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Mini Review

The Prevalence of Vitamin K Deficiency/Insufficiency, and Recommendations for Increased Intake

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Abstract

Vitamin K's bioavailability from food is poor, and this nutrient has small circulating in the blood compared to the other fat-soluble vitamins, is quickly metabolized and excreted, and has low tissue stores. Data indicates that measurements of prothrombin time, typically used to assess vitamin K status, is not a particularly accurate method for doing so, and that measurements of circulating undercarboxylated MGP levels is a more effective method.Use of this more accurate method has shown that some vitamin k deficiency or insufficiency has been seen in 97% of older subjects in a mixed population. Furthermore, research suggests that supplementation with 180µg/day vitamin K2 is associated with improved bone mineral retention and a decrease in arterial calcification.Considering the benefits associated with a higher intake of vitamin K2, and the lack of toxicity, it seems reasonable to suggest that recommendations for vitamin K2 be increased to 180µg/day for adults, up from its current adequate intake levels of 90-120µg/day for women and men, respectively

ABBREVIATIONS

GLA: γ-carboxyglutamic acid; VKDP: Vitamin K-Dependent Protein; OC: OsteoCalcin; MGP: Matrix Gla Protein; ucOC: Uncarboxylated fractions; dp-ucMGP: desphospho-uncarboxylated MGP

INTRODUCTION

Since its discovery in 1929, vitamin K has been primarily considered for its role as a haemostasiological (coagulation) cofactor, [1] although more recent research has identified a significant role with respect to bone and cardiovascular health [2]. In 2001 the U.S. Food and Nutrition Board[1] established the adequate intake (AI) levels of vitamin K for adults 19 years and older of 120 mcg/day for men and 90 mcg/day for women. Based upon data from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) [3] showing that the average daily dietary intake of vitamin K in adults 20 years and older of 122 mcg for women and 138 mcg for men, it would seem that most U.S. diets contain an adequate amount of vitamin K. In this case, however, there is data to suggest that many Americans may not, in fact, be obtaining sufficient vitamin K despite these survey results. The reasons for this are a function of vitamin K bioavailability from foods, its retention and transport, methods for assessing its status, research demonstrating the prevalence of undercarboxylated fractions of vitamin K-dependent proteins, and research suggesting benefit from a higher intake of vitamin K2.

Furthermore, with respect to chemical structure and pharmacokinetics which affects bioavailability, metabolism and perhaps impact on health outcomes, there are differences between two distinct forms of vitamin K: vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). These differences led Beulens *et al*., [4] to suggest that further investigations should be undertaken to determine whether a new daily intake level for vitamin K should consider each of these two forms.

The bioavailability of vitamin K from foods

One important consideration is the bioavailability of the K vitamins from foods, the primary source of which is considered to be phylloquinone (vitamin K1) from leafy green vegetables. [1] According to the Food and Agriculture Organization of the United Nations (FAO), [5] it has been estimated that absorption of phylloquinone (vitamin K1) from boiled spinach (eaten with butter) is no greater than 10 percent compared with an estimated

80 percent when phylloquinone is given in its free form. The poor absorption of phylloquinone from green leafy vegetables may be a function of its location in chloroplasts and tight association with the thylakoid membrane.

Conversely, when two servings daily of yogurt drink fortified with menaquinone (vitamin K2, 28 μg MK-7/yogurt drink) was consumed by healthy men and postmenopausal women, vitamin K status improved as measured by significant decreases in uncarboxylated osteocalcin and desphospho-uncarboxylated matrix Gla-protein. Consequently food fortification with MK-7 appears to be a viable strategy for improving vitamin K status [6].

Although it could be argued that intestinal microflora synthesize large amounts of menaquinones (vitamin K2), which are potentially available as a source of vitamin K, [7] there is a lack of hard experimental evidence documenting the site and extent of any absorption [8,9,10]. The overall evidence suggests poor bioavailability of bacterial menaquinones since they are mostly tightly bound to the bacterial cytoplasmic membrane and the largest pool is present in the colon, which lacks bile salts for their solubilization [8,9].

Vitamin K retention and excretion

Vitamin K is transported primarily mainly in lipoproteins in circulation.[11] Furthermore, relatively small amounts of vitamin K circulate in the blood compared to the other fat-soluble vitamins, and vitamin K is quickly metabolized and excreted. This is based upon measurements of phylloquinone whereby an oral dose is only retained at a level of 30% to 40%, while and 40% to 50% is excreted in the feces via bile and about 20% is excreted in the urine [11,12]. Vitamin K's relatively low blood levels and tissue stores [12] can be accounted for due to this rapid metabolism of the nutrient.

Methods for assessing vitamin K status

Due to its rapid metabolism, circulating phylloquinone levels is not dependable as measures of vitamin K status. In fact, plasma phylloquinone was found to be inconsistently correlated with phylloquinone intake when comparing women and men, [13] and patients with plasma phylloquinone concentrations slightly below the normal range have no clinical indications of vitamin K deficiency [14]. Nor is the assessment of vitamin K intake necessarily accurate due to biases inherent to dietary intake questionnaires, fluctuations in intake, and the bioavailability of this nutrient from food. Currently, prothrombin time is typically used to assess vitamin K status, but this is not routinely done except in individuals who take anticoagulants or have bleeding disorders. The problem is that changes in vitamin K intakes have rarely been shown to alter prothrombin time [15].

Rather, Theuwissen *et al*., [16] and Cranenburg *et al*., [17] identified measurements of circulating undercarboxylated MGP levels as a more effective method of assessing vitamin K status and also a better method for establishing appropriate intake levels. The reason for this is that vitamin K functions as a cofactor for the enzyme, γ-glutamylcarboxylase which in turn catalyses the carboxylation of the glutamic acid (Glu) to γ-carboxyglutamic acid (Gla) forming Gla-proteins or vitamin K-dependent proteins (VKDPs) [1] These VKDPs include osteocalcin (OC), also known as bone Gla protein (synthesized by osteoblasts) and matrix Gla protein (MGP, found in cartilage, bone, and soft tissue, including blood vessel walls) [18-25]. Now consider that, while uncarboxylated prothrombin reflects the hepatic vitamin K status, circulating uncarboxylated fractions of OC (uncarboxylated OC, ucOC) and MGP (desphospho-uncarboxylated MGP, dp-ucMGP) are recognized markers for the extra-hepatic vitamin K status and have been associated with osteoporotic fractures and arterial calcification, respectively [26-28].

Prevalence of ucMGP reflecting vitamin K deficiency/ insufficiency

A total of 452 community-dwelling men and women (age range 60–80 y; 421 whites, 14 blacks, 4 Hispanics, 11 Asians, and 2 Native Americans) participated in a randomized controlled trial [29]. These subjects were generally in good health and free from clinical cardiovascular disease and laboratory evidence of kidney or liver disease or osteoporosis. Of the 452 participants enrolled, 438 or 97% had notable measures of ucMGP and coronary artery calcium at baseline, which is comparable to the previously reported overall plasma ucMGP concentration of healthy adults of a similar age [17]. When supplemented with vitamin K, the circulating measures of vitamin K status ($P<0.001$), as well as vitamin K intake ($P=0.032$), were also significantly associated with ucMGP: there was a significant reduction ($P<0.0001$) in plasma ucMGP among older adults who received supplementation with vitamin K for three years compared with those who did not receive vitamin K. This data suggests that 97% of subjects may have been vitamin K deficient or insufficient, as reflected by their measures of ucMGP.

In addition, other research has shown that in healthy adults, circulating ucMGP levels gradually increased with age, with a significant rise seen above 40 years of age [30]. Similarly Cranenburg *et al*., [17] showed a trend of increasing ucMGP values with age, and significant higher values for elderly (66–80 years).

Benefits from a higher intake of vitamin K2

Data suggest that vitamin K2 (menaquinone, esp. MK-7) has advantages over vitamin K1 (phylloquinone). Well and Suttie [31] have demonstrated that phylloquinone has a relatively short half-life time,whereas research suggests that long-chain menaquinones have a longer half-life. Additionally, while phylloquinone and the MK-7 form of menaquinone were found to be well absorbed as dietary supplements, the long half-life of MK-7 resulted in much more stable serum levels, and 7- to 8-fold accumulation higher levels during prolonged intake [32].

In the population-based Rotterdam study, [33] which included 4807 subjects, dietary menaquinone intake was inversely related to all-cause mortality and severe aortic calcification, but phylloquinone intake was not related to any of the outcomes. Similarly, in a cross-sectional study [34] among 564 post-menopausal women found that menaquinone intake, but not phylloquinone intake, was associated with decreased relative risk of coronary calcification (p=0.03). Furthermore, research [16] found that circulating MK-7 concentrations only became significant starting with an intake of 90 μg/day, and research

by Dalmeijer *et al*., [30] demonstrated that undercarboxylated MGP decreased significantly (P< 0.001) by 31% and 46%, respectively, when subjects received 180 µg and 360 µg/day MK-7, respectively.

In addition, Knapen *et al*., [35] investigated long-term effects of supplementation with 180 µg/day MK-7 (MenaQ7, n=120) or placebo (n=124) on arterial stiffness in healthy postmenopausal women for three years in a double-blind, placebo-controlled trial. Measurements included Indices of local carotid stiffness, regional aortic stiffness and dp-ucMGP. After three years of supplementation with MK-7, measures of aortic stiffness significantly decreased. Compared to placebo, MK-7 decreased dp-ucMGP by 50%. Researchers concluded that long-term supplementation with MK-7 improves arterial stiffness in healthy postmenopausal women, especially those with high arterial stiffness.

This same dose of MK-7 was shown to have benefits in a placebo-controlled study by Knapen *et al*., [36] in 2013. For three years, healthy postmenopausal women (n = 244) received 180 µg MK-7/day MK-7 or placebo. DXA was used to assess various measures of bone density measurements, bone strength indices of the femoral neck were calculated, and ucOC was measured. The results were that 180 µg MK-7/day MK-7 significantly improved vitamin K status, decreased the age-related decline in bone mineral content and bone mineral density at the lumbar spine and femoral neck, improved bone strength and significantly decreased the loss in vertebral height of the lower thoracic region at the mid-site of the vertebrae.

Adverse effects and drug interactions

Additionally, there is no known toxicity associated with high doses of the vitamin K1 or K2, which is why no tolerable upper level (UL) of intake has been established for vitamin K1 or K2 by the Food and Nutrition Board, Institute of Medicine [1], or by the World Health Organization [37], and long-term high dosage therapy with vitamin K is not associated with increased thromboembolic events [38].

Nevertheless, it should be noted that excessive vitamin K intake, either from supplements or from changes in the diet, can reduce the anticoagulant effects of oral anticoagulants such as warfarin [39]. In fact, there are millions of patients on warfarin therapy for a variety of thrombogenic conditions such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, and prosthetic cardiac valves, which has resulted in significant risk for major bleeding. In such cases, vitamin K has served as one of the major reversing agent for patient's over-anticoagulated with warfarin [40].

Furthermore, in hemodialysis patients vitamin K antagonists are sometimes given to lower thrombosis tendency, but have side effects that enhance arterial calcifications. A study by Zaragatski et al., [41] found that Vitamin K2 treatment, additional to vitamin K antagonists, attenuated calcification in healthy rats and rats with chronic kidney disease induced using an adenine-enriched diet. Further research should be conducted to determine the potential value of concomitant treatment with vitamin K2 and vitamin K antagonists in hemodialysis patients.

Clearly, any patients on anticoagulant therapy should confer with their physician before increasing vitamin K intake.

DISCUSSION & CONCLUSION

Given that some vitamin k deficiency or insufficiency has been seen in 97% of older subjects in a mixed population as reflected by their measures of ucMGP [27], and considering the issues with vitamin K bioavailability from foods, its retention and transport, the benefits associated with a higher intake of vitamin K2, and the lack of toxicity, it seems reasonable to suggest that recommendations for vitamin K2 (esp. as MK-7) be increased to 180 µg/day for adults.

CONFLICT OF INTEREST

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