

Vitamin E: An Important & Controversial Nutrient

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Vitamin E is a fat-soluble vitamin with a well-established need in human health. Over the past decade or so, however, there has been a great deal of controversy surrounding whether supplementation with vitamin E increases or decreases the risk of heart disease and prostate cancer. This article will review the functions of vitamin E and research on the role of supplementation in human health, as well as address the aforementioned controversy.

Vitamin E Defined

From a scientific perspective, vitamin E is not just one compound (as is the case with other vitamins such as vitamin C), but rather a family of eight isomers, which include alpha-, beta-, gamma- and delta-e tocopherols. In this context, the term isomer refers to compounds with the same structural formula but different spatial arrangements of atoms.¹ The other four isomers are alpha-, beta-, gamma- and delta- tocotrienols (a family of natural compounds related to tocopherols). However, according to the Food and Nutrition Board, Institute of Medicine, vitamin E is defined as one specific compound, alpha-tocopherol. The reason for this is that alpha-tocopherol is the only form of vitamin E that is actively maintained in the human body and found in the largest quantities in blood and tissues.² Consequently, alpha-tocopherol is the only form that meets the latest recommended dietary allowance (RDA) and daily value (DV) for vitamin E. Nevertheless, the other tocopherols and tocotrienols do have value to human health.

Forms & Bioavailability

Vitamin E is measured in international units (IU), a unit of measurement based on biological activity or effect rather than weight (as is the case with nutrients measured in milligrams). Keeping this in mind, it is interesting to note that synthetic vitamin E (dl-alpha-tocopherol) is less bioavailable and only half the biological activity of natural vitamin E (d-alpha-tocopherol).³ That means that it takes twice as many milligrams of synthetic E to provide the same biological activity as would be found in natural E. Additionally, vitamin E is also available as tocopheryl esters using acetic or succinic acid. Alpha-tocopheryl acetate and succinate are more stable and easy to use in vitamin supplements. The bioavailability of alpha-tocopherol from succinate and acetate is equivalent to that of free alpha-tocopherol.⁴ For the rest of this article, the term "vitamin E" shall be considered to mean alpha-tocopherol or alpha-tocopheryl, unless otherwise stated.

Functions

The primary function of vitamin E is as an antioxidant. Since lipids (fats) are part of all cell membranes, fat-soluble vitamin E is ideally suited to quench free radicals that would otherwise compromise the integrity of cell membranes. Vitamin E also protects LDL cholesterol from oxidation, which is important since oxidized LDLs have been implicated in the development of cardiovascular diseases.⁵

In addition to its role as an antioxidant, vitamin E has also been shown to: 1) inhibit the activity of protein kinase C, a

cell-signaling molecule (may increase expression of oncogenes which promote cancer progression⁶), 2) affect the expression and activities of molecules and enzymes in immune and inflammatory cells, and 3) inhibit platelet aggregation and to enhance vasodilation (which promotes circulation).^{7,8} Finally research has shown that supplemental vitamin E was able to improve measures of immune function in the elderly^{9,10}, improve oxidative stress, improve insulin action and glucose disposal in diabetes¹¹⁻¹⁵ and slow progression of Alzheimer's in individuals with moderate neurological impairment.¹⁶

Intake

According to the National Health and Nutrition Examination Survey (NHANES) 2003-06, Americans' average dietary intake of vitamin E from food (including enriched and fortified sources) is 6.9 mg/day (10.35 IU). This intake is well below the current RDA of 15 mg/day (22.5 IU). This means that more than 90 percent of Americans do not meet RDA for vitamin E.¹⁷ If you compare it to the 30 IU DV for vitamin E, the results are even worse.

Cardiovascular Disease

Two large studies found that men and women who supplemented with at least 100 IU of natural vitamin E daily had significantly reduced risk of heart disease.^{18,19} A randomized, placebo-controlled, intervention trial of 39,876 women found that daily supplementation with 600 IU of natural vitamin E every other day for 10 years decreased cardiovascular-related deaths by 24 per-

cent, but had no effect on the incidence of various cardiovascular events²⁰ except for a 21 percent reduction in risk of venous blood clot.²¹ In addition, men who took at least 100 IU of natural vitamin E daily had a reduction in the progression of coronary artery atherosclerosis compared to those who took less vitamin E.²² Also, a randomized, placebo-controlled, intervention trial found that supplementing with 400 IU or 800 IU of synthetic vitamin E daily for 18 months reduced the occurrence of non-fatal heart attacks by 77 percent in heart patients.²³

By contrast, a large randomized trial found that supplementation with 400 IU of synthetic vitamin E every other day for eight years had no significant effect on the risk of major cardiovascular events.²⁴ Likewise, three other trials did not find significant risk reductions in cardiovascular disease with vitamin E supplementation in the following ranges: 37.5 IU (natural)²⁵, 400 IU (natural) (47)²⁶ or 225 IU (synthetic).²⁷ In a study of vascular disease in diabetes patients, daily supplementation with 400 IU of natural vitamin E for about seven years had no effect on major cardiovascular events, but there was a slightly increased risk of heart failure.²⁸

In an effort to determine an effective dose level, a clinical study²⁹ was conducted with individuals with high cholesterol and oxidative stress levels using placebo or the following daily doses of natural vitamin E: 100, 200, 400, 800, 1,600 or 3,200 IU/day for 16 weeks. A reduction in oxidative stress occurred only at 1,600 and 3,200 IU/day, both of which are above the 1,500 IU/day tolerable upper intake level (UL) for vitamin E.

So how does one interpret this seemingly contradictory research on vitamin E and cardiovascular disease when the jury still seems to be out? There are at least a couple of possibilities. One is that doses in the 100 IU range seem to consistently have had benefit for reduction of cardiovascular disease risk when larger or smaller doses did not. Another way is to take the research as an indication that vitamin E should be combined with other antioxidants rather than taken alone. (See the section on prostate cancer for elucidation on this concept.)

Yet another explanation may be that

tocotrienols, rather than alpha-tocopherol, offer better protection against the risk of cardiovascular disease. A two-month, randomized, placebo-controlled, blinded end point clinical study³⁰ examined the effects of placebo and 50, 100 and 200 mg daily of Tocomin Suprabio, a self-emulsifying palm oil-based preparation of the tocotrienols. Results showed that those in Tocomin Suprabio groups had a significantly reduced augmentation index (AI, a measure of arterial stiffness) compared to the placebo group, which did not show any reduction in their AI. Another 30-day study combining tocopherols, palm-based tocotrienols and palm olein showed a reduction in serum total cholesterol and low-density-lipoprotein cholesterol concentrations in all the volunteers.³¹

Prostate Cancer

A placebo-controlled intervention study that was designed to look at the effect of vitamin E supplementation on lung cancer development noted a 34 percent reduction in the incidence of prostate cancer in smokers given daily supplements of 37.5 IU/day synthetic vitamin E.³² A meta-analysis that combined the results of this study with three other randomized controlled trials associated vitamin E supplement use with a 15 percent lower risk of prostate cancer.³³

Conversely, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) involved 35,000 men randomly assigned to receive either: 1) selenium (L-(+)-selenomethionine) plus synthetic vitamin E (dl-alpha-tocopheryl acetate), 2) selenium plus placebo, 3) synthetic vitamin E plus placebo or 4) two placebos. When originally published in 2008³⁴, the results indicated that after almost five and half years, no significant differences were observed between any of the groups in relation to prostate cancer risk. However, subsequently an analysis of the study's participants published in *JAMA*³⁵ indicated that synthetic vitamin E supplements alone were associated with a 17 percent increase in the risk of prostate cancer, but that no increase in risk was observed in the combination selenium-vitamin E group.

In the opinion of this author, what the *JAMA* analysis really shows is that men

should take selenium with their vitamin E. In fact, the *JAMA* analysis is reminiscent of the flawed 1994 study in which smokers using beta-carotene were thought to be at a greater risk of lung cancer³⁶, although a more thorough follow-up analysis which looked at the diets and other dietary supplements taken revealed that the smokers' actual danger was due to low total antioxidant levels; not to the fact that they took beta-carotene.³⁷ This makes sense given the fact that antioxidants function interdependently, and so should be taken together. This is consistent with comments from Dr. Duffy MacKay of Council for Responsible Nutrition (CRN) about the *JAMA* analysis: "This reinforces the theory that vitamins work synergistically and that drug-like trials of nutrients, when used in isolation from other nutrients, may not be the most appropriate way to study them."³⁸ **VR**

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