

15

Vitamin E

Maret G. Traber

Introduction

Unlike most vitamins, which function as cofactors or have specific metabolic functions, vitamin E is unique in human nutrition because its major, if not sole, function is as an antioxidant. Consequently, vitamin E deficiency symptoms in target tissues are dependent not only upon vitamin E concentrations, but also on the degree of oxidative stress. This chapter will describe vitamin E structures and antioxidant properties; its distribution in food; its role in lipoprotein transport, delivery to tissues, and metabolism; and its safety and role in chronic disease prevention.

Definitions, Structures, and Antioxidant Activity

Vitamin E is the collective name for molecules that exhibit the antioxidant activity of α -tocopherol. Vitamin E was discovered in 1922 when it was found to be required by pregnant rats to prevent the resorption of fetuses.¹ At least eight different molecules (tocopherols and tocotrienols) have α -tocopherol antioxidant activity.² These forms vary in the number of methyl groups on the chromanol ring: trimethyl (α -), dimethyl (β - or γ -), and monomethyl (δ -). The tocopherols have a chromanol ring with a phytyl tail, while the tocotrienols have an unsaturated tail (Figure 1).

Vitamin E Form Required By Humans: α -Tocopherol

The naturally occurring form of α -tocopherol is *RRR*- α -tocopherol.² This nomenclature means that the chiral carbons are in the *R*-conformation at positions 2, 4', and 8'. Unlike most other vitamins, chemically synthesized α -tocopherol is not identical to the naturally occurring form. Synthetic α -tocopherol is called *all-rac*- α tocopherol (*all racemic* or *dl*) and contains an equal mixture of

eight different stereoisomers (*RRR*, *RSR*, *RRS*, *RSS*, *SRR*, *SSR*, *SRS*, *SSS*), all of which have equal antioxidant, but differing biologic activities.

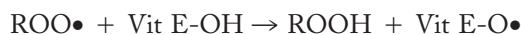
The 2 position of α -tocopherol (the junction of the ring and tail) is critical for α -tocopherol biologic activity. Only *2R*- α -tocopherol forms meet human vitamin E requirements.² *SRR*- α -tocopherol is prototypic of the 2*S*-forms and has been used to study synthetic vitamin E kinetics.

Vitamin E supplements often contain esters of α -tocopherol such as α -tocopheryl acetate, succinate, or nicotinate. The ester form prevents the oxidation of vitamin E and prolongs its shelf life. Following oral administration, these esters are readily hydrolyzed and α -tocopherol (unesterified form) is absorbed.³

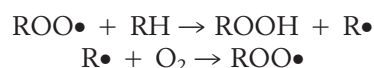
Antioxidant Activity

Vitamin E, a potent peroxy radical scavenger, is a chain-breaking antioxidant that prevents the propagation of free radicals in membranes and in plasma lipoproteins. When peroxy radicals ($\text{ROO}\bullet$) are formed, they react 1000 times faster with vitamin E (Vit E-OH) than with PUFA (RH).⁴ The hydroxyl group of tocopherol reacts with the peroxy radical to form the corresponding hydroperoxide and the tocopheroxyl radical (Vit E-O \bullet):

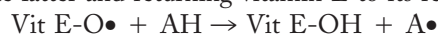
In the presence of vitamin E:



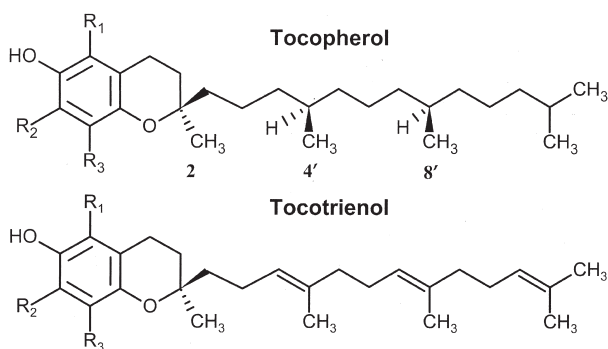
In the absence of vitamin E:



The tocopheroxyl radical (Vit E-O \bullet) reacts with vitamin C (or other hydrogen donors, AH), thereby oxidizing the latter and returning vitamin E to its reduced state:



This phenomenon has led to the idea of "vitamin E recycling," in which the antioxidant function of oxidized vitamin E is continuously restored by other antioxidants.



Compound	R ₁	R ₂	R ₃
α-tocopherol	CH ₃	CH ₃	CH ₃
β-tocopherol	CH ₃	H	CH ₃
γ-tocopherol	H	CH ₃	CH ₃
δ-tocopherol	H	H	CH ₃
α-tocotrienol	CH ₃	CH ₃	CH ₃
β-tocotrienol	CH ₃	H	CH ₃
γ-tocotrienol	H	CH ₃	CH ₃
δ-tocotrienol	H	H	CH ₃

Figure 1. Tocopherols and tocotrienols. Compounds with vitamin E antioxidant activity have a chromanol head with a hydroxyl group and varying numbers of methyl groups, as indicated. Tocopherols have 3 chiral centers in the phytyl tail at positions 2, 4', and 8'.

The “antioxidant network” depends upon the supply of aqueous antioxidants and the metabolic activity of cells. This interaction of vitamins E and C has been demonstrated in humans under oxidative stress. Specifically, cigarette smokers with the lowest plasma ascorbic acid concentrations had the fastest vitamin E disappearance rates.⁵

Further information concerning the reactions of tocopherols and tocotrienols *in vivo* and *in vitro* can be found in the extensive review by Kamal-Eldin and Appelqvist.⁶ Since the tocopheroxyl radical can be reduced back to tocopherol by ascorbate or other reducing agents, oxidized tocopherols are usually not found *in vivo*. Liebler et al.⁷ suggest that biologically relevant oxidation products formed from α-tocopherol include 4a,5-epoxy- and 7,8-epoxy-8a(hydroperoxy)tocopherones and their respective hydrolysis products, 2,3-epoxy-tocopherol quinone and 5,6-epoxy-α-tocopherol quinone. However, these products are formed during *in vitro* oxidation; their importance *in vivo* is unknown.⁸

Content of Foods

γ-Tocopherol is the most abundant tocopherol found in the US diet.⁹ However, α-tocopherol, not γ-tocopherol, and specifically only the 2*R*-forms of α-tocopherol, were defined by the Food and Nutrition Board of the US Institute of Medicine to meet human vitamin E requirements.² This change from the 1989 RDA makes vitamin E one of the most difficult nutrients to obtain from the diet. Only 8% of men and 2% of women in the United States had dietary vitamin E intakes¹⁰ that met the 2000 Estimated Average Requirement (EAR, 12 mg α-tocopherol/d).² Moreover, most individuals obtain dietary vitamin E from high-energy, high-fat foods that are not

Table 1. 2*R*-α-Tocopherol Contents of Foods

	Serving Size	mg/serving
Cereals ready-to-eat, fortified	1 cup	13.50
Sunflower seeds, dry roasted	1/4 cup	8.35
Almonds	1 oz (24 nuts)	7.33
Spinach, cooked	1 cup	6.73
Oil, sunflower	1 tbsp	5.59
Tomato sauce	1 cup	5.10
Oil, safflower	1 tbsp	4.64
Hazelnuts	1 oz	4.26
Carrot juice	1 cup	2.74
Beet greens, cooked	1 cup	2.61
Potato chips	1 oz	2.58
Potato, french fried	1 large	2.57
Sweet potato, canned	1 cup	2.55
Broccoli, chopped, cooked	1 cup	2.43
Oil, canola	1 tbsp	2.39
Peppers, sweet, red, raw	1 cup	2.35
Oil, olive	1 tbsp	1.94
Oil, soybean	1 tbsp	1.65

From: USDA National Nutrient Database for Standard Reference, Release 17

particularly α-tocopherol rich.¹⁰ Some examples of vitamin E food sources are shown in Table 1.

The richest dietary sources of vitamin E are edible vegetable oils.⁹ Most oils contain varying amounts of the tocopherols; few oils contain tocotrienols. α-Tocopherol is especially high in wheat germ oil, safflower oil, and sunflower oil. Soybean and corn oils contain predominantly γ-tocopherol, as well as some tocotrienols. Cottonseed oil contains both α- and γ-tocopherols in equal proportion. Palm oil contains large amounts of α- and γ-tocotrienols and some α-tocopherol. Nuts, especially almonds, are also good sources of vitamin E, while fruits and vegetables—good sources of antioxidants such as vitamin C, flavonoids and carotenoids—are not good sources of vitamin E. Indeed, the major food source of vitamin E is dessert.¹¹

Dietary Reference Intakes

Recommended Dietary Allowance for α-Tocopherol

In 2000, the Food and Nutrition Board published “Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.”² The Recommended Dietary Allowances (RDAs) represent the daily α-tocopherol

Table 2. Criteria and Dietary Reference Intake Values for Vitamin E by Life Stage Group (adapted from Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000. Available online at: <http://www.nap.edu/openbook/0309069351/html/index.html>. Accessed March 1, 2006.)

Life Stage Group	Criterion	EAR*	RDA†	AI‡	UL§
Premature infants					21
0–6 months	Average vitamin E intake from human milk			4	
7–12 months	Extrapolation from 0–6 months AI			5	
1–3 years	Extrapolation from adult EAR	5	6		200
4–8 years	Extrapolation from adult EAR	6	7		300
9–13 years	Extrapolation from adult EAR	9	11		600
14–18 years	Extrapolation from adult EAR	12	15		800
>18 years	Intakes sufficient to prevent hydrogen peroxide-induced erythrocyte hemolysis in vitro	12	15		1000
Pregnancy					
≤ 18 years	Adolescent EAR	12	15		800
19–50 years	Adult EAR	12	15		1000
Lactation					
≤ 18 years	Adolescent EAR plus average amount of vitamin E secreted in human milk	16	19		800
19–50 years	Adolescent EAR plus average amount of vitamin E secreted in human milk	16	19		1000

* EAR = Estimated Average Requirement: The intake that meets the estimated nutrient needs of half the individuals in a group.

† RDA = Recommended Dietary Allowance: The intake that meets the nutrient needs of almost all (97–98%) of individuals in a group.

‡ AI = Adequate Intake: The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status. For healthy infants receiving human milk, the AI is the mean intake.

§ UL = Tolerable Upper Intake Level: The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals.

intakes required to ensure adequate nutrition in 95% to 97.5% of the population, and are an overestimation of the level needed for most people in any given age or gender group (Table 2).²

The vitamin E requirement is based on the observation that only supplements containing α -tocopherol have been shown to reverse vitamin E deficiency symptoms in humans. The α -tocopherol amounts were based primarily on the amounts necessary to correct abnormal erythrocyte hemolysis in subjects who had consumed experimental vitamin E-deficient diets for 5 to 7 years.² Serum concentrations (in response to known supplemental vitamin E intakes) that prevented in vitro peroxide-induced erythrocyte hemolysis were used to determine EARs. Supplements containing either *RRR*- or *all-rac*- α -tocopherol were used to reverse vitamin E abnormal erythrocyte hemolysis, and therefore correction factors were developed to convert international units to milligrams of 2*R*- α -tocopherol.

The factors to convert international units to milligrams are 0.45 times the IU for *all-rac*- and 0.67 times the IU for *RRR*- α -tocopherol.² For example, if a vitamin E supplement is labeled 400 IU *dl*- α -tocopheryl acetate, then

400 times 0.45 equals 180 mg 2*R*- α -tocopherol, but if it is labeled 400 IU *d*- α -tocopheryl acetate, then 400 times 0.67 equals 268 mg 2*R*- α -tocopherol. These conversions are used only to estimate intakes relative to the RDA; different conversion factors are used to assess intakes relative to the upper limit (UL).

Safety and Upper Limits

The recommendation by the Food and Nutrition Board is that the UL for any supplements containing α -tocopherol is 1000 mg for adults.² Reports of adverse effects of vitamin E supplements in humans are sufficiently rare that data from multiyear studies in rats fed high dietary vitamin E levels were used to set the ULs.² No UL was set for infants, as food was recommended as the only vitamin E source for them. However, a UL of 21 mg/d was suggested for premature infants with birth weights of 1.5 kg, based on the adult UL. The ULs are also shown in Table 2.

The UL was set only for vitamin E supplements and not for food, because it is almost impossible to consume enough α -tocopherol-containing foods to achieve a daily

1000 mg intake for prolonged periods of time. The UL was defined for both 2*R*- and 2*S*- α -tocopherols, because all of the stereoisomeric forms in *all-rac*- α -tocopherol are absorbed and delivered to the liver. The appropriate conversion factors are different from those above for *all-rac*- α -tocopherol. The factors to convert international units to milligrams are 0.9 times the IU for *all-rac*- and 0.67 times the IU for *RRR*- α -tocopherol. The UL amounts given in IU are 1100 IU for *all-rac*- and 1500 IU for *RRR*- α -tocopherol. The UL for *RRR*- α -tocopherol is apparently higher, because each capsule of *RRR*- α -tocopherol contains fewer milligrams of α -tocopherol than does one containing *all-rac*- α -tocopherol.

A review of the literature on vitamin E safety has been published recently,¹² and confirms the findings from the Food and Nutrition Board. However, reports from three clinical trials have suggested adverse vitamin E effects in humans under special circumstances. One study was a 3-year, double-blind trial of antioxidants (vitamins E and C, β -carotene, and selenium) in 160 subjects on simvastatin-niacin therapy.¹³ In subjects taking antioxidants, there was less benefit of the drugs in raising high-density lipoprotein (HDL) cholesterol than was expected, and there was an increase in clinical end points (arteriographic evidence of coronary stenosis, or the occurrence of a first cardiovascular event, including death, myocardial infarction, stroke, or revascularization).¹³ The Women's Angiographic Vitamin and Estrogen (WAVE) Trial, was a randomized, double-blind trial of 423 postmenopausal women with at least one coronary stenosis at baseline coronary angiography. In the postmenopausal women on hormone replacement therapy, all-cause mortality was increased in women assigned to antioxidant vitamins compared with placebo (HR, 2.8; 95% CI, 1.1–7.2; $P = .047$).¹⁴ The "HopeToo" trial suggested that patients at high risk for coronary heart disease taking vitamin E were at increased risk of left-ventricular dysfunction.¹⁵ Interestingly, none of these trials had the same adverse effect of vitamin E. Moreover, a meta-analysis evaluating the relationship of vitamin E supplements with all-cause mortality could not define a mechanism for adverse vitamin E effects.¹⁶ Traber¹⁷ proposed that the adverse effects seen in clinical trials in patients consuming a variety of pharmaceutical agents were a result of vitamin E-mediated alterations in xenobiotic metabolism. This hypothesis is based on the increase in vitamin E metabolism in response to supplements and the potential for alterations in xenobiotic metabolism and disposition, as discussed below.

High vitamin E intakes are associated with an increased tendency to bleed.² It is not known if increased bleeding is a result of decreased platelet aggregation caused by an inhibition of protein kinase C by α -tocopherol, some other platelet-related mechanism, or decreased clotting due to a vitamin K and E interactions causing abnormal blood clotting.² Patients on anticoagulant ther-

apy should be monitored when taking vitamin E supplements to insure adequate vitamin K intakes.¹⁸

Biological Activities of the Tocopherols

Intestinal Absorption

All vitamin E forms are absorbed, along with fats, into intestinal cells and incorporated in chylomicrons for secretion into lymph.¹⁹ The major steps from micellar uptake to enterocyte trafficking and incorporation into chylomicrons are largely unknown. Fat malabsorption syndromes (e.g., cholestatic liver disease) and genetic abnormalities in either lipoprotein synthesis (e.g., abetalipoproteinemia) or the α -tocopherol transfer protein (α -TTP) (e.g., ataxia with vitamin E deficiency, or AVED) result in vitamin E malabsorption or abnormally low plasma α -tocopherol transport, respectively.¹⁹

Vitamin E absorption from supplements is poor when the supplement is consumed without fat, as was observed when vitamin E pills were consumed without food.²⁰ Moreover, vitamin E bioavailability is highly influenced by prandial status.²¹ However, the amount of dietary fat needed for optimal vitamin E absorption is unknown.

Lipoprotein Transport

Unlike other fat-soluble vitamins that have specific plasma transport proteins, vitamin E is transported nonspecifically in all of the plasma lipoproteins. Once chylomicron remnants containing dietary vitamin E reach the liver, only one form of vitamin E, α -tocopherol, is preferentially secreted by the liver into the plasma in very-low-density lipoproteins (VLDL).¹⁹ Once in the circulation, VLDL are delipidated to form low-density lipoproteins (LDL). During this process, vitamin E is transferred to HDLs, which can transfer vitamin E to all of the circulating lipoproteins.¹⁹ Thus, the liver, not the intestine, discriminates between tocopherols. All lipoproteins transport vitamin E, and all mechanisms for delivery of lipids from lipoproteins to tissues (e.g., receptors) deliver vitamin E along with the lipoprotein contents. This phenomenon was demonstrated in a porcine blood-brain barrier model in which both the SR-B1 receptor and lipoprotein lipase were demonstrated to deliver α -tocopherol to cells.²²

α -Tocopherol-Transfer Protein

The liver preferentially secretes α -tocopherol into plasma under the control of the hepatic α -TTP, as shown in patients with genetic α -TTP defects^{23,24} and in α -TTP-knockout mice (*Ttpa*^{-/-}).²⁵

Liver α -TTP has been isolated and its cDNA sequences reported.²⁶ α -TTP has been crystallized and the α -tocopherol-binding pocket identified.^{27,28} Interestingly, the pocket causes α -tocopherol to fold such that the 2 position is critical for the fit into the pocket.

Plasma Vitamin E kinetics

A kinetic model of vitamin E transport in plasma has been described.²⁹ In normal subjects, the fractional disappearance rates of *RRR*- α -tocopherol (0.4 ± 0.1 pools/d) were significantly ($P < 0.01$) slower than for *SRR*- α -tocopherol (1.2 ± 0.6 pools/d). The apparent half-life of *RRR*- α -tocopherol was about 48 h, while *SRR*- α -tocopherol had a half-life of approximately 13 h.²⁹

Vitamin E kinetics of α - and γ -tocopherols have also been studied.³⁰ Plasma γ -tocopherol exponential disappearance rates (1.39 ± 0.44 pools/d) were triple those of α -tocopherol (0.33 ± 0.11 ; $P < 0.001$). The γ -tocopherol half-lives were 13 ± 4 h, compared with 57 ± 19 h for α -tocopherol. Thus, *RRR*- α -tocopherol remains in the plasma about 4 times longer than does *SRR*- α -tocopherol or γ -tocopherol (Figure 2). The similarity in the disappearance rates for γ -tocopherol and *SRR*- α -tocopherol strongly support the idea that forms of vitamin E that are not actively re-secreted by α -TTP into the plasma are excreted or metabolized.

Biliary Excretion

Vitamin E does not accumulate in the liver to “toxic” levels, suggesting that excretion and metabolism are important in preventing adverse vitamin E effects. However, the regulation of hepatic vitamin E concentrations has not been extensively studied. α -Tocopherol is excreted into bile via multi-drug resistance gene 2 (MDR2, ABC

B4, or p-glycoprotein),³¹ an ATP-binding cassette transporter that also facilitates biliary phospholipid excretion.

The ATP-binding cassette transporter (ABCA1) mediates the α -tocopherol efflux from cells to HDL, similarly to “cholesterol reverse transport.”³² HDL has been shown to deliver α -tocopherol to the liver via scavenger receptor-BI (SR-BI).³³ In SR-BI-null compared with wild-type mice, plasma α -tocopherol concentrations increased, biliary α -tocopherol decreased, but liver α -tocopherol was unchanged; therefore, it appears that SR-BI-mediated hepatic α -tocopherol uptake is coupled to its biliary excretion.³⁴ Importantly, SR-BI protein is increased in vitamin E-deficient rats, suggesting that the liver can increase SR-BI to increase hepatic α -tocopherol delivery.³⁵ Under normal conditions, α -tocopherol transport via HDL to the liver would allow uptake of α -tocopherol into a liver pool destined for excretion in bile or perhaps metabolism.

Vitamin E Metabolism

The first vitamin E metabolites described were urinary “Simon metabolites,” which are oxidized, tail-shortened vitamin E metabolites.⁸ Unoxidized vitamin E metabolites, alpha-carboxyethyl hydroxychroman (α -CEHC) and γ -CEHC, are derived from α - and γ -tocopherol (as well as α - and γ -tocotrienols), respectively, and have been detected in urine, bile, and plasma,⁸ as well as liver homogenates.³⁶ Modern techniques to prevent in vitro oxidation have shown that Simon metabolites largely occur during in vitro sample handling.⁸

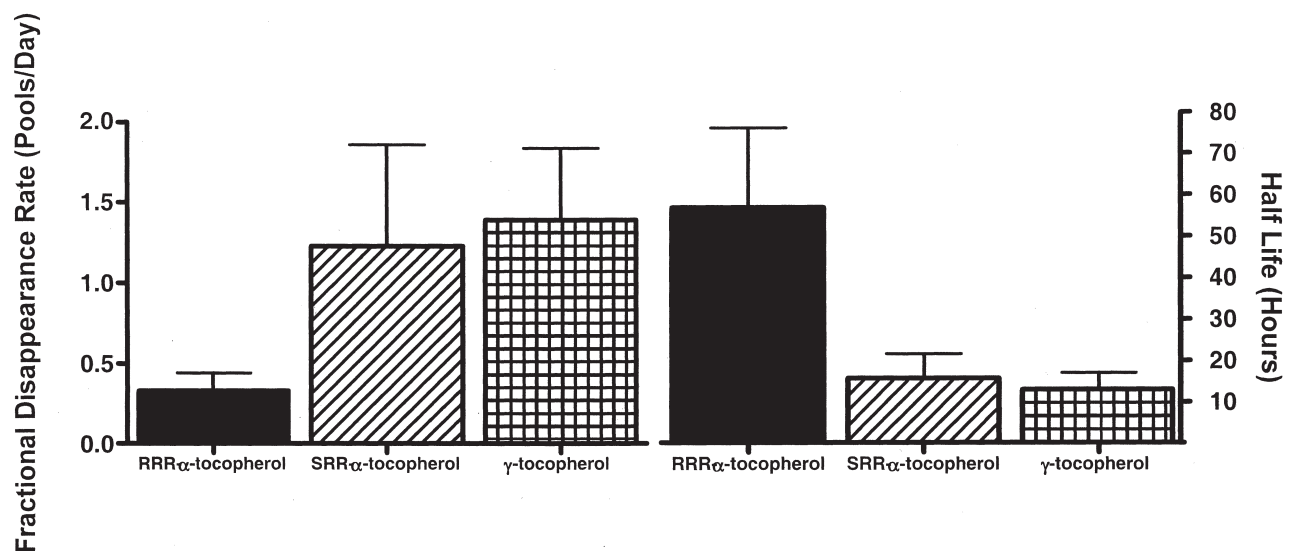


Figure 2. Plasma *RRR*- and *SRR*- α -tocopherol, and γ -tocopherol disappearance rates and half-lives. Vitamin E kinetics of *RRR*- and *SRR*- α -tocopherols (Traber MG, Ramakrishnan R, Kayden HJ. Human plasma vitamin E kinetics demonstrate rapid recycling of plasma *RRR*- α -tocopherol. Proc Natl Acad Sci U S A. 1994;91:10005–10008) and γ -tocopherol (Leonard SW, Paterson E, Atkinson JK, et al. Studies in humans using deuterium-labeled α - and γ -tocopherol demonstrate faster plasma γ -tocopherol disappearance and greater g-metabolite production. Free Radic Biol Med. 2005;38:857–866) have been studied. The fractional disappearance rates of *RRR*- α -tocopherol (0.4 ± 0.1 pools/d) were significantly ($P < 0.01$) slower than for *SRR*- α -tocopherol (1.2 ± 0.6) (Traber et al., 1994). Plasma γ -tocopherol exponential disappearance rates (1.39 ± 0.44 pools/d) were triple those of α -tocopherol (0.33 ± 0.11 , $P < 0.001$) (Leonard et al., 2005). The apparent half-life of *RRR*- α -tocopherol was about 48 h, while *SRR*- α -tocopherol had a half-life of approximately 13 h (Traber et al., 1994). The γ -tocopherol half-lives were 13 ± 4 h compared with 57 ± 19 h for α -tocopherol (Leonard et al., 2005).

Vitamin E metabolism is mediated by cytochrome P450s (CYPs), in that the tocopherols or tocotrienols are initially ω -oxidized by CYPs and then, following β -oxidation, are conjugated with sulfate or glucuronide and excreted in urine or bile.⁸

Hepatocytes produce γ -CEHC when incubated with γ -tocopherol. Initially, CYP3A appeared to be involved in γ -CEHC production because CYP3A stimulators and inhibitors appropriately altered vitamin E metabolism.^{37,38} Subsequently, CYP4F2 was demonstrated to be involved in the ω -oxidation of α - and γ -tocopherols.³⁹ In mice with widely ranging liver α - (from 0.7 to 16 nmol/g) and γ -tocopherol (0 to 13 nmol/g) concentrations, hepatic α -CEHC was undetectable, but γ -CEHC concentrations (0.1 to 0.8 nmol/g) were correlated with both α - and γ -tocopherol concentrations ($P < 0.004$).⁴⁰ However, when Cyp4f and Cyp3a protein concentrations were measured, there were no variations in Cyp4f protein expression, but Cyp3a protein was correlated ($P < 0.0001$) with liver α - but not γ -tocopherol concentrations. Apparently, α -tocopherol increases Cyp3a protein expression, γ -CEHC formation, and the excretion of both γ -tocopherol and γ -CEHC.⁴⁰ This important relationship between α -tocopherol and Cyp3a mRNA expression has also been observed elsewhere.⁴¹

The regulatory mechanisms of CEHC production have not been extensively studied. CEHC production from γ -tocopherol is much greater than that from α -tocopherol,³⁷ and studies in isolated hepatocytes or liver cell lines have not provided answers to the mystery of why α - and γ -tocopherols, despite their very similar structures and antioxidant activities, are metabolized differently by the liver. When equimolar amounts of labeled tocopherols (about 50 mg each d_6 - α - and d_2 - γ -tocopheryl acetates) were administered to normal subjects,³⁰ plasma d_6 - α -CEHC concentrations were below levels of detection for all subjects at all time points. Rates of plasma γ -CEHC and γ -tocopherol disappearance were not different from each other and were much faster than α -tocopherol disappearance.³⁰ These studies confirm that vitamin E metabolism is important in discriminating between various tocopherols and tocotrienols, and thus is a key regulator of vitamin E bioavailability.

Deficiency

Although rare, overt vitamin E deficiency occurs in humans as a result of genetic abnormalities in α -TTP or lipoprotein synthesis and as a result of various fat malabsorption syndromes.¹⁹ Vitamin E deficiency occurs secondary to fat malabsorption because vitamin E absorption requires biliary and pancreatic secretions.¹⁹

The large-caliber, myelinated axons in peripheral sensory nerves are the predominant target tissue in vitamin E deficiency in humans. A progressive peripheral neuropathy is observed, with a dying back of the large-caliber axons in the sensory neurons.⁴² In deficient humans, axo-

nal degeneration rather than demyelination is the primary sensory nerve abnormality. Thus, the axons degenerate first, then demyelination occurs.

Genetic defects in α -TTP are associated with a characteristic syndrome, AVED.¹⁹ The ataxia observed in these patients has also been mimicked in α -TTP-null mice.⁴³ Gene analysis using high-density nucleotide arrays have shown repressed expression of retinoic acid-related orphan receptor alpha (ROR- α) in the cortex of α -TTP-null mice.⁴⁴ ROR- α absence causes ataxia in mice⁴⁵; thus, some α -tocopherol actions may be mediated by ROR- α .

AVED patients have extraordinarily low plasma vitamin E concentrations (as low as 1/100 of normal), but if they are given vitamin E supplements, plasma concentrations reach normal levels within hours.⁴⁶ A dose of 800 to 1200 mg/d is usually sufficient to prevent further deterioration of neurologic function and, in some cases, improvements have been noted.^{42,47} Postmortem analysis of an AVED patient demonstrated that vitamin E supplementation did allow brain vitamin E accumulation and prevention of Purkinje cell loss.⁴⁸ If supplementation is halted, plasma vitamin E concentrations decrease within days to deficient levels. The biochemical defect in AVED patients, shown using deuterated tocopherols, demonstrated that hepatic α -TTP is required to maintain plasma RRR - α -tocopherol concentrations^{23,24} via secretion in VLDL. The molecular mechanism by which α -TTP facilitates α -tocopherol export from the liver remains under investigation.

Chronic Disease Prevention and Public Health Implications

Given that vitamin E deficiency is very rare and that vitamin E intakes by most Americans are much less than their estimated requirements, questions arise whether the dietary α -tocopherol recommendations are too high and, conversely, given the potential for adverse effects, is there any benefit to vitamin E supplementation? The questions would be easier to answer if there were specific metabolic pathways that required vitamin E such that a marginal deficiency could be defined. Certainly, signaling pathways and specific genes have been identified that are altered by low or high α -tocopherol concentrations,⁴⁹ but there is no consensus concerning such effects, and they are difficult to separate from changes in oxidative stress-dependent mechanisms. One area of particular importance is that of impaired immune function in the elderly that can be improved with vitamin E supplementation, which is discussed further in the chapter in this volume on vitamin E.⁵⁰ Again, it is not clear if this result in the elderly a situation in which long-term suboptimal intakes of vitamin E allow increased oxidative stress to alter T-cell function. Similarly, aged patients with eye disease (macular degeneration) benefited from the daily use of a dietary

supplement that included vitamin E.⁵¹ Eyes are an extension of the nervous system, and vitamin E is particularly necessary for the maintenance of normal nerve function. It is therefore quite provocative that vitamin E supplements were associated with a decreased risk of amyotrophic lateral sclerosis,⁵² and that supplements have been reported to delay the progression of Alzheimer's disease.⁵³

Oxidative stress increases plasma vitamin E disappearance caused by endurance exercise⁵⁴ and in cigarette smokers.⁵ Vitamin E supplementation decreases F2-isoprostanes, a measure of lipid peroxidation in exercisers⁵⁵ and in hypercholesterolemics.⁵⁶ Moreover, supplementation with both vitamin E and C slows atherosclerosis progression,⁵⁷ which is not surprising given that this is an oxidative stress disorder⁵⁸ and that low vitamin C status allows faster vitamin E disappearance.⁵

Summary

Taken together, these findings suggest that long-term suboptimal vitamin E intakes will indeed allow the accumulation of oxidative damage. It is generally agreed that chronic diseases are associated with increased oxidative damage.² What remains an open question is whether vitamin E supplements in excess of daily requirements will decrease the risk of chronic disease. Although many vitamin E supplementation studies carried out in patients with various kinds of chronic diseases have failed to show benefit, these studies have largely attempted to reverse existing disease. The question of whether increased oxidative stress as a result of suboptimal vitamin E intake increases the risk of chronic disease has not yet been answered.

Acknowledgments

This work was supported by a National Institutes of Health grant (NIH DK59576).

References

1. Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science*. 1922;56:650–651.
2. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000. Available online at: <http://www.nap.edu/openbook/0309069351/html/index.html>. Accessed March 1, 2006.
3. Cheeseman KH, Holley AE, Kelly FJ, et al. Biokinetics in humans of RRR- α -tocopherol: the free phenol, acetate ester, and succinate ester forms of vitamin E. *Free Radic Biol Med*. 1995;19:591–598.
4. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, α -tocopherol, and ascorbate. *Arch Biochem Biophys*. 1993;300:535–543.
5. Bruno RS, Ramakrishnan R, Montine TJ, et al. α -Tocopherol disappearance is faster in cigarette smokers and is inversely related to their ascorbic acid status. *Am J Clin Nutr*. 2005;81:95–103.
6. Kamal-Eldin A, Appelqvist LA. The chemistry and antioxidant properties of tocopherols and tocotrienols. *Lipids*. 1996;31:671–701.
7. Liebler DC, Burr JA, Phillips L, Ham AJ. Gas chromatography-mass spectrometry analysis of vitamin E and its oxidation products. *Anal Biochem*. 1996;236:27–34.
8. Brigelius-Flohé R, Traber MG. Vitamin E: function and metabolism. *FASEB J*. 1999;13:1145–1155.
9. Eitenmiller R, Lee J. *Vitamin E: Food Chemistry, Composition, and Analysis*. New York: Marcel Dekker; 2004.
10. Maras JE, Bermudez OI, Qiao N, et al. Intake of α -tocopherol is limited among US adults. *J Am Diet Assoc*. 2004;104:567–575.
11. Ma J, Hampl JS, Betts NM. Antioxidant intakes and smoking status: data from the continuing survey of food intakes by individuals 1994–1996. *Am J Clin Nutr*. 2000;71:774–780.
12. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr*. 2005;81:736–745.
13. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583–1592.
14. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA*. 2002;288:2432–2440.
15. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293:1338–1347.
16. Miller ER 3rd, Paston-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142:37–46.
17. Traber MG. Vitamin E, nuclear receptors and xenobiotic metabolism. *Arch Biochem Biophys*. 2004;423:6–11.
18. Corrigan JJ Jr, Ulfers LL. Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. *Am J Clin Nutr*. 1981;34:1701–1705.
19. Traber MG. Vitamin E. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*. Baltimore: Williams & Wilkins; 1999; 347–362.
20. Leonard SW, Good CK, Gugger ET, Traber MG. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *Am J Clin Nutr*. 2004;79:86–92.

21. Iuliano L, Micheletta F, Maranghi M, et al. Bioavailability of vitamin E as function of food intake in healthy subjects: effects on plasma peroxide-scavenging activity and cholesterol-oxidation products. *Arterioscler Thromb Vasc Biol.* 2001;21:E34–E37.
22. Goti D, Balazs Z, Panzenboeck U, et al. Effects of lipoprotein lipase on uptake and transcytosis of low density lipoprotein (LDL) and LDL-associated alpha-tocopherol in a porcine in vitro blood-brain barrier model. *J Biol Chem.* 2002;277:28537–28544.
23. Traber MG, Sokol RJ, Burton GW, et al. Impaired ability of patients with familial isolated vitamin E deficiency to incorporate alpha-tocopherol into lipoproteins secreted by the liver. *J Clin Invest.* 1990;85:397–407.
24. Traber MG, Sokol RJ, Kohlschütter A, et al. Impaired discrimination between stereoisomers of α -tocopherol in patients with familial isolated vitamin E deficiency. *J Lipid Res.* 1993;34:201–210.
25. Terasawa Y, Ladha Z, Leonard SW, et al. Increased atherosclerosis in hyperlipidemic mice deficient in alpha-tocopherol transfer protein and vitamin E. *Proc Natl Acad Sci U S A.* 2000;97:13830–13834.
26. Arita M, Sato Y, Miyata A, et al. Human alpha-tocopherol transfer protein: cDNA cloning, expression and chromosomal localization. *Biochem J.* 1995;306:437–443.
27. Meier R, Tomizaki T, Schulze-Briese C, et al. The molecular basis of vitamin E retention: structure of human alpha-tocopherol transfer protein. *J Mol Biol.* 2003;331:725–734.
28. Min KC, Kovall RA, Hendrickson WA. Crystal structure of human α -tocopherol transfer protein bound to its ligand: Implications for ataxia with vitamin E deficiency. *Proc Natl Acad Sci U S A.* 2003;100:14713–14718.
29. Traber MG, Ramakrishnan R, Kayden HJ. Human plasma vitamin E kinetics demonstrate rapid recycling of plasma RRR- α -tocopherol. *Proc Natl Acad Sci U S A.* 1994;91:10005–10008.
30. Leonard SW, Paterson E, Atkinson JK, et al. Studies in humans using deuterium-labeled α - and γ -tocopherol demonstrate faster plasma g-tocopherol disappearance and greater g-metabolite production. *Free Radic Biol Med.* 2005;38:857–866.
31. Mustacich DJ, Shields J, Horton RA, et al. Biliary secretion of alpha-tocopherol and the role of the mdr2 P-glycoprotein in rats and mice. *Arch Biochem Biophys.* 1998;350:183–192.
32. Oram JF, Vaughan AM, Stocker R. ATP-binding cassette transporter A1 mediates cellular secretion of alpha-tocopherol. *J Biol Chem.* 2001;276:39898–39902.
33. Mardones P, Quinones V, Amigo L, et al. Hepatic cholesterol and bile acid metabolism and intestinal cholesterol absorption in scavenger receptor class B type I-deficient mice. *J Lipid Res.* 2001;42:170–180.
34. Mardones P, Strobel P, Miranda S, et al. Alpha-tocopherol metabolism is abnormal in scavenger receptor class B type I (SR-BI)-deficient mice. *J Nutr.* 2002;132:443–449.
35. Witt W, Kolleck I, Fechner H, et al. Regulation by vitamin E of the scavenger receptor BI in rat liver and HepG2 cells. *J Lipid Res.* 2000;41:2009–2016.
36. Leonard SW, Gumprich E, Devereaux MW, et al. Quantitation of rat liver vitamin E metabolites by LC-MS during high-dose vitamin E administration. *J Lipid Res.* 2005;46:1068–1075.
37. Birringer M, Pfluger P, Kluth D, et al. Identities and differences in the metabolism of tocotrienols and tocopherols in HepG2 cells. *J Nutr.* 2002;132:3113–3118.
38. Parker RS, Sontag TJ, Swanson JE. Cytochrome P4503A-dependent metabolism of tocopherols and inhibition by sesamin. *Biochem Biophys Res Commun.* 2000;277:531–534.
39. Sontag TJ, Parker RS. Cytochrome P450 omega-hydroxylase pathway of tocopherol catabolism: Novel mechanism of regulation of vitamin E status. *J Biol Chem.* 2002;277:25290–25296.
40. Traber MG, Siddens LK, Leonard SW, et al. α -Tocopherol modulates Cyp3a expression, increases γ -CEHC production and limits tissue γ -tocopherol accumulation in mice fed high γ -tocopherol diets. *Free Radic Biol Med.* 2005;38:773–785.
41. Kluth D, Landes N, Pfluger P, et al. Modulation of Cyp3a11 mRNA expression by alpha-tocopherol but not gamma-tocotrienol in mice. *Free Radic Biol Med.* 2005;38:507–514.
42. Sokol RJ. Vitamin E deficiency and neurological disorders. In: Packer L, Fuchs J, eds. *Vitamin E in Health and Disease.* New York: Marcel Dekker; 1993; 815–849.
43. Yokota T, Igarashi K, Uchihara T, et al. Delayed-onset ataxia in mice lacking alpha-tocopherol transfer protein: model for neuronal degeneration caused by chronic oxidative stress. *Proc Natl Acad Sci U S A.* 2001;98:15185–15190.
44. Gohil K, Godzdanker R, O’Roark E, et al. Alpha-tocopherol transfer protein deficiency in mice causes multi-organ deregulation of gene networks and behavioral deficits with age. *Ann N Y Acad Sci.* 2004; 1031:109–126.
45. Steinmayr M, Andre E, Conquet F, et al. *Staggerer* phenotype in retinoid-related orphan receptor alpha-deficient mice. *Proc Natl Acad Sci U S A.* 1998;95: 3960–3965.
46. Sokol RJ, Kayden HJ, Bettis DB, et al. Isolated vitamin E deficiency in the absence of fat malabsorption—familial and sporadic cases: characterization and investigation of causes. *J Lab Clin Med.* 1988; 111:548–559.
47. Gabsi S, Gouider-Khouja N, Belal S, et al. Effect of vitamin E supplementation in patients with ataxia

- with vitamin E deficiency. *Eur J Neurol.* 2001;8:477–481.
48. Yokota T, Uchihara T, Kumagai J, et al. Postmortem study of ataxia with retinitis pigmentosa by mutation of the alpha-tocopherol transfer protein gene. *J Neurol Neurosurg Psychiatry.* 2000;68:521–525.
 49. Azzi A, Gysin R, Kempna P, et al. Regulation of gene expression by alpha-tocopherol. *Biol Chem.* 2004;385:585–591.
 50. Meydani SN, Leka LS, Fine BC, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA.* 2004;292:828–836.
 51. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119:1417–1436.
 52. Ascherio A, Weisskopf MG, O'Reilly E J, et al. Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol.* 2005;57:104–110.
 53. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med.* 1997;336:1216–1222.
 54. Mastaloudis A, Leonard SW, Traber MG. Oxidative stress in athletes during extreme endurance exercise. *Free Radic Biol Med.* 2001:911–922.
 55. Mastaloudis A, Morrow JD, Hopkins DW, et al. Antioxidant supplementation prevents exercise-induced lipid peroxidation, but not inflammation, in ultramarathon runners. *Free Radic Biol Med.* 2004;36:1329–1341.
 56. Davi G, Alessandrini P, Mezzetti A, et al. In vivo formation of 8-Epi-prostaglandin F2 alpha is increased in hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 1997;17:3230–3235.
 57. Salonen RM, Nyssonen K, Kaikkonen J, et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. *Circulation.* 2003;107:947–953.
 58. Diaz MN, Frei B, Vita JA, Keaney JFJ. Antioxidants and atherosclerotic heart disease. *N Engl J Med.* 1997;337:408–416.
-