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A MINI-OVERVIEW OF VITAMIN E

By
TOSSON A. MORSY[1*] and ABDULLAH D. ALANAZI[2]**
Faculty of Medicine, Ain Shams University, Cairo 11566, Egypt[1] and Department of Biological Science and Humanities, Shaqa University, P.O. Box 1040, Ad-Dawadimi 11911, Saudi Arabia[2] (*Correspondence: tossonmorsy@ med.asu.edu.eg or morsy egypt 2014@gmail.com, orcid.org/0000-0003-2799-2049 & **aalanazi@su.edu.sa)

Abstract

Vitamin E (tocopherol) is a fat-soluble vitamin with antioxidant properties; it protects cell membranes from oxidation and destruction, found in a variety of foods including oils, meat, eggs, and leafy vegetables. Their serums levels are strongly influenced by concentration of serum lipids, and do not accurately reflect tissue vitamin levels. Effective vitamin E levels are calculated as the ratio of serum alpha-tocopherol per gram total lipids.

Absorption of dietary vitamin E requires effective pancreatic exocrine function and fat absorption, unless provided in a synthetic water-soluble form. Also, a specific protein (alpha-tocopherol transfer protein) is required for effective transport and use. Signs and symptoms of vitamin E deficiency include hemolysis, neuromuscular disorders, ataxia, and peripheral neuropathy. Because of an abundance of tocopherols in the human diet, its deficiency is rare except in individuals with pancreatic insufficiency or other conditions causing substantial fat malabsorption, or protein-energy malnutrition and may be caused by rare genetic defects affecting vitamin E metabolism or transport. No syndrome of acute vitamin E toxicity has been described. In premature infants, high-dose vitamin E treatment was associated with increased risk for sepsis. Chronic intake of supplements in excess of 400 IU daily has been associated with increased risk of hemorrhage and all-cause mortality.

Key words: Vitamin E, Action, Requirements, Deficiency, Toxicity, Therapeutic role

Introduction

Vitamins are a number of chemically unrelated families of organic substances that cannot be synthesized by humans but need to be ingested in the diet in small quantities to prevent metabolism disorders. They are divided into water-soluble and fat-soluble vitamins (Tab. 1).

Evans and Bishop (1922) discovered a substance that was deficient in rats fed a diet that contained lard and that resulted in infertility (Traber, 2000). The deficiency was corrected when a lipid extract of cereals was added to the diet; this was termed the "anti-sterility factor" (Evans, 1963). In 1925, vitamin E was officially recognized as the fifth vitamin. A few years later the name tocopherol from the Greek word of "toc" (child) and "phero" (to bring forth) was coined to describe its role as an essential dietary substance in normal fetal and childhood development. In 1969, the FDA formally recognized vitamin E as an essential nutrient for humans. Vitamin E is a fat-soluble compound and an antioxidant and protects cell membranes from oxidation and destruction (Mason, 1980). It is the collective term for four tocopherols (α-, β-, γ-, and δ-tocopherols) and four tocotrienols (α-, β-, γ-, & δ-to cotrienols) found in food, with antioxidant activities, but cannot be interconverted, and only α-tocopherol meets the human vitamin E requirement (Traber, 2007).

Review and Discussion

Sources: Vitamin E is found in a variety of foods including oils, meat, eggs, and leafy vegetables. Its major dietary sources are vegetable oils and nuts as well as soybean, sunflower, corn, walnut, cottonseed, palm, and wheat germ oils contain relatively higher amounts (more than 50mg vitamin E/100g oil) of vitamin E than other oils (Sheppard *et al*, 1980).

Chemistry: There are a number of biologically active vitamin E compounds in nature. Approximately eight naturally occurring vitamin E compounds were described, including alpha-, beta-, gamma-, and delta- tocoph-

erol. The only forms of tocopherol that are efficiently maintained in human plasma are four of the many isomers of α-to-copherol (RRR-, RSR-, RRS-, & RSS- α-to-copherol, which are present in "all racemic" synthetic vitamin E; only the RRR-form is present in foods). These are the forms of vitamin E that are most biologically active, and are the forms to which the Recommended Daily Allowances apply. Synthetic vitamin E supplements containing all the eight isomers of α-tocopherol (All racemic) has approximately half of the activity of "natural source" vitamin E. However, all of the isomers of α-tocopherol may contribute to the potential adverse effects of supplemental vitamin E, and are included in the calculation of an upper limit for supplementation (Huang and Appel, 2003). Gamma-tocopherol is transported less efficiently than α-tocopherol, but is more abundant in the US diet, so similar tissue levels are achieved from dietary vitamin E. Pharmacological doses of α-tocopherol taken in supplements reduce levels of gamma-tocopherol in plasma (Burton *et al,* 1983).

Actions: Vitamin E works as a free radical scavenger, protecting polyunsaturated fatty acids (PUFA), a major structural component of the cell membranes, from peroxidation. In the past few decades, there was an increasing interest in the role of free radicals and anti-oxidants in atherosclerosis and carcinogenesis (Jialal *et al,* 1995). Deficiency of vitamin E has been connected to cardiovascular events. Low-density lipoprotein (LDL) plays a central role in these hypotheses. When LDL is exposed to oxidative stress, it undergoes a cascade of changes affecting the vascular endothelium, thereby facilitating atherogenesis (Hodis *et al,* 1995). This theory is referred to as the oxidative modification hypothesis, and has fueled epidemiologic studies and clinical trials in cardiology to determine the role of antioxidants, such as vitamin E, in prevention and treatment of atherosclerotic cardiovascular disease (Stampfer and Rimm, 1995). However, trials of vitamin E supplementation have generally showed no effect in heart disease prevention.

Gamma-tocopherol has unique anti-inflammatory activities, mediated by reductions in prostaglandin E2 (Jiang *et al,* 2000). High doses of vitamin E (as α-tocopherol) reduce levels of gamma-tocopherol, perhaps explaining the adverse effects of pharmacological doses of vitamin (Rimm *et al,* 1993).

Some functions of vitamin E are independent of the antioxidant/radical scavenging activity, including inhibition of cell proliferation, platelet aggregation, and monocyte adhesion. Several other effects at the molecular level have been identified, but the clinical implications of these actions have not been established (Zingg and Azzi, 2004).

Metabolism: Like other fat-soluble vitamins, bioavailability of vitamin E depends upon physiologic mechanisms for fat digestion and absorption. This process requires lipolytic function of pancreatic enzymes (Traber *et al,* 1990). Pancreatic esterases are the enzymes responsible for breaking down the tocopheryl-ester bonds between vitamin E and fatty acids (Nakamura *et al,* 1975). Within the intestinal mucosal cells, chylomicrons are produced from phospholipids, triglycerides, apolipoproteins, and fat-soluble vitamins. Synthesis of chylomicrons is needed for transport of vitamin E via the liver lymphatic system (Cohn *et al,* 1988a). Within hepatocytes, chylomicron remnants are broken down by lysosomes, and RRR- α-tocopherol is preferentially secreted into the bloodstream, packaged within VLDL molecules. The transport protein for α-tocopherol is named α-tocopherol transfer protein (A-TTP) (Cohn *et al,* 1988b)

Requirements: Dietary vitamin E content is variable and proportional to vegetable oil intake. American diets of 2000 to 3000 kcal /day contain 7 to 10mg of α-tocopherol equivalents. However, this is likely an underestimate because dietary fat intake is commonly under-reported.

Healthy population: The United States National Academy of Sciences Food and Nutri-

tion Board recommended 15mg of dietary α-tocopherol units per day for adolescents and adult men and women. This is the equivalent of 22 International Units (IU) of "natural-source" vitamin E (RRR- α-tocopherol), or 33 IUs of the synthetic form (all-rac-alpha-tocopherol). In children, the recommended daily allowance rises from 6mg at 1 to 3 years of age to 15mg by 14 to 18 years. Although the requirements are stated in terms of α-tocopherol equivalents, a substantial portion, which provided as gamma-tocopherol if dietary sources are used. So, dietary vitamin E has advantages over vitamin E taken as a supplement (Yoshida *et al,* 1992).

Cholestatic disease: Patients with cholestasis or pancreatic exocrine insufficiency are at risk for vitamin E deficiency because of malabsorption of fat and fat-soluble vitamins. The patients with cholestasis also tend to have hyperlipidemia, which strongly influences vitamin E levels, so assessment of their vitamin E status requires simultaneous measurement of alpha-tocopherol and serum lipids (Traber *et al* 1986). If vitamin E deficiency is diagnosed, these patients are treated with large oral doses of vitamin E. Water-miscible vitamin E (d-α-tocopherol glycol 1000 succinate, TPGS) is most effective in these patients. However, water-miscible preparations have not been shown to be superior for patients with cystic fibrosis who are taking concurrent pancreatic enzyme supplements (Soltani-Frisk *et al,* 2001).

Typical supplementation regimens for infants and children with cholestasis are 25 to 50 int. units/kg/day of vitamin E (α-tocopherol), or 15 to 25 int. units/kg/day of water-miscible vitamin E (Feranchak and Sokol, 2007).

The prevalence of vitamin E deficiency in adults with cholesteric liver diseases has not been well defined. It is probably most common in patients with severe and prolonged primary biliary cirrhosis, in who estimates of vitamin E deficiency range from 10 to 50% (Muñoz *et al*, 1989). For patients with significant cholestasis (e.g., bilirubin >2.0mg/dL), routine monitoring of vitamin E levels is recommended, with vitamin E replacement as needed (Lindor *et al*, 2012).

Deficiency: Vitamin E deficiency is uncommon in humans except in unusual circumstances due to the abundance of tocopherols in the diet. Individuals eating a vegetarian or vegan diet typically are not at increased risk for vitamin E deficiency. Individuals with fat malabsorption and steatorrhea are at risk for deficiency of all lipid-soluble vitamins (Farrell, 1980). These included cirrhosis, cholesteric liver disease, cystic fibrosis, small bowel bacterial overgrowth, and pancreatic insufficiency, celiac disease, and Crohn disease. Deficiency degree is generally proportional to magnitude and steatorrhea duration (Sokol *et al,* 1983).

There are also several genetic disorders that lead to vitamin E deficiency. As an example, a genetic defect in the A-TTP (α-tocopherol transfer protein) is associated with neurologic deficits and is known as ataxia with vitamin E deficiency (AVED). Affected patients have symptoms similar to Friedreich's ataxia (Ben Hamida *et al,* 1993). These patients sometimes respond to oral supplementation of vitamin E in doses of 800 to 1200mg/day. More often, supplementation serves to prevent the disease progression (Sokol, 1993).

In adults and children, vitamin E deficiency can cause neuromuscular disorders and hemolysis. Low serum levels of vitamin E (defined as below 0.5mg/dL) may cause no appreciable symptoms, or may manifest as subtle neurologic abnormalities. Neuromuscular disorders associated with vitamin E deficiency are mostly of the neuropathic and myopathic type (Kumar, 2007). The neuropathy generally consists of a spinocerebellar syndrome, with variable involvement of the peripheral nerves. Clinical manifestations were ataxia, hyporeflexia, and loss of proprioceptive and vibratory sensation (Oski and Barness, 1967). A skeletal myopathy and pigmented retinopathy also might be present (Natta and Machlin, 1972).

Vitamin E deficiency can shorten the lifespan of red blood cells. In premature infants, vitamin E deficiency may cause a hemolytic anemia (Ray *et al,* 2007). Congenital hemolytic disorders such as thalassemia, sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency (G-6-PD), and spherocytosis may be associated with low vitamin E plasma levels, likely because of increased oxidant stress and antioxidant consumption (Walter *et al,* 2006). Oral therapy with vitamin E supplementation may be of benefit, but efficacy was not proved (Rachmilewitz *et al,* 1979).

Excess and toxicity: The long-term effects and the safety of vitamin E supplementation are unclear. Most studies suggest that doses of vitamin E supplementation in doses of 100 to 400 IU per day are safe for most patients (Hathcock, 1997). But, other reports caution against the use of higher doses. One study, for example, found a higher evidence of mortality due to hemorrhagic strokes in vitamin E supplementation. Others were caution against the vitamin E use in patients with an increased propensity to bleeding or on oral anticoagulants as warfarin (Jaja *et al,* 2005). Animal models have showed impaired absorption of fat-soluble vitamins A & K with large vitamin E supplements. Large oral supplements of vitamin E were associated with necrotizing enterocolitis in infants. Vitamin E may impair the hematologic response to iron in children with iron-deficiency anemia (Finer *et al,* 1984).

A meta-analysis examined dose-response relationship between the vitamin E and overall mortality in a total of 19 randomized clinical trials that included a total of 135,967 participants. Doses of vitamin E ranged from 16.5 to 2000 IU/day (median, 400 IU). Vitamin E supplementation with a dose ≥400 IU/day was associated with a significantly increased risk of all-cause mortality (95% CI 3-74 per 10,000 persons). Thus, the patients without special indications should not take vitamin E supplements for the prevention of disease (Miller *et al,* 2005).

Therapeutic Actions: Typical dosing of vitamin E is given in terms of α-tocopherol (15mg of α-tocopherol = 22 IU of natural vitamin E or 33 IU of synthetic vitamin E).

1- Cancer: Various effects of vitamin E were reported on certain cancers, particularly within subgroups such as smokers (Kirsh *et al,* 2006), but randomized trials did not support a protective effect. Randomized trials of vitamin E in cancer prevention include: Women's Health Study followed 39,876 apparently healthy women ages 45 and older for a mean of 10.1 years (Lee *et al,* 2005). Compared with placebo, supplementation with 600 IU of natural-source vitamin E on alternate days had no effect on the incidence of all cancer (relative risk (RR 1.01, 95% CI 0.94-1.08) or on breast cancer (RR 1.00), lung cancer (RR 1.09), colon cancer (RR 1.00), or cancer death (RR 1.12). The Polyp Prevention Study observed no reduction in colorectal polyps among subjects randomized to receive vitamin E (Greenberg *et al,* 1994). The HOPE-TOO trial found no effect of vitamin E supplementation (400IU daily) on cancer incidence nor cancer deaths after a median follow-up of seven years (Lonn *et al,* 2005). An analysis of 7627 women who were free of cancer at random assignment in the Women's Antioxidant Cardiovascular Study did not find effect of vitamin E (600IU every other day) on the cancer incidence after a mean follow-up of 9.4 years (Lin *et al,* 2009). In contrast to these negative trials, the ATBC Cancer Prevention Study observed a 32% decrease in prostate cancer incidence & 41% decrease in prostate cancer mortality among men randomized to 50mg (75 IU) of α-tocopherol (vitamin E) for five to eight years compared with placebo (Heinonen *et al,* 1994).

However, subsequent large randomized trials found no reduction in prostate cancer incidence with vitamin E supplementation: The select trial followed 35,533 men (ages 50 and older for African American men and ages 55 and older for other men) for a median of 5.5 years. Compared with placebo, vit-

amin E supplementation (400 IU daily) had no effect on rates of prostate cancer (hazard ratio [HR] 1.13, 95% CI 0.95-1.35) or total cancer (HR 1.03, CI 0.91-1.17). The Physicians' Health Study II followed 14,641 male physicians ages 50 and older for an average of 8.0 years (Lippman *et al,* 2009). Compared with placebo, vitamin E supplementation (400IU every other day) had no effect on the prostate cancer incidence (HR 0.97, CI 0.85-1.09) or total cancer (HR 1.04, CI 0.95-1.13). Supplementation with vitamin E does not appear to be beneficial in preventing cancer, but Peh *et al.* (2016) concluded that with the concerted efforts in synthesizing novel vitamin E analogs and clinical pharmacology of vitamin E, it was likely that certain vitamin E isoform(s) could be therapeutic agents against human diseases besides cancer. Kaidar-Person *et al.* (2018) reported that the use of pentoxifylline & vitamin E of treatment or prevention of radiation-induced fibrosis in breast cancer patients and that this regimen may reduce RT-associated toxicity.

2- Dermatology, Vitamin E is an important fat-soluble antioxidant used for more than 50 years in dermatology. It is an important ingredient in many cosmetic products, protects the skin from various deleterious effects due to solar radiation by acting as a free-radical scavenger. Experimental studies showed that vitamin E has anti-tumorigenic and photoprotective properties, with a paucity of controlled clinical studies providing a rationale for well-defined dosages and clinical indications of vitamin E usage in dermatological practice (Keen and Hassan, 2016).

3- Cardiovascular disease: Nearly all randomized trials of vitamin E did not show any benefit for primary or secondary prevention of CHD (Vivekananthan *et al,* 2003). Also, vitamin E supplementation may increase the risk of heart failure (Lonn *et al,* 2005). Wang and Xu (2019) added that higher vitamin E may increase the risk of CAD/MI and safety and efficacy of vitamin E supplementation use should be reevaluated. Fan *et al.* (2019) found that genetically elevated vitamin E was associated with increased risk of coronary artery disease, suggested an adverse causality between circulating vitamin E and coronary artery disease.

4- Stroke: The evidence did not suggest that vitamin E supplements protect against stroke. Ascherio *et al.* (1999) in an observational study including 43,738 men, showed no association between supplemental vitamin E (250 IU or more daily) and stroke risk. In the randomized ATBC study, which followed 22,271 male smokers for a median of six years, vitamin E supplementation 50mg (75 IU) had no overall effect on stroke risk. However, in a subgroup analysis, vitamin E increased the risk for subarachnoid hemorrhage and decreased the risk for ischemic stroke particularly in men with hypertension (Leppala *et al*, 2000). Lonn *et al.* (2001) in a study of 732 high-risk patients from HOPE trial, supplementation with vitamin E had no effect on progression of carotid intimal medial thickness over an average follow-up of 4.5 years. However, Salonen *et al.* (2003) in a six-year randomized trial of daily supplementation with vitamin E (136 IU) and vitamin C (250mg slow release) in 520 people showed a significant improvement in the average annual increase in carotid artery intima-media thickness compared with placebo (.010mm vs. .014mm), and clinical implications were unclear. Cheng *et al.* (2018) from observational studies on associations between vitamin E intake & stroke risk remain controversial, they concluded the meta-analysis provides evidence that a higher dietary vitamin E intake is associated with a lower stroke risk.

5- Dementia: Although observational studies suggested that increased dietary intake of vitamin E or vitamin E supplementation might protect against the development of Alzheimer disease and vascular dementia (Engelhart *et al,* 2002), in randomized trials vitamin E supplementation did not appear to affect the risk of dementia (Kang *et al,* 2006). Farina *et al*. (2017) found no evidence that the α-tocopherol form of vitamin E given to

people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD, but, a moderate quality evidence from a single study that it may slow functional decline in AD. Gugliandolo *et al.* (2017) in animal models found that high vitamin E doses and prolonged supplementation seemed to be associated with better Alzheimer results. They added that a higher intake of foods rich in vitamin E, which contain a combination of different forms, was associated with a better cognitive function, but clear results about vitamin E efficacy in AD required.

6- Infection: Studies have reported that supplementation with vitamin E improved the immune response (Serafini, 2000). Such an effect is of particular interest in elderly people, in whom an age-related decline in immune response may increase the risk of infections and their complications. But, clinical trials that have examined the use of vitamin E to prevent infections in the elderly have not found clinical benefits. Large, randomized, placebo-controlled studies did notfind reduction in the incidence of respiratory infections when either institutionalized (Meydani *et al,* 2004) or non-institutionalized elderly patients received daily vitamin E supplements experienced a respiratory infection, those who received vitamin E (200IU/day) had a significantly longer total illness duration (19 vs. 14 days), more symptoms, and a higher frequency of fever and activity restriction (Graat *et al,* 2002). Meydani *et al.* (2018) suggested that on the basis of mechanistic studies showed that biological plausibility, correction of a major cellular dysfunction in older adults, and strong evidence from several animal and a few human studies indicating a reduction in risk and morbidity from infections. Cordero *et al.* (2018) reported that the potential complementary use of vitamin E to ameliorate sensory and autonomic dysfunctions associated with spinal cord injury, and identified promising newcellular and functional targets of its neuroprotective effects.

7- Viral infection: Influenza is an acute infectious disease that exerts a very great effect on human society, causing huge medical and economic losses. Influenza usually occurs in annual seasonal (winter) outbreaks or epidemics (in moderate temperature climates). Moreover, influenza pandemics periodically attack the populations of all continents. People of all ages are affected, but the prevalence is greatest in school-age children. The disease's severe course, complications, and mortality were greatest in infants, elderly, and those with underlying illnesses-chronic pulmonary or cardiovascular diseases, and diabetes mellitus. The severe complications include hemorrhagic bronchitis or pneumonia (primary viral or secondary bacterial). Besides, fulminant fatal influenza viral pneumonia can occur, with death proceeding in as little as 48 hours after the initial flu symptoms (WHO, 2010). The pathogenesis of influenza virus infection is associated with two general processes in the human body: (i) local lung damage due to viral replication in the columnar ciliary epithelium of bronchi and bronchioles, which led to progressive damage of the alveolar cells, bronchopneumonia (viral or combined viral-bacterial), massive bronchitis (including bronchiolitis), and the like, as the major causes of death (Taubenberger and Morens, 2008), (ii) a dramatic inflammatory burst that induces among other processes an increase in reactive oxygen species generation, causing extensive damage in cellular membranes, predominantly in the small vessels, arterioles, and capillaries (Berrri *et al,* 2013). Besides, extra-pulmonary complications affect many organs and tissues, as heart, brain, middle ear, liver, and endocrines, even stomach and kidneys, though was rare (Papic *et al,* 2012). Among the antioxidants tested in influenza virus infections in mice, vitamin E occupies the leading position because of its efficacy in preventing oxidative damage via its free-radical scavenging activity. Although vitamin E is not possessing specific antiviral action, its antioxi-

dant effect probably plays important role in lung and liver protection. Attention should be paid to the synergistic character of antiviral effect of the combination vitamin E and oseltamivir. Vitamin E could be recommended as a component in multitarget influenza therapy (Mileva and Galabov, 2018).

8- Venous thromboembolism: Vitamin E high doses may interfere with vitamin K and affect the coagulation. A secondary analysis from the Women's Health Study found that women randomly assigned to receive 600 IU vitamin E every other day had a lower risk of venous thromboembolism (VTE) than in women received placebo with hazard ratio 0.79, 95% CI 0.66-0.94 (Glynn *et al,* 2007). Lutsey (2012) reported that the evidence suggested a relation between dietary intake and the vitamin E risk was relatively weak overall. Gan *et al.* (2017) highlighted lack of inhibitory effect on platelet aggregation after short-term supplementation of PTT mixture in participants with metabolic syndrome. Other non-antioxidant functions of vitamin E were also presented, as its anti-inflammatory effects, role in prevention of cardio-vascular diseases and cancer, as well as protective functions against neurodegenerative and other diseases (Szymańska *et al,* 2017).

Because of concerns about raised risks of bleeding, the Institute of Medicine recommends a Tolerable Upper Intake Level (UL) for vitamin E consumption from supplements. Recommended upper limit is 1000mg of α-tocopherol daily (approximately 1,500 IU of natural source or 1,100 IU of synthetic vitamin E) for adults without fat malabsorption or other cause of vitamin E malabsorption. The UL in children rises from 200mg/ day at 1 to 3 years to 600mg daily at 9 to 13 years. Because of increasing evidence showed adverse effects of pharmacologic vitamin E doses, it is possible that this UL is too high and not recommend supplementation near this level except when indicated to correct deficiency (Bjelakovic *et al,* 2012).

Therapeutic Actions: The benefit of vitamin E supplementation on cancer, cardiovascular disease, stroke, dementia, and liver diseases (such as nonalcoholic fatty liver disease) continue to be evaluated. A benefit of supplementation in cardiovascular disease appeared to be unlikely.

In premature infants, hemolytic anemia is a common abnormality encountered in the presence of vitamin E deficiency. Vitamin E therapy slightly increases hemoglobin concentrations and reduces the incidence of periventricular hemorrhage (Brion *et al,* 2003). However, the risk of sepsis also was increased with high-dose supplementation, regardless of whether administered by intravenous or oral routes. A few studies suggest some benefit in preventing retinopathy of prematurity, but overall the evidence is inconclusive (Tasman *et al,* 2006).

Association between development of Alzheimer disease and vitamin E deficiency was suggested (Grundman, 2000). But, randomized trials suggest that vitamin E supplementation does not affect the risk of cognitive impairment or dementia, but a possible role in slowing progression of Alzheimer disease (Tabet and Birks, 2000). Although controversial, few studies support potential benefits of vitamin E supplementation in treating cataracts and/or age-related macular degeneration (Evans, 2006). A study suggested benefit in preventing or treating tardive dyskinesia (Lohr, and Caligiuri 1996). A meta-analysis concluded that it may protect against deterioration of tardive dyskinesia, but probably did not improve symptoms (Soares and McGrath, 2001).

Serum vitamin E levels are strongly influenced by concentration of serum lipids, and not accurately reflect tissue vitamin levels (Bieri *et al,* 1983). Thus, effective vitamin E levels are calculated as the following ratio: Effective serum vitamin E level = α-tocopherol/ (cholesterol + triglycerides). A normal ratio is >0.8mg α-tocopherol/gm total lipids. For patients with normal serum lipids levels, serum α-tocopherol levels provide an adequate estimate of vitamin E sufficiency. α-tocopherol levels of less than 0.5mg/dL or

5µg/mL, or 11.5µmol/L are considered deficient. In a USA national survey, the 5th percentile for vitamin E serum levels was 0.62 mg/dL or14.3µmol/L, and the 25th percentile was 0.79mg/dL or 18.5µmol/L (Trevithick *et al,* 1993).

Recommendations

Patients without special indications must avoid taking daily supplements containing high doses (>400 IU) of vitamin E (Grade 2B). Individuals with severe pancreatic insufficiency or cholesteric liver disease may have vitamin E deficiency due to fat malabsorption. For such patients, vitamin E supplementation was recommended (Grade 1 A). Doses of about 25 to 50int. units/kg/ day are generally effective in children. Alternatively, water miscible vitamin E can be used to maximize absorption, at a dose of 15 to 25 int. units/kg/day.

Vitamin E supplementation does not support in prevention or treatment of cancers, cardiovascular and cerebrovascular disease, dementia, and retinopathy of prematurity. Weak evidence suggests a possible role in slowing the progression of Alzheimer disease, tardive dyskinesia, and macular degeneration. In premature infants, vitamin E supplementation may reduce the risk of periventricular hemorrhage, but also increases the risk of sepsis. It does not improve outcomes in healthy children or adults. High-dose supplementation may increase mortality and the risk of hemorrhage.

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Table 1: Water-soluble and fat-soluble vitamins

Vitamins	Function	Deficiency syndrome
Water-soluble		
B1, thiamine	Thiamine pyrophosphate	Beriberi
B2, riboflavin	Flavine adenine dinucleotide	
Niacin, nicotinic acid	Nicotinamide adenine dinucleotide	Pellagra
B6, pyroxidine, pyridoxa	Transaminase cofactor	Anemia
B12, cobalamin	One carbon transfer	Pernicious anemia
Folate	One carbon transfer	Megaloblastic anemia
Biotin	Pyruvate carboxlase cofactor	
Pantothenate	Coenzyme A	
C ascorbate	Antioxidant, collagen synthesis	Scurvy
Fat-soluble		
A	Vision, epithelial differentiation	Xerophthalmia
Retinol		
Retinal		
Retinoic acid		
D	Prohormone for calcium regulation	Rickets, osteomalacia
Cholecalciferol		
Ergocalciferol		
E	Antioxidant	
Tocopherols		
K	Clotting factors, bone proteins	Hemorrhagic disease
Phylloquinone		
Menaquinone		
Menadione		