The Virtual Free Radical School

Tocopherol (Vitamin E) in Health and disease

by

VERIS

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The worldwide VERIS Research Information Service disseminates nutritional information, emphasizing the potential health-enhancing benefits of antioxidants and botanicals. VERIS began in 1985 as one of the first science-based resources for information on natural ingredients found in dietary supplements and foods, and continues to serve in this role as a credible communications resource.

Tocopherol (Vitamin E) in Health and disease

Overview: Vitamin E is an essential fat-soluble vitamin. Recently, the National Academy of Sciences defined vitamin E as the 2*R* stereoisomers of alpha-tocopherol. However, past classifications of vitamin E included a group of eight compounds – alpha-, beta-, gamma- and delta-tocopherols and tocotrienols. The naturally occurring *d*-alpha-tocopherol has the highest biological activity. **This presentation will review functions, absorption and transport, intake and requirements, forms, deficiency states and safety of vitamin E.** This presentation will also provide an overview of the current research status of vitamin E's role in preventing or minimizing oxidative damage associated with the development of cancer, coronary heart disease, cataracts and Alzheimer's disease.

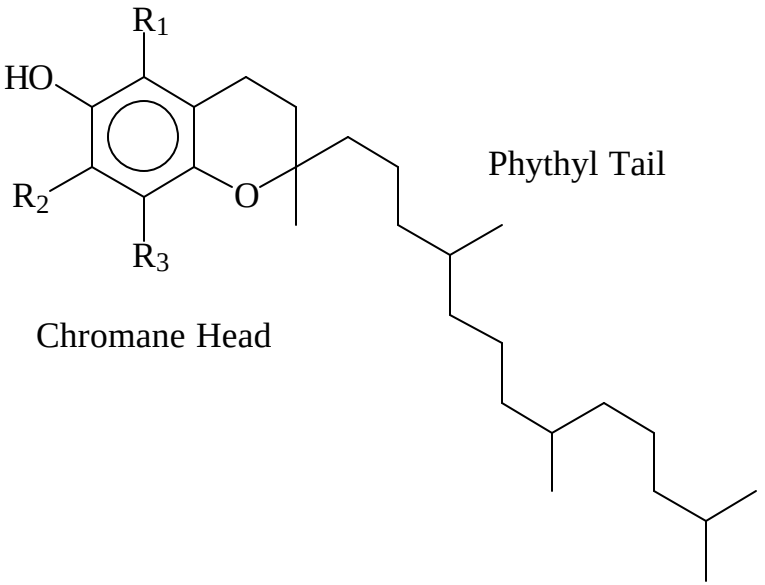
Functions of Vitamin E

- Chain-breaking antioxidant
- Protects cell membranes
- Enhances immune response
- Regulates platelet aggregation
- Regulates protein kinase C activation

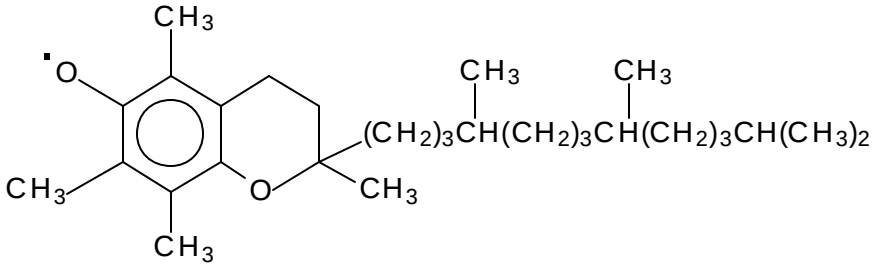
Notes to Functions

- Vitamin E is the major chain-breaking antioxidant in body tissues and is the first line of defense against lipid peroxidation, protecting cell membranes from free radical attack through its free radical quenching activity.
- Vitamin E protects polyunsaturated fats in cell membranes that are important for membrane structure and function.
- Increased intake of vitamin E enhances immune response.
- Vitamin E regulates platelet aggregation by inhibiting platelet cyclooxygenase activity and thus decreases prostaglandin production. It also has a role in regulation of protein kinase C activation.

Vitamin E as an antioxidant



R· + TOH ¾ ® RH + TO·



	R_1	R_2	R_3
α	CH_3	CH_3	CH_3
β	CH_3	H	CH_3
γ	H	CH_3	CH_3
δ	H	H	CH_3

Absorption and Transport

- Dependent on ability to absorb fat
- Absorbed into lymphatic system
- Component of chylomicrons
- Alpha-tocopherol is major tocopherol in plasma
- Positive association between serum lipid and tocopherol levels
- Normal range is 0.5-1.6 mg/dl

Notes to Absorption and Transport

The ability of an individual to **absorb vitamin E is dependent on the ability to absorb fat.**

Vitamin E is absorbed into the lymphatic system from the intestines and enters the blood as a component of the chylomicrons. **The majority of vitamin E in plasma is in the low-density lipoproteins.** Alpha-tocopherol is the major tocopherol in adult plasma and accounts for approximately 87% of the total tocopherol concentration.

There is a positive association between serum lipid levels and tocopherol levels. **Vitamin concentrations in body tissues vary considerably.** Adipose tissue and adrenal glands have the highest levels. Vitamin E levels in plasma range from 0.5-1.6 mg/dl in normal populations. In general, a 10-fold increase in vitamin E intake will double plasma concentrations.

Clinical Deficiency States

- Susceptible groups
  - Patients with malabsorption syndromes
  - Premature infants
  - Patients on TPN
- Characterized by progressive neurological syndrome
  - Gait disturbances
  - Absent or altered reflexes
  - Limb weakness
  - Sensory loss in arms and legs
- Improved neurological function with vitamin E therapy

Notes to Clinical Vitamin E deficiency

A. Malabsorption Syndrome

Clinical vitamin E deficiency that is alleviated by vitamin E administration is seen in individuals with chronic malabsorption syndrome, premature infants and patients on total parenteral nutrition (TPN).

Conditions that interfere with normal digestion, absorption or transport of fat have been associated with low serum levels of vitamin E. Serum vitamin E concentrations can be less than 20% of normal in individuals with **malabsorption syndromes** such as celiac disease, cystic fibrosis and biliary atresia.

Patients with abetalipoproteinemia (an inherited disorder marked by absence of lipoproteins in the blood and low levels of chylomicrons) frequently have very low serum vitamin E concentrations, below measurable levels.

Notes to Clinical Vitamin E deficiency

B. Neurological Syndrome

A progressive **neurological syndrome** can develop due to long term, severe vitamin E deficiency and is characterized by gait disturbances, absent or altered reflexes, limb weakness and sensory loss in the arms and legs. Symptoms of neurological dysfunction develop within 18-24 months in children with vitamin E deficiency but symptoms in vitamin E-deficient adults usually require 10-20 years of fat and vitamin E malabsorption. **Neurological function has been shown to improve with appropriate vitamin E therapy** and progressive neurological damage may be prevented by initiation of vitamin E therapy at an early age in children with chronic cholestatic disease.

Notes to Clinical Vitamin E deficiency

C. Premature Infants

Newborn infants, especially those that are premature, are susceptible to vitamin E deficiency due to inadequate body stores, impaired absorption and reduced transport capacity in the blood due to low LDL levels at birth.

Plasma vitamin E levels are frequently low in patients on total parenteral nutrition as the major source of vitamin E in the parenteral solution is the fat emulsion, which provides primarily γ- and δ-tocopherols that are much less biologically active forms of tocopherol.

Thus, alpha-tocopherol supplementation is required for patients on total parenteral nutrition.

Sources, Intakes and Requirements

- Vegetable oils, sunflower seeds and nuts are the richest dietary sources
- Average daily intake is 15 I.U. in men and 11.4 I.U in women (NHANES III)
- DRI and RDA is 15 mg alpha-tocopherol (22.5 I.U.)
- Optimal vitamin E intakes may be 100-400 I.U. per day

Notes to Sources, Intakes and Requirements

A. Sources

The richest dietary sources of vitamin E are vegetable oils (primarily soy, sunflower and corn oils), sunflower seeds and nuts.

Results of a national survey (NHANES III) showed an average daily vitamin E intake of 10 mg (15 I.U.) for men and 7.6 mg (11.4 I.U.) for women. However, a number of individuals in the survey had intakes considerably below the average.

Notes to Sources, Intakes and Requirements

B. Requirements

Determination of **vitamin E requirements** is complicated by whether requirements should focus only on prevention of deficiency symptoms or on amounts necessary to prevent lipid peroxidation. In studies of healthy individuals consuming diets considered to be adequate, supplementation with vitamin E in amounts considerably above those needed to prevent deficiency resulted in a significant decrease in a marker of oxidative damage.

Notes to Sources, Intakes and Requirements

C. Recommendations

The 1989 **Recommended Dietary Allowance** (RDA) for vitamin E was 10 mg (15 I.U.) for men and 8 mg (12 I.U.) for women. The 2000 RDA, which is also the **Dietary Reference Intake** (DRI) for vitamin E, is 15 mg alpha-tocopherol (22.5 I.U.) for both men and women.

Dietary vitamin E intakes of 10-30 mg per day will maintain serum vitamin E concentrations in the normal range. However, a number of studies have shown that vitamin E intakes considerably above these recommended levels have a beneficial role in prevention of chronic diseases and conditions in which free radical-mediated cell damage is implicated in their development. Additional dose-dependent studies will help to determine optimal vitamin E intakes, which may be in the range of 100-400 I.U. per day.

Efficacy of Natural-Source *vs* Synthetic Vitamin E

- Natural-source is a single isomer (d-alpha-tocopherol)
- Synthetic is a mixture of eight isomers
- Natural-source has twice the bioavailability of synthetic

Notes to Natural-Source *vs* Synthetic Vitamin E

Vitamin E is the exception to the paradigm that natural and synthetic vitamins are equivalent. **Natural-source vitamin E** (RRR-alpha-tocopherol or d-alpha-tocopherol) is derived from vegetable oils and is a single isomer. Synthetic vitamin E (all-rac-alpha-tocopherol or dl-alpha-tocopherol) **is a mixture of eight isomers**, only one of which is d-alpha-tocopherol. The 2000 National Academy of Sciences report recognizes four of the eight isomers (2R isomers) to have vitamin E activity and the other four isomers to have none.

Research suggests that the lungs, red blood cells, blood plasma and brain demonstrate preferential retention of natural-source vitamin E. Physiological differences between natural-source and synthetic vitamin E relate to preferential retention of d-alpha-tocopherol in blood and tissues compared to other tocopherols. Human studies using deuterated tocopherols have shown that **the bioavailability of natural-source vitamin E is approximately twice that of synthetic vitamin E.**

Protective Role in Disease Prevention

There is extensive evidence implicating oxidative damage in the development of degenerative diseases and conditions. A number of studies have evaluated the role of vitamin E, alone or in combination with other antioxidants, in preventing or minimizing oxidative damage associated with development of cancer, coronary heart disease, cataracts and Alzheimer's disease.

Cancer

- Majority of epidemiologic studies showed an inverse association between vitamin E status and subsequent risk of certain cancers
- Intervention trials have shown mixed results
  - Reduced cancer incidence and decreased mortality rate from stomach and esophageal cancers in China
  - No decrease in recurring colorectal tumors in U.S.
  - Improvement in precancerous oral lesions in U.S.
  - Decreased incidence and mortality of prostate cancer but not lung cancer in Finland

Notes to Cancer

Results of **animal studies suggest that vitamin E and other antioxidants alter cancer incidence and growth** by acting as anticarcinogens, quenching free radicals or reacting with their products.

Numerous studies have examined the relationship between levels of vitamin E and other antioxidants and cancer incidence. The majority of epidemiologic studies have shown an inverse association between dietary vitamin E intakes or serum concentrations and the subsequent risk of certain cancers. However, a protective effect of vitamin E may not be fully demonstrated in all epidemiologic studies evaluating serum vitamin E concentrations and cancer risk as the range of dietary intake of vitamin E in a specific population may be narrow.

Notes to Cancer

A limited number of **intervention trials** have also evaluated the **role of vitamin E and other antioxidants in cancer prevention**, with mixed results. In a large study in China, there was a decreased incidence of cancer, and reduced mortality from stomach and esophageal cancer in the group supplemented with vitamin E, beta-carotene and selenium. There was no evidence that beta-carotene or vitamins C and E decreased the incidence of new colorectal tumors in a U.S. study of patients who had a colorectal tumor removed before entering the study.

In a multi-center U.S. trial that evaluated vitamin E treatment in patients with precancerous lesions in the oral cavity, almost one-half had clinical responses (at least 50% disappearance of lesions) and another one-fourth had histologic responses (improvement in the degree of abnormal tissue). Vitamin E supplementation decreased the incidence and mortality rate of prostate cancer but not lung cancer in a primary prevention trial in Finland.

Coronary Heart Disease

- Increased vitamin E intakes associated with decreased risk of coronary heart disease in epidemiologic studies
- Dose-dependent resistance of LDL to oxidation with vitamin E supplementation
- In 2 of 3 secondary prevention trials, vitamin E showed protective effects

Notes to Coronary Heart Disease

Results of animal studies suggest that vitamin E and other antioxidants alter cancer incidence and growth by acting as Animal studies and **epidemiologic data suggest that reduced antioxidant protection may increase the risk of coronary heart disease and increased intake of vitamin E and other antioxidants may have a role in prevention of the disease.** The majority of epidemiologic studies have shown that increased vitamin E intakes or blood levels are associated with a decreased risk of coronary heart disease. In two large Harvard-based epidemiologic studies, subjects who took daily vitamin E supplements of 100 I.U. or more for at least two years had a significantly reduced risk of coronary heart disease compared to subjects who did not supplement with vitamin E.

Notes to Coronary Heart Disease

Supplemental vitamin E intakes have been shown to decrease the susceptibility of low-density lipoprotein (LDL) to oxidative damage. Oxidative modification of LDL is implicated in the initiation of coronary heart disease. Resistance of LDL to oxidation increased in a dose-dependent manner during vitamin E supplementation. The maximum effect of vitamin E in decreasing susceptibility of LDL to oxidation was observed at daily intakes of at least 400 I.U.

Notes to Coronary Heart Disease

A limited number of intervention trials have also evaluated the **effects of supplementation with vitamin E, alone or in combination with other antioxidants, on risk or progression of coronary heart disease** in various groups, with mixed results.

In three secondary prevention trials of vitamin E supplementation, in which patients had diagnosed coronary heart disease or were at high risk for the disease, a U.K. study showed protective effects against subsequent heart attacks, a study in Italy showed some benefits and the third conducted in a number of countries showed no significant benefits.

Based on a review of all available research evidence, **vitamin E may have a role in prevention of coronary heart disease**, the leading cause of death in developed countries.

Cataracts

- Vitamin E delayed or minimized cataract development in animal models
- Epidemiologic data suggest a relationship between blood vitamin E levels and cataract risk
- Decreased cataract risk associated with vitamin E supplementation

Notes to Cataracts

Oxidative damage is considered to be an early, significant event in the development of most cases of senile cataract, which affects the elderly and is the most common type of cataract. Results of **animal studies have shown that vitamin E is able to arrest and reverse cataract development to some extent.** In isolated animal lenses and in a number of animal models, vitamin E delayed or minimized cataract development induced by experimental oxidative stress.

Epidemiologic data suggest an inverse relationship between blood levels of vitamin E and other antioxidants and cataract risk. Two studies showed a significant decrease in cataract risk in subjects who regularly took vitamin E supplements compared to those who did not. Leading investigators who have studied the relationship between nutrition and cataracts have suggested that although moderate supplementation with **vitamin E will not prevent cataracts, it may delay the onset and slow the progression of cataract development**.

Alzheimer's Disease

- Increased vitamin E intakes or blood levels associated with reduced risk of Alzheimer's disease
- Vitamin E or selegiline slowed disease progression in multicenter trial
- Current practice guidelines recommend vitamin E or selegiline for patients with moderate disease
- Vitamin E may be preferred from a safety standpoint

Notes to Alzheimer's Disease

Oxidative damage is also implicated in brain aging and in development of certain degenerative conditions affecting the brain, such as Alzheimer's disease. **Studies have shown that increased intakes or blood levels of vitamin E were associated with reduced risk of Alzheimer's disease.**

A multicenter two-year trial evaluated the effects of vitamin E or the drug selegiline on disease progression in patients with moderately severe Alzheimer's disease. Study results showed that either vitamin E or selegiline slowed the progression of the disease compared to the placebo group. The researchers concluded that cost and convenience may be involved in treatment decisions since both vitamin E and selegiline were effective.

Notes to Alzheimer's Disease

The Alzheimer's Disease Cooperative Study has initiated a three-year multicenter trial in patients with mild cognitive impairment to evaluate whether vitamin E can prevent or delay the clinical diagnosis of Alzheimer's disease.

Current clinical practice guidelines from the American Psychiatric Association recommend that vitamin E or selegiline be considered for patients with moderate Alzheimer's disease to delay the mental deterioration and that vitamin E may be preferred from a safety standpoint.

Safety

- Few side effects in double-blind, controlled human studies
- Could affect blood clotting in patients on blood thinners
- No other specific side effects
- UL set at 1,000 mg per day for adults
- Vitamin E is safe and well tolerated over wide range of intakes and time periods

Notes to Safety

Since vitamin E intakes considerably above those needed to prevent deficiency are taken by many individuals over long periods of time to help prevent free radical-mediated conditions and diseases and to maintain health, safety is an important consideration. In double-blind, placebo-controlled human studies, very few observed side effects were seen with oral daily intakes of 600-3200 I.U. for three weeks to six months. **Side effects associated with vitamin E were also uncommon in other human studies.**

Notes to Safety

Although high vitamin E intakes have not been demonstrated to cause abnormalities in blood clotting in normal adults, they may intensify an existing blood coagulation defect produced by vitamin K deficiency due to malabsorption or blood thinners. In two clinical trials of patients on blood thinning drugs, vitamin E intakes of 100 or 400 I.U. in one study and 800 or 1,200 I.U. in the other study did not significantly affect blood clotting in these groups. Based on potential effects of vitamin E on blood clotting, **the Tolerable Upper Intake Level (UL)** set by the National Academy of Sciences in 2000 for all forms of alpha-tocopherol **is 1,000 mg per day for adults**. Since vitamin E supplementation could potentially affect blood clotting in patients on blood thinners, high vitamin E dosages may be contraindicated for these patients or should be used only under medical supervision.

Except for a vitamin K interaction in patients on blood thinners, there are no specific side effects associated with vitamin E intake. Thus, based on a review of both animal and human data, oral vitamin E is safe and well tolerated over a wide range of intakes and over long periods of time.

Summary

- Increasing research evidence implicates oxidative damage in development of various degenerative diseases and conditions.
- As the major fat-soluble antioxidant, vitamin E is protective against oxidative damage.
- The majority of epidemiologic evidence suggests that increased intakes or blood levels of vitamin E are associated with decreased risk of certain types of cancer, coronary heart disease, cataracts and Alzheimer's disease.
- A limited number of intervention trials have shown mixed but frequently beneficial effects of vitamin E supplements at intakes considerably above levels required to prevent deficiency symptoms.
- Research results suggest that the bioavailability of natural-source vitamin E is approximately twice that of synthetic vitamin E.
- A review of safety data has shown that oral vitamin E is safe and well tolerated over a wide range of daily intake levels.

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