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VITAMIN E IN HUMANS: Demand and Delivery

Maret G. Traber
Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, California 94720

Helmut Sies
Institut für Physiologische Chemie I, Heinrich-Heine-Universität Düsseldorf, Postfach 101007, D-40001-Düsseldorf, Germany

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ABSTRACT

How much vitamin E is enough? An established use of supplemental vitamin E in humans is in the prevention and therapy of deficiency symptoms. The cause of vitamin E deficiency, characterized by peripheral neuropathy and ataxia, is usually malabsorption—a result of fat malabsorption or genetic abnormalities in lipoprotein metabolism. Genetic abnormalities in the hepatic α-tocopherol transfer protein also cause vitamin E deficiency—defects in this protein cause an impairment in plasma vitamin E transport. Impaired delivery of vitamin E to tissues, thereby, results in deficiency symptoms. Also discussed is the use of supplemental vitamin E in chronic diseases such as ischemic heart disease, atherosclerosis, diabetes, cataracts, Parkinson's disease, Alzheimer's disease, and impared immune function, as well as in subjects receiving total parenterol nutrition. In healthy individuals, a daily intake of about 15–30 mg of α-tocopherol is recommended to obtain "optimal plasma alpha-tocopherol concentrations" (30 μM or greater).

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INTRODUCTION

How much vitamin E is enough? Where does it come from? Where does it go? What does it do? In this review, we evaluate the literature on vitamin E in humans from the aspect of what is known about needs for vitamin E and how those needs are met. We also consider ways in which vitamin E might be beneficial in large supplemental doses.

An established supplemental vitamin E use in humans is for prevention and therapy of vitamin E deficiency. Vitamin E deficiency occurs in premature infants with hemolytic anemia; it has also been reported in low-birth-weight babies nourished with unfortified formula high in polyunsaturated fatty acids (PUFA) (74), or when the transfer of vitamin E from the mother to the fetus is insufficient (74). In infants and children, deficiency can also occur secondary to fat malabsorption (116).

Vitamin E deficiency can occur as a result of defects at various steps during delivery from the diet to the tissues, e.g. (*a*) by malabsorption from the diet, (*b*) from defects in plasma lipoprotein transport, in delivery to cells and to subcellular sites, and (*c*) during enhanced loss resulting from (oxidative) metabolism. In adults, vitamin E deficiency most often occurs secondary to enteropathies such as fat malabsorption (steatorrhea), pancreatic insufficiency, hepatobiliary tract diseases, short bowel syndrome, gastrectomy, or abetalipoproteinemia (116).

Assessment of vitamin E status is complicated. The problem becomes even more complex when considering what the optimal levels of vitamin E intake are in the normal population. Epidemiologic evidence suggests that supplementation with 100 mg or more of vitamin E for two years or longer results in a decreased risk of cardiovascular disease (107, 121). Decreased risk of cancer in response to vitamin E supplementation has also been reported (9, 15, 17). Nonetheless, a number of clinical trials have shown that vitamin E supplements (even more than 1 g/day) only raise plasma concentrations of α-tocopherol about two- to threefold (38, 61, 65, 66, 103, 105). Thus, measurements of plasma vitamin E concentrations may not adequately describe vitamin E status.

In this review, we delineate the mechanisms for delivery of vitamin E to the tissues and illustrate how defects in these mechanisms can result in vitamin E deficiency in humans. Further, we consider what the likely mechanisms are that result in delivery of vitamin E to tissues, and how these might add to our understanding of how supplemental vitamin E in amounts in excess of those that can be obtained from the diet might protect against chronic diseases such as heart disease and cancer.

Vitamin E Structures

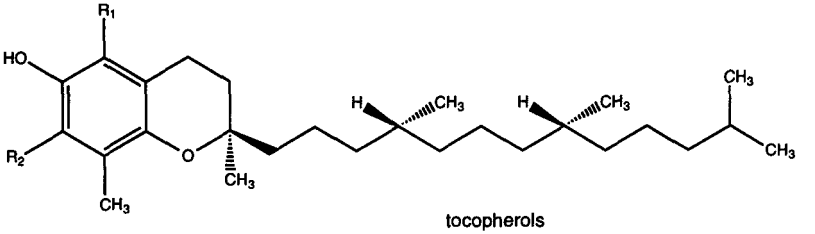
Vitamin E was first described by Evans & Bishop (44) at the University of California, Berkeley, in 1922. The term vitamin E includes all tocol and tocotrienol derivatives, which exhibit the biological activity of α-tocopherol, as reviewed by Sheppard et al (112). Tocopherols include mono (δ-), di (β- or γ-), and trimethyl (α-) tocols (Figure 1). The biologically most active form is *RRR*-α-tocopherol (formerly called d-α-tocopherol). α-Tocopherol is also synthesized commercially for use in animal nutrition and in human vitamin E supplements by condensation of trimethyl hydroquinone with isophytol (71). α-Tocopherol comprises eight stereoisomers, arising from the three chiral centers (labeled 2, 4′, and 8′) (Figure 1) and is designated *all-rac*-α-tocopherol (previously called d,l-α-tocopherol). Vitamin E supplements are marketed as mixed tocopherols, α-tocopherol, or α-tocopheryl esters (acetate, nicotinate, or succinate).

In nature, vitamin E is synthesized only by plants, and the richest dietary sources of vitamin E are edible vegetable oils (112). These oils contain all four homologues—α-, β-, γ-, and δ-tocopherols—in varying proportions. *RRR*-α-tocopherol is especially high in wheat germ oil, safflower oil, and sunflower oil, whereas soybean and corn oils contain predominantly γ-tocopherol, as well as some tocotrienols. Cottonseed oil, as well as palm oil, contains both α- and γ-tocopherols in equal proportion. In addition, palm oil contains large amounts of both α- and γ-tocotrienols. As an aside, γ-tocotrienol has been found to increase the turnover of the rate-limiting enzyme in cholesterol synthesis (96).

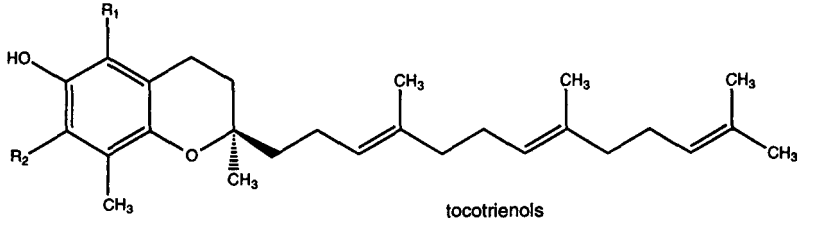
Unprocessed cereal grains and nuts are also good sources of vitamin E; fruits and vegetables contain smaller amounts. Meats, especially animal fat, also contain vitamin E.

Vitamin E Antioxidant Activity

Vitamin E functions as an antioxidant to protect lipids against oxidative damage (22, 131). It especially protects PUFA within phospholipids of biological membranes and in plasma lipoproteins (23). The phenolic hydroxyl group of tocopherol reacts with an organic peroxyl radical to form the corresponding organic hydroperoxide and the tocopheroxyl radical (Vit E-O•):



tocopherols



tocotrienols

Figure 1 Chemical structure of tocopherols and tocotrienols. For α, R_1 and $R_2 = CH_3$; for β, $R_1 = CH_3$ and $R_2 = H$; for γ, $R_1 = H$ and $R_2 = CH_3$; and for δ, R_1 and $R_2 = H$.

$$ROO\bullet + \text{Vit E-OH} \rightarrow ROOH + \text{Vit E-O}\bullet.$$

Thereby, the chain of peroxidation reactions is effectively interrupted; the generated organic hydroperoxide can subsequently be detoxified via nonradical reactions.

Tocopheroxyl radicals can be reduced to tocopherol by interaction with reductants serving as hydrogen donors, AH:

$$\text{Vit E-O}\bullet + AH \rightarrow \text{Vit E-OH} + A\bullet.$$

Biologically important hydrogen donors, demonstrated in vitro to regenerate tocopherol from the tocopheroxyl radical, include ascorbate (vitamin C) and thiols (156), especially glutathione (see 84, 92, 114, 115 for discussion).

Tocopherols, especially α-tocopherol, can also react with singlet oxygen (45, 48, 67, 91, 127). Light is emitted when singlet oxygen spontaneously returns to the triplet ground state; however, in the presence of tocopherols, the excited state of oxygen is deactivated without light emission. Instead, chemical quenching results along with the formation of various oxidation products. Loss of α-tocopherol has also been reported upon exposure to nitric oxide (32).

In addition to its antioxidant function, reported structure-specific effects of α-tocopherol on specific enzyme activities, or on membrane properties, have

been reviewed (148). The most recent work in this respect is on the regulation of vascular smooth muscle cell proliferation and protein kinase C activity (16, 122), and on the suppression of arachidonic acid metabolism via phospholipase inhibition (99).

BIOKINETICS

To function effectively, vitamin E must be absorbed, transported, delivered to cells, and integrated into lipid droplets and into cellular membranes and organelles of all tissues. The major steps along this pathway are important to understanding the physiologic antioxidant functions of vitamin E (73, 97), as illustrated in Figure 2. These are also potential sites where defects can result in vitamin E deficiency.

Absorption

The absorption of vitamin E from the intestinal lumen is dependent upon processes necessary for digestion of dietary fats and uptake into enterocytes.

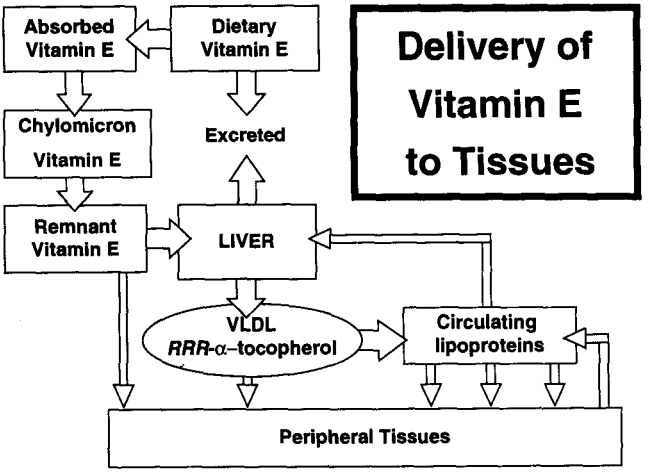


Figure 2 Delivery of vitamin E to tissues. This scheme shows the path of dietary (or supplemental) vitamin E as it is absorbed and secreted in chylomicrons; the chylomicrons then are transformed into remnants in the circulation, which can deliver dietary vitamin E to the liver. The liver is central in this scheme because it sorts the various forms of vitamin E preferentially selecting *RRR*-α-tocopherol for secretion in very low density lipoproteins (VLDL); excess α-tocopherol, as well as other forms of vitamin E, are excreted into bile. VLDL are catabolized in the circulation; as a result, other circulating lipoproteins become preferentially enriched with *RRR*-α-tocopherol. Tissues can acquire vitamin E during triglyceride-rich lipoprotein (chylomicron and VLDL) catabolism, as well as by uptake of low density lipoproteins (LDL) via the LDL receptor, or by transfer from vitamin E-rich lipoproteins to membranes.

Pancreatic esterases are required for release of free fatty acids from dietary triglycerides. Esterases are also required for the hydrolytic cleavage of tocopheryl esters (90), a common form of vitamin E in dietary supplements. The apparent absorption of *RRR*-α-tocopherol in humans was studied using deuterated forms of vitamin E and was found to be similar whether administered as the free phenol, the acetyl ester, or the succinyl ester (29).

Bile acids are needed for the formation of mixed micelles, delivering the various products of lipolysis together with free cholesterol to the intestinal mucosa. Bile acids are absolutely essential for vitamin E absorption (49, 117). In the absence of either pancreatic juice or bile, the appearance of vitamin E in the lymphatic system is poor. In the absence of both secretions, only negligible amounts of vitamin E are absorbed (49, 56, 117, 119). Thus, vitamin E deficiency occurs in patients with biliary obstruction, cholestatic liver disease, pancreatitis, or cystic fibrosis.

Even in healthy individuals, the efficiency of absorption is low (about 15–45%), estimated using radioactively labeled α-tocopherol (14). The relative uptake decreases with increasing amounts of ingested vitamin E, as shown using thoracic duct cannulated rats (145).

The movement of vitamin E through the absorptive cells is not well understood: It is thought to involve diffusion processes; no intestinal tocopherol transfer proteins have been described. In the intestinal mucosa, chylomicrons are formed as vehicles for transport, consisting of triglycerides, free and esterified cholesterol, phospholipids, proteins and apolipoproteins [especially apolipoprotein (apo) B48], fat-soluble vitamins (including vitamin E), and carotenoids. Studies of patients with hypobetalipoproteinemia or abetalipoproteinemia have demonstrated that a defect in either apoB (both apoB100 and apoB48) synthesis or incorporation of triglycerides into apoB-containing particles results in an impaired absorption of vitamin E (72, 149). Indeed, transgenic mice that have had their gene for apoB knocked out develop severe neurologic and developmental abnormalities, thought to arise from vitamin E deficiency (59, 60).

Transport and Distribution

Vitamin E enters the circulation from the intestine in chylomicrons via the lymphatic pathway, i.e. the thoracic duct. The transfer of vitamin E from chylomicrons is regulated by complex mechanisms that control lipid and lipoprotein metabolism. One important enzyme in chylomicron catabolism is lipoprotein lipase, which is bound to the endothelial lining of capillaries. This enzyme hydrolyzes triglycerides, releasing fatty acids (33), and has been shown to hydrolyze retinyl esters (13). Although vitamin E is not esterified in vivo, apparently lipoprotein lipase acts as a transfer protein for vitamin E (147). Some vitamin E is transferred to the various tissues (likely adipose tissue,

muscle, skin, and perhaps brain) by this enzyme-mediated mechanism. It should, however, be noted that lipoprotein lipase-deficient patients do not become vitamin E deficient (147). This is likely due to two factors: (*a*) these patients have very high plasma tocopherol concentrations, as a result of their extraordinarily high circulating lipid levels (often more than 10 times higher than normal), which could allow exchange to tocopherol-poor membranes; and (*b*) there are redundant mechanisms for delivery of vitamin E to tissues, as discussed below.

During chylomicron catabolism, various forms of vitamin E are distributed to all of the circulating lipoproteins, as was demonstrated using *RRR*-α-, *SRR*-α-, and γ-tocopherols labeled with differing amounts of deuterium (136, 137). This process occurs rapidly during the delipidation of triglyceride-rich lipoproteins. As the chylomicron contents are hydrolyzed, excess surface is created. The resultant surface is transferred to high density lipoproteins (HDL), which can readily exchange surface components with other lipoproteins (53, 83, 146). Transfer proteins may be involved: Neutral lipid transfer protein, which exchanges cholesteryl ester for triglyceride from HDL to triglyceride-rich lipoproteins, does not promote vitamin E transfer (53). However, phospholipid transfer protein reportedly potentiates this activity (75).

The conversion of chylomicrons to remnant particles results in the distribution of newly absorbed vitamin E to all of the circulating lipoproteins and ultimately to tissues. It is likely this enrichment of lipoproteins with vitamin E (not only α-tocopherol but other forms, especially the major dietary source of vitamin E, γ-tocopherol) that is the mechanism by which these forms of vitamin E are delivered to tissues. Handelman et al (55) have shown that the adipose tissue γ-tocopherol content can be modified by dietary means, but this process takes more than two years for much change to occur.

After partial delipidation by lipoprotein lipase and acquisition of apoE, chylomicron remnants are taken up by the liver parenchymal cells. The precise mechanisms for chylomicron remnant uptake remain under intense investigations because several pathways involving lipoprotein lipase, apoE, and low density lipoprotein (LDL) receptor-related protein, as well as the LDL receptor, are involved (57, 130). The remnants taken up by the liver likely contain a major portion of absorbed tocopherols.

Liver

In the liver, newly absorbed dietary lipids are incorporated into nascent very low density lipoproteins (VLDL). A number of studies have demonstrated that the liver is responsible for the control and release of *RRR*-α-tocopherol into human plasma (136, 137, 140, 143, 144, 152, 153) and, consequently, for its delivery to peripheral tissues.

The liver synthesizes VLDL by mechanisms that remain largely unknown. It has been suggested that VLDL form when newly synthesized apoB100-rich particles coalesce with separately synthesized triglyceride-rich droplets (54). Both of these components are necessary for VLDL assembly. In the absence of apoB100, VLDL is not secreted from the liver; in the absence of triglyceride, apoB100 is degraded (104). Thus, the genetic defect in the triglyceride transfer protein (157) results in the recessive form of abetalipoproteinemia. These patients have a normal gene for apoB100 and normal to high amounts of messenger RNA for apoB100, yet they are unable to secrete VLDL (78). They become vitamin E deficient because they absorb vitamin E poorly as a result of an inability to synthesize apoB-containing chylomicrons, and they do not secrete apoB-containing lipoproteins containing vitamin E from the liver (104). Thus, studies using deuterated tocopherols in five patients with abetalipoproteinemia demonstrated that large doses of vitamin E (2 g) do little to raise plasma concentrations—these remained less than 1/100 of normal (149).

It is clear, however, that the VLDL particles secreted by the liver are preferentially enriched in *RRR*-α-tocopherol. When cynomolgus monkeys were fed equimolar amounts of *RRR*-, *SRR*-α-, and *RRR*-γ-tocopherols (labeled with different amounts of deuterium) and sacrificed 24 h later, their livers secreted nascent VLDL particles that were preferentially enriched (>80%) with *RRR*-α-tocopherol (151).

During liver disease, vitamin E metabolism may become deranged. Patients with alcoholic liver disease or hemochromatosis were found to have somewhat decreased plasma α-tocopherol concentrations (154). Experiments in rats have also demonstrated that chronic alcohol administration diminishes liver α-tocopherol (12). A significant decrease (37%) in the plasma vitamin E/lipid ratio was also observed in patients with Wilson's disease, who had elevated serum free copper (>10 g/dl) (154).

α-*Tocopherol Transfer Protein*

The central role of the liver in maintaining plasma vitamin E concentrations and the discrimination between the different homologues and stereoisomers are dependent upon the hepatic α-tocopherol transfer protein (Table 1). This protein recognizes the following features of vitamin E (see Figure 1): (*a*) the fully methylated, intact chromane ring with the free 6-OH group; (*b*) the presence of the phytyl side-chain; and (*c*) the *R* stereochemical configuration at the 2 position (as discussed in 135).

The protein was first identified (27), purified, and characterized (109, 158) from rat liver cytosol. Recently, the α-tocopherol transfer protein was isolated from human liver cytosol (77) and its complementary DNA sequence was

Table 1 Vitamin E deficiency in humans caused by mutations in the alpha-tocopherol transfer protein[a]

α-Tocopherol transfer protein
Gene mutations were found in AVED and FIVE deficiency patients
Detected only in liver
Complementary DNA predicts 278 amino acids
Molecular mass 31,749
Exhibits α-tocopherol transfer activity
Structural similarities
94% to rat α-tocopherol transfer protein
47.4% to retinaldehyde binding protein in retina
37.4% to SEC14 protein present in golgi complex
Localized to 8q13.1-13.3 region chromosome 8

[a]Adapted from References 2, 93. AVED, Ataxia with vitamin E deficiency; FIVE, familial isolated vitamin E deficiency.

reported (2). The human protein has 94% homology to the rat protein, and some homology both to the retinaldehyde binding protein in the retina and to sec14, a phospholipid transfer protein (2). The gene has been localized to the 8q13.1-13.3 region of chromosome 8 (2, 39).

Two different groups of patients have been described to have a genetic defect in the α-tocopherol transfer protein. Patients with sporadic, as well as familial, isolated vitamin E (FIVE) deficiency were described to have impaired incorporation of *RRR*-α-tocopherol into nascent VLDL (152). Furthermore, a number of these patients were found to have an impaired ability to discriminate between *RRR*- and *SRR*-α-tocopherols (153). FIVE deficiency patients have normal plasma vitamin E concentrations if they are given vitamin E supplements (about 1 g/day). If supplementation is halted, then plasma vitamin E concentrations falls to less than 1/100 of normal within days. These patients are characterized by a progressive peripheral neuropathy with a specific dying back of the large caliber axons of the sensory neurons, which results in ataxia (118).

The other group of patients (identified from a large number of inbred Tunisian families) was instrumental in the characterization of the genetic defect in the α-tocopherol transfer protein in humans. These patients were first thought to have Friedreich's ataxia (5, 6), but now their disorder is termed ataxia with vitamin E deficiency (AVED). When their genetic defect was characterized, they were found to have defects on chromosome 8, not 9 (where defects have been reported). Subsequent investigation demonstrated that members of the family affected with neurologic abnormalities also had extraordinarily low plasma vitamin E (5). This unusual defect was mapped to the same location (chromosome 8) as was the α-tocopherol transfer protein (93). Interestingly, in most of the Tunisian patients, the terminal 10% of the protein was deleted (93).

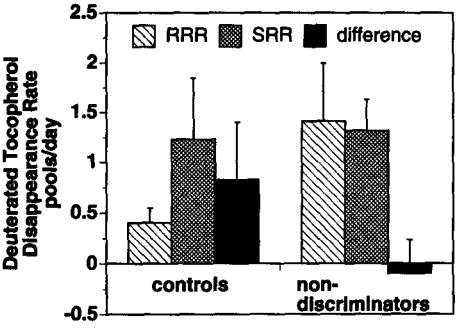


Figure 3 Comparison of the disappearance rates of *RRR*- and *SRR*-α-tocopherols in controls and nondiscriminator patients. Subjects were given equal amounts of *RRR*- and *SRR*-α-tocopherols labeled with different amounts of deuterium, and the plasma concentrations of deuterated tocopherols followed. Shown are the rates of disappearance of each of the isotopes in controls ($N = 6$) and nondiscriminator patients ($N = 3$). The differences between the rates *RRR*- and *SRR*-α-tocopherols measure the rates the liver must resecrete *RRR*-α-tocopherols into the plasma to maintain its apparent slower rate of disappearance. These calculations were described previously (150).

The severity of the neurologic disorder resulting from the defect in the tocopherol transfer protein and the ease with which vitamin E-deficiency symptoms can be prevented with supplemental vitamin E has prompted Belal et al (4) to advocate measurement of plasma vitamin E in patients with peripheral neuropathy or ataxia. It also prompted them to encourage early and vigorous vitamin E supplementation in children whose parents have a defect in the protein and in patients with these neurologic symptoms and subnormal plasma vitamin E levels.

In normal subjects, both *RRR*- and *SRR*-α tocopherols labeled with differing amounts of deuterium are secreted similarly in chylomicrons; but by 24 h, their plasma is enriched preferentially with *RRR*-α-tocopherol. However, in patients with FIVE deficiency, deuterated tocopherol concentrations attained a maximum concentration at a time that was coincident with the maximum in chylomicrons. Subsequently, plasma concentrations of both *RRR*- and *SRR*-α-tocopherols decreased rapidly. The fractional disappearance rates of deuterium-labeled *RRR*- and *SRR*-α-tocopherols in the three nondiscriminator patients were 1.4 ± 0.6 and 1.3 ± 0.3 pools/day, respectively (Figure 3) (150). In six controls, fractional disappearance rates of deuterium-labeled *RRR*-α-tocopherol (0.4 ± 0.1 pools/day) were significantly ($P < 0.01$) slower than for *SRR*-α-tocopherol (1.2 ± 0.6). The differences (0.8 ± 0.6 pools/day) between these two rates in control subjects estimate the rate of resecretion of *RRR*-α-tocopherol into the plasma by the liver. Although labeled *RRR*-α-tocopherol

would appear to leave the plasma slowly, both forms of vitamin E leave the plasma rapidly. Recycling of *RRR*-α-tocopherol by the liver accounts for salvage of nearly one pool of α-tocopherol per day (150).

Lipoproteins

Lipoproteins transport vitamin E in plasma (as discussed above and in 73, 139). There are no specific transport proteins for vitamin E in plasma. Thus, major mechanisms for the delivery of lipids to tissue are also major mechanisms for the delivery of vitamin E to tissues (Figure 2).

As mentioned above, lipoprotein lipase functions as a transfer protein for vitamin E, transferring tocopherols along with fatty acids during lipolysis of chylomicrons and VLDL (147). Although a majority of the VLDL remnants [intermediate density lipoproteins (IDL)] is returned to the liver, the remainder is converted by the lipase to LDL. During the conversion of these triglyceride-rich to lower density lipoproteins, there is also transfer of surface components, and presumably vitamin E, to HDL. Vitamin E spontaneously transfers from HDL to other lipoproteins (83, 146).

Delivery of vitamin E to tissues can also take place via the LDL receptor (141). LDL particles transport cholesterol and other components into cells via LDL receptors that bind two proteins, apoB100 in LDL and apoE in IDL and HDL (19). Thus, delivery of cholesteryl linoleate is accompanied by the simultaneous delivery of vitamin E.

Uptake and Retention in Tissues

The rate at which newly absorbed vitamin E is taken up by various tissues is not uniform. There are tissues in which the turnover is fast, e.g. plasma, red blood cells, and liver, and there are other tissues in which the turnover is slow, e.g. muscle, testes, brain, and spinal cord (24). Neural tissues resist losing their vitamin E, as shown using adult dogs fed a vitamin E-deficient diet (101, 102). Weanling rats on a vitamin E-deficient diet do not show abnormalities in neurologic function for up to 40 weeks, possibly because of their efficient retention of vitamin E in the neural tissue (100).

Mobilization, Metabolism, Elimination

No organ functions as a storage organ for α-tocopherol, releasing it on demand. The bulk of vitamin E in the body is localized in the adipose tissue (142) but is not readily mobilized from it (110).

Because the tocopheroxyl radical can be reduced back to tocopherol by ascorbate or other reducing agents, the flux through the radical pathway may be much larger than the flux through the pathway of further metabolism. Liebler & Burr (80) studied oxidation of α-tocopherol in vitro using peroxyl

radicals generated from the azo initiator, azobis(2,4-dimethylvaleronitrile) in acetonitrile, hexane, or phospholipid liposomes and suggest that biologically relevant products formed in liposomes include 4a,5-epoxy- and 7,8-epoxy-8a(hydroperoxy)tocopherones and their respective hydrolysis products, 2,3-epoxy-α-tocopherol quinone and 5,6-epoxy-α-tocopherol quinone.

The primary oxidation product is the tocopheryl quinone, which can be conjugated to yield the glucuronate after prior reduction to the hydroquinone. The glucuronate can be excreted into bile or further degraded in the kidneys to the tocopheronic acid and processed for urinary excretion (40). Further oxidation products, including dimers, trimers, and other adducts, have been described. Schultz et al (111) described a novel urinary metabolite of α-tocopherol (2,5,7,8-tetramethyl-2(2′carboxyethyl)-6-hydroxychromane), which is excreted in the urine when large supplemental doses of *RRR*-α-tocopherol are fed to humans. Doses in excess of 50 mg of vitamin E exceed the plasma threshold of 7–9 mol of α-tocopherol/g of total lipid and result in excretion of this metabolite. Schultz et al (111), therefore, suggest that the excretion of the metabolite indicates saturation of the plasma binding capacity for α-tocopherol.

The major route of ingested tocopherols is fecal elimination, due to the low intestinal absorption. Forms of vitamin E not preferentially used, such as synthetic racemic isomer mixtures or γ-tocopherol (144), are eliminated during the process of nascent VLDL secretion in the liver and are thought to be excreted into bile (73).

VITAMIN E SUPPLEMENTATION IN HUMANS IN RELATIONSHIP TO DISEASE STATES

Administration of large, supplemental vitamin E doses to subjects with vitamin E deficiency, or to those at risk for vitamin E deficiency, is generally recognized as an important preventative measure, because the peripheral neuropathy resulting from vitamin E deficiency is so devastating (116), and because supplemental vitamin E is virtually nontoxic (8, 69, 86). A recommendation for supplemental vitamin E for the general population is much more controversial. The traditional approach to vitamin dosages has been to recommend amounts that can be obtained from the diet that are sufficient to prevent deficiency symptoms in 98% of the individuals in the population (47). However, antioxidant nutrients, such as vitamins E and C, perhaps should be considered differently. These may have beneficial effects in pharmacologic amounts and may provide protective effects against free radical damage, which potentiate chronic diseases. This concept is addressed in the following section.

Ischemic Heart Disease

Plasma vitamins E and A are inversely correlated with mortality from ischemic heart disease in cross-cultural epidemiology (50). In 12 of 16 different populations in Europe, there was no evidence of an expected relation to total cholesterol (r^2 = 0.04; P = 0.53), blood pressure (r^2 = 0.01; P = 0.80), or smoking (r^2 = 0.002; P = 0.89). However, vitamin E accounted for 63% of the differences in mortality (r^2 = 0.63; P = 0.0002; Figure 4). Similar results were obtained for lipid-standardized plasma vitamin E (r^2 = 0.62; P = 0.0003), including four hypo- or hypercholesterolemic populations. With the combination of the four variables—lipid-standardized vitamin E, cholesterol, blood pressure, and smoking—in a multiple regression analysis, the differences in mortality in the 16 European populations could be predicted by 87% (r^2 = 0.87; P = 0.0001).

The relationship between risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene was examined in a population case-control study in Edinburgh of 110 patients with angina, identified by the Chest Pain Questionnaire, and 394 control subjects selected from a sample of 6000 men aged 35–54 (106). Plasma concentrations of vitamins C and E and carotene were significantly inversely related to the risk of angina. There was no significant relationship to vitamin A. Smoking was a confounding factor. The inverse relationship between angina and low plasma carotene disappeared and that with plasma vitamin C was substantially diminished after adjustment for smoking. Vitamin E remained independently and inversely related to the risk

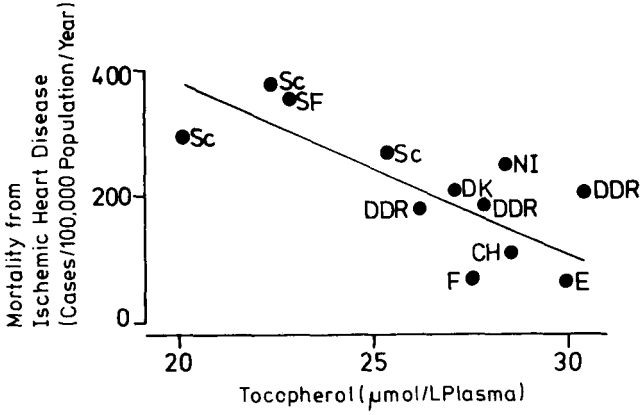


Figure 4 Inverse correlation between age-specific mortality from ischemic heart disease and the plasma level of α tocopherol (r^2 = 0.63) in 12 European populations with normal plasma cholesterol (220–240 mg/dl). Abbreviations: Sc, Scotland; SF, Finland; DDR, Germany; DK, Denmark; F, France; NI, Ireland; CH, Switzerland; E, Spain. Adapted from Gey et al (50).

of angina after adjustment for age, smoking habit, blood pressure, lipids, and relative weight. The adjusted odds ratio for angina between lowest and highest quintiles of vitamin E concentrations was 2.68 (95% confidence interval 1.07–6.70; $P = 0.02$).

Hodis et al (58) reported on a subgroup analysis of the on-trial antioxidant vitamin intake database acquired in the Cholesterol Lowering Atherosclerosis Study, a randomized, placebo-controlled, serial angiographic clinical trial evaluating the risk and benefit of colestipol-niacin on coronary artery disease progression. They found that subjects with supplementary vitamin E intake of 100 IU per day or greater demonstrated less coronary artery lesion progression than did subjects with supplementary vitamin E intake of less than 100 IU per day for all lesions ($P = 0.04$) and for mild/moderate lesions ($P = 0.01$). They, however, emphasized that a carefully designed, randomized, serial arterial imaging end point trial is needed to verify these results.

Atherosclerosis

One fundamental circulatory disorder is atherosclerosis, and several studies suggest that oxidized LDL are atherogenic (124, 125). LDL particles are not only rich in cholesterol, they also contain about 1300 molecules of PUFA (linoleic, arachidonic, and docosahexaenoic acids) per molecule (42, 43). These PUFA are susceptible to peroxidation by oxidative attack through oxygen radicals. Oxidized LDL stimulate the recruitment of monocytes/macrophages in the subendothelial space of the vessel wall (10, 31). These macrophages can then take up oxidatively modified LDL via the scavenger receptor to form lipid-containing foam cells, characteristic constituents of early atherosclerotic foci in the vessel wall. Oxidized LDL also contain cytotoxic components that can generate damage to endothelial cells (126).

In principle, the oxidation of LDL is a process of lipid peroxidation. Peroxidation products formed within the LDL particles could then react with the amino acid side chains of apoB and form new epitopes that have affinity not to the classic LDL receptor, but rather to the scavenger receptor (76). LDL are protected by α-tocopherol (about six molecules per LDL particle; γ-tocopherol is also present), ß-carotene, lycopene, α-carotene, zeaxanthin, cryptoxanthin, and phytofluene: overall, about 6 to 14 molecules of antioxidant per particle, with considerable variation between individuals (42).

During oxidative stress in vitro, human LDL rapidly loose their antioxidants and then are devoid of protection or, as stated by Brown and Goldstein, "left to the mercy of oxygen" (20). After exhaustion of antioxidants, lipid peroxidation proceeds. This period of time, called induction period or lag phase, has been used as a measure of resistance to oxidation. If LDL (42) [or biological membranes, in general (25)] are enriched with tocopherol in vitro, then the lag

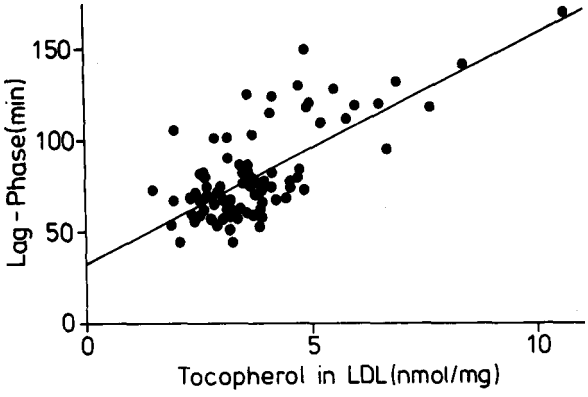


Figure 5 Correlation between the resistance to oxidation (lag phase) of LDL and the content of α-tocopherol in LDL ($r^2 = 0.51$). Twelve individuals received the doses RRR-α-tocopherol daily over the course of three weeks. The correlation coefficient (r^2) indicates the percentage of scatter of measured values that can be explained by α-tocopherol ($r^2 = 1.0$ means full explanation of total scatter). Modified from Dieber-Rotheneder et al (37).

phase, or resistance to oxidation, increases proportionally with the tocopherol content.

Supplementation of healthy adults with vitamin E increased α-tocopherol in subsequently isolated LDL (37), with a significant correlation between the tocopherol content and their resistance to oxidation (Figure 5). A doubling of the LDL α-tocopherol content increased resistance to oxidation by 1.5–fold. In a randomized, placebo-controlled study conducted over a period of eight weeks, Jialal et al (65) tried to ascertain the minimum dose of α-tocopherol that would decrease the susceptibility of LDL to oxidation. α-Tocopherol in doses in excess of 200 IU/day was effective. However, the individual differences are considerable, suggesting that other factors (e.g. the carotenoids or the levels and composition of PUFA) are important as well.

One controversial aspect of vitamin E is in respect to studies of the oxidation of LDL. In some in vitro systems, high concentrations of vitamin E can act as a pro-oxidant (87, 89). In the absence of water-soluble antioxidants (i.e. ascorbate or urate) during oxidation of LDL, α-tocopherol acts as a chain-transfer agent. The α-tocopheroxyl radical formed on the surface of LDL moves into the LDL core, where it abstracts hydrogen from a cholesteryl ester with a polyunsaturated fatty acid molecule to form a peroxyl radical (18, 62, 128). In this scenario, vitamin E does not function as a chain-breaking antioxidant, but rather as a propagator of lipid peroxidation in the lipid core. These studies emphasize the importance of the interaction of vitamins E and C, because

ascorbate can regenerate α-tocopherol from the α-tocopheroxyl radical, as discussed above. It is not known whether or not there are microenvironments in which oxidants have destroyed the water-soluble antioxidants, and thus α-tocopherol present in LDL could function as a pro-oxidant in vivo.

Kalyanaraman et al (68) have investigated the role of α-tocopherol during oxidation of LDL with peroxide and horseradish peroxidase. They found a simultaneous loss of tocopherol and appearance of conjugated dienes, suggesting that during this type of oxidation α-tocopherol could act as a pro-oxidant. However, addition of extra α-tocopherol to the LDL prior to oxidation was protective and did not increase LDL oxidation. Kalyanaraman et al (68) suggested that the peroxide and horseradish peroxidase system generates a free radical on the apoB protein, which is able to initiate lipid peroxidation. The peroxyl radical then reacts with α-tocopherol to form the α-tocopheroxyl radical. The observation that higher concentrations of α-tocopherol can reduce the initial rate of conjugated diene formation suggests that α-tocopherol can also react directly with the oxidant responsible for lipid oxidation. Thus, it appears that vitamin E in LDL most likely does not act as a pro-oxidant.

Surveys of endogenous antioxidant defenses in human plasma (129) and of the therapeutic potential of vitamin E in the pathogenesis of spontaneous atherosclerosis (64) suggest only a benign role for vitamin E. Taken together, we can state that by now the hypothesis that oxidatively modified LDL play a major role in the development of arteriosclerosis is well-founded. The finding that vitamin E and other antioxidants can decrease LDL oxidation in vitro is of great interest and has major implications for future use of vitamin E in disease prevention.

Diabetes

Long-standing diabetes mellitus is very frequently associated with characteristic vascular complications, either as microangiopathy in capillaries or arterioles or as macroangiopathy in larger arteries; clinical manifestations are diabetic retinopathy, nephropathy, and neuropathy. Increased platelet aggregation and thromboxane A_2 levels observed in diabetic patients were normalized through vitamin E supplementation (70, 155). In studies carried out with insulin-dependent (type I) diabetic patients, platelet thromboxane production was decreased in 22 patients who received 400 mg of *all-rac*-α-tocopheryl acetate for four weeks (52). Similar results were obtained by monitoring malondialdehyde release and the oxidative conversion of arachidonate in nine patients receiving 1 g of vitamin E daily for 5 weeks (30). Thus, vitamin E supplementation may represent a therapeutic means to prevent or delay the development of diabetic vascular complications. However, to evaluate the clinical usefulness of such an approach, DeMaio et al (34) carried out a

long-term, large-scale clinical trial to determine whether or not vitamin E supplementation would prevent restenosis after percutaneous transluminal coronary angioplasty; they found no effect. Paolisso et al (94, 95), however, have found that vitamin E potentiates insulin function in diabetic patients. Thus, the question of clinical usefulness of vitamin E in diabetes remains elusive.

Cataracts

Cataracts are the leading cause of blindness worldwide, the vast majority of which are of the senile variety. Spector (120) has reviewed the evidence that oxidative stress induces maturity onset cataracts and lens opacification. He suggested that the epithelial cell layer is the initial site of attack by oxidative stress, and that putative drug therapy to prevent the development of cataracts should be initiated at a very early stage, when individuals are in their early 50s, well before the prevalence of maturity onset cataract becomes significant.

Comparison of the self-reported consumption of supplementary vitamins by 175 cataract patients with that of 175 individually matched, cataract-free subjects (108) showed that the cataract-free subjects used significantly more supplementary vitamins C and E ($P < 0.01$ and 0.004, respectively). Similarly, subjects without senile cataracts had a higher antioxidant status (vitamin C, vitamin E, and carotenoids) than persons with cataracts had (63). Using glutathione-depleted L-buthionine(S,R)-sulfoximine (BSO)-treated newborn rats, Maitra et al (82) investigated the effect of α-lipoic acid, a powerful antioxidant, on cataract formation and found that a dose of 25 mg/kg of body weight prevented cataracts in 60% of the animals. These experimental data show that the level of antioxidant protection in the eye is critical for the prevention of cataracts.

Parkinson's Disease and Alzheimer's Disease

Afflictions of the nervous system, in general, are of interest with respect to vitamin E therapy, in view of the neurochemical, neurophysiological, and neuropathological information obtained from studies of vitamin E deficiency (88, 116). For example, there is evidence that links oxygen free radicals and Parkinson's disease (134). However, the serum levels of vitamin E and the vitamin E/cholesterol ratios were found not to be significantly lower in the patients with Parkinson's disease than in the control subjects (46). Furthermore, the conclusion from the DATATOP study (a multi-center trial of more than 800 patients) was that Deprenyl® (10 mg per day) but not vitamin E (2000 IU per day) delays the onset of disability associated with early, otherwise untreated, Parkinson's disease (133). In contrast, Dexter et al (36) studied four

patients with vitamin E deficiency and sensory ataxia and found reduced [^{18}F]dopa uptake in both putamen and caudate in the two most severely affected patients. They concluded that severe and prolonged vitamin E deficiency results in loss of nigrostriatal nerve terminals and support the hypothesis that oxidative stress may contribute to the etiology of Parkinson's disease.

In an analysis of brain antioxidants in patients with Alzheimer's disease or patients with Parkinson's disease (1), midbrain tocopherol levels were doubled in both of these groups as compared with the control group. Regarding Alzheimer's disease, experimental work has shown that metal-catalyzed oxidation confers amyloidogenicity to amyloid protein precursor fragments (41), and vitamin E protects nerve cells from amyloid ß protein toxicity (3).

Immune Function

Lymphocytes and mononuclear cells have the highest vitamin contents of any circulating cells (7). Machlin (81) stated that therefore it is not surprising that vitamin E has a profound effect on the immune system. Possible explanations for the immune-enhancing properties of vitamin E are alterations in eicosanoid metabolism and alterations in membrane fluidity of immune cells. Moreover, antioxidant properties may explain the decrease in self-destruction of neutrophils during the oxidative burst.

Two studies indicate that vitamin E may be of considerable importance in maintaining or enhancing the immune system in the elderly. In a prospective epidemiological study (28), it was found that 66% of subjects over 60 years of age, with plasma tocopherol levels of less than 1.35 mg/dl, experienced at least three infections over a 3-year period. In contrast, only 37% of subjects with plasma tocopherol over 1.35 mg/dl had at least three infections. Based on the dose-response, an intake of 40–60 IU of vitamin E per day is necessary to attain blood levels this high. In a double-blind study in healthy elderly (60–85 years) subjects, those given 800 IU of vitamin E per day had enhanced delayed-type hypersensitivity and lymphocyte mitogen responses compared with placebo control subjects (85). Measurements of selenium and vitamin E status in institutionalized elderly people as compared with those who were healthy showed diminished values (26). It was concluded that aging per se had a minimal effect on the selenium and vitamin E status, but that intercurrent illness and decreased food intake can lead to diminished levels in elderly people. An immune-enhancing effect of vitamin E in humans could have considerable public health implications and warrants continued investigation. Results from a randomized controlled trial on dietary supplementation of elderly long-stay patients with vitamins A, C, and E suggested that supplementation with physiological doses in combination can improve cell-mediated immunity (98).

Patients Receiving Total Parenteral Nutrition

Patients receiving total parenteral nutrition (TPN) ideally are provided with all of their required nutrients—vitamin E is given as part of a vitamin mix and as a component of a lipid emulsion, which also provides essential fatty acids, as well as calories. Most intravenous preparations of lipid emulsions are made with soybean oil (to provide polyunsaturated fats), which contains 6–10 times as much γ- as α-tocopherol. Previously, the γ-tocopherol content of the lipid emulsions (35, 51) has been used to calculate the total vitamin E intake based on the premise that γ-tocopherol has 10% of the biologic activity of α-tocopherol (21). However, this may not be valid, because there are specific mechanisms for maintaining plasma α-tocopherol, not γ-tocopherol, concentrations.

The evaluation of vitamin E status of TPN patients receiving lipid emulsions suggests that they may be receiving inadequate amounts of vitamin E. Firstly, TPN patients have been demonstrated to have elevated levels of exhaled pentane and ethane, markers of lipid peroxidation in vivo (79), suggesting increased oxidation of vitamin E as well. Secondly, TPN patients have adipose tissue α-tocopherol concentrations that are half of normal, suggesting a depletion of tissue stores of vitamin E (123). Thus, patients who receive 10 IU of vitamin E in addition to the tocopherols in the soybean oil lipid emulsions appear to be in negative vitamin E balance. How can this be?

Infusion of PUFA may lead to an increased requirement for vitamin E. In normal subjects receiving lipid emulsions, γ-tocopherol levels in plasma are only elevated during the infusion (138). Subsequently, plasma γ-tocopherol concentrations rapidly decreased; at 24 h postinfusion, γ-tocopherol concentrations were one fifth those of α-tocopherol (138). Furthermore, during lipid infusion there is a redistribution of α-tocopherol from LDL and HDL to triglyceride-rich lipoproteins, which are rapidly catabolized. Patients on long-term TPN may be depleting tissue stores of vitamin E because the lipid emulsions remove α-tocopherol from the plasma lipoproteins, returning it to the liver. Thus, current TPN lipid emulsions provide a high intake of PUFA, which results in increased requirements for lipid-soluble antioxidants without providing sufficient α-tocopherol.

CONCLUDING REMARKS

Increasing evidence implicates free radical–mediated cell and tissue damage in the pathogenesis of various degenerative diseases and conditions. The susceptibility of the body to peroxidative damage is related to the balance between the prooxidant load and the adequacy of antioxidant defenses. A disbalance in favor of the prooxidants has been termed oxidative stress (113). Research continues on the protective effects of vitamin E and the other biologic anti-

oxidants in counteracting or preventing oxidative damage. The knowledge available to date, largely based on animal studies and human epidemiology, suggests that tocopherols carry out essential functions in slowing or preventing degenerative disease processes.

The amounts of vitamin E (10 mg of α-tocopherol equivalents) recommended by the Food and Nutrition Board of the National Research Council (47) are estimated to meet requirements and prevent deficiency symptoms in normal humans. These amounts can be obtained by eating a wide variety of foods rich in vitamin E. With all the caveats, an optimum plasma level of α-tocopherol of 30 μM or greater has been defined (11). To maintain this plasma level, on average, a daily dietary intake of about 15–30 mg of α-tocopherol is required. These amounts could be obtained from dietary sources, if one made a concerted effort to eat foods high in vitamin E (112). In contrast, the amounts of supplemental vitamin E suggested as protective from epidemiologic studies (15, 17, 107, 121) are vastly in excess of those that could be obtained from the diet. To date, no controlled studies have been reported that demonstrate clinical efficacy of dietary supplements of vitamin E. Indeed, no decrease in the incidence of lung cancer among male smokers was observed in response to 5–8 years of dietary supplementation with 50 IU of vitamin E (132). Thus, recommendation of supplementary vitamin E in excess of dietary amounts awaits the results of ongoing, large-scale, randomized trials of primary and secondary prevention. Furthermore, the interpretation of these studies will be rendered difficult because of the multiple lines of antioxidant defense.

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