Vitamin E

Vitamin E		Women	Men	Children		
α-TE/d				2-5 y	6-9 y	10-13 y
Recommended intake	RI	8	10	5	6	7/8
Average requirement	AR	5	6			
Lower intake level	LI	3	4			
Upper intake level	UL	300	300			

Introduction

Vitamin E has traditionally been used as a common term for four tocopherols (alpha-, beta-, gamma-, delta-tocopherol) and four tocotrienols (alpha-, beta-, gamma-, delta-tocotrienol) that were demonstrated to have varying levels of biological activity in experimental animal studies (Traber 2006). However, alpha-tocopherol is the only form that is recognized to meet human requirements. Alpha-tocopherol is a required nutrient for humans because it is needed for prevention of vitamin E deficiency symptoms including neuropathy and hemolytic anemia (Traber and Stevens 2011). In NNR 2012 vitamin E activity is confined to alpha-tocopherol. Previously vitamin E activity has been expressed as alpha-tocopherol equivalents (alpha-TE) also including estimated small amounts of activity suggested by animal experiments to be provided by other tocopherols and tocotrienols.

The naturally occurring form of alpha-tocopherol is RRR-alpha-tocopherol. Synthetic alpha-tocopherol, all-rac-alpha-tocopherol or dl-alpha-tocopherol contains an equal mixture of eight different stereoisomers. All of the stereoisomers have equal antioxidative activities, but only those with the 2R-configuration (RRR-, RSR-, RRS- and SRR) have high biological function activity. Due to lower affinity of 2S-isomers by alpha-tocopherol transport protein (alpha-TTP) relative bioavailability of the synthetic form of alpha-tocopherol is, however, suggested to be only a half of that of the natural alpha-tocopherol (Food and Nutrition Board 2000). This means that only alpha-tocopherol in foods and 2R-alpha-tocopherols in vitamin E preparations contribute vitamin E activity. For commercially available vitamin E preparations, the following conversion factors were suggested: 0.5 for all-rac-alpha-tocopherol, 0.455 for all-rac-alpha-tocopheryl acetate and 0.91 for RRR-alpha-tocopheryl acetate (Burton et al 1998, Horwitt 1999). In older literature 1 alpha-TE corresponds 1.49 IU.

Dietary sources and intakes

Vegetable oils, vegetable oil-based spreads, nuts and seeds, and egg yolk are good food sources of vitamin E. The alpha-tocopherol content is highest in sunflower oil followed by corn and rapeseed oil, olive and soybean oil. In addition vegetable oils contain variable amounts of other tocopherols and tocotrienols. Corn oil, soybean oil and also rapeseed oil are high in gamma-tocopherol. On average approximately half of alpha-tocopherol in the diet of Finnish adults was provided by cereal and bakery products and fat spreads, oils, and dressing (Paturi et al 2008). Among the EPIC study participants from the Nordic countries added fats contributed most to vitamin E (alpha-TE) intake, followed by cereal and cereal products and cakes (Jenab et al 2009). Other important sources were fruits, vegetables and fish and shellfish.

In recent dietary surveys from the Nordic countries mean dietary intake of vitamin E (alpha-tocopherol) among adult populations vary between 7-10 mg per day (Becker and Pearson 2002, Lyhne et al 2005, Pedersen et al 2010, Konstantinova et al 2007, Paturi et al 2008). When expressed per energy intake dietary alpha-tocopherol of adults in the Nordic countries ranges from 7 to 12 mg/10 MJ. During pregnancy intake of vitamin E is higher and most of women use supplements containing vitamin E (Arkkola et al 2006, Prasad et al 2010, Haugen et al 2008). Alpha-tocopherol intake of children ranges between 7 to 11 mg/10 MJ (Lyhne et al 2005, Pedersen et al 2010, Enghart Barbieri et al 2006, Hoppu et al 2010) and do not greatly differ from that of adults.

Physiology and metabolism

The uptake, transport and tissue delivery of alpha-tocopherol involves molecular, biochemical and cellular processes closely related with overall lipid and lipoprotein metabolism (Rigotti 2007). Presence of bile salts, pancreatic enzymes and formation of micelles are prerequisites for vitamin E absorption. In order to obtain maximal absorption vitamin E should be given at meals and both the amount of fat and food matrix influence vitamin E absorption. However, knowledge of vitamin E absorption is incomplete. In balance studies with small radioactive doses of alpha-tocopherol absorption in normal subjects have ranged between 55 to 79% (Traber and Stevenson 2011, Chuang et al 2011), whereas much lower figure of 33% was reported based on observed changes in plasma labeled alpha-tocopherol after administration of stable isotope labeled dose of alpha-tocopherol (Bruno et al 2006). Large individual variation in human responses to vitamin E has been described.

Absorbed vitamin E is transferred within chylomicrons or bound to HDL into the liver where alpha-TTP preferentially binds alpha-tocopherol and is essential for the selective resecretion of alpha-tocopherol (Brigelius-Flohe 2009). The metabolism of vitamin E is tightly regulated and unlike other fat-soluble vitamins there is no toxic accumulation in the liver. Alpha-tocopherol that is not released into circulation is excreted into the bile via transporters upregulated with alpha-tocopherol or it is metabolized via the cytochrome P450 system also regulated with alpha-tocopherol and excreted in bile or urine. The major route of excretion of alpha-tocopherol is feces with small amounts excreted in urine (Chuang et al 2011). Turnover of vitamin E is slow; in a kinetic study with tracer marked RRR-alpha-tocopherol in healthy men and women the mean half-life of the dose in plasma was 44 days and in red blood cells 96 days tracked for 460 days (Chuang et al 2011).

Although no tissue serves as a vitamin E store, depletion of body vitamin E takes decades rather than weeks (Traber 2007). Non-alpha-tocopherols and tocotrienols are rapidly

metabolized thereby preventing their tissue accumulation and limiting increases in their plasma concentrations (Traber 2010). In human tissues alpha-tocopherol is the most common tocopherol and contributes about 90% of the total amount of tocopherols and tocotrienols in plasma (Piironen et al 1983) and 50-80% in other tissues (Burton et al 1998). Recently water-soluble alpha-tocopheryl phosphate has been shown to appear in minute amounts in foods and tissues (Gianello et al 2005).

Main biochemical function of alpha-tocopherol has been suggested to be its antioxidant activity. As a chain-breaking antioxidant alpha-tocopherol may prevent propagation of free radicals in membranes and in plasma lipoproteins (Traber and Atkinson 2007). In addition several other important biological functions including modulation of cell signaling and gene expression are ascribed to vitamin E (Zingg 2007). Alpha-tocopherol may modulate activity of several enzymes most of which are membrane bound or activated by membrane recruitment, especially those affecting cell proliferation, membrane trafficking and metabolism of xenobiotics (Brigelius-Flohe 2009). Genes involved in the metabolism and excretion of vitamin E are regulated by alpha-tocopherol itself. Ultimate biological function of vitamin E remains to be revealed (Brigelius-Flohe and Galli 2010).

Vitamin E is suggested to affect health through its antioxidant activity, immune enhancement, inhibition of platelet aggregation and anti-inflammatory function with much of this evidence relaying on cell studies and findings from animal experiments. Evidence of decreased oxidative stress with alpha-tocopherol supplementation in humans is inconsistent (Dragsted 2008). The effect of vitamin E on biomarkers of oxidative stress appears to depend on the circumstances, most importantly on the level of baseline oxidative stress (Block et al 2008). Differences in the individual responses to alpha-tocopherol are also suggested to arise due to genetic factors (Belisle et al 2009, Farbstein et al 2011).

High vitamin E intake has been associated with prolonged bleeding suggesting that high amount of vitamin E may interfere in the blood clotting system especially with simultaneous use of aspirin or treatment with anticoagulants (Liede et al 1998, Swedish Medical Products Agency 2000). It is hypothesized that sharing the same metabolic pathways vitamin E intake may affect K vitamin status (Booth et al 2004, Traber 2008).

Vitamin E and chronic diseases

Importance of vitamin E has been proposed in several chronic diseases such as cardiovascular diseases, cancer, dementia, as well as other diseases associated with increased oxidative stress and inflammation.

Observational studies have provided some evidence suggesting lower risk of coronary heart disease with higher intake of vitamin E, whereas randomized clinical studies do not, overall, provide support for significant or clinically important effect of vitamin E supplementation on coronary heart disease (Ye and Song 2008, Mente et al 2009) or stroke (Bin et al 2011). However, single beneficial or adverse effects have been reported in some studies. Although supplementation of healthy women with 600 IU (400 mg) of a natural form of vitamin E every other day for 10 years did not affect occurrence of cardiovascular events, a significant 24% decrease in cardiovascular deaths was found, and women aged 65 years benefitted most of the vitamin E supplementation (Lee et al 2005). Those supplemented with vitamin E had

also 21% lower risk for vascular thromboembolism (Glynn et al 2007). Among women at high risk for cardiovascular diseases those with prior cardiovascular disease were suggested to benefit from 600 IU vitamin E supplementation every other day (Cook et al 2007). In another study of high risk population daily supplementation with 400 IU alpha-tocopherol did not prevent major cardiovascular events instead an increased risk for heart failure was found (Lonn et al 2005). In line with the results from the ATBC study (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994) increased risk for hemorrhagic stroke was reported among healthy physicians who received 400 IU (270 mg) alpha-tocopherol every other day for 8 years (Sesso et al 2008).

The significance of vitamin E in cancer prevention has been investigated in several clinical trials, none of which has provided evidence for overall protection from cancer (Goodman et al 2011). The decreased prostate cancer risk associated with 50 mg daily dose of dl-α-tocopheryl acetate (among middle-aged Finnish male smokers (Heinonen et al 1998), has not been supported by findings from other large-scale controlled trials (Jiang et al 2010). On the contrary, in post-trial analyses increased risk of prostate cancer was reported among men who had received a daily supplement of 400 IU all-rac-alpha-tocopherol acetate (270 mg) on average for 5.5 years (Klein et al 2011). Neither there is any evidence from randomized controlled trials that vitamin E supplementation would be effective against other cancers including lung, breast, colorectal and upper gastrointestinal or any other types of cancer when given for 5 to 10 years to middle-aged and elderly men and women in doses ranging from 50 mg of synthetic alpha-tocopherol per day to 400 IU daily amount of natural form alpha-tocopherol (Virtamo et al 2000, Malila et al 2002, Lonn et al 2005, Lee et al 2005, Gaziano et al 2009, Linn et al 2009, Lippman et al 2009). Results from observational studies of alpha-tocopherol in cancer prevention are inconsistent (Ju et al 2010).

There is some evidence from observational studies to indicate a putative role of vitamin E in preventing cognitive impairment, but findings from a few intervention studies have provided little support for that (Morris 2012). In observational studies reduced risk of type 2 diabetes by higher intake of antioxidants was mainly attributed to vitamin E (Hamer and Chida 2007), but beneficial effect of vitamin E supplementation has not been confirmed in randomized trials (Song et al 2009). Observational studies of vitamin E and the risk of cataract and age-related maculopathy have shown mixed results, and only very limited effect of vitamin E supplementation alone or in combination with other antioxidants on incidence or progression of cataracts or age-related macular degeneration have been revealed (Chiu and Taylor 2007). Supplementation with alpha-tocopherol above the recommended levels is suggested to improve immune function and decrease respiratory tract infections, especially in the aged (Wu and Meydani 2008), however, results of a few randomized trials are inconsistent. Individual differences in the effects of vitamin E supplementation on respiratory tract infections are suggested in part to be conveyed by genetic factors (Belishle et al 2010).

Requirement and recommended intake

Vitamin E deficiency due to low dietary intake has not been described in normal, healthy individuals. However, deficiency may be caused due to prolonged fat malabsorption, due to genetic defects in lipoprotein transport or genetic defect in hepatic alpha-tocopherol transfer protein. In addition premature very low birth weight infants are in danger to become deficient and neurological disorders detected in protein-energy malnutrition are suggested to be related with vitamin E deficiency (Traber 2007). In premature children, symptoms such as haemolytic anaemia, trombocytosis and oedema have been reported (Hassan et al 1966).

Clinical symptoms in adults include peripheral neuropathy, ataxia and skeletal myopathy. In adults, prolonged low intakes of vitamin E have been shown to increase haemolytic tendency in vitro without any clinical symptoms (Horwitt et al 1963) a property that can be used as a criterion of vitamin E adequacy.

A new approach to estimate requirement of humans was reported by Bruno et al (2006) based on plasma alpha-tocopherol kinetics study among healthy adults given a 22 mg dose of stable isotope labeled alpha-tocopherol with different amounts of fat. The estimated rate of alpha-tocopherol delivery to tissues was 5 mg per day. Given 33% absorption, the amount of dietary vitamin E needed daily to replace irreversible losses would be $\leq$15 mg/day; with higher absorption, the alpha-tocopherol requirement would be smaller (Bruno et al 2006). These findings seem to support current daily recommended intakes for vitamin E adopted by US Food and Nutrition Board (2000).

In absence of more specific measures, the plasma concentration of alpha-tocopherol is regarded as the most adequate indicator of vitamin E status (Horwitt 1999; Morrissey and Sheehy 1999). Since the plasma lipid level influences the alpha-tocopherol concentration, correction for plasma lipids may be warranted in subjects with high lipid levels when assessing vitamin E status in populations. However, plasma levels may not necessarily display peripheral vitamin E status and may therefore be of limited validity (Huebbe et al 2011).

The vitamin E requirement is partly related to the PUFA intake, since the antioxidant function of vitamin E is critical for the prevention of oxidation of tissue PUFA (Valk and Hornstra 2000). In general higher need of vitamin E at higher intake of PUFA is not a practical problem since most foods rich in PUFA also are rich in vitamin E.

Adults

Among adults, the criteria for establishing requirement and recommended intake are the plasma concentration of alpha-tocopherol or the relationship to PUFA intake. Data from studies by Horwitt et al. (Horwitt 1963) showed an increased haemolytic tendency in subjects with a plasma alpha-tocopherol concentration below 12 µmol/L, corresponding to a tocopherol:total cholesterol ratio of 2.25 µmol/mmol (Commission of the Europe Communities 1993). However, the in vitro haemolytic response was dependent on the PUFA content of the diet and the limited number of subjects makes this limit uncertain. A plasma level above 16.2 µmol/L has been suggested as an indicator of acceptable vitamin E status (Morrissey and Sheehy 1999).

Data from Nordic populations show that average alpha-tocopherol intakes of 6-10 mg per day are associated with mean plasma alpha-tocopherol concentrations of 23-28 µmol/L among adults (Piironen et al 1983, Ylönen et al 2003, Wallström et al 2001, Tomten and Høstmark 2009). Clearly higher concentrations with a range between 33-46 µmol/L have been reported among hyperlipidemic subjects (Sarkkinen et al 1993, Hallikainen et al 2000a, 2000b, Korpela et al 2006, Heggen et al 2010). Among a small group of sub-elite runners with irregular menstrual cycle alpha-tocopherol in serum was low (15.7 µmol/L; 2.7 µmol/mmol total lipids) apparently partly due to low vitamin E intake, 5 mg/day (Tomten and Høstmark 2009) and post-exercise osmotic fragility of erythrocytes was increased at low serum alpha-tocopherol concentration. Low vitamin E status has been observed in high consumers of alcohol (Bjørneboe et al 1988) and occasional cases of neurological symptoms with ataxia

due to vitamin E deficiency have been reported in the Nordic countries (Gjerde et al 1998; Koht et al 2009). Otherwise available data indicate that vitamin E status is sufficient in the Nordic populations at current vitamin E intakes. Among older smoking men lowest mortality during 19 years was reported for those whose serum alpha-tocopherol values adjusted for cholesterol at baseline were between 13-14 mg/L (30.2-32.5 µmol/L) after which no further benefit was noted (Wright et al 2006). These serum values approximately corresponding to 13 mg daily intake of vitamin E might indicate vitamin intake level which may be sufficient to give protection from chronic diseases and protect from premature death (Traber and Stevens 2011). However, these findings may not be generalized to other groups.

The relationship between vitamin E and PUFA intake could also be used as a criterion for the recommended intake. Based on suggested requirement 0.6 alpha-TE/g PUFA (Valk and Hornstra 2000) and an average PUFA level of 5 % of energy intake (E%), an intake of 7 and 9 mg alpha-tocopherol/d for women and men, respectively, would be sufficient. The Scientific Committee on Food considered a ratio of 0.4 alpha-TE/g total PUFA to be adequate (Commission of the Europe Communities 1993) for adults provided vitamin E does not fall below 4 mg/d for adult men and 3 mg/d for adult women. Based on this ratio, the estimated average requirement would thus be 5 and 6 mg alpha-tocopherol/d for women and men, respectively.

In the absence of signs of vitamin E inadequacy in the general Nordic population and as no new data supporting changes have emerged, the recommended intake from 2004 is maintained. The RI of vitamin E is set to 8 alpha-tocopherol/d for women and 10 alpha-tocopherol/d for men. As no human data are available on the biopotency, apart from antioxidative activity, of tocopherols and tocotrienols other than the 2R-isomers of alpha-tocopherol, the reference values only apply to the 2R-isomers. A number of studies suggest that besides alpha-tocopherol, other tocopherols and tocotrienols may have important functions and beneficial effects (Aggarwal et al 2010, Ju et al 2010) but thus far evidence of their importance in human health is limited.

Children

The recommended intakes for infants and children are generally based on the vitamin E content in breast milk and the relationship between alpha-tocopherol and linoleic acid or total PUFA (Aggett et al 1998). The Scientific Committee on Food considered a ratio of 0.4 alpha-TE/g total PUFA to be adequate also for children (Commission of the European Communities 1993). In NNR 2012, the recommended intakes are based on a ratio of at least 0.6 alpha-TE/g total PUFA and a mean intake of PUFA corresponding to 5 E%.

Pregnancy and lactation

The recommended intake value for pregnancy is set to10 alpha-TE, which is applicable in the last two trimesters and covers the increased intake of energy and PUFA. The recommended intake during lactation (11 alpha-TE/d) also includes the extra need to cover secretion in breast milk.

Reasoning behind the recommendation

In the absence of signs of vitamin E inadequacy in the general Nordic population, and as no new data supporting changes have emerged, the recommended intake of vitamin E remains unchanged, i.e. 8 alpha-TE/d for women and 10 alpha-TE/d for men.

The recommended intakes for infants and children are generally based on the vitamin E content in breast milk and the relationship between alpha-tocopherol and linoleic acid or total PUFA (Aggett et al 1998). In NNR 2012, the recommended intakes are based on a ratio of at least 0.6 alpha-TE/g total PUFA and a mean intake of PUFA corresponding to 5 E%.

The recommended intake value for pregnancy is set to 10 alpha-TE, which is applicable in the last two trimesters and covers the increased intake of energy and PUFA. The recommended intake during lactation (11 alpha-TE) also includes the extra need to cover secretion in breast milk.

Upper intake levels and toxicity

Toxicity of vitamin E is low apparently due to efficient inbuilt metabolic control which prevents any excess accumulation of vitamin in the body. No adverse effects have been described from intakes provided by food sources. Few adverse effects of vitamin E supplementation have been reported in clinical trials and vitamin E supplements in amounts ≤1600 IU (1073 mg RRR-alpha-tocopherol) were suggested to be safe for most adults (Hathcock et al 2005). This amount corresponds to the upper safe limit set at 1000 mg alpha-tocopherol per day in the US recommendations (9=Food and Nutrition Board 2000). The Scientific Committee on Food (36=Scientific Committee on Food 2003) has proposed an upper level of alpha-tocopherol of 300 mg/d for adults. This level is mainly based on effects of increased intakes of vitamin E supplementation on blood clotting and includes an uncertainty factor. This UL was included in NNR 2004 and is also used in NNR 2012.

Concern of potential harm of vitamin E supplementation was raised by findings from the ATBC study suggesting increased mortality due to hemorrhagic stroke (37=The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994). An increased risk of hemorrhagic stroke was reported recently in another study of men in USA supplemented with 400 IU (270 mg) synthetic alpha-tocopherol every other day (Sesso et al 2008). Thus high amount of vitamin E may interfere in the blood clotting system especially with simultaneous use of aspirin. Depending on the circumstances decreased blood clotting may also be beneficial as suggested by decreased risk of vascular thromboembolism described among healthy women given 600 IU (400 mg) supplement of a natural form of alpha-tocopherol every other day (Glynn et al 2007).

A small but statistically significant increased mortality among those supplemented with vitamin E was demonstrated in two meta-analyses of randomized clinical trials (Miller et al 2005, Bjelakovic et al 2007). Increased mortality was suggested among subjects supplemented with doses of 400 IU per day (270 mg) or higher, and a dose-response analysis showed progressively increased all-cause mortality already as vitamin E doses exceeded 150 IU/day (100 mg) (Miller et al 2005). Generalization of these findings, largely based on studies in patients with chronic diseases to healthy adults is, however, uncertain. Although the causal relationship between vitamin E supplementation and increased mortality remains to be unclear, this possibility is a reason to be cautious in relation to vitamin E supplementation.

Taken together, available scientific data suggest that there are no benefits of high intakes of vitamin E. Although the risks associated with high supplemental intakes of vitamin E remain unclear, available data suggest some potential risks. In the absence of clear health benefits,

prolonged intake of supplemental vitamin E does not seem to be justified for the general population.

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