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Chapter

Relation between Vitamin K and Osteoporosis

Sawsan Jaghsi

Abstract

Vitamin K is an essential fat-soluble vitamin. The role of vitamin K as a cofactor involved in blood coagulation is well demonstrated. In the past two decades, vitamin K has been receiving more attention due to its role in bone health and metabolism. Vitamin K plays a role in activation of vitamin K-dependent proteins, which are involved not only in blood coagulation but in bone metabolism and the inhibition of arterial calcification. Numerous studies have exhibited the importance of vitamin K in bone health. The bone mineral density (BMD) does not remain steady with age, particularly declining after menopause. Osteoporosis is a metabolic bone disease of reduced bone density, fragile bone, and elevated susceptibility to fracture. A greater understanding of the biological linkages between vitamin K and bone may conduce to new treatment for osteoporosis that may improve bone density and prevent the adverse outcomes of osteoporosis.

Keywords: vitamin K, phylloquinone, menaquinone, bone mineral density, osteoporosis, Gla protein

1. Introduction

Vitamin K is an important fat-soluble vitamin. The discovery of vitamin K was in Germany in 1929 by Henrik Dam in his research on sterol metabolism, and he suggested the name vitamin K on the basis of its role in coagulation (koagulation in German spelling).

The exact function of vitamin K in the human body was discovered in the 1970s with the discovery of γ-carboxyglutamic acid (Gla), an amino acid found in all vitamin K proteins [1].

Gamma glutamyl carboxylase is an enzyme that located in the endoplasmic reticulum and mediates the posttranslational conversion of glutamyl to γ-carboxyglutamyl residues in vitamin K-dependent proteins; this enzyme needs vitamin K as a cofactor for this conversion; thus the important role of vitamin K appears in tissues that contain vitamin K-dependent protein to make them a functional protein [2].

During the last two decades, the researches have focused on the role of vitamin K in osteoporosis [3], cardiovascular disease [4], diabetes [5], and cancer [6] besides its role on coagulation [7].

In the liver there are several vitamin K-dependent proteins which all play a role in hemostasis. In addition to the hepatic tissue, bone tissue contains vitamin K-dependent proteins such as osteocalcin (bone Gla protein) and matrix Gla protein (MGP). Mineral binding capacity of osteocalcin needs vitamin K for adding mineral to the bone matrix in normal bone growth and development [8].

Studies have reported that vitamin K plays a role in bone metabolism in other mechanisms. There is an evidence that vitamin K positively affects calcium balance and increase of calcium retention [9]. Vitamins K and D work synergistically on bone metabolism, the form of osteocalcin that osteoblasts produce is undercarboxylated osteocalcin, and this process is upregulated by vitamin D, while carboxylation of osteocalcin is mediated by vitamin K [10].

Vitamin K is shown to decrease bone resorption by osteoclasts and inhibits production of bone-resorbing agents such as interleukin-6 [11] and prostaglandin E2 [12].

Osteoporosis is a metabolic bone disease of reduced bone density, fragile bone, and elevated susceptibility to fracture. Genetic factors, age, sex, race, general health, exercise, cigarette smoking, alcohol abuse, hormone replacement therapy, and nutrition are some of the factors that influence an individual's risk of osteoporosis [13].

The aim of the present paper is to summarize the present knowledge on vitamin K and bone metabolism, emphasize the role of vitamin K in bone health, and evaluate vitamin K as a diagnostic and therapeutic marker in osteoporosis.

2. Types of vitamin K

Vitamin K refers to a family of compounds with a common chemical structure of 2-methyl-1,4-naphthoquinone (**Figure 1**) [14].

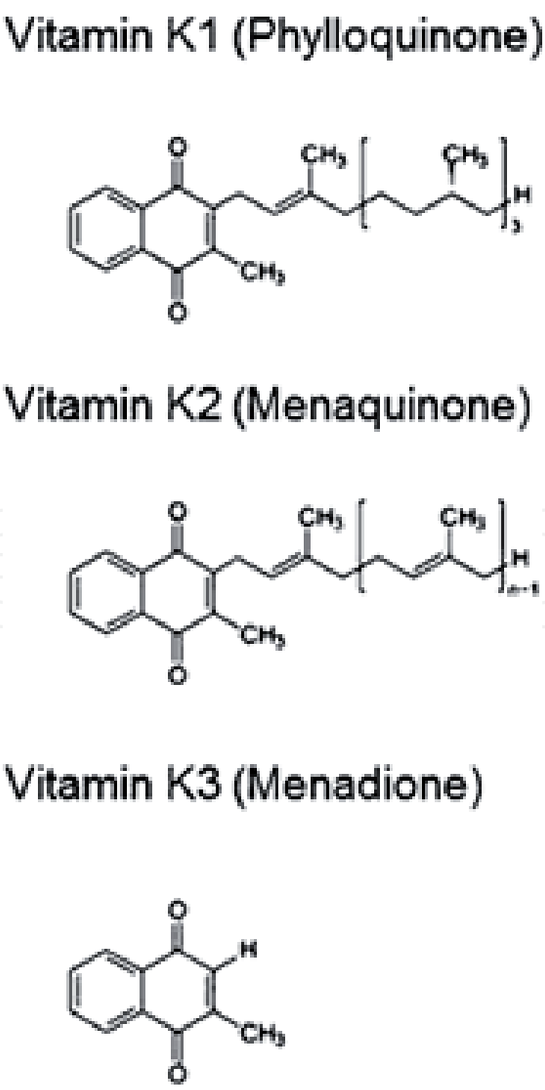

Figure 1.
Structure of the main forms of vitamin K.

These compounds include:

1. Vitamin K1 (phylloquinone)

2. Vitamin K2 (menaquinones)

3. Vitamin K3 (menadione) [7]

3. Sources of vitamin K

Vitamin K1 (phylloquinone) comes from vegetables, especially green leafy vegetables such as spinach, vegetable oils, broccoli, and some fruits [1].

Vitamin K2 (menaquinone) forms a subfamily in which it has an unsaturated isoprenyl side chain (may range from 1 to 13 isoprene residues). The various menaquinones are generally denoted as MK-n, where n symbolizes the number of isoprene residues in the side chain and is designated as MK-4 through MK-13, established upon the length of their side chain. The most well-studied menaquinones are MK-4, MK-7, MK-8, MK-9, and MK-10 that all occur in the human diet.

Menaquinones (except MK-4) are of microbial origin, and relatively high concentrations are only found in a few food items. Natto (a traditional Japanese food made from fermented soybeans) has high amounts of menaquinones (almost exclusively MK-7). Other fermented foods, such as cheese, also contain menaquinones. However, the forms and amounts of vitamin K in these foods likely vary relying on the strains of bacteria utilized to make the foods.

Bacteria in the human gut produce most of the menaquinones, especially the long-chain menaquinones; the amount of vitamin K that the body acquires in this manner is unclear.

Menadione is a synthetic form of vitamin K. It has increased toxic risk, so it is not a commonly supplemented form of vitamin K [1, 15].

4. Absorption and transport of vitamin K

In the intestine vitamin K is incorporated into mixed micelles, and it is absorbed by enterocytes. From there, vitamin K is combined into chylomicrons, released into the lymphatic capillaries, transported to the liver, and then packed again into very-low-density lipoproteins. In the circulation, vitamin K is carried mainly in lipoproteins [16].

5. Recommended intake

The AI for vitamin K1 is 120 mcg/day for men and 90 mcg/day for women as it was determined by the Institute of Medicine in the United States in 2001 [17].

These current AI values are established upon the hepatic vitamin K demanded for activation of coagulation factor and absence of abnormal bleeding. There was not any DRI for vitamin K2 or an upper limit intake level for vitamin K1 at that time. Clinical trials have used vitamin K supplements at doses much higher than the DRI levels (10 mg for vitamin K1 and 45 mg for vitamin K2) and found no evidence of toxic effects. However, trials which have used supplements of 45 mg/day of MK-4 demonstrate incidences of skin appendage lesions [18, 19].

6. Serum vitamin K concentration

Vitamin K is being absorbed via chylomicrons; in addition it is distributed via lipoproteins. The menaquinones with longer side chain are partitioned into LDL, whereas others including vitamin K1 are in the triglyceride rich fragment [20]. Vitamin K does appear to bioaccumulate in various tissues following oral ingestion, and it appears to have a relatively short time in the body prior to being excreted in comparison with the fat-soluble vitamins [16].

The major form of vitamin K in serum is vitamin K1, and it has a relative rapid half-life relative to MK-4, whereas MK-7 and other long-chain menaquinones have a very extended half-life and greater bioactivity [21].

The normal range of circulating concentrations of vitamin K1 is 05–2.5 nM/L (0.22–1.22 ng/ml) without taking any supplements [22]. However the range of vitamin K1 in patients and healthy adults was 0,22–8.88 nM/L (0.09–3.96 ng/ml) as reported in several clinical studies [23].

7. Bone uptake

Osteoblasts appear to take vitamin K which is transported via lipoproteins, and this uptake is facilitated by the LDL receptor which is expressed on these bone cells (LRP1 and, to a fewer degree, VLDLR) with the competence of the triglyceride fraction in giving its phylloquinone being greater than HDL but less than LDL, and the uptake is relying on ApoE. Hence it is thought that genetic variations in ApoE can affect vitamin K status. This region contains several Gla proteins such as matrix Gla protein and osteocalcin which need vitamin K to be effective [24].

Delivery of vitamin K to the bone tends to be less than in the liver, as in instances where vitamin K-dependent proteins (Gla) are totally γ-carboxylated in the liver, while they are not in the bone [20].

8. Vitamin K functions

Vitamin K plays a biological role as a cofactor of gamma glutamyl carboxylase, which mediates γ- carboxylation of glutamic acid residues (Glu) to γ-carboxyglutamic acid (Gla) on vitamin K-dependent protein. The Y-carboxylation of the vitamin K-dependent proteins Gla proteins is essential for their function.

Gla proteins or vitamin K-dependent proteins are a group of proteins that have calcium-binding characteristics and are existing in the extracellular matrix or in body fluids.

These proteins are included in blood clotting, bone mineralization, cartilage, and other soft tissues; and they have an important role in supporting the health of bones, joints, and blood vessels [3]. Some studies have suggested that vitamin K has anticancer [6], anti-inflammatory, and antioxidant characteristics [25].

There are seven different vitamin K-dependent proteins which all regulate coagulation; prothrombin (Factor II) is the most well-known target protein which was the first protein to be discovered to be γ-carboxylated by vitamin K. Afterwards factors VII, IX, and X as well as proteins C, S, and Z were discovered [8].

9. Vitamin K deficiency

There are not enough studies to determine a limit or threshold for concentration of vitamin K in serum that indicate deficiency or insufficiency [24].

Vitamin K deficiency is rare among adults, and it is determined clinically by bleeding because of low activation of coagulation proteins and is often estimated by measurement of undercarboxylated prothrombin concentration in serum released from the liver. Its concentration increases with the degree of severity of vitamin K deficiency [26].

Vitamin K deficiency is usually limited to people with liver and pancreas disease, cystic fibrosis, digestive disorders, disorders of fat malabsorption, chronic malnutrition, and alcohol dependency or those taking drugs that interfere with vitamin K metabolism such as vitamin K antagonist anticoagulants, bile acid sequestrants, certain types of antibiotics, and anticonvulsants [27].

The more common condition is subclinical vitamin K deficiency that results in increased levels of undercarboxylated or even uncarboxylated Gla proteins in serum. This occurs when serum vitamin K concentration is ≤0.5 nM/L [28] or serum undercarboxylated osteocalcin is ≥4.0 ng/mL [26].

Gla proteins that are not fully carboxylated are not activated and do not execute their role in the bone, cartilage, and soft tissue mineralization. Low vitamin K intake and low serum vitamin K concentrations are associated with increased risk of osteoporosis, cancer, and aortic calcification as observed by several studies [27–29].

10. The role of vitamin K in the bone

10.1 Mechanisms dependent on the Y-carboxylation via GGCX enzyme

Several vitamin K-dependent proteins have been verified. Some of them exist in the skeleton and cartilage such as osteocalcin, matrix Gla protein, Gla-rich protein, protein S, and gas 6 [30].

Osteocalcin is the first Gla protein discovered that originated from extrahepatic tissues. It is mainly produced by osteoblasts and has been suggested to affect bone metabolism by regulating osteoblast activity and bone mineralization [31].

Osteocalcin has three glutamic acid (Gla) residues which undergo gamma carboxylation by a process dependent on vitamin K; the Y-carboxylation of osteocalcin is necessary for its function. Y-carboxylated osteocalcin shows a high affinity to hydroxyapatite and bone matrix, contributing to bone formation. It has been shown that decarboxylated osteocalcin cannot bind calcium, thus emphasizing the importance role of vitamin K in the activation protein [32].

The percentage of overall osteocalcin that remained uncarboxylated (% ucOC) is a biomarker of vitamin K status (more carboxylation indicates a better status, less carboxylation indicates a worse status), and osteocalcin continually gets carboxylated up until a daily intake of around 1000mcg phylloquinone. Dietary recommendations (120 μg/day for men, 90 μg/day for women) are based on saturation of the coagulation system. Requirements to maintain bone Gla protein function and bone formation might be higher [33, 34].

Some studies have demonstrated that elevated concentration of undercarboxylated osteocalcin in serum is a predictor of fractures [35, 36].

MGP is included in the organic matrix and mobilization of calcium in the skeleton. It is mainly synthesized in the bone, cartilage, dentine, and soft tissues, including blood vessels, and is also found in the brain, heart, kidney, liver, lung, and spleen [37, 38].

10.2 Mechanisms independent of the Y-carboxylation via GGCX enzyme

Studies also reported that vitamin K prevents bone resorption through a mechanism totally different from that of Y-carboxylation. Vitamin K is shown to improve

bone mineralization and decrease bone resorption by osteoclasts [39]. Other vitamin K roles have also been reported such as it can promote fracture reparation by stimulating bone formation and decrease calcium excretion by urine [3]. These results confirm the significant role of vitamin K in bone metabolism.

Vitamin K also functions as a ligand of steroid and xenobiotic receptor (SXR) and its murine homolog, pregnane X receptor (PXR), which after heterodimerization with the vitamin A receptor (RXR) induces the target genes including tsukushi (*Tsk*), matrilin-2 (*Matn2*), and *CD14*. *Tsk* encodes a protein that has a collagen-accumulating effect, and Matn2 is a protein comprising an extracellular matrix like collagen, whereas *CD14* regulates osteoblastogenesis and osteoclastogenesis.

Msx2 is another vitamin K-induced SXR-dependent gene identified, which induces osteoblast differentiation. Induction of these genes is not repressed by warfarin treatment, indicating a GGCX-dependent mechanism is not involved [30].

It has been reported that osteoporosis is linked with oxidative stress. Moreover, supplementation of vitamin K as an antioxidant vitamin could effectively reduce levels of oxidative stress, with possibly advantageous influence on bone, as displayed in several experimental models [27].

It is possible that higher levels of vitamin K suppress IL-6 secretion from inflammatory stressors, although the mechanisms underlying this are not currently known [11]. In addition, vitamin K also represses osteoclast activity, therefore averting the breakdown of bone [40].

11. Studies on vitamin K and the bone

Osteoporosis is a metabolic bone disease of reduced bone density, fragile bone, and elevated susceptibility to fracture [41]. Risk factors for osteoporosis contain genetic, nutrition, and hormone [3].

It is a common disease affecting 1 in 3 women and 1 in 12 men, resulting in substantial morbidity, excess mortality, and health and social services spending. It is therefore important to improve strategies for prevention and treatment osteoporosis in both men and women [42].

Some studies showed that the administration of vitamin K led to an increase of bone mineral density (BMD) in osteoporotic patients (Vermeer et al. [43]). In addition, administration of vitamin K was found to prevent bone loss and reduce the incidence of fractures (Shiraki et al. [44]).

A survey investigating vitamin K intake data from the fifth Korea National Health and Nutrition Examination Survey reported that low dietary vitamin K intake was related to low bone mineral density in subjects who were included (2785 men, 4307 women aged over 19 years). In addition, there was a reduction in risk for osteoporosis as vitamin K intake increased in women, but this effect was not continued after adjusting factors. This survey recommended increasing the dietary VK intakes for preserving BMD [45].

A study by Fujita et al. [46] observed that high intake of natto, fermented soybean high in phylloquinone, and MK-7 was associated with higher BMD, which was also demonstrated in a study by Ikeda et al. [47].

A cross-sectional study (3199 middle-aged Scottish females included) reported that females in the highest quartile of dietary intake of vitamin K1 (162 mcg/day) have a significantly higher lumbar spine (L2–L4) BMD and left femoral neck BMD against the lowest quartile (59 mcg/day) [48]. In vitro experiments by Hara et al. showed that vitamin K inhibits bone resorption induced by IL-la, PGE, PTH, and vitamin D3 in a dose-dependent manner [12].

Several studies have shown the relation between vitamin K and bone mineral density; a study by Kanai et al. reported that postmenopausal women with decreased bone mineral density (mean BMD, 0.73 g/cm2) had significantly lower levels of vitamin K1 and MK-7 than women with normal bone density (mean BMD, 0.99 g/cm^2) [49].

In our study we found that serum vitamin K1 level was significantly lower in the postmenopausal osteoporotic women group than in the normal control group, the mean serum vitamin k1 level was significantly lower in the postmenopausal osteoporotic women group than in the normal control group (mean = 0.794 vs. 3.61 ng/ml, P < 0.0001), and serum vitamin k1 concentration was positively correlated with lumbar spine BMD among postmenopausal osteoporotic women (R = 0.533, p = 0.009) and in postmenopausal healthy control (R = 0.563, p = 0.02). Diagnostic sensitivity and specificity of vitamin k1 for osteoporosis were 90 and 98%, respectively (cutoff value: 0.853 ng/ml). The area under the ROC curve (AUC) value for vitamin k1 was 0.984; the odd ratio result was 18.66 [50]. The same result was reported also by Heiss et al. [51].

These findings may suggest a role of vitamin K in bone metabolism. And therefore it has been thought that it might be effective for treating osteoporosis. Furthermore, Booth et al. [52] found that low plasma vitamin K1 concentrations were associated with low spine BMD among postmenopausal women not using estrogen replacement. These findings suggest a protective role of vitamin K in the skeleton in women. In addition, poor vitamin K nutritional status (low plasma phylloquinone concentrations and high serum %ucOC) was correlated with low BMD at the hip among men.

High incidence of vertebral fractures has reported to be contrarily correlated with BMD of lumbar spine and vitamin k1 concentration in the study on 379 Japanese women of 30–88 years to 4 years [53].

Vitamin K was found to increase bone mineral density in an in vivo osteoporosis model. A study by Hodges et al. deduced that osteoporotic patients had decreased levels of vitamin K and increased levels of non Y-carboxylated osteocalcin [54].

The relations between vitamin K intake and bone mineral density are not coherent in observational studies [27].

Fang et al. showed that vitamin K supplements did not have influence on BMD at the femoral neck, but there was an increase in mean lumbar spine BMD by 1.3% (95% CI: 0.5–2.1) after supplementation for 6–36 months.

In this meta-analysis, seven studies utilized vitamin K1 with portions ranging from 0.2 to 10 mg/day. Ten studies utilized vitamin K2 (eight used MK-4 with portions of 15–45 mg/day, and two studies utilized MK-7 with portions of 0.2–3.6 mg/day), and after studies with high risk of bias have been excluded, the writer deduced that supplementation with vitamin K did not have significant effect on lumbar spine BMD in their subgroup analysis; they found that supplementation with vitamin K2 increased mean lumber spine BMD by 1.8% (95% CI, 0.9–2.8). No such influence was realized for studies with vitamin K1 supplementation [19].

It has been reported that osteoporosis is related to oxidative stress. Moreover, supplementation of vitamin K, as an antioxidant vitamin, could effectively decrease levels of oxidative stress, with possibly beneficial effect on the bone, as displayed in several experimental models [55].

Vitamin K is necessary for bone health. In fact, low vitamin K intake, low vitamin K circulating levels, and high undercarboxylated osteocalcin levels are all related with excessive hip fractures risk in observational studies [15].

More studies are required regarding the influences of vitamin K on diagnosis and management of osteoporosis and similarly on BMD.

12. Conclusion

Studies suggest that vitamin K has a role in bone metabolism and it may contribute in maintaining BMD and diagnosing osteoporosis. Studies have demonstrated that in the healthy population, all clotting factors are synthesized in their active form, whereas the synthesis of other Gla proteins is sub-optimal in non-supplemented subjects. Prolonged subclinical vitamin K deficiency is a risk factor for osteoporosis. Present recommendations for dietary intake are based on the daily dose required to prevent bleeding. Scientific data suggests that new, higher recommendations for vitamin K intake should be formulated.

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