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The health benefits of vitamin K

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ABSTRACT

Vitamin K has important functions within the body, some of which are still being discovered. Research has shown that vitamin K is an anticalcification, anticancer, bone-forming and insulin-sensitising molecule. Recent data indicate that subclinical vitamin K deficiency is not uncommon. Additionally, vitamin K antagonists such as warfarin may cause detrimental side effects, which may partly be blunted through vitamin K supplementation.

INTRODUCTION

Vitamin K is a fat-soluble vitamin, important for the function of numerous proteins within the body, such as the coagulation factors (II, VII, IX, X and protein C and protein S), osteocalcin (a bone-forming protein) and matrix-Gla protein (MGP) (an anticalcification protein), to name a few.[1–3] Vitamin K exists naturally as vitamin K_1 (phylloquinone) and vitamin K_2 (menaquinone, MK-4 through MK-10).[2–5] Vitamin K_1 is mainly found in green leafy vegetables as well as olive oil and soyabean oil, whereas vitamin K_2 (menaquinone) is found in small amounts in chicken, butter, egg yolks, cheese and fermented soyabeans (better known as natto).[2 6–9]

Vitamin K_1 and vitamin K_2 are required for the γ-glutamyl carboxylation of all vitamin K-dependent proteins.[2] Despite the fact that mammalian bacterial intestinal flora are able to produce vitamin K_2, the amount produced is thought to be negligible.[2] The adequate intake (AI) for vitamin K has been proposed to be 90 µg/day for women and 120 µg/day for men.[2 10] However, it has been speculated that the AI for vitamin K (90–120 µg/day) is not sufficient to induce complete carboxylation of all vitamin K-dependent proteins.[2 11 12]

VITAMIN K DEFICIENCY

The measurement and treatment of vitamin K deficiency based on blood tests is not perfect. Plasma phylloquinone concentrations fluctuate based on recent dietary intakes.[2 13] Despite the fact that a high percentage of undercarboxylated osteocalcin indicates poor vitamin K status, this value can also vary based on recent vitamin K intake and supplementation[2 14] and may not indicate chronic vitamin K status. Moreover, a normal carboxylated MGP protein in the serum may not necessarily indicate a normal vitamin K status, as carboxylated MGP in the serum could be normal, but suboptimal in the arteries (where vitamin K_2 is needed to prevent vascular calcification.)

VITAMIN K AND BONE HEALTH

Osteoporosis is a leading contributor of fractures worldwide, causing more than 8.9 million fractures annually.[15] Moreover, Osteoporosis affects an estimated 200 million women worldwide (approximately 1/10th of women aged 60, 1/5th of women aged 70, 2/5ths of women aged 80, and 2/3rds of women aged 90).[15] One in 3 women and 1 in 5 men over 50 will experience an osteoporotic fracture.[15] Additionally, 61% of all osteoporotic fractures occur in women.[15] It has been predicted that the incidence of hip fracture is expected to increase by 310% in men and 240% in women by 2050; thus, the economic toll of osteoporosis is expected to significantly increase.[15] Indeed, it has been estimated that there is a 40% lifetime risk for fractures affecting the hip, forearm and vertebrae (similar to the risk for cardiovascular disease),[15] with nearly 75% of these types of fractures occurring in patients aged 65 years age and above.[15 16] Osteoporosis has been shown to account for more days spent in the hospital than diabetes, heart attacks or breast cancer.[15] It is also a major cause of disability, which has been shown to be greater than that caused by cancer (except lung cancer) and comparable to or greater than disability from rheumatoid arthritis, asthma and high blood pressure related heart disease.[15] The overall mortality within the first 12 months after a hip fracture is approximately 20%, being higher in men than women.[15] Moreover, men make up 20–25% of all hip fractures,[15] and have an estimated 30% lifetime risk of experiencing an osteoporotic

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fracture when over 50, similar to the lifetime risk of developing prostate cancer.[15] Fragility fractures are the primary cause of hospitalisation and/or death for US adults ≥age 65 and above.[15] Furthermore, 44% of nursing home admissions are due to fractures.[15] It is obvious that osteoporosis is extremely common and this condition leads to disability, costs and even death. Thus, preventing and treating this disease is of utmost importance. However, the recently updated USA Preventive Services Task Force (USPSTF) has recently stated that there is insufficient evidence that calcium and vitamin D prevent a fracture in premenopausal women or in men who have not experienced a fracture and now recommends against daily supplementation with 400 IU or less of vitamin D3 and 1000 mg or less of calcium for the primary prevention of fractures in non-institutionalised postmenopausal women. Thus, unless you are an institutionalised postmenopausal woman or you have already experienced a fracture, the USPSTF does not recommend calcium and vitamin D for preventing a first-time fracture, as there is a lack of evidence. The USPSTF also states that "Daily supplementation with ≤400 IU of vitamin D3 and ≤1000 mg of calcium has no net benefit for the primary prevention of fractures" and that "Evidence is lacking regarding the benefit of daily supplementation with >400 IU of vitamin D3 and >1000 mg of calcium for the primary prevention of fractures in postmenopausal women, and the balance of benefits and harms cannot be determined."[17] Thus, what else can a clinician prescribe to help to prevent osteoporosis and its consequences? A broad amount of data seems to indicate substantial potential for supplementary vitamin K. However, currently few guidelines recommend vitamin K therapy for prevention or treatment of osteoporosis.

Vitamin K_1 (5 mg daily) given to 440 postmenopausal women with osteopenia for 2 years in a randomised, placebo-controlled, double-blind trial caused a greater than 50% reduction in clinical fractures (9 vs 20, p=0.04) versus placebo, despite the fact that there was no improvement in bone mineral density.[18] Moreover, there was a 75% reduction in cancer incidence with vitamin K_1 (3 vs 12, p=0.02). The benefit of vitamin K on bone is thought to be unrelated to increasing BMD but rather increasing bone strength.[19] A recent meta-analysis has shown that vitamin K_2 (45 mg/day) significantly reduces hip (77% reduction), vertebral (60% reduction) and all non-vertebral fractures (81% reduction).[20] Whether the results of vitamin K_2 at a dose of 45 mg can be translated to over the counter doses of vitamin K_1 (such as 1–5 mg) is still a matter of debate, but vitamin K_1 on its own has already been shown to reduce fractures and cancer in a clinical trial, although more data are needed to confirm these benefits.

Box 1 The health benefits of vitamin K (box 1)

Bone health

May help to prevent fractures due to osteopenia and osteoporosis[18–20]

Trial evidence

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Cancer (especially liver cancer)

May help to prevent liver cancer and death in patients with liver cirrhosis and hepatocellular carcinoma (HCC)[54–61]

Trial evidence

Five randomised controlled trials tested vitamin K_2 (45 or 90 mg/day) in patients with HCC. Vitamin K_2 significantly improved 1-year overall survival, (RR=1.03, 95% CI 1.00 to 1.05, p=0.03)[74]

Vascular calcifications

May help to prevent vascular calcifications (especially in patients on warfarin)[5 26 75]

Trial evidence

Significantly delayed the development of coronary artery calcium in a 3-year, double-blind, randomised controlled trial of 452 patients.

In a 3-year, double-blind, placebo-controlled trial, vitamin K_1 (along with vitamin D) significantly delayed the deterioration of arterial elasticity[37] in 181 postmenopausal women. This was not found with vitamin D alone.

Coronary heart disease (CHD)

May reduce the risk of CHD, CHD mortality and all-cause mortality[5 26 76]

Insulin sensitivity

May help improve insulin sensitivity[40]

Warfarin international normalised ratio (INR)

May help to stabilise INR in patients on warfarin[41]

VITAMIN K AND VASCULAR CALCIFICATIONS

Coronary artery calcium (CAC) has been shown to have increasing prevalence as kidney function declines.[3] Indeed, CAC prevalence has been reported in 13% of 'healthy' patients without renal disease,[21] 40% of patients with chronic kidney disease patients not on dialysis,[21] 57% of patients starting dialysis[22] and 83% of patients on long-term dialysis.[23] Diets lacking vitamin K can precipitate the development of vitamin K deficiency in as little as 7 days.[24] Additionally, subclinical vitamin K deficiency is not uncommon, especially in patients receiving warfarin.[25] Cross-sectional and cohort data have shown a lower risk of coronary heart disease (CHD), CHD mortality, all-cause mortality and severe aortic calcifications with higher vitamin K_2 (menaquinone) intake[5 26] (box 1). This was not shown with vitamin K_1 intake (phylloquinone, the major dietary source of vitamin K.[26 27] Thus, dietary vitamin K_1 intake, without vitamin K_2, may not be sufficient to suppress arterial calcifications and/or reduce risk for subsequent cardiovascular events and death. The menaquinone form of vitamin K (ie, vitamin K_2) has been presumed to be

more effective than vitamin K_1 at preventing and reversing arterial calcifications. It has been proposed that a substantial amount of apparently healthy patients are subclinically vitamin K deficient based on undercarboxylated osteocalcin and MGP,[25] presumably increasing the risk of vascular calcifications, cancer and osteoporosis.

Low vitamin K status (indicated by undercarboxylated MGP) is associated with increased vascular calcifications, and these levels can be improved by effective vitamin K supplementation[28–32] It was long believed that vitamin K was only involved in forming coagulation factors (ie, maintaining haemostasis). However, other vitamin-K dependent proteins (containing γ-carboxyglutamate or Gla) are dependent on vitamin-K carboxylation for functionality.[33] Vitamin K acts as a cofactor in the conversion of glutamate into Gla. Gla-containing proteins (MGP and osteocalcin) regulate many anticalcification and bone-forming processes in the body, which are dependent on vitamin K in order to be produced. Low levels of vitamin K impair activation of osteocalcin and decrease the activity of osteoblasts (cells important for building bone).[33 34] Thus, vitamin K is vital to the functionality of proteins such as osteocalcin (important for building bone), (MGP, the most potent arterial calcification inhibitor known) and the growth-arrest sequence-6 protein (Gas6, involved in cell growth regulation[35]

Vitamin K has been shown to significantly delay the development of CAC in a 3-year, double-blind, randomised controlled trial of 452 patients (229 patients on vitamin K_1 and 223 patients in the control group).[36] All patients were assigned to a multivitamin (containing 1.6 mg thiamine, 1.8 mg riboflavin, 2.1 mg vitamin B-6, 3 µg vitamin B12, 75 mg vitamin C, 12 mg vitamin E, 6 mg pantothenic acid, 20 mg niacin, 160 µg folate and 30 µg of biotin) as well as calcium (600 mg calcium carbonate) and vitamin D (cholecalciferol 400 IU). In the intention-to-treat (ITT) analysis, CAC progression at baseline and at year 3 was measured in 388 participants, which indicated no difference in the progression of CAC. However, a secondary analysis of 295 participants who were compliant with their supplements (predefined as ≥85% adherence over 3 years) showed a significantly decreased progression of CAC in the vitamin K_1 group (500 µg) compared to the control group ($p=0.03$). Moreover, in adherent participants with a CAC >10 at baseline (ie, patients with pre-existing arterial calcification), patients assigned to vitamin K_1 had a 6% less progression in CAC than those in the control group ($p=0.04$), whereas there was no benefit of vitamin K_1 in patients without baseline CAC. Despite the fact that serum MGP increased in the vitamin K_1 group, whereas MGP was decreased in the control group (treatment effect: $p\leq0.03$ in ITT and secondary analyses), neither baseline nor change in MGP predicted the change in CAC, suggesting that the benefit of vitamin K on CAC progression is not related to increases in serum MGP. However, since the assay for serum MGP did not differentiate between carboxylated versus undercarboxylated forms of MGP (and it is assumed that only the carboxylated form of MGP is functional as a calcification inhibitor), interpretation of serum MGP is severely problematic. Baseline osteoprotegerin (OPG) concentrations were positively predictive of change in CAC ($p=0.004$ in ITT adjusted for treatment), corroborating previous evidence suggesting that patients with higher calcification scores have higher baseline serum OPG concentrations. This study also indicated that there was no influence of vitamin K_1 on circulating OPG, interleukin 6 and C reactive protein and controlling for the 3-year change in cytokines did not alter the significance of treatment effect on change in CAC. Thus, the effect of vitamin K on CAC might be independent of changes in serum cytokine levels (but not necessarily ruling out vitamin K's benefit on the blunting of the effects of these cytokines). Despite the fact that vitamin K_1 has a beneficial effect on CAC in older men and women, larger studies powered for clinical end points (stroke, myocardial infarction and death) are needed to assess the risks and benefits of vitamin K therapy.

Vitamin K administration has been shown to significantly delay the progression of CAC and, in addition, it has also been shown to significantly delay the deterioration of arterial elasticity.[37] In another 3-year, double-blind, placebo-controlled trial, vitamin D and vitamin K were investigated. The trial included 181 postmenopausal women who were given (1) a placebo, (2) a supplement containing minerals and vitamin D, or (3) the same supplement with the addition of vitamin K_1. The vitamin K_1 group had a significant increase in the distensibility coefficient (8.8%, $p<0.05$), compliance coefficient (8.6%, $p<0.05$), elasticity (13.2%, $p<0.01$) and a decrease in pulse pressure (−6.3%; $p<0.05$). There was no significant difference between the vitamin D and mineral group without vitamin K and the placebo group. In summary, vitamin K_1 along with vitamin D has beneficial effects on arterial elasticity.

VITAMIN K AND WARFARIN

Since warfarin directly leads to the inhibition of vitamin K, it would be presumed that there could be increased arterial calcifications in patients given warfarin. In fact, many preclinical and prospective studies have shown increased calcifications with patients on warfarin compared to those not receiving warfarin. Furthermore, most individuals taking warfarin are counselled to avoid vitamin K-containing foods, such as green leafy vegetables, which may lead to an even further increase in CAC.[36] Vitamin K deficiency can be exacerbated further when warfarin is initiated.[38] The negative impact that warfarin can have on the body has long been recognised.[39]

Warfarin has been shown to cause severe arterial calcifications in the aorta and the carotid arteries of rats. However, when high-dose therapy with vitamins K_1 or K_2 (100 µg/g of chow) was given, the progression of

calcifications ceased and there was also a 37% reduction in prior calcifications induced by warfarin. Moreover, high-dose vitamin K_1 or vitamin K_2 restored arterial distensibility back to that seen in control rats.[38] Thus, animal data indicate that vitamin K (K_1 or K_2) may be able to reverse arterial calcifications and at the same time improve arterial compliance. Warfarin has been shown to prevent the conversion of vitamin K_1 to vitamin K_2.[40–42] Since warfarin was stopped prior to the introduction of high-dose vitamin K_1 or K_2, it is uncertain if either would have prevented these calcifications during concomitant warfarin administration. However, previous data have shown that vitamin K_2 is more effective than vitamin K_1 at preventing arterial calcifications during concomitant warfarin treatment in rats.[34] Thus, if further trials are performed, vitamin K_1 and K_2 should be tested.

Women taking warfarin during the first trimester of their pregnancy may give birth to children with punctate calcifications in the axial skeleton, proximal femurs and calcanei. It has been presumed that prenatal vitamin K deficiency induced by warfarin may be the underlying cause of these calcifications.[43 44] Indeed, several studies indicate a connection between warfarin and arterial calcifications.

Thirty six patients, 19 on warfarin for more than 10 years and 17 controls from five different thrombosis services in the Netherlands, were studied. Patients on warfarin had over a threefold increase in femoral artery calcifications compared to the control group (77.8% vs 25%, respectively). Also, patients on warfarin had a significantly higher carotid intima-media thickness compared with controls (p=0.04). The authors concluded that warfarin was associated with increased arterial calcifications and may increase atherosclerotic development[45]

Warfarin has been associated with a 1.71-fold increase in mitral valve calcium (MVC), mitral annular calcium (MAC) or aortic valve calcification on two-dimensional echocardiograms compared to controls. In a population of 1155 patients, MVC, MAC and aortic valve calcium was present in 65% of patients with warfarin compared to only 52% of patients who were not on warfarin (p<0.0001).[46]

Forty five aortic valves were examined after cardiac replacement surgery to look at calcified deposits. In the warfarin group, during a period of approximately 1–3 years in duration, there was significantly more calcium content contained within the aortic valves of patients with warfarin compared to the control group. Patients receiving preoperative warfarin treatment had a twofold increase in calcifications compared to non-treated patients. The authors concluded that warfarin might induce cardiovascular calcifications.

Finally, multislice spiral CT was used to determine if patients on warfarin have a significantly greater amount of coronary calcification compared to controls. Indeed, patients on warfarin had increased coronary calcium, determined by a significantly higher Agatston score (1561+/−1141) compared to controls (738+/−978) (p=0.024 for the difference).[48] Moreover, patients on warfarin had significantly more valvular calcium compared to patients without anticoagulation treatment (valvular Agatston score 2410±1759 vs 1070±1085, p=0.002). Thus, warfarin seems to be associated with increased valvular and coronary calcium in patients with aortic valve disease, which may be related to warfarin's inhibition of vitamin-K's ability to carboxylate anticalcification proteins, particularly MGP.

Evidence that somewhat challenges the above data is The Warfarin and Coronary Calcification Study. This study of 70 patients found no significant relationship between duration of warfarin treatment and CAC score.[49] Therefore, larger randomised controlled trials are required to determine if warfarin increases the risk of vascular calcifications. When vitamin K_1 is given to patients with warfarin, a more stable international normalised ratio (INR) has been noted. This has been shown in one retrospective and two prospective studies.[41]

VITAMIN K AND INSULIN SENSITIVITY

In a 3-year randomised, double-blind, controlled trial of 355 patients, vitamin K significantly improved insulin sensitivity in men with diabetes. Vitamin K is involved in pancreatic β-cell proliferation, insulin sensitivity, production of adiponectin and increased glucose tolerance, all of which may have contributed to these results. As a vitamin K inhibitor, warfarin may potentially negate these effects. In summary, vitamin K may improve insulin sensitivity in men with diabetes.[40]

VITAMIN K AND CANCER

Vitamin K_2 has been shown to inhibit the growth of human cancer cell lines, including hepatoma lines, as well as to treat myelodysplastic syndrome.[50–53] Two trials seem to indicate that vitamin K_2 45 mg/day reduces the development of hepatocellular carcinoma (HCC) in patients with liver cirrhosis and that vitamin K_2 significantly reduces the recurrence of HCC in patients following the curative treatment of HCC with an associated reduction in all-cause mortality in these patients.[54–61] The possible reduction in mortality with vitamin K_2 may be explained by multiple mechanisms. The mechanisms responsible include (1) activation of growth-inhibiting proteins requiring vitamin K_2, such as prothrombin,[62] (2) arylation pathways,[63] (3) activation of growth arrest genes such as gas 6,[64] and (4) and increased c-Jun and c-Myc mRNA expression in hepatoma cells.[57]

Preventing the recurrence of HCC is an important strategy, especially considering the fact that even after patients undergo curative therapy recurrence rates remain high.[65] While triple combination therapy with boceprevir or telaprevir, pegylated interferon (IFN) and ribavirin is effective for the treatment of hepatitis C virus

(HCV), information on preventing HCC development and/or recurrence as well as all-cause mortality is lacking.[66 67] Moreover, this combination therapy is expensive, requires injections (IFN) and is often not well tolerated due to adverse events (ie, fever and pancytopenia). Conversely, vitamin K_2 45 mg once daily is less expensive, orally administered and safe, as it is currently used for the treatment of osteoporosis.[55 68] In these trials, there were few if any adverse events associated with vitamin K_2 45 mg once daily, even out to approximately 8 years of duration. However, not all of the trials were blinded and most trials included a relatively small number of patients (n=40–61); however, follow-up was quite long (median=36 months to mean 65 months). Finally, all trials were performed in Japanese patients, and thus these data may not be generalisable to those of other ethnicities.

More information is needed to further evaluate the use of vitamin K_2 45 mg once daily on top of current optimal medical therapy in patients with HCV, liver cirrhosis or HCC, especially in those who are resistant to current therapies. Combining vitamin K_2 with an ACE inhibitor (perindopril) has shown synergistic effects on HCC recurrence and survival, and thus this combination should also be further explored.[60] Moreover, additional studies should be explored combining vitamin K_2 with acyclic retinoids, as this combination has also shown positive results on human HCC cell lines.[69] The Health Benefits of vitamin K have been summarised in box 1.

VITAMIN K AND HAEMODIALYSIS

Pilkey *et al*[70] demonstrated that 29% of patients with haemodialysis have coexisting subclinical vitamin K deficiency. Later, Cranenburg *et al*,[71]while evaluating vitamin K status and intake in such patients, reported subnormal levels in 45% of study participants. Finally, in the recent VItamin K Italian (VIKI) dialysis study, 23.5% of patients were found to be vitamin K deficient, and this deficiency was found to be the strongest predictor of vertebral fractures (OR: 2.94; 95% CI 1.38 to 6.26).[72] Other data have shown that vitamin K_2 may improve bone remodelling in patients with haemodialysis with low serum parathyroid hormone levels.[73] Supplementing with at least 200 µg menaquinone-7 (a form of vitamin K_2) daily may help to achieve near maximal protection from vascular calcification, osteoporosis and cancer (measured by maximal gamma carboxylation of vitamin K dependent proteins).[35]

CONCLUSION

Vitamin K has a plethora of potential implications, including prevention and treatment of arterial calcifications, coronary heart disease and cancer, improvements in bone strength and reduced risks of fractures as well as improvements in insulin sensitivity. Additionally, vitamin K may even play a vital role in the stabilisation of INR control for patients on warfarin. On the basis of previously presented data, warfarin may increase arterial calcifications and osteoporosis through the inhibition of vitamin K. Larger trials should be performed to further elucidate the negative long-term health consequences of warfarin and if these can perhaps be prevented through the institution of supplemental vitamin K.

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Competing interests Dr DiNicolantonio works for a company that sells vitamin K but he does not directly profit from their sales. JHO'K has a major ownership interest in CardioTabs, and is also founder and Chief Medical Officer for this nutriceutical company that has products containing vitamin K.

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Notes