Micronutrient concentrations and subclinical atherosclerosis in adults with HIV

Dear Sir:

Falcone et al (1) examined serum micronutrient concentrations along with surrogate markers of atherosclerosis in a cohort of HIV-infected adults. They reported that “the highest tertile of serum vitamin E concentration was associated with higher common and internal carotid intima-media thickness (c-IMT) and coronary artery calcium (CAC) scores (P < 0.05 for c-IMT and CAC)” (p 1213). They concluded that “elevated serum vitamin E concentrations ... may increase the risk of cardiovascular complications in HIV-infected adults” (p 1213). However, we believe that the authors’ conclusion that vitamin E is adversely affecting atherosclerosis is not convincing, is based solely on associations that cannot establish causation, and has no mechanistic basis. Furthermore, on the basis of current descriptions of adverse consequences of highly active antiretroviral therapy drugs (2), the authors’ recommendation that HIV-infected subjects should limit vitamin E intake may be harmful.

Serum α-tocopherol (vitamin E) concentrations are closely regulated by the α-tocopherol transfer protein and are highly dependent on serum lipid concentrations because α-tocopherol is nonspecifically transported by lipoproteins, as reviewed previously (3). Moreover, correlations between vitamin E intakes and serum α-tocopherol concentrations are confounded by a strong correlation with serum cholesterol concentrations (4).

There may be health benefits to higher serum α-tocopherol concentrations. Wright et al (5), in their 19-y follow-up study of 29,092 Finnish male smokers aged 50–69 y who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, found that “Men in the higher quintiles of serum α-tocopherol [at baseline] had significantly lower risks of total and cause-specific mortality than did those in the lowest quintile [relative risk (RR) = 0.82 (95% CI: 0.78, 0.86) for total mortality and 0.79 (0.72, 0.86), 0.81 (0.75, 0.88), and 0.70 (0.63, 0.79) for deaths due to cancer, cardiovascular disease, and other causes, respectively; P for trend for all <0.0001]” (p 1200). The mean (±SD) serum α-tocopherol concentrations in the patients with HIV (1) were 1182.0 ± 714.7 µg/dL (equivalent to 11.8 ± 7.1 mg/L), equal to the midrange in the Wright et al study (5), and the HIV patients’ highest concentrations (>12.2 mg/L) were similar to the highest quintile in the Wright et al study (>13.5 mg/L). Notably, none of these serum concentrations is particularly high because it has been well documented that serum α-tocopherol does not increase >2 to 3-fold in response to vitamin E supplements (6).

Because vitamin E is an antioxidant (3), and atherosclerotic lesions contain oxidized lipids (7), it was assumed by many investigators that antioxidant supplements would decrease heart disease risk. However, the Heart Outcomes Prevention Evaluation (HOPE) Study was the first of many randomized controlled intervention studies to show that vitamin E supplements given to high-risk patients did not decrease heart disease incidence (8). However, subsequent subgroup analysis of patients from the HOPE trial showed that in haptoglobin 2-2 genotype (Hp 2-2) diabetic participants given vitamin E supplements there was a “statistically significant reduction in the risk of CV death (0.45 [0.23–0.90]) and nonfatal myocardial infarction (0.57 [0.33–0.97])” (p 2767) (9). Importantly, Milman et al (10) in a separate study showed that vitamin E supplementation (400 IU) reduced cardiovascular events in Hp 2-2 individuals with diabetes. Haptoglobin is a major antioxidant protein; therefore, Hp 2-2 individuals have less antioxidant protection. Thus, in subjects with observed inadequate antioxidant protection, vitamin E supplementation is beneficial in decreasing heart attack risk.

Given that the ranges of serum α-tocopherol concentrations are similar in the Falcone et al (1) and Wright et al (5) studies, what is the explanation for the association of higher progression of atherosclerosis biomarkers in the patients with HIV? Falcone et al (1) note that “Patients in the higher tertiles of serum vitamin E were more likely ... to have higher serum triglyceride (P ≤ 0.001) and total and LDL-cholesterol (P ≤ 0.001) concentrations” (p 1215). We believe that the elevated concentrations of circulating total cholesterol (212 ± 55.9 mg/dL), and triglycerides (273 ± 244 mg/dL), in patients with the highest serum vitamin E concentrations (Table 2 in reference 1) is the cause for their increased progression of atherosclerosis. Given that serum α-tocopherol concentrations increase with serum cholesterol concentrations (4), Wright et al (5) adjusted serum α-tocopherol for total cholesterol concentrations. It is surprising that Falcone et al (1) did not correct their serum α-tocopherol concentrations for circulating lipids. Thus, in our opinion, the authors were misled in the interpretation of their data because α-tocopherol is transported in the serum in lipoproteins and increases in parallel with increasing lipid concentrations (3). Moreover, atherosclerosis progression may be aggravated by the highly active antiretroviral therapy drugs, which inhibit in vitro cholesterol efflux from human macrophage–derived foam cells (2). Remarkably, this effect is reversed by vitamin E (2). Thus, the authors’ recommendation for limits on vitamin E (1) may adversely affect the health of persons with HIV.

Neither author declared a conflict of interest.

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REFERENCES


Reply to MG Traber and B Frei

Dear Sir:

We appreciate Traber and Frei’s interest in our work. The effect of vitamin E on the progression of atherosclerosis is a complex and controversial area of research involving underlying physiologic processes, which remain to be fully elucidated (1).

We clearly state in our study’s limitations that the results show an association between serum concentrations of vitamin E and atherosclerosis and do not suggest causation. On the basis of our cross-sectional study design, any elaboration on an underlying mechanism of action would have been speculative.

The reference to the Heart Outcomes Prevention Evaluation (HOPE) Study (2, 3) is interesting, but we point out that this trial was in a very specific population (ie, in those with haptoglobin deficiency), which is quite distinct from the patients infected with HIV in our study. We also note that we adjusted our multivariate analysis for potential confounders such as serum total cholesterol, serum triglycerides, and serum LDL.

We agree that both HIV infection itself and selected antiretroviral agents may alter lipid metabolism. Moreover, our study underlines that additional factors are likely implicated in cardiovascular risk stratification in this complex patient population. We would, however, emphasize that the study by Wang et al (4) reports an in vitro effect, which may or may not be sustained in vivo.

We also note that our recommendations are based on the fact that it is common for some individuals infected with HIV to take pharmacologic doses of selected micronutrients, which may not be of benefit.

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REFERENCES