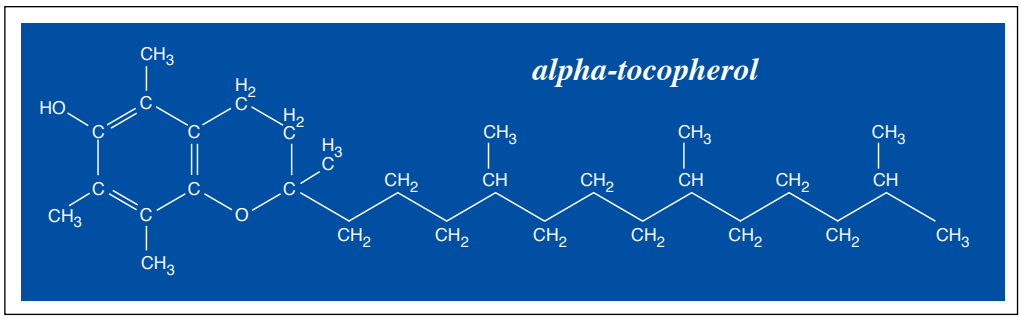
Mixed Tocopherols

Introduction

Vitamin E is a generic term used to describe all tocopherol and tocotrienol derivatives that exhibit the biological activity of alpha-tocopherol. While alpha-tocopherol is considered to be responsible for the majority of the biological action of vitamin E, beta-, gamma-, and delta-tocopherol also occur naturally in food. Tocopherols are oily, yellow liquids found in the seeds, leaves, and other lipid-containing parts of plants. Alpha-tocopherol is found largely in the chloroplasts of plant cells, while other tocopherols are found primarily outside of the chloroplasts. This compartmentalization implies different activities for the various tocopherol molecules in plants.

Vitamin E is known for its antioxidant, immune-enhancing, anti-inflammatory, and anti-platelet aggregation effects. Vitamin E is used clinically to prevent cardiovascular disease, cancer, cataracts, complications of diabetes, and to improve immune function. Although the majority of research has been on alpha-tocopherol, investigations are being performed on the contributions of beta-, gamma-, and delta-tocopherol to the action of vitamin E.



Pharmacokinetics

Tocopherols are absorbed in the small intestine (primarily the jejunum) by passive diffusion. After absorption, tocopherols enter the lymphatic system and are subsequently transported to the liver in chylomicrons. In the liver, they are bound to tocopherol transfer protein for distribution to other tissues. Tocopherols concentrate in adipose compartments of various tissues such as the liver, heart, adrenal glands, brain, and nervous system. Tocopherols are excreted through the feces, skin, and urine.

Although gamma-tocopherol is the most abundant tocopherol in the American diet, alpha-tocopherol is found in the serum and red blood cells of healthy volunteers in the highest concentration.[1] Gamma-tocopherol is also found in both plasma and red cells, while beta- and delta-tocopherol are found in the plasma only in minute amounts.

The predominance of alpha-tocopherol in the serum appears to be due to its preferential binding to tocopherol transfer protein.[2] Because of this binding affinity, most of the absorbed beta-, gamma-, and delta-tocopherol is secreted into bile and excreted in the feces. Alpha-tocopherol is largely excreted in the urine. Supplementation with high doses of alpha-tocopherol has been shown to deplete the plasma levels of gamma-tocopherol,[3] and may do the same with other tocopherols.

Mechanisms of Action

A major biochemical activity of tocopherols is protection from free radicals and products of oxygenation. Specifically, tocopherols appear to detoxify lipid peroxy radicals, as well as block the reactivity of singlet oxygen radicals.[4] Vitamin E works in conjunction with other antioxidant nutrients to quench free radicals. Vitamin E also inhibits lipoxygenase, an enzyme responsible for the formation of pro-inflammatory leukotrienes. Tocopherols appear to inhibit platelet aggregation through inhibition of protein kinase C[5] and increased action of nitric oxide synthase.[6]

Anti-cancer actions of vitamin E have demonstrated a difference in activity for individual tocopherols. Alpha-tocopherol inhibits production of protein kinase C and collagenase,[7] two enzymes that facilitate cancer cell growth. Gamma-tocopherol has been shown to have superior growth inhibitory effect on human prostate cancer cell lines when compared to alpha-tocopherol.[8] Delta-tocopherol has exhibited growth inhibitory activity against mouse mammary cancer cell lines, while alpha- and gamma-tocopherol has not.[9]

Clinical Indications

Cardiovascular Disease

Epidemiological studies have demonstrated an inverse relationship between vitamin E intake and cardiovascular disease risk.[10,11] However, randomized and controlled trials have reported conflicting results as to whether vitamin E supplementation reduces atherosclerosis progression and cardiovascular disease events.[12,13] Recent studies looking at mixed tocopherols for the prevention of cardiovascular disease have indicated mixed tocopherols may have a stronger inhibitory effect on lipid peroxidation than alpha-tocopherol alone.[14] Mixed tocopherols were also superior to alpha-tocopherol in protecting rat myocytes from hypoxia-reoxygenation damage.[15] Another study showed the combination of alpha-, gamma-, and delta-tocopherol inhibited human platelet aggregation and lipid peroxidation more than the three tocopherols in isolation, suggesting a synergistic platelet-inhibitory effect.[6]

In the Cambridge Heart Antioxidant Study (CHAOS), 202 patients with angiographically proven atherosclerosis were given d-alpha-tocopherol (800 IU per day, 400 IU per day, or placebo) While vitamin E (alpha-tocopherol) reduced the risk of nonfatal myocardial infarction by 77 percent, there was a non-significant excess of cardiovascular deaths in the vitamin E group. Most deaths, however, occurred in the early period after diagnosis; when early deaths were excluded there were fewer deaths among vitamin E-supplemented individuals. All causes of mortality were also not significantly higher in the vitamin E group.[16] In a follow-up trial, no beneficial preventive effect was seen with supplementation of 400 IU per day vitamin E for 4.5 years.[12]

Treatment of patients with intermittent claudication with 300 IU d-alpha-tocopherol acetate for 2-5 years improved walking distance compared to vasodilating or anticoagulant medications.[17]

Cancer Prevention

Supplementation of male smokers for 5-8 years with 50 IU d,l-alpha-tocopherol led to a 32-percent reduction in prostate cancer incidence and a 41-percent reduction in prostate cancer mortality compared to placebo.[18] A non-significant, 22-percent reduction in colon cancer incidence was also seen in the treatment group in this trial.[19] Vitamin E, in combination with other antioxidant vitamins, has been shown to reduce the recurrence rate of bladder cancer[20] and colorectal adenomas[21] compared to placebo. A number of animal and *in vitro* studies have outlined the anti-cancer potential of vitamin E.[22,23] Several mechanisms of vitamin E are considered important in this regard, including stimulation of wild-type p53 tumor suppressor gene, down-regulation of mutant p53, activation of heat shock proteins, and an anti-angiogenic effect mediated by blockage of transforming growth factor-alpha.[22]

Gynecological Conditions

In women with dysmenorrhea, supplementation with 50 mg alpha-tocopherol three times per day for two menstrual cycles reduced symptoms in 68 percent of women, compared with 18 percent of those taking placebo.[24] Another double-blind trial found supplementation with 400 IU vitamin E per day improved symptoms of premenstrual syndrome.[25] In breast cancer survivors, supplementation with 800 IU per day led to a significant reduction in hot flash symptoms compared to women taking placebo.[26]

HIV/AIDS

Research in murine AIDS using a 15-fold increase in dietary vitamin E (160 IU/L liquid diet) demonstrated normalization of immune parameters that are altered in HIV/AIDS.[27] Vitamin E has also been shown to protect against bone marrow toxicity, a well established side effect of AZT.[28] A study of the effects of d-alpha-tocopherol on bone marrow cultures from stage IV AIDS patients revealed similar findings.[29]

Immunity

Vitamin E may enhance certain clinically-relevant *in vivo* indexes of T-cell-mediated function in healthy elderly persons. In 88 free-living, healthy subjects at least 65 years of age, 200 mg per day vitamin E improved antibody response to various vaccines. No adverse effects were observed with vitamin E supplementation. [30] Vitamin E may enhance resistance to viral diseases, as was shown in a study of 209 elderly subjects. Higher plasma vitamin E levels correlated with a reduced number of infections over a three-year period.[31]

Diabetes

Fuller et al found vitamin E, at a dosage of 1,200 IU daily in the form of tocopheryl acetate, elicited significant reductions in LDL oxidation, but had no significant effect on lowering plasma glycosylated protein or glycosylated hemoglobin in diabetes.[32] Kuznetsov et al found normalization of lipid peroxidation in hypertensive diabetics with alpha-tocopherol acetate.[33] Douilet et al found a significant protective effect of vitamin E and selenium on the kidneys of diabetic rats. Plasma lipid peroxides, glucose, and triglycerides were also decreased.[34] Cary and McCarty report on 19/20 diabetic patients who had improvement or no progression of retinopathy when supplemented with 500 mcg selenium, 800 IU vitamin E, 10,000 IU vitamin A, and 1 g vitamin C daily for several years.[35]

Researchers divided 80 diabetics suffering from complications into four groups. One group served as the control group; one received lipoic acid 600 mg daily; one received 1,200 IU d-alpha-tocopherol; and the fourth received 100 mcg selenium. All groups treated with antioxidants showed significant diminution of urinary albumin and thiobarbituric acid (a reactive species and indicator of oxidative processes). Neuropathy symptoms regarding thermal and vibratory senses were significantly improved.[36]

Drug-Nutrient Interactions

High doses of vitamin E might potentiate the effects of drugs that interfere with platelet aggregation or blood clotting, such as warfarin. It may be advisable to reduce the dosage of supplemental vitamin E when taking these medications, or adjust the dosage of both warfarin and vitamin E for optimal therapeutic effect.

Side Effects and Toxicity

The toxicity of oral vitamin E supplementation is understood to be quite low. Supplementation with 3,200 IU vitamin E for nine weeks was well tolerated in one double-blind trial, with the only adverse effects reported being intestinal cramps and diarrhea.[37] Patients who self-administered 100-800 IU vitamin E for an average of three years were found to have no significant toxic effects, including no abnormalities of the liver, kidneys, blood sugar, or coagulation pathways.[38]

One published case report from 1974 described a patient taking warfarin who developed prolonged bleeding times on self-administration of 1,200 IU vitamin E per day.[39] This abnormality resolved on discontinuation of vitamin E. However, two clinical trials, one double-blind, did not find any reduction of warfarin effect with vitamin E administration at doses up to 1,200 IU.[40,41] A complete review of the toxicity of vitamin E supplementation can be found in Bendich and Machlin.[42]

Dosage

The optimal supplementation dosage of mixed tocopherols is undetermined, and no specific recommendations have been made; however, 200 - 1,200 IU is the most commonly prescribed dosage. The recommended daily intake of vitamin E (d-alpha tocopherol) is 22.4 IU, and the suggested upper limit is 1,490 IU daily.[43] The synthetic form of vitamin E, d,l-alpha tocopherol, is one-half the potency of natural d-alpha-tocopherol; therefore, the dosage of synthetic vitamin E should be adjusted accordingly.

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