See corresponding article on page 1200.

How much vitamin E? . . . Just enough![1,2]

Maret G Traber

"Although initial studies have indicated that antioxidants may reduce oxidative stress, human intervention studies do not support a beneficial effect of antioxidant supplements." That sentence, from a review by Blomhoff (1), could be a quotation from any number of recent publications. Indeed, this editorial is focused on a recent report in the Journal by Wright et al (2), investigators of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a study that is infamous for showing that β-carotene supplements were associated with a greater risk of lung cancer in Finnish smokers (3). This adverse finding prompted many investigators to question the benefit of antioxidant supplements. Some investigators even advocated that vitamin E supplements should be avoided, despite reports that 93% of men and 96% of women in the United States do not consume the recommended daily amount of dietary vitamin E (4).

Vitamin E, a nutrient required by humans, has been mired in controversy largely because its major, if not sole, function is to act as a chain-breaking, lipid-soluble antioxidant. With such an amorphous physiologic function, the definition of specific vitamin E requirements and thus the formulation of dietary vitamin E recommendations have been difficult. The Food and Nutrition Board, in its latest revision of dietary nutrient intakes (5), asked the question, "What is the optimal antioxidant intake for the reduction of chronic disease risk?" This is a very different question from "What is the minimum amount of a nutrient required to prevent a deficiency symptom?" And that difference brings us to the crux of the problem of determining "how much vitamin E is enough?"

The primary symptom of vitamin E deficiency in humans, observed in subjects with a genetic defect in the hepatic α-tocopherol transfer protein, is a dying back of the sensory neurons that causes a peripheral neuropathy, ataxia, and ultimately death (6). These neurologic abnormalities have not been observed in subjects consuming diets low in vitamin E, nor are there biomarkers other than nonspecific in vitro measures of oxidative stress that have diagnostic value in assessing vitamin E status. Thus, the 2000 dietary reference intake (DRI) for vitamin E (5) is calculated from data gathered in the 1960s from experimentally vitamin E–depleted men. Greater peroxide-dependent erythrocyte hemolysis, assessed in vitro, was observed in the men with serum vitamin E concentrations <5 mg/L (11 μmol/L) than in the men with concentrations >5 mg/L. That concentration is important because data from the third National Health and Nutrition Examination Survey (*see* Table F-2 in reference 5) showed that <5% of the surveyed US population had serum vitamin E concentrations <5 mg/L (11 μmol/L).

The previous approach of setting requirements by estimating the amount of vitamin E necessary for a reversal of symptoms of vitamin E deficiency is different from an approach that focuses on establishing the amount of vitamin E necessary to reduce the risk of chronic diseases or on questioning whether greater vitamin E intakes actually do reduce such risks. Oxidative stress is associated with chronic diseases largely because inflammatory responses have an oxidative stress component. Thus, decreasing oxidative stress by increasing antioxidant intakes ought to decrease the cellular damage caused by reactive oxygen species created during inflammatory reactions, thereby protecting tissues against injury, and thus, hypothetically, reducing the incidence of chronic disease. However, most vitamin E supplementation intervention trials have not shown a reduction in the risk of chronic disease, although two studies did show such a reduction (7, 8).

The latest findings from the ATBC Study, in the article by Wright et al (2), are, therefore, unexpected. The ATBC Study sought to evaluate whether supplementation with vitamin E [50 IU *all-rac*-α-tocopheryl acetate (3)] and β-carotene (20 mg) would reduce the incidence of lung cancer. Wright et al describe a cohort of 29 092 men who were followed prospectively for 19 y, during which time 13 380 of these men died. It is striking that the authors report that the men in the highest quintile of baseline serum concentrations of α-tocopherol had significantly lower risks of total and cause-specific mortality, including cardiovascular disease and cancer, than did the men in the lowest quintile of baseline serum concentrations of α-tocopherol. Wright et al also noted that those with higher serum concentrations of vitamin E had significant reductions in mortality due to lung or prostate cancer, ischemic or hemorrhagic stroke, and respiratory disease.

With respect to vitamin E requirements for reducing the risk of chronic diseases, it is important to note that significant reductions in risk were observed as serum α-tocopherol values increased from 9.1 mg/L (21 μmol/L) to ≈13 mg/L (30 μmol/L) (2). The baseline characteristics of the subjects (aged 50–69 y) showed that the middle 3 quintiles had serum α-tocopherol concentrations of 10–11 mg/L (23–26 μmol/L), 11.2–12.1 mg/L (26–28 μmol/L), and 12.2–13.5 mg/L (28–31 μmol/L). These data

[1] From the Linus Pauling Institute, Oregon State University, Corvallis, OR.

[2] Reprints not available. Address correspondence to MG Traber, Linus Pauling Institute, Oregon State University, Corvallis, OR 97331-6512. E-mail: maret.traber@oregonstate.edu.

from the Finnish male smokers show a distribution of serum vitamin E concentrations similar to that reported for American men (*see* Table F-2 in reference 5). Specifically, serum α-tocopherol concentrations were reported for American men aged 51–70 y in selected percentiles of this population group; men in the 25th percentile had serum α-tocopherol concentrations of 9.8 mg/L (23 μmol/L), those in the 50th percentile had concentrations of 11.2 mg/L (26 μmol/L), and those in the 75th percentile had concentrations of 14.6 mg/L (34 μmol/L). The optimum relative reduction in mortality observed in the ATBC Study group occurred at serum α-tocopherol concentrations of $\geq$13–14 mg/L (30–33 μmol/L; 2). Wright et al (2) noted that the relative homogeneity of the ATBC Study cohort limited potential confounding; thus, education, physical activity, BMI, blood pressure, and alcohol and energy intakes did not confound the observed associations, which led them to posit that the higher vitamin E intakes were responsible for the benefits observed.

We now have a critical piece of information—that is, serum α-tocopherol concentrations of 13–14 mg/L (30–33 μmol/L) optimally reduce mortality due to chronic disease. Now all we have to do is estimate how much α-tocopherol to consume to achieve that serum concentration. In general, serum α-tocopherol concentrations are poorly correlated with dietary vitamin E estimates, increase with increasing serum lipid concentrations, and appear to be regulated by the α-tocopherol transfer protein (5); thus, estimates of the vitamin E intake necessary to achieve a certain serum concentration of α-tocopherol have varied widely. Using a dose-response design, Deveraj et al (9) showed that normolipidemic subjects have serum α-tocopherol concentrations of 8.6 mg/L (20 μmol/L) that could be raised to 14.2 mg/L (33 μmol/L) by the consumption of 100 IU vitamin E supplements [to estimate the milligrams of 2*R*-α-tocopherol in a vitamin E supplement, multiply the dose by 0.45 mg/IU if the supplement is *all-rac*- (ie, synthetic) or by 0.67 mg/IU if the supplement is *RRR*- (ie, natural) α-tocopherol (3)]. In the Framingham Study, half of the elderly subjects had plasma concentrations of α-tocopherol of $\geq$13 mg/L (30 μmol/L), but these higher plasma concentrations were also associated with a combination of dietary and supplemental vitamin E intakes (10). The estimated dietary vitamin E intake in the ATBC baseline study needed to achieve the middle quintile of serum concentrations of 11.1 to 12.1 mg α-tocopherol/L (25.8–28 μmol/L) was 12 mg α-tocopherol, a dietary value not significantly different from the estimated average requirement (12 mg) proposed by the Food and Nutrition Board (5). However, 12 mg vitamin E is an amount that is greater than that estimated to be consumed by 93% of men and 96% of women in the United States (4).

And so we are left with the good news that the serum concentration of α-tocopherol is associated with decreased chronic disease risk, but we still do not know how much vitamin E to recommend for consumption to achieve that concentration. It may be that large vitamin E supplements are not necessary to achieve optimal serum α-tocopherol concentrations, in that the vitamin E recommended dietary allowance of 15 mg/d may yield optimal serum concentrations to achieve significant reductions in chronic disease mortality. However, 15 mg/d may be a vitamin E intake that is achieved only with supplements, given the dietary habits of most Americans (11) and the observation that vitamin E–rich food sources are less popular foods, such as nuts, seeds, and vegetable oils, including olive, sunflower, or safflower oils.

The author had no personal or financial conflict of interest with respect to the study by Wright et al.

REFERENCES

1. Blomhoff R. Dietary antioxidants and cardiovascular disease. Curr Opin Lipidol 2005;16:47–54.
2. Wright ME, Lawson KA, Weinstein SJ, et al. Higher baseline serum concentrations of vitamin E are associated with lower total and cause-specific mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Clin Nutr 2006;84:1200–7.
3. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: effects of baseline characteristics and study compliance. J Natl Cancer Inst 1996;88:1560–70.
4. Maras JE, Bermudez OI, Qiao N, Bakun PJ, Boody-Alter EL, Tucker KL. Intake of alpha-tocopherol is limited among US adults. J Am Diet Assoc 2004;104:567–75.
5. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press, 2000.
6. Ouahchi K, Arita M, Kayden H, et al. Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein. Nat Genet 1995;9:141–5.
7. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996;347:781–6.
8. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:56–65.
9. Devaraj S, Adams-Huet B, Fuller CJ, Jialal I. Dose-response comparison of RRR-alpha-tocopherol and all-racemic alpha-tocopherol on LDL oxidation. Arterioscler Thromb Vasc Biol 1997;17:2273–9.
10. Vogel S, Contois JH, Tucker KL, Wilson PW, Schaefer EJ, Lammi-Keefe CJ. Plasma retinol and plasma and lipoprotein tocopherol and carotenoid concentrations in healthy elderly participants of the Framingham Heart Study. Am J Clin Nutr 1997;66:950–8.
11. Gao X, Wilde PE, Lichtenstein AH, Bermudez OI, Tucker KL. The maximal amount of dietary alpha-tocopherol intake in U.S. adults (NHANES 2001–2002). J Nutr 2006;136:1021–6.