Does High-Dose Vitamin E Kill People?

A meta-analysis of 19 vitamin E studies, scheduled to be published in January 2005 in The Annals of Internal Medicine, concluded that high-dose vitamin E supplementation (400 IU per day or more) may increase all-cause mortality and should be avoided. The article’s conclusions, which were widely circulated in the media two months before the scheduled publication of the article, created quite a stir. Many frightened patients stopped taking vitamin E or called to ask whether they should stop. Numerous practitioners also contacted me, wondering what to tell the patients who were jamming their phone lines with new-onset tocopherolphobia.

After reviewing a pre-publication copy of the meta-analysis I have concluded that it contains important flaws that call its conclusions into question. In addition to the researchers’ acknowledgement that their findings may apply only to people with chronic illnesses (as opposed to healthy people), other limitations of the study are discussed below. The report does serve to remind us, however, of what this author and others have been saying for many years: that not all commercially available forms of vitamin E may be entirely safe for all people at all dosage levels.

In the new study, researchers combined the results of 19 previously published vitamin E supplementation trials that included a total of 135,967 participants. The patients in the various studies were randomly assigned to take vitamin E (in doses ranging from 16.5 to 2,000 IU per day) or a placebo for at least one year. Most of the patients had one or more chronic diseases (such as heart disease, diabetes, Parkinson’s disease, Alzheimer’s disease, or kidney failure) or were at high risk of developing heart disease. In the 19 studies combined, the risk of death due to any cause did not differ significantly between people assigned to vitamin E and those assigned to placebo. However, the effect of vitamin E supplementation on mortality differed according to how much vitamin E was used. In the low-dose studies (less than 400 IU per day) vitamin E supplementation was associated with a small and not statistically significant reduction in the death rate. In the 11 high-dose studies (400 IU per day or more), on the other hand, those who took vitamin E had a 4% increase in risk of death, an increase which, though small, was statistically significant. Based on these findings, the researchers recommended that people limit their vitamin E intake to less than 400 IU per day.

For a number of reasons, that recommendation may be unwarranted. In some of the high-dose studies, certain aspects of the study design preclude any meaningful conclusion about vitamin E. For example, in the Age-Related Eye Disease Study (AREDS), participants received not only vitamin E, but also 80 mg of zinc and 2 mg of copper per day, as well as other nutrients. Supplementing with large doses of zinc (80 mg per day is a fairly large dose) for long periods of time can lead to copper deficiency, which can increase the risk of heart disease and other chronic illnesses. Although copper was also supplemented, it was given in the form of cupric oxide, an insoluble compound that cannot be absorbed by humans. The increase in mortality found in this study could have been due to zinc-induced copper deficiency, and may have had nothing to do with vitamin E supplementation.

In another high-dose vitamin E study (Cambridge Heart Antioxidant Study), the results were complicated by the fact that the vitamin E and placebo groups were not comparable. Even though assignment to the two groups was done randomly, the vitamin E group had significantly higher serum cholesterol levels and significantly greater percentages of participants with high blood pressure, diabetes, cigarette smoking, and severe coronary artery disease, compared with the placebo group. Thus, the people taking vitamin E were sicker than those taking the placebo, a fact that could account for the slight increase in mortality seen in the vitamin E group.

In a third high-dose study (the MRC/BHF Heart Protection Study), participants received synthetic beta-carotene in addition to vitamin E. Researchers have questioned the safety of synthetic beta-carotene (which is chemically different from food-derived beta-carotene), particularly for people who smoke cigarettes or drink alcohol. Previous studies have shown that supplementing with synthetic beta-carotene increases the risk of lung cancer among smokers and increases alcohol-induced liver damage in laboratory animals. It is possible that the increase in mortality found in the MRC/BHF Heart Protection Study was due to the use of synthetic beta-carotene, and had nothing to do with vitamin E.

The three studies mentioned in the previous paragraphs included a total of more than 27,000 participants, fully two-thirds of all of the patients in the 11 high-dose vitamin E studies. Consequently, the conclusion that high-dose vitamin E is dangerous is based primarily on the results of these three apparently flawed studies.

If any adverse effects of high-dose vitamin E do exist, they might be...
Editorial

Why Support AAHF?

Because the government should not restrict our access to integrative medical treatments and dietary supplements.

Did you know that 1 letter = 100 voices?

www.healthfreedom.net

1.800.230.2762 • 703.759.6711 (fax) • office@healthfreedom.net

JOIN: Become a member.*

ACT: Write Congress from our on-line Legislation Action Center. Tell them to support the Access to Medical Treatment Act and to protect DSHEA.

BE: PART OF THE SOLUTION:

AAHF is your politically active voice at the federal level fighting for your right to access a full range of health care treatment and prevention methods.

*Mention this ad and receive 10% off of membership for new members. Expires 12/31/04. Not applicable with any other offers.

Explained by the type of vitamin E used in the research studies. Vitamin E (also called tocopherol) occurs naturally in food in four different forms, known as alpha-, beta-, gamma-, and delta-tocopherol. Although approximately 70% of the vitamin E in food is in the form of gamma-tocopherol, most of the nutritional supplements on the market contain only alpha-tocopherol, and all 19 studies included in the meta-analysis used alpha-tocopherol by itself.

While alpha-tocopherol has a number of biochemical actions (such as preventing the oxidation of LDL cholesterol and inhibiting platelet aggregation) that would be expected to prevent heart disease, certain functions are performed better by gamma-tocopherol. For example, the formation of nitric-oxide-derived free radicals, which appears to be a factor in the pathogenesis of heart disease, is inhibited to a greater extent by gamma-tocopherol than by alpha-tocopherol. In addition, gamma-tocopherol is a more potent inhibitor of platelet aggregation than alpha-tocopherol. Moreover, gamma-tocopherol possesses certain anticancer effects that are not shared by alpha-tocopherol. Supplementing with large doses of alpha-tocopherol alone has been found to deplete gammatocopherol. Consequently, whatever positive effects are produced by alphatocopherol supplementation might be counterbalanced by a reduction of gamma-tocopherol levels in the body, a reduction that would presumably be more pronounced when using higher doses of pure alpha-tocopherol.

If high-dose alpha-tocopherol does adversely affect some people, one might reasonably expect that "mixed tocopherols," which contain all four naturally occurring forms of vitamin E, would not have the same negative effects. Although mixed tocopherols are more expensive than alpha-tocopherol, the available evidence suggests that mixed tocopherols are the preferable form of vitamin E, both in terms of safety and effectiveness.

While all of the 19 studies considered in the meta-analysis used alpha-tocopherol, not all of them used the same type. Alpha-tocopherol is commercially available in two forms: D-alpha-tocopherol (also called RRR-alpha-tocopherol; the form that occurs in food and in the body) and D,L-alpha-tocopherol (also called all-rac-alpha-tocopherol; an equal mixture of D-alpha-tocopherol and its mirror image, L-alpha-tocopherol). The D,L mixture is less expensive to manufacture than the D- form, and is frequently used in research studies. L-alpha-tocopherol does not occur naturally in food or in the body and has little or no vitamin E activity; preliminary evidence suggests that it may even interfere with some of the effects of D-alpha-tocopherol. Moreover, not much is known about the long-term safety of L-alpha-tocopherol. Of note, in the only large, high-dose study in the meta-analysis (other than the flawed studies mentioned previously) that used the naturally occurring D-alpha-tocopherol (the Heart Outcomes Prevention Evaluation), the mortality rates in the vitamin E and placebo groups were identical. Thus, if there is a small negative effect of high-dose vitamin E, it might be attributable in part to the use of the unnatural D,L-mixture.

The issues raised in this editorial cast doubt on the reliability of the new study's conclusions. Of course, if the only good thing one could say about high-dose vitamin E is that it probably does not kill people, then there would be no point to this discussion. Years of research, however, suggests that vitamin E may help prevent heart attacks, slow the progression of Alzheimer's disease, reduce the deleterious effects of air pollution, and aid in the treatment of intermittent claudication, fibrocystic breast disease, premenstrual syndrome, childhood epilepsy, certain forms of chronic hepatitis, osteoarthritis, and infertility. Nearly all of these studies used 400 IU or more of vitamin E per day. Whether lower doses of mixed tocopherols would be as effective as higher doses of alphatocopherol should be a topic of future research.

Alan R. Gaby, MD

References

1. Baker DH. Cupric oxide should not be used as a copper supplement for either animals or humans. J Nutr 1999;129:2278-2279.