Vitamin K

The term vitamin K describes a class of fat-soluble vitamers, each of which function as a cofactor for the γ-carboxylase enzyme. Carboxylation of specific glutamic acid residues enables vitamin K–dependent proteins to bind calcium, which confers their function. Vitamin K is required for normal coagulation because several proteins in the coagulation cascade are vitamin K dependent. Additional vitamin K–dependent proteins have been identified in other tissues, such as cartilage, bone, and vascular tissue, suggesting that vitamin K is involved in multiple aspects of human health and disease.

Deficiency

Newborns are given vitamin K at birth to prevent vitamin K–deficient bleeding, which can otherwise occur because vitamin K does not cross the placenta (1). Beyond the neonatal period, vitamin K deficiency is rare. A recent analysis of the 2011–2012 NHANES indicated that vitamin K intakes have overall declined in the last 2 decades and, indeed, over half of adults >70 y old do not meet vitamin K dietary recommendations (2). Although this does not manifest as overt vitamin K deficiency, low vitamin K intakes and status have been linked to increased risk of certain age-related comorbidities, such as cardiovascular disease. However, results of vitamin K supplementation trials have been equivocal (3).

Dietary Recommendations

There is >1 naturally occurring form of vitamin K. Phylloquinone (vitamin K1) is plant-based, and menaquinones (collectively referred to as vitamin K2) are mostly synthesized by bacteria. Menaquinones differ structurally from phylloquinone in the saturation and length of their side chain, with the side chain length differentiating the menaquinone forms. Menaquinone-4 (MK4), for example, has an unsaturated side chain containing 4 isoprenoid units. The current Adequate Intakes (AIs) for vitamin K are based on the median phylloquinone intakes reported in NHANES III (1988–1994) and have not been revisited since 2001. The current AIs expressed as micrograms phylloquinone per day are: infants 0–6 mo, 2.0 μg/d; 7–12 mo, 2.5 μg/d, 1–3 y, 30 μg/d; 4–8 y, 55 μg/d; 9–13 y, 60 μg/d; 14–18 y, 75 μg/d; ≥19-y females, 90 μg/d; and ≥19-y males, 120 μg/d (4, 5). There are no increases during pregnancy or lactation. Some have recently suggested there should be a separate dietary requirement for menaquinones (6), claiming some menaquinones have unique beneficial properties. However, this claim is not well supported by the scientific literature (3). Some menaquinones are now being incorporated into food composition databases, including the USDA's Food Data Central, but the overall menaquinone content of the food supply has not yet been comprehensively analyzed, which is necessary to better understand the contribution of these forms to total vitamin K intakes and ultimately, overall health.

Food Sources

Green leafy vegetables and vegetable oils are the main dietary sources of phylloquinone. Mixed dishes and convenience foods were also recently identified as important contributors to phylloquinone intake in the United States, presumably from the addition of oils during food preparation, which challenges the assumption that phylloquinone intake is a marker of a healthy diet (2). MK4 is found in some animal-based foods, and phylloquinone is converted to MK4 in certain tissues (7). Menaquinones 5 to 13 are synthesized by some bacteria and are present in some fermented dairy products, meat, and vegetables (7–9). Menaquinones are also synthesized by bacteria in the colon, but their contribution to vitamin K nutritional status is not substantial because their absorption from the colon is poor (10).

Clinical Uses

With the exception of vitamin K being given to newborns prophylactically to prevent vitamin K–deficient bleeding (1), vitamin K is not used for clinical purposes.

Toxicity

There are no known toxicities associated with vitamin K in healthy individuals. People taking the vitamin K antagonist Coumadin (warfarin) should work with their health care provider to monitor their vitamin K intakes.

Recent Research

The same menaquinones that are produced by gut bacteria are also abundant in the food supply. However, little is known about how dietary vitamin K influences the gut microbiota. Mice fed a low-vitamin-K diet had a significantly different cecal microbial composition compared with mice fed diets supplemented with phylloquinone or different menaquinone forms. Surprisingly, the form of vitamin K in the diet did not influence the cecal microbial composition, suggesting the amount of vitamin K in the diet is more influential than the form consumed because the gut bacteria remodel what is absorbed (10). A similar pattern is emerging with respect to composition and distribution of vitamin K metabolites in nonhepatic tissues. Through use of stable isotopes in mouse models, it was determined that intakes of phylloquinone and various menaquinones, individually and in combination, had equivalent conversion to MK4 in nonhepatic tissues, such as brain (11). Through use of CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) technology, it has been established that

UbiA prenyltransferase domain containing 1 (UBIAD1) is the sole enzyme responsible for the conversion of various quinones to MK4 (12). UBIAD1 is a critical enzyme in the cholesterol biosynthesis pathway, and UBIAD1-deficient mice fail to thrive. However, these UBIAD1-deficient mice do not develop signs of overt vitamin K deficiency, which has been interpreted as an indication that these animals obtain sufficient vitamin K to support carboxylation of the hepatic vitamin K–dependent coagulation protein but that MK4 is involved in nonrelated physiological roles that influence these animals' ability to thrive. The UBAID1-deficient mouse model offers a unique opportunity to elucidate the roles of MK4 beyond that of carboxylation of vitamin K-dependent proteins (12).

Joint tissues contain multiple vitamin K–dependent proteins, including matrix Gla protein (MGP). Calcium deposition in cartilage can be characteristic of osteoarthritis (13), and MGP inhibits soft tissue calcification when it is carboxylated, which requires vitamin K. In recent population-based studies, warfarin use was associated with a 2–3-fold higher risk of knee and hip osteoarthritis development and progression, and with a 1.6-fold higher risk of joint replacement, compared with treatment with anticoagulants that are not vitamin K antagonists (14, 15). Higher vitamin K intakes and vitamin K status have also been associated with a lower prevalence (16) and progression (17) of osteoarthritis. Randomized clinical trials designed to evaluate the effect of vitamin K supplementation on osteoarthritis are needed.

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Abbreviations used: AI, Adequate Intake; MGP, matrix Gla protein; MK4, menaquinone-4; UBIAD1, UbiA prenyltransferase domain containing 1.

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