL to in vitro oxidation (45–47). In animal studies, vitamin E was shown to retard atherosclerotic lesion development (48, 49).

Observational data suggested that the habitual use of vitamin E supplements (50–52), vitamin E dietary intake (53), and plasma vitamin E concentrations (54) were associated with decreased risk of developing CVD. Early small intervention trials suggested beneficial effects of vitamin E supplementation for CVD outcomes (55, 56).

More recent randomized placebo-controlled intervention trials do not support the original observations regarding vitamin E. With few exceptions, a large series of primary and secondary prevention trials have reported no significant benefit of moderate- to high-dose vitamin E supplementation on cardiovascular outcomes [see reviewers and meta-analyses (3, 18, 52, 57, 58)]. These data were recently confirmed in a well-controlled randomized intervention trial assessing the effect of vitamins E and C on risk of major cardiovascular events (59). In addition, concern has been raised about potential adverse effects of vitamin E doses in excess of 400 IU per day, the level initially identified as efficacious in observational studies (60). A recent review of these data concluded that the low-bias risk trials (ranked as having high-methodological quality) were more likely to report increased all-cause mortality in the vitamin E-supplemented group, whereas the high-bias risk trials (ranked as having low-methodological quality) were more likely to report decreased all-cause mortality in the vitamin E supplemented group events (3).

At this time, the data do not support the use of vitamin E supplements to reduce CVD risk.

GENERAL COMMENTS AND CONCLUSIONS

Despite observational data suggesting strong associations between carotenoids, folic acid, and vitamin E, or metabolites altered by these nutrients, and decreased CVD risk, most intervention data using nutrient supplements at or above the Recommended Dietary Allowance values (61, 62) have not supported these relationships. There are also some data to suggest that unexpected adverse consequences may result from supplementation with nutrients traditionally thought to have a low risk of toxicity. The

data for vitamin D is not yet adequate to evaluate a potential relationship to CVD risk.

Although there has been considerable speculation about why the discrepancy exists between the observational and interventional data, there are no clear answers (63). Observational data are known to be vulnerable to potential residual confounding with diet and lifestyle patterns (19). For example, individuals who report using nutrient supplements are also more likely to eat "healthier" diets, exercise more, and smoke cigarettes less than those who report not using nutrient supplements (64–68). There is also an underlying suspicion of publication bias against studies having either null or negative outcomes (19, 69). Intervention data suffer from concerns about over-reliance on secondary rather than primary prevention, insufficient intervention and follow-up periods, inappropriate supplement doses, and unsuitable cohorts for testing the hypothesis. Furthermore, we are just beginning to appreciate the effect of genotypic differences within and among cohorts.

At this time, the data are insufficient to recommend the routine use of any nutrient supplement to prevent or treat CVD. From the lessons learned in the recent past, however, we are in a good position to adjudicate new potential relationships as they emerge.▮

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