Vitamin E[1]

Vitamin E refers to the plant-derived, lipid-soluble antioxidants: tocopherols and tocotrienols. They terminate the chain reaction of lipid peroxidation. Vitamin E biological activity is different from its antioxidant activity, and there is a preference for α-tocopherol. This preference is achieved through the selective degradation and excretion of other vitamin E forms and the selective retention of α-tocopherol, mediated by the hepatic α-tocopherol transfer protein (α-TTP). Hepatic α-TTP facilitates the selective incorporation of α-tocopherol into circulating lipoproteins that distribute the vitamin to nonhepatic tissues. α-TTP is therefore considered to be the major regulator of vitamin E status in humans.

Deficiencies: Vitamin E deficiency occurs in humans as a result of genetic abnormalities in α-TTP or in lipoprotein synthesis or occurs secondary to fat malabsorption. Genetic defects in α-TTP are associated with a characteristic syndrome, ataxia with vitamin E deficiency (AVED). More than 20 mutations in α-TTP have been identified in human AVED patients.

Diet recommendations: The vitamin E dietary reference intake (DRI) for adult men and women (and individuals 14–18 y) was set in 2000 at a daily estimated average requirement (EAR) of 12 mg α-tocopherol and an recommended daily allowance (RDA) of 15 mg. There are no increases for pregnancy, but for lactation the RDA is 19 mg/d. The adequate intake (AI) for infants (0–6 mo) was estimated to be 4 mg and for 7 through 12 mo to be 5 mg. The RDA for children 1 to 3 y is 6 mg; for those 4–8 y, it is 7 mg and 11 mg for those 9 to 13 y.

Plant-synthesized α-tocopherol is *RRR*-α-tocopherol; chiral carbons are in the *R*-conformation at positions 2, 4′, and 8′. Chemical synthesis results in an equal mixture of 8 different stereoisomers (*RRR*, *RSR*, *RRS*, *RSS*, *SRR*, *SSR*, *SRS*, *SSS*) that is called *all-rac*-α-tocopherol. The 2 position of α-tocopherol, the junction of the ring and tail, is critical for in vivo α-tocopherol vitamin activity. Only 2*R* forms meet human requirements.

Food sources: Major dietary vitamin E sources, as commonly eaten portions [USDA National Nutrient Database for Standard Reference, Release 24 (January 2012; http://www.nal.usda.gov/fnic/foodcomp/search/)] are fortified ready-to-eat cereals; nuts, especially almonds; seeds, such as sunflower seeds; greens, such as spinach; and vegetable oils, especially sunflower and safflower.

Clinical uses: Humans with defects in the *TTPA* gene (encoding α-TTP) have extraordinarily low (1/100 of normal) plasma vitamin E concentrations, but if they are given vitamin E supplements, plasma concentrations normalize within hours; if supplementation is halted, plasma vitamin E concentrations decrease within days to deficient levels. A daily α-tocopherol dose (800–1200 mg) is usually sufficient to prevent further deterioration of neurologic function, and in some cases, improvements have been noted. Postmortem analysis of a brain from a vitamin E–supplemented AVED patient demonstrated vitamin E accumulation and prevention of Purkinje cell loss.

Vitamin E deficiency due to impaired lipoprotein synthesis or fat malabsorption syndromes (e.g., abetalipoproteinemia, cystic fibrosis, short bowl disorder, choleastasis, and inherited defects in bile acid synthesis) is also treated with daily vitamin E supplements (100 mg/kg body weight).

The benefit of vitamin E supplements in individuals who are not vitamin E deficient is controversial. In the elderly, impaired immune function was improved with vitamin E supplementation. Patients with macular degeneration benefited from a supplement cocktail that included vitamin E. Vitamin E supplements have decreased heart attack risk in those with the haptoglobin 2–2 genotype, which results in a dysfunctional protein and causes increased oxidation by free heme. A follow-up study of the Alpha-Tocopherol Beta-Carotene Cancer Prevention trial showed that men at baseline who consumed 12 mg α-tocopherol daily (equivalent to the vitamin E EAR) had considerably lower risk of total and cause-specific mortality 13 y later.

Toxicity: The upper limit of tolerable intakes (UL) is 1000 mg/day, equivalent to 1100 IU synthetic or 1500 IU natural vitamin E. The UL was based on the adverse effect of an increased bleeding tendency observed in rat studies. This tendency to bleed was found to have beneficial effects in preventing venous thrombosis in a trial of vitamin E supplements in women.

Subsequent to the publication of the DRI, there have been several meta-analyses evaluating the outcomes of human vitamin E supplementation trials. Thus far, there have been no uniform mechanisms identified for the claim in meta-analyses of increased mortality associated with vitamin E supplements.

Recent research

Vitamin E in the central nervous system: Vitamin E deficiency manifests primarily as cerebellar ataxia in humans, underscoring the unique sensitivity of the central nervous system to oxidative stress. Interestingly, α-TTP is expressed in the cerebellum. α-Tocopherol supplementation in α-TTP

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knockout mice normalizes its status in all tissues *except* the brain. Thus, a unique relationship exists between *localized* vitamin E levels, expression of α-TTP, oxidative stress, and optimal cerebellar function. The detailed description of this relationship and the molecular mechanisms that underlie it are critical research questions.

Homeostasis: An important fundamental question in vitamin E biology is "are there compensatory mechanisms in response to oxidative stress to increase α-tocopherol concentrations or distribution?." Provocatively, brain α-TTP expression levels respond to oxidative stress, but liver α-TTP does not.

Fertility: Vitamin E was discovered as an essential dietary factor for reproductive health in female rodents. Surprisingly, very little is known regarding human vitamin E status and reproductive health. In mice, α-tocopherol sufficiency is essential for placentation. α-TTP is expressed in the uterine wall of pregnant female mice and in the human placenta. Research in this field is of great importance because 96% of U.S. women do not meet vitamin E EAR.

Interactions with other nutrients: The untoward effects of vitamin E supplements on blood clotting may result from vitamin E and K interactions because these supplements increase undercarboxylation of prothrombin, suggesting lower vitamin K activity. More than 90% of dietary, plant-derived vitamin K is phylloquinone (vitamin K1) with a 20-carbon phytyl side chain that is identical to that of tocopherol. Phylloquinone is converted to menadione and then to MK-4 (extrahepatic tissue vitamin K). Based on their similar structures, vitamins E and K likely share the same pathways for metabolism and excretion. Possible mechanisms for the vitamin E and K interaction have been proposed, but none have been proven.

The interactions of vitamins E and C are likely dependent on their roles as antioxidants; vitamin C can regenerate tocopherol from the tocopheroxyl radical. When α-tocopherol kinetics were evaluated in cigarette smokers, smokers had higher F_2-isoprostane concentrations and faster plasma α-tocopherol disappearance rates than nonsmokers. When smokers received vitamin C supplementation (500 mg twice daily) for 2 weeks, α-tocopherol disappearance rates were normalized. Thus, in smokers with greater oxidative stress, additional vitamin C is needed to restore the α-tocopheroxyl radical to its reduced form. Importantly, vitamin C supplementation did not change F_2-isoprostane concentrations, showing that α-tocopherol does not prevent radical formation or the initial oxidation of fatty acids, but halts the chain reaction of lipid peroxidation.

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For further information

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