



Position Paper on Vitamin E: Comment on HOPE-TOO Published Results

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EXECUTIVE SUMMARY

- *A recent study published in JAMA has raised concern regarding long-term vitamin E supplementation.*
- *A closer look at this study within the context of other vitamin E research suggests that careful interpretation is warranted.*
- *Several opinion leaders in the health industry have not deemed vitamin E supplementation unsafe as a result of this study.*
- *A specific, high-risk population was selected for this study; therefore, these results do not negate the numerous positive benefits vitamin E supplementation may have for healthy individuals.*
- *Diet and exercise information were not provided in this study, leading to potential misinterpretation of the findings. The one-system, one-drug approach to medicine lacks the complexity of integration of all body systems that Functional Medicine aims to address.*
- *The human body works best with an antioxidant mixture, similar to that found in nature, versus high amounts of isolated compounds.*
- *Vitamin E (alpha tocopherol) is just one member of a family of potential bioactive compounds; other tocopherol compounds, especially gamma tocopherol, have been shown to have beneficial biological activity different from alpha tocopherol, and warrant further scientific investigation.*

Recent JAMA Study: HOPE-TOO

Due to the recent publication in the March 16, 2005 issue of the *Journal of the American Medical Association* entitled, "Effects of Long-Term Vitamin E Supplementation on Cardiovascular Events and Cancer: A Randomized Controlled Trial," there has been heightened negative press coverage on vitamin E.¹ This trial, known as the Heart Outcomes Prevention Evaluation Study Extension (HOPE-TOO), included high-risk individuals with vascular disease or diabetes who ingested 400 IU. of natural vitamin E in supplement form for seven years, and reported the following conclusions:

- There was no significant difference in the number of cancers or cancer deaths between those taking vitamin E and placebo. No data were available on specific cancers.
- Patients in the vitamin E group had an overall *higher risk of heart failure* (519 subjects in the vitamin E group vs. 443 in placebo group out of a total sample size of 7,030) and *hospitalization for heart failure* (203 subjects in the vitamin E group vs. 146 in placebo group out of a total sample size of 7,030).

A Balanced Review of Vitamin E Literature

It is valuable to put these findings in the context of the previous work on vitamin E and cardiovascular health. A review of the vitamin E literature, as it pertains to cardiovascular health, suggests there have been a mixture of results, both positive and negative, which could be due to a number of factors, including dose, form (i.e., natural or synthetic, or antioxidant combinations), and/or study cohort (i.e., healthy subjects or individuals with chronic disease or risk factors). Another issue is that compliance was not mentioned, other than the measurement of two-year plasma levels of vitamin E in randomly selected subjects (163 in the vitamin E group and 34 in the placebo group). The HOPE-TOO study was seven years long, and there is a high degree of probability that subjects' compliance tapered off the longer the study progressed.

It is worthwhile to mention that there have been quite a number of positive published studies on the effects of vitamin E on cardiovascular health and cancer. Therefore, this study may not warrant as much caution as has been generated by the popular press. As these particular results have not been noted in other studies, it remains speculative as to whether vitamin E supplementation poses true cardiovascular risk or whether this outcome was a chance effect. In a number of human clinical trials, there have been positive results documented on the effects of vitamin E on cardiovascular health in healthy individuals, possibly due to its protective effect on preventing or reducing oxidation of low-density lipoprotein (LDL) cholesterol. Epidemiological and clinical studies have supported the role of vitamin E in stimulating the regression of existing arterial lesions and its protective effect against the development of atherosclerosis.²⁻⁴

For example, observational studies have demonstrated a relationship between lowered rates of cardiovascular disease and higher vitamin E intake. In the Nurses Health Study (n=87, 245 female nurses), it was suggested that the incidence of cardiovascular disease was 30% to 40% lower among nurses with the highest intake of vitamin E from diet and supplements.⁵ Cardiac risk reduction was associated specifically with long-term (> 2 years) supplemental vitamin E, and not dietary vitamin E or short-term (< 2 years) vitamin E supplementation. A similar correlation between vitamin E intake and reduced coronary heart disease risk was found in 39,910 men taking at least 100 I.U. of vitamin E in supplemental form for at least two years.⁶ Finally, another study with 5,133 Finnish men and women aged 30-69 years and initially free from cardiovascular disease reported an inverse association between dietary vitamin E intake and coronary mortality in both men and women.⁷

What Do Opinion Leaders Recommend?

Opinion leaders such as the Council for Responsible Nutrition, the National Cancer Institute (part of the National Institutes of Health) and the Institute of Medicine do *not* regard vitamin E as unsafe as a result of these findings.

Additionally, the Council for Responsible Nutrition has “urged caution” in interpreting the results from the HOPE-TOO trial.⁸ They contend that these results may be limited to the specific cohort that was studied in the trial—high-risk individuals over the age of 55 years with either vascular disease or diabetes. Upon entry into the study, these subjects already had cardiovascular disease or strong risk factors and were taking medications (e.g., beta-blockers, aspirin, lipid-lowering agents, diuretics, calcium channel blockers). Therefore, this study was designed to assess the role of vitamin E in preventing cardiovascular risk outcomes in high-risk patients rather than evaluating the protective effect of vitamin E against cardiovascular disease in healthy individuals.

In response to the HOPE-TOO study findings, the Council for Responsible Nutrition has conveyed to consumers that vitamin E is very safe, and that supplementation with vitamin E has been suggested to provide health benefits such as protection against oxidative stress and inflammation. In addition, the National Cancer Institute is currently sponsoring ongoing long-term studies (e.g., Selenium and Vitamin E Cancer Prevention Trial, also known as SELECT) investigating vitamin E supplementation and its role in preventing specific types of cancer. These studies have not been halted as a result of these recent findings. Furthermore, the Food and Nutrition Board of the Institute of Medicine has designated vitamin E intakes are safe up to 1000 mg (equivalent to 1500 I.U. of natural vitamin E—almost 4 times the amount used in the HOPE-TOO trial).

Support for the Functional Medicine Approach

In the HOPE-TOO study report, details regarding diet, exercise/activity and lifestyle were not included. Very often, pharmaceutical-based medicine lacks the integration of nutritional components and exercise regimens. As a result, rather than assist the patient to recovery, the drug treatment adds to the patient's chemical toxicity, and burdens cellular metabolism, creating potential metabolic dysfunctions. The manner in which such an altered body system handles a natural compound like vitamin E could be drastically different. For example, the fact that most of the HOPE-TOO study participants were on medications may have impacted the body's interaction with vitamin E.

In contrast, Functional Medicine teaches that individuals have unique biochemistry and that health is determined by an integration of approaches for the emotional, cognitive, and physical processes rather than the performance of one isolated organ system responding to a supra-active, synthesized compound. Most practitioners can appreciate the role that diet plays in a person's state of wellness, and that changing diet and lifestyle may have tremendous effects on study results. Having diet and exercise information available on these study participants would have been beneficial for looking at potential interactions on all levels. For example, it is well-known that vitamin E is a fat-soluble vitamin that would be best absorbed when taken with a fat-containing, mixed meal; however, we do not know how study participants were instructed to take vitamin E.

Antioxidants Work Better Together

Although much of the research to date focuses on the potential benefit of single antioxidant nutrients, it has become clear that the best protection against oxidative stress comes from a wide assortment of interrelated antioxidants and antioxidant cofactors.⁹ In other words, the human body utilizes an integrated antioxidant system composed of several players that work together as a team. The reducing potential of each individual member of the antioxidant defense team is enhanced when a full complement of players is available. For example, some evidence suggests a poor concentration of any single one of the antioxidants vitamin C, vitamin E, or beta-carotene, appears to increase the risk of cardiovascular disease. Additionally, the combination of several suboptimal concentrations may have an additive or even synergistic effect on increasing risk.

Conversely, it has been suggested that, under certain conditions, an excess of any one type of antioxidant in the absence of balance with the others may actually be counter-protective.¹⁰ Moreover, the relative importance of a given antioxidant may vary with different disease conditions because the type or types of reactive oxygen species generated are likely to differ, and because varying levels of specific antioxidants exist within the different tissues of the body.

Reconsideration for all of the Tocopherols

Along the lines of creating balance within antioxidants, a final aspect to consider is that although vitamin E (alpha tocopherol) has been recognized as the key tocopherol for its antioxidant effects, it is just one member of the tocopherol family. Along with alpha tocopherol, the vitamin E family also includes beta, gamma, and delta tocopherols. Early studies indicated that alpha tocopherol was specific among the tocopherols in playing a role in fertility of laboratory animals. Due to this specialized activity, combined with it being the predominant form in human tissues, alpha tocopherol became the lead tocopherol, with biologists almost completely disregarding the other, "minor" tocopherols for basic and clinical research.¹¹

Recent findings have demonstrated that this conventional approach to tocopherols needs strong reconsideration. Novel, beneficial effects have been reported for the other tocopherols, especially gamma tocopherol, which has different features compared with those of alpha tocopherol. Some of the benefits of gamma tocopherol are linked not to its antioxidant potential, but to its anti-inflammatory, anti-cancer, and sodium excretion functions, and data are emerging that the other forms of vitamin E may also play non-antioxidant roles.¹¹⁻¹³ Large doses of alpha tocopherol can displace gamma tocopherol in plasma and other tissues to a significant degree,¹⁴⁻¹⁶ so a combination of these tocopherols, and perhaps the others, is recommended, as it better reflects the ratios found in a healthy diet.

These findings may signal a paradigm shift in tocopherol research and may contribute to human health in ways not previously recognized. Data warrant further experimental and epidemiological evaluation of the other tocopherols, and their metabolism, especially with respect to cardiovascular health and cancer biology.

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