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The Role of Tocopherols in Health

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6 The Role of Tocopherols in Health

Richard S. Bruno

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6.1 INTRODUCTION

Vitamin E is the term that describes eight lipophilic, naturally occurring compounds including four tocopherols and four tocotrienols (Figure 6.1). Tocopherols have a saturated phytol tail, whereas tocotrienols have an unsaturated tail. Within each class, four forms exist as α-, β-, γ-, and δ- that differ based on the number and position of methyl groups present on the chromanol head. When the chromanol head is fully methylated and the phytol tail is saturated, this vitamer is identified as α-tocopherol. The most abundant forms of vitamin E found biologically and in the diet are α- and γ-tocopherol. Structurally, they are similar and differ only in that γ-tocopherol has an unsubstituted position on the chromanol head (Figure 6.1). Thus, due to the dietary and biological abundance of these vitamin E forms, a considerable body of knowledge has accumulated since their discovery. This
chapter will therefore focus on these vitamin E forms, although greater emphasis will be placed on α-tocopherol because this is the only form of vitamin E that is essential for humans.

6.2 HISTORY

Vitamin E was discovered in 1922 as a compound necessary to sustain reproductive ability in rodents. Evans and Bishop determined that rodents fed diets containing rancid fat (i.e., vitamin E deficient) produced offspring that were mostly sterile in the first generation and completely sterile in the second generation, and fetal resorption occurred despite the presence of normal ovarian structure and function. Around this time period, the same conclusion was formed by Barnett Sure, who was performing similar dietary experiments, but he coined the term “vitamin E” because vitamins A, B, C, and D were already identified. Further work led to the isolation of α-tocopherol from wheat germ, which exhibited biologic activity of vitamin E. In the subsequent year, β- and γ-tocopherols were isolated from vegetable oils, but these vitamin E homologs were demonstrated to have lower biological activity than α-tocopherol. While these non-α-tocopherol forms of vitamin E reportedly have vitamin E biological activity, compound purity and the sensitivity of analytical methods utilized have been questioned. For example, commercially available γ-tocopherol is typically ~97% pure, with much of the “contamination” attributed to α-tocopherol. Thus, some early research regarding vitamin E biological activity may need to be reconsidered.

Historically, the fetal resorption assay has been used to define vitamin E biological activity despite this assay being laborious. However, the assay provides useful information since it quantifies the amount of vitamin E necessary to maintain the maximal number of live fetuses. While vitamin E deficiency can be induced in laboratory animals, it is quite difficult to do so in humans. Horwitt and others studied the effects of chronically low vitamin E intakes among hospitalized patients. After nearly 2 years of the 6-year-long investigation, circulating vitamin E decreased into the

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**FIGURE 6.1** Vitamin E structures: tocopherols and tocotrienols. Vitamin E consists of four tocopherols and four tocotrienols. α-tocopherol, either naturally occurring or from synthetic preparations, is widely consumed in supplement form. Synthetic preparations of α-tocopherol contain eight stereoisomers (2R forms: RRR, RSR, RRS, RSS; 2S forms: SRR, SSR, SRS, SSS) due to the three chiral centers (denoted by asterisks) present on the phytol tail, whereas naturally occurring α-tocopherol exists solely in the RRR configuration.
deficient range, but overt signs of clinical deficiency did not develop despite increased sensitivity of
erthrocytes to hydrogen peroxide–induced hemolysis.

Despite the efforts of chronic dietary vitamin E restriction in humans, symptoms of vitamin E
deficiency (i.e., peripheral neuropathy, spinocerebellar ataxia, skeletal myopathy, pigmented
retinopathy) have not been observed in the laboratory. Further, humans usually become vitamin E
deficient only secondary to other pathologies, including fat maldigestion disorders,11 dysfunctional
lipid metabolism,12 and severe protein-energy malnutrition.13 However, the discovery of the
α-tocopherol transfer protein and its rarely occurring mutation have led to the identification of
vitamin E deficiency independent of other pathologies in humans,14 which has been confirmed in
α-tocopherol transfer protein knock-out mice.15

### 6.3 FUNCTIONS

#### 6.3.1 Antioxidant

The most well-known function of vitamin E is its chain-breaking antioxidant activity that
terminates the cyclic propagation of lipid peroxidation (Figure 6.2).16 Indeed, vitamin E is a peroxyl
radical scavenger that protects polyunsaturated fatty acids from lipid peroxidation.17 Vitamin E
“outcompetes” the propagation reactions such that a single vitamin E molecule should be able to
protect ~1000 lipid molecules from the chain reaction propagation step.18 This phenomenon is
attributed to the higher rate constant between vitamin E and peroxyl radicals compared with the
reaction rate between PUFA and peroxyl radicals. When vitamin E scavenges peroxyl radicals,
it loses an electron while terminating the propagation reaction, and becomes oxidized to form a
tocopheroxyl radical (Figure 6.2). Tocopheroxyl radicals can then: (1) undergo additional oxidation to
generate a tocopherol quinone,19 (2) react with another radical to yield a non-reactive product, (3) be
recycled to a native tocopherol by other antioxidants (e.g., vitamin C),2 or (4) theoretically reinitiate
lipid peroxidation through a process referred to as tocopherol-mediated peroxidation.20

Of all the tocopherols, α-tocopherol has the strongest antioxidant activity based on a technique
that assesses the inhibited autooxidation of styrene (i.e., peroxyl radical generation).21 Antioxidant
activities of tocopherols are as follows: α > γ > β > δ, with respective rate coefficients of 320, 140,
130, and $44 \times 10^4$ (M$^{-1}$ s$^{-1}$). α-Tocopherol likely exhibits superior antioxidant activity because it contains three methyl groups (Figure 6.1) on the chromanol head that function to stabilize phenoxyl radicals. Other tocopherols are lacking one or more methyl groups and hence have lower antioxidant activity. In agreement, β- and γ-tocopherol each have two methyl groups but at differing positions on the chromanol head, and each has approximately the same antioxidant activity.

Despite *in vitro* antioxidant activity of each vitamin E form, whether each form exhibits *in vivo* antioxidant function is questionable because of considerable differences in bioavailability. Although there are eight forms of vitamin E, only α- and γ-tocopherols are generally detected in tissues and plasma of non-users of dietary supplements (discussed further under the “Bioavailability” section). In fact, plasma α-tocopherol concentrations ($\sim$20–40 µmol/L) are significantly higher than those of γ-tocopherol ($\sim$1–5 µmol/L), whereas the other six vitamin E forms are generally low (<500 nmol/L) or undetectable in human plasma. Thus, the more abundant forms of α- and γ-tocopherol are more likely to exhibit an *in vivo* antioxidant function.

Oxidative stress results in the imbalance between free radicals and antioxidant defenses in favor of the former. Excess free radicals are implicated to damage various biomolecules including proteins, DNA, and lipids. Conversely, antioxidants that scavenge free radicals, such as α- and γ-tocopherol, would be expected to undergo oxidation to result in their more rapid depletion from biological systems. This phenomenon has been demonstrated *in vitro* such that vitamin E can be oxidized by oxidant-rich cigarette smoke or by peroxynitrite. However, considerably less is known regarding the effects of oxidative stress on vitamin E in humans. This, in part, is due to the availability of few experimental human models to evaluate the extent to which oxidative stress alters vitamin E concentrations.

In an effort to define the impact of oxidative stress relative to the antioxidant function of vitamin E, investigators have evaluated alterations in vitamin E utilization in several human cohorts. These have included exercising individuals, cigarette smokers, and persons with metabolic syndrome. Although each is unique in clinical presentation, these cohorts are characterized by acute vs. chronic oxidative stress and relatively low vs. relatively high oxidative stress responses. For example, smokers represent a model of chronic high oxidative stress from the direct effects due to cigarette smoke itself, but also from the indirect effects of smoke-induced activated inflammatory responses. Aerobic exercise acutely increases the magnitude of oxidative stress due to increased mitochondrial oxygen consumption and electron transport flux. And, metabolic syndrome is associated with low-grade, chronic inflammation. Nonetheless, smoking, exercise, and metabolic syndrome are associated with increased oxidative damage markers, including F$_2$-isoprostanes that are considered the “gold standard” measure of oxidative damage.

The effects of oxidative stress on vitamin E utilization were evaluated in smokers and nonsmokers who ingested 150 mg of deuterium-labeled α-tocopherols for 6-days. Post-supplementation, smokers and nonsmokers achieved similar plasma concentrations of labeled α-tocopherols. However, during the post-supplementation period, smokers’ plasma α-tocopherol disappearance rates were significantly faster than those of nonsmokers (Table 6.1), and they had plasma α-tocopherol half-lives that were

<table>
<thead>
<tr>
<th>Clinical Model</th>
<th>Plasma α-Tocopherol Rate of Disappearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise vs. Sedentary$^{28}$</td>
<td>22% faster</td>
</tr>
<tr>
<td>Smokers vs. Nonsmokers$^{30}$</td>
<td>13% faster</td>
</tr>
<tr>
<td>Metabolic Syndrome vs. Healthy$^{29}$</td>
<td>15% slower</td>
</tr>
</tbody>
</table>

TABLE 6.1 α-Tocopherol Pharmacokinetics in Several Free-Living Human Models of Oxidative Stress
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~10 hours shorter in duration. Smokers’ α-tocopherol disappearance rates were also inversely correlated with their plasma vitamin C concentrations (further discussion under “α- and γ-Tocopherol Interactions with Vitamin C”). In other words, smokers with the lowest vitamin C concentrations had the fastest rates of α-tocopherol disappearance, suggesting that greater vitamin C status helps to conserve vitamin E. A separate placebo-controlled, crossover study therefore evaluated vitamin C or placebo supplementation for 2 weeks in smokers and nonsmokers prior to oral administration of a single dose of deuterium-labeled α- and γ-tocopherols. Similar to prior work, smokers during the placebo phase had faster plasma α- and γ-tocopherol disappearance rates. However, vitamin C supplementation completely normalized smokers’ α- and γ-tocopherol disappearance rates to those occurring in nonsmokers. It was therefore concluded that: (1) oxidative stress depleted/oxidized α- and γ-tocopherol to respective tocopheroyl radicals, and (2) vitamin C recycled α- and γ-tocopheroyl radicals to their reduced tocopherol forms to preserve vitamin E status. Such studies in smokers and nonsmokers have improved our understanding that α- and γ-tocopherol function as antioxidants in vivo and that they act along with vitamin C as members of the antioxidant network.

Aerobic exercise also increased rates of α-tocopherol disappearance (Table 6.1). This was established in ultramarathon runners who completed two trials in which they ingested deuterium-labeled α-tocopherols prior to a 50-km race or during a sedentary period that occurred 1 month after the race. Relative to the sedentary trial, disappearance rates of deuterium-labeled α-tocopherol were faster during the exercise trial. The accelerated rate of α-tocopherol depletion also occurred in association with exercise, nearly doubling circulating isoprostanes from the pre-race period, whereas isoprostanes were unaffected throughout the sedentary trial. Thus, exercise-induced lipid peroxidation depleted α-tocopherol consistent with its antioxidant function.

α-Tocopherol pharmacokinetics have also been evaluated in persons with metabolic syndrome compared with healthy adults (Table 6.1). At study enrollment, metabolic syndrome persons had dyslipidemia (i.e., low HDL-C, high total cholesterol, LDL-C, and triglycerides), insulin resistance, lower vitamin C status, and higher levels of lipid peroxidation and circulating inflammatory biomarkers. When their α-tocopherol pharmacokinetics were evaluated following the oral ingestion of deuterium-labeled α-tocopherol, metabolic syndrome persons actually had slower rates of α-tocopherol disappearance. These rates remained slower even after α-tocopherol disappearance rates were normalized to circulating lipids. While slower lipoprotein clearance could contribute to slower α-tocopherol elimination, data showed that α-tocopherol was poorly enriched into chylomicrons and VLDL. This resulted in an overall lower α-tocopherol bioavailability and suggested that intestinal and hepatic inflammatory responses impair α-tocopherol trafficking along the gut-liver axis.

Many studies have considered the impact of oxidative stress on α-tocopherol disappearance. An alternative approach to evaluate the antioxidant function of α-tocopherol is to consider its dose- and time-dependent impact on oxidative stress. Seminal studies by Roberts and colleagues demonstrated that F2-isoprostanes are lowered in a time-dependent manner by α-tocopherol in persons with hypercholesterolemia. However, it required a minimum of 16 weeks at a dose of 3200 IU/d. In a dose-response study (0, 100, 200, 400, 800, 1600, and 3200 IU/d), a minimum of 1600 IU/d was required to lower F2-isoprostanes by 35%, whereas 3200 IU lowered F2-isoprostanes by 49%. These data were deemed important for the planning of interventions in which α-tocopherol would be applied to improve morbidities that are driven by oxidative stress, particularly lipid peroxidation.

6.3.2 Non-Antioxidant

6.3.2.1 α-Tocopherol

Separate from the direct antioxidant function of α-tocopherol, it may also function in cell signaling. Protein kinase C is involved in cell proliferation and differentiation and may be inhibited by α-tocopherol in smooth muscle cells, monocytes, and platelets. Other proteins altered in expression by α-tocopherol include VCAM-1 and ICAM-1, which influence cardiovascular disease risk. Vitamin E has also been suggested to regulate both COX-1 and phospholipase A2.
Treatment with α-tocopherol dose-dependently increased the production of vasodilator prostanoids (prostaglandin I₂ and prostaglandin E₂) in human aortic endothelial cells, which occurred by inhibiting COX activity without affecting the expression of COX-1 or -2. An anti-inflammatory benefit of α-tocopherol supplementation to lower C-reactive protein and monocyte interleukin-6 concentrations was also observed in healthy persons and type 2 diabetics. In agreement, α-tocopherol decreased TNF-α from activated human monocytes as well as NF-κB binding activity. In one study, however, NF-κB was inhibited by α-tocopherol succinate, but not by either α-tocopherol or α-tocopheryl acetate. In contrast, a separate study showed that dietary α-tocopheryl acetate supplementation decreased hepatic NF-κB activation in a rodent model of phenobarbital-induced oxidative stress.

6.3.2.2 γ-Tocopherol

γ-Tocopherol, as well as its physiological metabolite, γ-CEHC (γ-carboxyethyl-hydroxy-chroman; Figure 6.3), is also reported to exhibit anti-inflammatory activity. γ-tocopherol and γ-CEHC inhibited COX activity in lipopolysaccharide-stimulated macrophages and interleukin-1β-stimulated epithelial cells. However, the γ-CEHC concentrations (10–50 µmol/L) used in these experiments exceeded physiological concentrations. γ-Tocopherol treatment also decreased the synthesis of prostaglandin E₂ and leukotriene B₄ at the site of inflammation in a rodent model of arthritis. Further, γ-tocopherol supplementation, but not α-tocopherol, inhibited protein nitration and spared vitamin C in rats subjected to zymosan-induced inflammation.

In humans, animals, and in vitro models, γ-tocopherol has been shown to be nitrated by reactive nitrogen species to yield nitro-γ-tocopherol (5-NO₂-γ-tocopherol; Figure 6.3). γ-Tocopherol, but not α-tocopherol, readily scavenges reactive oxides due to the subtle structural differences between these vitamers in that γ-tocopherol has an unsubstituted position on the chromanol head (Figure 6.1). Indeed, nitro-γ-tocopherol is the major product formed from the reaction between γ-tocopherol and peroxynitrite. It has been suggested that nitro-γ-tocopherol is a biomarker of nitrative stress and/or γ-tocopherol functions to protect other biomolecules, such as tyrosine, from nitration.

In patients with coronary artery disease, nitro-γ-tocopherol was elevated in the plasma and in carotid-artery atherosclerotic plaques. Measures from post-mortem brains of Alzheimer’s patients showed increased nitro-γ-tocopherol levels. Cigarette smoke is rich in both reactive oxygen species and nitric oxide. Not only does smoke exposure in vitro provoke the formation of nitro-γ-tocopherol, but it also decreases nitric oxide levels in vivo.
of nitro-γ-tocopherol, plasma concentrations of nitro-γ-tocopherol in smokers are approximately double those from nonsmokers.23

6.4 DIETARY SOURCES

6.4.1 Food

Vitamin E biosynthesis occurs in plants, thereby making it nutritionally essential for humans and animals. α- and γ-Tocopherol are the predominant vitamin E forms found in food.54 Figure 6.4 illustrates the α- and γ-tocopherol content in some commonly consumed foods. Notably, α-tocopherol is most abundantly found in almonds, safflower oil, sunflower seeds, and canola oil, whereas abundant sources of γ-tocopherol include certain vegetable oils (soybean and canola) and nuts (walnuts, peanuts, pecans). In the typical American diet, however, α-tocopherol is consumed limitedly.55 The majority of α-tocopherol is largely ingested from relatively non–nutrient dense foods that are not particularly rich in α-tocopherol, but their frequency of consumption is relatively high. For example, cakes, cookies, and pies are leading dietary contributors of α-tocopherol. Further, due to the high consumption of γ-tocopherol–rich food items in the American diet, it is estimated that γ-tocopherol represents nearly 70% of the total vitamin E intake.56 This is attributed to the number of food products formulated with soybean oil.57

6.4.2 Dietary Supplements

The majority of vitamin E supplements contain α-tocopherol, although γ-tocopherol supplements are increasingly common. The latter, however, generally contain a mixed tocopherol/tocotrienol formulary with γ-tocopherol as the predominant form. Regarding α-tocopherol, most supplements and fortified foods contain synthetic α-tocopherol (all rac-α-tocopherol, commonly labeled as dl-α-tocopherol) rather than naturally occurring α-tocopherol (RRR-α-tocopherol, labeled as d-α-tocopherol). Although natural and synthetic compounds are similar in their bioactivity for many

FIGURE 6.4 α- and γ-tocopherol content of select foods.
dietary supplements, this is not the case with α-tocopherol. α-tocopherol has three chiral centers (carbon positions 2, 4', and 8′; Figure 6.1), which yields eight stereoisomers (2R forms: RRR, RSR, RSS, RRR; 2S forms: SSR, SSR, SRS, SSS). Synthetic α-tocopherol supplements actually contain eight equimolar amounts of each stereoisomer, whereas naturally occurring α-tocopherol is exclusively RRR-α-tocopherol. 

The issue surrounding natural versus synthetic α-tocopherol concerns their substantial difference in bioavailability. Intestinal absorption and chylomicron enrichment or secretion does not differ between natural and synthetic α-tocopherol forms. However, the liver actually discriminates between these forms to potentiate natural α-tocopherol bioavailability compared with synthetic α-tocopherol. This liver-level discrimination between α-tocopherol forms is attributed to the α-tocopherol transfer protein, which facilitates the preferential secretion of RRR-α-tocopherol or 2R forms of α-tocopherol as part of very low-density lipoprotein (VLDL). By contrast, 2S forms of α-tocopherol have limited affinity toward the α-tocopherol transfer protein and are not appreciably secreted as part of VLDL but are rather directed toward catabolism to form α-CEHC. The difference in bioavailability between natural and synthetic α-tocopherols was illustrated in several studies performed in healthy humans who simultaneously ingested equal amounts of deuterium-labeled natural (d₆-RRR-α-tocopheryl acetate) and synthetic (d₆-all rac-α-tocopheryl acetate) α-tocopherols. In these studies, plasma concentrations of naturally occurring α-tocopherol (d₆-α-tocopherol) were approximately two times higher than those of synthetic α-tocopherol (d₆-α-tocopherol). Moreover, plasma d₆-α-CEHC and urinary d₆-α-CEHC were significantly higher (1.7–4.7 times) than that of d₆-α-CEHC. This supports that synthetic α-tocopherol is limited in its bioavailability because it is preferentially catabolized (synthesis of CEHC is discussed further under “Hepatic Metabolism”).

### 6.5 HUMAN REQUIREMENTS AND DIETARY INTAKE

Vitamin E dietary requirements exist only for α-tocopherol because the other seven vitamin E forms are poorly recognized by the α-tocopherol transfer protein and are not interconverted to α-tocopherol. The Recommended Dietary Allowance (RDA) for men and women is 15 mg/day of α-tocopherol. This intake level achieves circulating α-tocopherol concentrations that limit hydrogen peroxide–induced erythrocyte lysis. Dietary requirements also consider the stereochemistry of α-tocopherol. Since 2S-stereoisomers of α-tocopherol are not well maintained in plasma or tissues, they do not contribute to vitamin E requirements, and thus, dietary recommendations only consider 2R-stereoisomers.

Since vitamin E is a lipophilic, chain-breaking antioxidant, it would be expected that diets rich in PUFAs would increase vitamin E requirements. Although studies in humans are lacking, those in animals indicate that vitamin E deficiency occurs more readily when dietary lipid unsaturation is increased. This has led to the suggestion that at least 0.6 mg of α-tocopherol per gram of PUFA should be ingested, but studies in humans are needed to confirm this benefit.

Compared with dietary recommendations, most Americans fail to consume diets with adequate α-tocopherol. Indeed, >90% of American men and women do not consume diets that meet the Estimated Average Requirement (EAR; 12 mg/d) for α-tocopherol. Data from the National Health and Nutrition Examination Survey also indicate that median α-tocopherol intakes from food alone for men and women (19–30 years) were only 9.4 and 6.4 mg, respectively. However, these values might be underestimated due to several measurement errors. These include underreporting of total energy and fat intake, the amounts of fats and oils used in food preparation, the uncertainty of the specific oils consumed, and inaccuracies in the food composition databases. Nonetheless, Americans likely do not meet dietary α-tocopherol recommendations, and the available data concerning intakes are likely inaccurate.

Because diet assessment is limited for evaluating α-tocopherol adequacy, circulating α-tocopherol is an important biomarker of status that must be considered. An observation made in humans undergoing chronic depletion of α-tocopherol was that overt clinical deficiency did not occur
but that the susceptibility of hydrogen peroxide–induced hemolysis was greater when circulating α-tocopherol decreased to <12 µmol/L. In the United States, <1% of adults who are non-users of dietary supplements have circulating α-tocopherol <12 µmol/L, suggesting that vitamin E deficiency is not much of concern. However, if >30 µmol/L α-tocopherol is used as a cut-off of adequacy, then inadequate vitamin E status occurs in >80% of the population. This cut-off level has potential relevance because it is associated with the EAR of α-tocopherol, and data from large-scale observational studies suggest that α-tocopherol at >30 µmol/L is associated with a lower risk of mortality. While this makes for a compelling case to achieve higher circulating α-tocopherol, caution is needed in interpreting α-tocopherol as a biomarker of adequacy. This is because hyperlipidemia likely “traps” α-tocopherol in the circulation, resulting in physiological deficiency at target tissues. For this reason, it has been indicated that novel biomarkers of α-tocopherol adequacy are needed.

6.6 BIOAVAILABILITY

6.6.1 DIGESTION AND ABSORPTION

Since vitamin E is lipophilic, its absorption from the intestinal lumen is dependent on the same processes that enable fat digestion and uptake into the enterocytes (Figure 6.5). In addition to pancreatic esterases that are required to cleave fatty acids from triglycerides, bile acid secretion is equally important to promote the formation of mixed-micelles that enable vitamin E absorption. In fact, the absence of either results in poor vitamin E absorption, which is why vitamin E deficiency occurs in patients secondary to biliary obstruction, cholestatic liver disease, pancreatitis, or cystic fibrosis.

Following enterocyte uptake, vitamin E absorption into the lymphatic system is dependent on chylomicron synthesis and secretion (Figure 6.5). In the enterocytes, chylomicrons containing...

FIGURE 6.5 Vitamin E bioavailability. Dietary vitamin E, including all tocopherols and tocotrienols, are similarly incorporated into micelles, absorbed at the small intestine, and packaged into chylomicrons prior to lymphatic transport. Chylomicrons containing newly absorbed vitamin E can be catabolized by lipoprotein lipase to facilitate the transfer of vitamin E to peripheral tissues or lipoproteins. The majority of vitamin E, as part of a chylomicron remnant, is taken up at the liver in a receptor-mediated process. The liver, through the actions of α-tocopherol transfer protein (α-TTP), then preferentially packages and secretes VLDL containing mostly α-tocopherol (α-T) into the circulation. Other vitamin E forms (E) are secreted from the liver to a much lesser extent and are otherwise directed for elimination as vitamin E catabolites (i.e., CEHCs; carboxyethyl-hydroxychromanols).
triglycerides, cholesterol, phospholipids, and apolipoprotein are synthesized. During that process, vitamin E is incorporated into chylomicrons and secreted into the lymph (Figure 6.5). In healthy individuals, the absorption of vitamin E was estimated to range between 15% and 45% when using radioactive α-tocopherol. However, in thoracic-duct-cannulated rats, the absorption of vitamin E became less efficient with increasing amounts of α-tocopherol ingested. The bioavailability of α-tocopherol was examined in healthy humans who consumed test meals of varying lipid amounts (0–11 g fat) along with deuterium-labeled $\text{RRR-}\alpha$-tocopherol (22 mg) that was impregnated into apple pieces. Data indicated that dietary fat dose-dependently increased α-tocopherol bioavailability, with up to a threefold increase when 11 g of fat was co-ingested with the deuterium-labeled α-tocopherol. Further, at least 33% of the dose was absorbed during the 11-g fat trial, and because there was a linear relationship between dietary fat level and absorption, it was estimated that 0.33 mg of α-tocopherol was absorbed for each gram of fat consumed. However, despite demonstrating the importance of total fat on α-tocopherol bioavailability, the optimal quantity or type of fat was not determined in these studies.

6.6.2 Hepatic Secretion

Differences in plasma concentrations between various vitamin E forms were initially attributed to differences in intestinal absorption. However, the application of deuterated tocophers provides an understanding that differences in circulating vitamin E forms are not attributable to their enterocyte uptake or their secretion as part of chylomicrons. The liver is actually responsible for the preferential secretion of α-tocopherol into the plasma, with VLDL containing newly absorbed vitamin E (primarily as α-tocopherol).

Hepatic discrimination of the various vitamin E forms is attributed to the function of the α-tocopherol transfer protein. This protein was first identified by Catignani and Bieri, purified and characterized from liver, and later crystallized. The α-tocopherol transfer protein is expressed mainly in the liver and functions to preferentially transfer/secrete α-tocopherol from the liver (Figure 6.5) to the plasma by a mechanism that is incompletely understood. In comparison to α-tocopherol, other vitamin E forms bind with significantly less affinity to this protein (Table 6.2), thus explaining the hepatic discrimination of various vitamin E forms. In the absence of functional α-tocopherol transfer protein, such as in α-tocopherol transfer protein knock-out mice or humans with a genetic defect, the result is vitamin E deficiency.

### Table 6.2

<table>
<thead>
<tr>
<th>Vitamin E Form</th>
<th>α-Tocopherol Transfer Protein Binding Affinity (% of $\text{RRR-}\alpha$-Tocopherol)</th>
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<tbody>
<tr>
<td>$\text{RRR-}\alpha$-Tocopherol</td>
<td>100</td>
</tr>
<tr>
<td>β-Tocopherol</td>
<td>38</td>
</tr>
<tr>
<td>γ-Tocopherol</td>
<td>9</td>
</tr>
<tr>
<td>δ-Tocopherol</td>
<td>2</td>
</tr>
<tr>
<td>α-Tocopherol acetate</td>
<td>2</td>
</tr>
<tr>
<td>α-Tocopherol quinone</td>
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</tr>
<tr>
<td>$\text{SRR-}\alpha$-Tocopherol</td>
<td>11</td>
</tr>
<tr>
<td>α-Tocotrienol</td>
<td>12</td>
</tr>
</tbody>
</table>


Note: The α-tocopherol transfer protein has the highest binding affinity for naturally occurring stereoisomer of α-tocopherol ($\text{RRR-}\alpha$-tocopherol).
6.6.3 Hepatic Metabolism

Hepatic excretion of \( \alpha \)- and \( \gamma \)-tocopherol occurs via two predominant pathways. They can either be excreted intact or in their oxidized forms into bile. Alternatively, tocopherols can be catabolized in a cytochrome P450-dependent manner to yield a final excretory product, CEHC (\( \alpha \)- or \( \gamma \)-carboxyethyl-hydroxychroman; Figure 6.3) that is eliminated in either the urine or bile. Tocopherol metabolism occurs predominately in the liver. The specific P450 enzyme responsible for initiating the metabolism of tocopherols has been widely investigated,\(^{86-90}\) with evidence pointing to cytochrome P450 4F2.\(^{91,92}\) Tocopherol metabolism is initiated by \( \omega \)-hydroxylation of the phytyl tail, followed by several cycles of \( \beta \)-oxidation that each remove two carbon units from the phytyl tail until the final product, CEHC, is produced. CEHC is then often glucuronidated or sulfated prior to biliary or urinary excretion.

\( \alpha \)- and \( \gamma \)-tocopherols are catabolized at different rates. This was exemplified in healthy humans who ingested equal amounts of deuterium-labeled \( \alpha \)- and \( \gamma \)-tocopherol.\(^{93}\) Data show that plasma \( \gamma \)-tocopherol disappeared three times faster than \( \alpha \)-tocopherol. Further, plasma deuterium-labeled \( \alpha \)-CEHC was undetectable, whereas plasma deuterium-labeled \( \gamma \)-CEHC was readily detectable. The rates of disappearance of \( \gamma \)-CEHC and \( \gamma \)-tocopherol were also similar, suggesting that \( \gamma \)-tocopherol disappearance is largely attributed to its P450-mediated metabolism.

Although the diet contains mostly \( \gamma \)-tocopherol, human plasma contains significantly more \( \alpha \)-tocopherol compared with \( \gamma \)-tocopherol. This is explained by the higher binding affinity of the \( \alpha \)-tocopherol transfer protein to \( \alpha \)-tocopherol compared with \( \gamma \)-tocopherol (Table 6.2). Since \( \gamma \)-tocopherol is not well recognized by the \( \alpha \)-tocopherol transfer protein, it is more actively metabolized to \( \gamma \)-CEHC than \( \alpha \)-tocopherol is catabolized to \( \alpha \)-CEHC.\(^{93}\) In fact, plasma \( \gamma \)-CEHC concentrations are generally in the range of 50–150 nmol/L, whereas \( \alpha \)-CEHC concentrations are either low (<5 nmol/L) or undetectable in non-users of dietary supplements.\(^{62}\) However, \( \alpha \)-tocopherol supplementation not only increases circulating \( \alpha \)-tocopherol, it also increases \( \alpha \)-CEHC.\(^{94}\) Increased urinary \( \alpha \)-CEHC is also predicted by higher intakes of \( \alpha \)-tocopherol, which supports its potential use as a biomarker of \( \alpha \)-tocopherol adequacy.\(^{95}\) Because CEHC is a truncation of the tocopherol’s phytyl tail, CEHC retains antioxidant activity,\(^{96}\) but whether this is important to human health is unclear.

6.7 Deficiency

Dietary intakes of \( \alpha \)-tocopherol are rarely low enough in the American diet to induce vitamin E deficiency symptoms (\( \gamma \)-tocopherol is not essential). The first reports of vitamin E deficiency in children were characterizations of children with fat malabsorption syndromes such as abetalipoproteinemia, cholestasis, and cystic fibrosis.\(^{76}\) In vitamin E-deficient persons without any apparent lipid absorption or lipoprotein metabolism dysfunction,\(^{97}\) they had a defect in the gene that encodes the \( \alpha \)-tocopherol transfer protein. Thus, vitamin E could be absorbed, packaged into chylomicrons, and taken up by the liver (Figure 6.5), but could not be secreted from the liver due to the absence of the hepatic \( \alpha \)-tocopherol transfer protein. In \( \alpha \)-tocopherol transfer protein-knockout mice, vitamin E deficiency occurs in association with reproductive difficulties.\(^{15}\) These mice are also more susceptible to atherosclerosis. Oxidative stress, induced by hyperoxia, also decreases \( \alpha \)-tocopherol transfer protein mRNA expression, but without affecting protein expression.\(^{98}\) Zinc deficiency in rats decreased \( \alpha \)-tocopherol absorption and plasma \( \alpha \)-tocopherol concentrations,\(^{99}\) but it is unclear if zinc is required for \( \alpha \)-tocopherol transfer protein expression. Importantly, dietary protein is critical for maintaining vitamin E status consistent with protein restriction in rats decreasing mRNA and protein levels of the \( \alpha \)-tocopherol transfer protein in association with decreased \( \alpha \)-tocopherol concentrations.\(^{100}\)

6.8 Toxicity

The tolerable upper limit (UL) of intake for vitamin E is 1000 mg/d.\(^{1}\) Below this threshold is considered to pose limited adverse risk or health effects in nearly all individuals of the general population.\(^{101}\) In agreement, no important adverse effects have been attributed to vitamin E intakes.
up to 3200 IU/d.\textsuperscript{102} In contrast, a meta-analysis investigating the health benefits of α-tocopherol supplementation in a variety of populations (i.e., patients with cardiovascular disease, renal failure, and Alzheimer’s) suggested a lower dietary threshold (<400 IU) to minimize adverse effects.\textsuperscript{103} However, these findings have been disputed by several reports.\textsuperscript{104–108} For example, in a meta-analysis that similarly used the clinical endpoint of “all-cause mortality” (n = 57 randomized-controlled trials with >246,000 participants), a relative risk of 1.0 was reported for the relationship between vitamin E supplementation (up to 5500 IU/d) and mortality risk.\textsuperscript{105} This indicates that vitamin E neither provided a benefit or detriment. Others also report a lack of relationship between α-tocopherol supplementation (up to 800 IU/d) with all-cause or cardiovascular-related mortality.\textsuperscript{106–108} In a meta-analysis that used a function index of vascular health, it was suggested that α-tocopherol supplementation improves brachial artery flow-mediated dilation and that a significant inverse relationship was observed between pre-supplementation plasma α-tocopherol concentrations and the improvement of vascular function.\textsuperscript{109}

### 6.9 α- AND γ-TOCOPHEROL INTERACTIONS WITH VITAMIN C

Despite vitamin C being water soluble and vitamin E being fat soluble, these antioxidants can interact.\textsuperscript{110} Ascorbic acid either spares α-tocopherol from oxidation\textsuperscript{24,111,112} or regenerates a reduced α-tocopherol from its oxidized form (α-tocopheroxyl radical) via a recycling mechanism.\textsuperscript{110,113} Because α-tocopherol is lipophilic, α-tocopheroxyl radicals form within micellar and bilayer membrane systems and are “recycled” to α-tocopherol by ascorbic acid that is located within the aqueous phase.\textsuperscript{110} Specifically, the α-tocopheroxyl radical likely migrates to the membrane-aqueous interface where it interacts with hydrophilic ascorbic acid.\textsuperscript{118,110}

Demonstration of a vitamin C–vitamin E interaction was not observed in guinea pigs fed two doses of deuterium-labeled α-tocopherol and three doses of ascorbic acid.\textsuperscript{114} This was attributed to a lack of oxidative stress in the guinea pigs that would preclude appreciable oxidation of α-tocopherol. By contrast, findings of a randomized controlled trial indicated that co-supplementation with vitamin C and α-tocopherol, but not individual antioxidants, significantly reduced carotid artery intima-media thickness among hypercholesterolemic male smokers.\textsuperscript{115,116} The interaction between vitamins C and E was further supported by a placebo-controlled trial in smokers and nonsmokers who were provided vitamin C or placebo for 2 weeks prior to the oral administration of deuterium-labeled α- and γ-tocopherols.\textsuperscript{32} During the placebo study arm, plasma disappearance of both α- and γ-tocopherol was faster among smokers compared with nonsmokers. Among the smokers, who had increased plasma F\textsubscript{2α}-isoprostanes that were unaffected by short-term vitamin C supplementation, plasma disappearance rates of α- and γ-tocopherol were normalized to the slower rates observed in nonsmokers. These findings indicated that cigarette smoke–induced oxidative stress accelerated oxidative loss of vitamin E, whereas improved vitamin C status “recycled” α- and γ-tocopheroxyl radicals to their respective tocopherol forms to ameliorate vitamin E disappearance. This work was considered to provide the first direct evidence in vivo that vitamins C and E work together as co-antioxidants.\textsuperscript{117}

### 6.10 ROLE IN CHRONIC DISEASE PREVENTION

Oxidative stress is defined as an imbalance between antioxidant defenses and the magnitude of reactive oxygen/nitrogen species, and is implicated in numerous chronic disorders.\textsuperscript{118} This phenomenon arises from diminished antioxidants, increased reactive oxygen/nitrogen species generation, or in many cases, from a combination of both. Because of vitamin E’s antioxidant function, numerous investigations have assessed its potential role to manage the risk of chronic diseases, particularly heart disease, certain cancers, and Alzheimer’s disease.

#### 6.10.1 CARDIOVASCULAR DISEASE

Heart disease continues to be the leading cause of mortality in the United States with >635,000 deaths annually.\textsuperscript{119} Oxidative stress is well implicated in atherosclerosis.\textsuperscript{120} A key atherogenic initiator is the oxidation of LDL. This occurs in the subendothelial space of the vascular wall following the
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translocation of LDL from the circulation across the single-cell endothelial layer. This prompts macrophage-mediated uptake of oxidized LDL and the formation of lipid-laden foam cells, and drives pro-inflammatory responses that provoke endothelial dysfunction and injury that provoke atherogenesis.

Epidemiological data suggest that circulating α-tocopherol is inversely related to cardiovascular risk.\textsuperscript{121,122} Individuals with coronary risk factors such as hypertriglyceridemia and low HDL also have low circulating α-tocopherol.\textsuperscript{123} The cardioprotective role of α-tocopherol is supported by studies showing that the susceptibility of LDL to oxidation is alleviated by a supplementation regimen that enriches α-tocopherol in LDL.\textsuperscript{124,125} α-tocopherol also inhibits smooth muscle cell proliferation, platelet adhesion and aggregation, and endothelial monocyte adhesion.\textsuperscript{126}

Despite the promise of epidemiological evidence, randomized controlled trials examining α-tocopherol on cardiovascular risk have yielded inconsistent outcomes. Many clinical trials have reported neutral benefits of α-tocopherol, whereas others indicate that α-tocopherol supplementation lowers cardiovascular risk. These include the CHAOS trial,\textsuperscript{127} the SPACE trial,\textsuperscript{128} the Transplant Associated Arteriosclerosis Study,\textsuperscript{129} and the ASAP study.\textsuperscript{115} The CHAOS and SPACE trials evaluated the effects of α-tocopherol alone, whereas the other two investigated co-treatment of α-tocopherol and ascorbic acid. The CHAOS study showed a 47% reduction in coronary artery disease–associated death and nonfatal myocardial infarction by α-tocopherol supplementation. Although it occurred without statistical significance, the SPACE trial reported a 39% decrease in coronary artery disease–related mortality while observing a significant 70% decrease in myocardial infarction rate. In the Transplant Associated Arteriosclerosis Study, α-tocopherol and ascorbic acid co-treatment significantly reduced evidence of atherosclerosis. Similarly, hypercholesterolemic patients from the ASAP study had slower rates of intima media thickening with co-supplementation but not by either antioxidant alone. The benefits of α-tocopherol and ascorbic acid were most pronounced in men who smoked compared with nonsmokers. The Women’s Health Study, a placebo-controlled trial examining α-tocopherol supplementation for 10 years, indicated no cardioprotective benefit of α-tocopherol.\textsuperscript{130} However, among older women (>65 years of age) who represented only 10% of the cohort but accounted for 31% of all study endpoints, there was a significant reduction in major cardiovascular events in association with a 49% lower risk of cardiovascular-related death.

\subsection{6.10.2 Alzheimer’s Disease}

Because lipid peroxidation–related oxidative stress is implicated in Alzheimer’s disease, it has been hypothesized that α-tocopherol would prevent or slow its etiologic progression. This is consistent with brain tissue containing large amounts of PUFAs that are susceptible to lipid peroxidation in agreement with evidence that patients with Alzheimer’s disease have increased concentrations of the lipid peroxidation biomarker malondialdehyde.\textsuperscript{131}

Studies \textit{in vitro} indicate that α-tocopherol attenuates hydrogen peroxide–mediated cytotoxicity\textsuperscript{132} and amyloid β-protein-induced cell death.\textsuperscript{133} Similar benefits also occur in association with limiting NFκB inflammation.\textsuperscript{134} Studies in rodents support that supplementation increases brain α-tocopherol concentrations\textsuperscript{135,136} and improves cognitive performance in aged rats.\textsuperscript{137} Supplementation of α-tocopherol in rodents also alleviates neurotoxin-induced oxidative stress that is otherwise associated with impaired water maze performance.\textsuperscript{138} Others also report that α-tocopherol in rodents protects against brain lipofuscin accumulation\textsuperscript{139} and hippocampal ischemic neural damage.\textsuperscript{140}

A prospective observational study in older adults suggested that vitamin E supplement users have a lower risk of Alzheimer’s disease.\textsuperscript{141} In a separate prospective study, vitamin E from food, but not supplements, and no other antioxidants were associated with a lower risk of Alzheimer’s disease.\textsuperscript{142} Data from participants of the Chico Health and Aging Project also suggested that higher intakes of α-tocopherol equivalents (i.e., vitamin E derived from tocopherols and tocotrienols) were associated with a reduced incidence of Alzheimer’s disease.\textsuperscript{143} α- and γ-Tocopherol were also reported to have independent associations with lower Alzheimer’s disease risk, and intakes of either tocopherol were associated with slower rates of cognitive decline.
Based on these findings, it is not surprising that several randomized controlled trials have investigated vitamin E in the treatment or prevention of Alzheimer’s disease. The PREADViSE trial was concluded as a cohort study, but was initiated as a double-blind randomized clinical trial investigating α-tocopherol, selenium, or their combined use. Neither α-tocopherol alone nor selenium prevented dementia among 3786 persons >60 years of age who continued into the cohort study from an initial population of 7540 men who were enrolled into the intervention. In a separate double-blind, placebo-controlled trial in patients with mild to moderate Alzheimer’s disease, α-tocopherol (2000 IU/d) compared with placebo resulted in slower cognitive decline. This differed from the outcome of another report indicating that α-tocopherol supplementation (2000 IU/d; 3 years) failed to protect against the progression from mild cognitive impairment to Alzheimer’s disease in patients having an amnestic subtype of mild cognitive impairment at the time of enrollment. Consistent with these disparities, it has been suggested that the benefits of α-tocopherol in Alzheimer’s disease patients may be dependent upon whether an antioxidant effect can be observed. A separate line of evidence, which has been investigated limitedly, also suggests that γ-tocopherol may have a role to protect against Alzheimer’s disease. Specifically, γ-tocopherol scavenges peroxynitrite to form nitro-γ-tocopherol (Figure 6.3). In the brain of post-mortem Alzheimer disease patients, levels of 5-nitro-γ-tocopherol were reported to be increased by 2–3-fold.

6.10.3 Cancer

Dietary antioxidants have received attention based on evidence that intakes of fruits and vegetables are inversely related to cancer incidence. Antioxidants such as vitamin E may have an antioxidant benefit consistent with oxidative stress disrupting apoptotic processes and provoking DNA damage. Most studies examining vitamin E on cancer risk have focused on α-tocopherol, although γ-tocopherol has received some attention. Regardless of the vitamin E form, there is a lack of evidence to support an anti-cancer benefit of α-tocopherol in humans, although studies in vitro are generally supportive.

6.10.3.1 Lung and Prostate Cancers

The ATBC trial tested whether α-tocopherol and β-carotene supplementation, alone and in combination, would protect against lung cancer development in a cohort of >29,000 male smokers. One of the largest nutrition interventions in history, this trial was terminated prematurely because β-carotene increased lung cancer incidence; α-tocopherol had no effect on lung cancer incidence. In a secondary analysis of the ATBC trial, α-tocopherol was suggested to lower prostate cancer incidence among those receiving supplements. This preventative effect of α-tocopherol was lost, however, when data were examined from the post-intervention follow-up period, suggesting that the benefits ceased when supplementation was terminated. In the CARET trial, which provided β-carotene and retinol for a potential benefit on lung cancer risk, it was observed that low serum α-tocopherol was associated with a higher risk of prostate cancer. These findings and others led to the planning of SELECT, which examined prostate cancer incidence in >35,000 men who were randomized in a double-blind, placebo-controlled manner to receive selenium and α-tocopherol (alone and in combination) for 7–12 years. After a median follow-up period of 5.5 years, neither selenium nor vitamin E, alone or in combination, affected prostate cancer risk. Because interim data analysis indicated that supplementation was unlikely to yield a favorable outcome, SELECT was terminated, and participants were instructed to cease using supplements. However, data collection continued during the post-intervention follow-up phase. Compared with placebo, the prior use of α-tocopherol supplements alone was associated with a 17% higher risk of developing prostate cancer. These outcomes were disappointing because evidence in vitro indicated favorable effects of α-tocopherol on prostate cancer risk. Separate evidence also supports that γ-tocopherol inhibits prostate tumor cell growth to a greater extent than α-tocopherol, and that γ-tocopherol induces
apoptosis in androgen-responsive prostate cancer cells while dysregulating sphinolipid metabolism in association with increased death of prostate cancer cells.\textsuperscript{160}

6.10.3.2 Colon Cancer

The gastrointestinal tract is thought to be a major site on which antioxidants could exert protective benefits.\textsuperscript{161} Epidemiological studies examining vitamin E relative to colon cancer risk have been inconsistent, although patients with colon cancer often have lower circulating vitamin E concentrations.\textsuperscript{162,163} Secondary analysis of the ATBC trial suggested a lower incidence of colorectal cancer, but a greater frequency of cancers of the stomach.\textsuperscript{151} Findings of the Women’s Health Study similarly indicated that long-term \( \alpha \)-tocopherol supplementation had no effect on the incidence of total cancer, including colon cancer as well as cancer-related mortality.\textsuperscript{130} These works in relation to other studies have suggested that perhaps \( \gamma \)-tocopherol has greater potential compared with \( \alpha \)-tocopherol for colon cancer prevention,\textsuperscript{164} but this has not been rigorously examined through controlled trials.

6.11 CONCLUSIONS

Considerable effort has been invested to establish vitamin E requirements, define its trafficking and metabolism along the gut-liver axis, and understand its potential role to alleviate chronic disease risk. Clear evidence supports its antioxidant function, especially in relation to terminating the cyclic progression of lipid peroxidation, and its interaction with the antioxidant vitamin C. Despite these mechanistic insights, the available evidence is less clear regarding its role to manage chronic disease risk. This suggests that dietary \( \alpha \)-tocopherol supplements may have limited benefit for most individuals and that focus is needed to target those persons with compromised vitamin E status. Depending on the index of adequacy used, up to \( \sim \)80\% of Americans may have suboptimal circulating \( \alpha \)-tocopherol even though overt vitamin E deficiency is rarely observed. Because a substantial proportion of Americans fail to achieve recommended intakes of dietary \( \alpha \)-tocopherol, and often obtain it from foods that are low in \( \alpha \)-tocopherol, dietary modification is encouraged to obtain \( \alpha \)-tocopherol from \( \alpha \)-tocopherol-rich foods (Figure 6.4). Further study is also needed to establish the health benefits of \( \gamma \)-tocopherol. Despite \( \gamma \)-tocopherol having antioxidant activity in humans, it is not actively maintained in the circulation relative to \( \alpha \)-tocopherol but rather preferentially catabolized to \( \gamma \)-CEHC. Future studies need to examine the independent and additive benefits of \( \gamma \)-tocopherol and \( \gamma \)-CEHC, and whether \( \gamma \)-tocopherol has a clear health-promoting role that can be demonstrated through carefully controlled clinical trials.

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