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Review

Vitamin K and osteoporosis: Myth or reality?

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ABSTRACT

Vitamin K is a liposoluble vitamin. The predominant dietary form, phylloquinone or vitamin K1, is found in plants and green vegetables; whereas menaquinone, or vitamin K2, is endogenously synthesized by intestinal bacteria and includes several subtypes that differ in side chain length. Aside from its established role in blood clotting, several studies now support a critical function of vitamin K in improving bone health. Vitamin K is in fact required for osteocalcin carboxylation that in turn regulates bone mineral accretion; it seems to promote the transition of osteoblasts to osteocytes and also limits the process of osteoclastogenesis. Several observational and interventional studies have examined the relationship between vitamin K and bone metabolism, but findings are conflicting and unclear. This systematic review aims to investigate the impact of vitamin K (plasma levels, dietary intake, and oral supplementation) on bone health with a particular interest in bone remodeling, mineral density and fragility fractures.

Contents

1. Introduction . . . 58
2. Materials and Methods. . . . 58
3. Vitamin K. . . . 58
   3.1. Structure and Sources . . . 58
   3.2. Vitamin K Status in Humans . . . 58

Abbreviations: VK, Vitamin K; OC, Osteocalcin; RCTs, Randomized Control Trials; BMD, Bone Mineral Density; BTM, Bone Turnover Markers; VD, Vitamin D; Gla, γ-carboxyglutamic acid; PT, Prothrombin Time; MGP, Matrix Gla Protein; Gas-6, Growth arrest-specific 6 protein; ucOC, undercarboxylated OC; cOC, carboxylated OC; RANKL, Receptor Activator of Nuclear factor Kappa B Ligand; ODF, Osteoclast Differentiation Factor; SXR, Steroid and Xenobiotic Receptor; PXR, Pregnane X Receptor; FFQ, Food Frequency Questionnaire; BALP, Bone Alkaline Phosphatase; CTX, C-terminal Telopeptide of type 1 collagen; P1NP, Procollagen I Intact N-Terminal; NTX, N-terminal Telopeptide of type 1 collagen; QUS, Quantitative Ultrasound; BMC, Bone Mineral Content; CI, Confidence Interval; RR, Relative Risk; HR, Hazard Ratio; OR, Odds Ratio; DXA, Dual-energy X-ray absorptiometry; VKAs, VK antagonists; PTH, Parathormone.

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3.3. Dietary Intake . . . 59
3.4. Bioavailability . . . 59
4. Vitamin K and Osteoporosis . . . 59
4.1. Physiological Action of Vitamin K in Bone . . . 59
4.2. Vitamin K and Bone Remodeling . . . 60
4.3. Vitamin K and BMD . . . 61
4.4. Vitamin K and Bone Quality . . . 63
4.5. Vitamin K and Bone Fractures . . . 66
5. Vitamin K Antagonists and Bone Health . . . 66
6. Conclusion and Major Limitations . . . 68
Author Contributions . . . 68
Conflicts of Interest . . . 68
References . . . 68

1. Introduction

The fundamental role of vitamin K (VK) in blood clotting is well established [1–5]. However, the past two decades have seen increasing evidence supporting that VK also plays an important part in bone health. Indeed, VK is needed to carry out the process of osteocalcin (OC) carboxylation [6], it seems to promote the osteoblast-to-osteocyte transition and also limit osteoclastogenesis [7].

Some cross-sectional and randomized control trials (RCTs) have reported that VK plasma levels show a positive correlation with bone mass and a negative one with fracture risk. It has been clearly demonstrated that optimal vitamin D (VD) repletion is necessary to maximize the response to anti-resorbers regarding both bone mineral density (BMD) changes and anti-fracture efficacy [8], but we do not know exactly whether optimal VK status affects the response to anti-osteoporotic drugs. Moreover, most of the studies published on this topic are characterized by several important limitations and provide contrasting evidence. VK supplementation is therefore still not globally recommended to contrast post-menopausal bone loss, although an exception is Japan where it has already been approved for the prevention and treatment of osteoporosis [9].

This systematic review aims to investigate the impact of VK (plasma levels, dietary intake, and oral supplementation) on bone health. In particular, the focus is on the relation between VK and bone remodeling, bone mineral density and bone fragility fractures.

2. Materials and Methods

PubMed, MEDLINE and Cochrane databases were searched according to PRISMA guidelines [10] to identify publications on VK and bone health. Articles investigating the different forms of VK and their effect on bone metabolism were included. Names of different forms of VK such as Phylloquinone (K1), Menaquinone (K2), Menaquinone-4 (MK-4) and Menaquinone-7 (MK-7) were matched with bone turnover markers (BTM), in particular OC, BMD, and bone fragility fractures. Publications in English only were included.

3. Vitamin K

VK is a liposoluble vitamin discovered in 1929 by Henrik Dam, and its name derives from the German word *koagulation*. VK plays a central role in the liver where it is required for the synthesis of functionally active forms of several coagulation factors [11]. Its emerging role in modulating bone metabolism will be discussed in this review.

3.1. *Structure and Sources*

VK exists in two forms that share a methylated naphthoquinone nucleus (menadione) and have a variable aliphatic side chain at the 3′ position.

Phylloquinone (K1) is the predominant form found in human diet and is synthesized by plants and green vegetables, like kale, spinach, broccoli and some fruits and herbs. Certain types of oil such as soybean and canola also contain large amounts of K1 (Table 1) [12].

Menaquinones (K2) consist of several subtypes that differ in the length of the side chain which may range from 1 to 13 residues of unsaturated isoprene: the *n* in the acronym MK-n reflects the number of isoprene residues in the aliphatic side chain. K2 is endogenously synthesized by intestinal bacteria, so it has a more confined distribution in the diet than K1 and it is found in some cheese, eggs, meat and *natto* (fermented soybeans commonly consumed in Japan that are the richest source with a content of 775 mcg/100 g) [13–15].

K1 can be converted into menaquinone-4 (MK4) and accumulated in extrahepatic tissues. It has also been demonstrated that this conversion occurs following oral or enteral administration, but not parenteral or intracerebroventricular administration [16].

3.2. *Vitamin K Status in Humans*

VK status is still not a straightforward estimation. It can be measured in plasma, but an abnormal lipid profile may affect the results. Moreover, VK is a soluble vitamin with many isoforms and VK plasma values alone may not be sufficient to assess the real VK status. VK content of an adult human liver is about 200–300 nmol [17]. It is not clear whether liver storage may be an indicator of VK status, in fact, liver may or