Vitamin K

Vitamin K is the collective term for compounds with vitamin K activity and having the common 2-methyl-1,4-naphtoquinone ring structure.

Vitamin K occurs naturally in two forms. Phylloquinone or vitamin K1 (2-methyl-3-phytyl-1,4-naphtoquinone) is synthesised by plants. Menaquinones or vitamin K2 (multi-isoprenyl-quinones, several species) are primarily produced by bacteria. Both forms are found in animal tissues.

Dietary sources and intake

Leafy green vegetables, vegetable oils and vegetable margarines are the main sources of phylloquinone (Booth & Suttie 1998, Koivu-Tikkanen 2001, Shearer & Newman 2008). Menaquinones are found in liver, chicken, egg yolk and certain cheeses. Natto, a fermented soybean preparation, is particularly rich in menaquinone-7. Based on HPLC analyses of vitamin K in a large number of food products and food intake data from various sources in Finland, an average intake of 120 µg/day has been calculated (Koivu-Tikkanen 2001, Piironen et al. 1997). In a nationally representative nutrition monitoring study in Finland, it was estimated that the mean vitamin K intake is 90 µg/day in women and 100 µg/day in men aged 25-64 years (Paturi et al. 2007). In the Norwegian Hordaland study, it was estimated that intake of phylloquinone is 130 µg/day and that of menaquinones is 15-20 µg/day in women and men aged 47-50 years based on food frequency data (Apalset et al. 2010). Using food records, smaller phylloquinone intake (60-70 µg/day) has been reported in Danish women aged 45-58 years (Rejnmark et al. 2006).

Physiology and metabolism

Compounds with vitamin K activity are required as cofactors for the carboxylation of glutamic acid to γ-carboxyglutamic acid (Gla) needed for the synthesis of factors II (prothrombin), VII, IX, and X, and proteins C, S, and Z, all involved in the coagulation of blood (Suttie 1993). The presence of Gla in these proteins enables them to bind calcium. Several Gla-containing proteins have been identified in bone, including osteocalcin, matrix-Gla-protein, protein S and growth-arrest-specific gene (Gas6) protein. Osteocalcin is most likely involved in the regulation of bone mineral maturation, but otherwise the exact function of these proteins in bone is not known. Matrix Gla protein is involved in regulation of soft-tissue calcification. In addition, a number of other Gla-containing proteins with unknown functions have been identified in several tissues. (Cranenburg et al. 2007, Shearer & Newman 2008, Booth 2009).

Vitamin K is absorbed in the jejunum and ileum. It is estimated that 80% of purified phylloquinone is absorbed (Shearer et al. 1974). However, bioavailability from food sources

is considerably less. Absorption of phylloquinone from food sources was found to be 10-15% of phylloquinone absorbed from tablet or suspension (Gijsbergs et al. 1996, Garber et al. 1999). Bioavailability of phylloquinone from kale was appr. 5% as assessed using stable isotope (Novotny et al. 2010). Fat malabsorption decreases the absorption of vitamin K significantly and bleeding is an early sign of this condition.

Absorbed vitamin K is transported by chylomicrons in the lymph and is mainly taken up by the liver. In addition to liver, vitamin K is stored in other organs like bone tissue, heart, pancreas (Shearer&Newman 2008) and fat tissue (Shea et al. 2010). Compared to other fat soluble vitamins, the total body pool is small. Turnover of phylloquinone is rapid, but somewhat slower for menaquinones. Hepatic reserves are rapidly depleted when dietary vitamin K is restricted. A more or less continuous supply is thus required to maintain satisfactory body stores.

Because of poor placental transport of vitamin K and consequent deficiency in the newborn, haemorrhage, sometimes also intracranial, may occur during the neonatal period.

Vitamin K and osteoporosis

The association between phylloquinone intake or status and risk of fracture has been investigated in several observational studies and majority of them show inverse association (Booth 2009). The association between phylloquinone intake and bone mineral density has been less consistent. Several randomized clinical trials have assessed the effect of phylloquinone supplementation (doses 200 µg/d-5 mg/d) on bone mineral density and hip fracture, the majority reporting no effect of the supplementation (Bolton-Smith et al. 2007, Booth et al. 2008, Binkley et al. 2009, Cheung et al. 2008). One study has reported protective effect of phylloquinone in postmenopausal women (Braam et al. 2003). Earlier interventions using pharmacological doses of menaquinone-4 carried out in Japan supported prevention of fractures, however, the quality of trials has been criticised (Cockayne 2006). Recent trials in other populations have not indicated a significant effect of menaquinones on bone mineral density (Knapen et al. 2007, Binkley et al. 2009, Emaus et al. 2010). In a meta-analysis of the effect of long-term treatment by oral anticoagulant on bone density, no differences were found any site apart from lower bone density in the ultradistal radius (Caraballo et al. 1999). Furthermore, poorer health of the anticoagulant users as compared to non-users can be an important confounder in the association between oral anticoagulants and bone health (Woo et al. 2008).

Vitamin K and atherosclerosis

Vitamin K-dependent matrix Gla protein inhibits vascular calcification suggesting a role for vitamin K in atherosclerosis. However, human data from observational studies have been inconsistent (Erkkilä & Booth 2008, Rees et al. 2010). High phylloquinone intake can reflect generally heart healthy diet, instead of direct effect. A randomized clinical trial has suggested that phylloquinone supplementation slows the progression of coronary artery calcification among healthy adults who have existing calcification (Shea et al. 2009), but there has not been effect on carotid intima-media thickness (Braam et al. 2004). Others have reported that menaquinones confer a protective effect (Gast et al. 2009). However, more studies are needed before recommendations can be made based on cardiovascular health outcomes.

Vitamin K and other health effects

Anticarcinogenic effects of vitamin K have been reported in animal and cell studies. An observational study suggests an association between menaquinones intake and reduced risk of cancer (Nimptsch et al. 2010). In addition, a role for vitamin K against insulin resistance has been proposed; however, human data are still limited (Yoshida et al. 2008, Beulens et al. 2010). Vitamin K is also suggested to reduce inflammation (Shearer &Newman 2008, Booth 2009).

Requirement and recommended intake

Clinical deficiency is normally not detected after the first few months of life in otherwise healthy individuals. Deficiency has been seen in connection with malabsorption, antibiotic treatment and parenteral nutrition without vitamin K supplementation.

Determination of the requirement for vitamin K has been difficult since it is not possible to induce clinical deficiency symptoms on a vitamin K depletion diet. Bacterial synthesis in the intestine is not sufficient, however, to maintain normal serum levels of vitamin K. The traditional, insensitive method to evaluate vitamin K status has been to determine the concentration of coagulation factors, most often measured as prothrombin time. Newer biomarkers of vitamin K status include serum concentrations of phylloquinone, the degree of carboxylation of vitamin K-dependent proteins and urinary vitamin K metabolites (Booth & Suttie 1998, Booth 2009, Harrington et al. 2007). The Food and Nutrition Board (2001) determined that these methods could not be used in the assessment of requirement because of uncertainty surrounding their true physiological significance and the lack of sufficient dose-response data. Therefore, the American DRIs, 120 and 90 µg/day for men and women respectively, are based on self-reported median vitamin K dietary intake in apparently healthy population groups (Food and Nutrition Board 2001). A depletion-repletion study on 10 young men showed that a reduction of phylloquinone in the diet from the normal level of 80 µg/day to about half that level resulted after 3 weeks in reduced plasma phylloquinone, increase in undercarboxylated prothrombin in plasma and reduced urinary excretion of Gla (Suttie et al. 1988). Supplementation by 50 µg/day reversed these changes. However, in another study similar amount did not bring the plasma phylloquinone levels back to original after depletion diet (Ferland et al. 1993). Healthy young individuals on intakes of about 60 to 80 µg/day (corresponding to 1 µg/kg/day) have shown no signs of clinical deficiency, indicating that this intake is adequate for the majority of individuals based on our current understanding of vitamin K's function in blood coagulation (Suttie et al. 1988, Jones et al. 1991, Bach et al. 1996, National Research Council 1998). However, studies indicate that this amount might be insufficient to support adequate carboxylation of extrahepatic vitamin K-dependent proteins (Binkley et al. 2002, Booth et al. 2001, Booth et al. 2003, Bügel et al. 2007, Schurgers et al. 2007).

Breastfed newborns are at risk of haemorrhage. Vitamin K concentrations in human milk have ranged from 0.85 to 9.2 µg/L with a mean of 2.5 µg/L (Food and Nutrition Board 2001). Using the average concentration as a basis, it could be extrapolated to a recommended intake of about 2 µg/kg/day. All newborns should routinely be given vitamin K (as a 1 mg intramuscular dose, or as weekly oral doses) to avoid haemorrhage during the neonatal period and oral prophylaxis should be continued for the 3 first months (Hansen et al. 2003, Van Winckel et al. 2009).

Upper intake levels and toxicity

No evidence of toxicity associated with high intakes of any form of natural vitamin K has been reported. The Scientific Committee on Food of the European Commission concludes in their report that there is no evidence of adverse effects associated with supplementary intakes of vitamin K in the form of phylloquinone of up to 10 mg/day for limited periods of time (Scientific Committee on Food 2003). This is supported by Cheung et al. 2008 who reported no increased adverse effects in women receiving daily 5 mg phylloquinone for 4 years. Synthetic analogues such as menadione have been associated with liver damage and haemolytic anaemia and should not be used therapeutically.

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