Original Research Paper

Volume-8 | Issue-8 | August-2018 | PRINT ISSN No 2249-555X

Health Science

VITAMIN K IN WOMEN'S HEALTH

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ABSTRACT In the last decades data about the importance of vitamin K in human health became even more interesting. Vitamin K includes a group of lipophilic substances called quinones which are different from a biochemical point of view and in respect of their pharmacological profile, as regards their use as supplements. In particular, vitamin K2 seem to be the most intriguing because of its large involvement in bone maintenance in postmenopausal women. However, according to recent studies, vitamin K may represent an "omnipotent vitamin", considering the growing interest in different fields, such as cardiovascular pathologies and oncogenesis. Anyway, the most solid evidence concern bone health. We review and discuss the impact of vitamin K, particularly vitamin K2, on female bone homeostasis and we also synthesize new highlights about vitamin K status in general women's health and their possible future therapeutic implications.

KEYWORDS : vitamin k2, osteoporosis, bone, osteocalcin, fracture

Introduction

Vitamin K refers to a group of fat-soluble compounds called quinones including phylloquinone or phytonadione (vitamin K1), menaquinones (vitamin K2), menadione (vitamin K3) [1]. All these compounds are characterized by the common 2-methyl-1,4-naphthoquinones ring binding a different side chain in position 3, consisting in substituent R group [2]. For example, vitamin K1 has a partially saturated polyisoprenoid group (phytyl R group), while vitamin K2 shows a repeating, unsaturated trans-polyisoprenyl R group. Vitamin K3 presents a simpler structure, without an aliphatic R group chain; it is considered a minor active syntetic form of vitamin K, even if some authors hypotisized it may derive from intestinal bacterial vitamin K1 cleavage [3].

Vitamin K1 is the major type of dietary vitamin K, mainly found in green leafy vegetables: on the contrary, vitamin K2 is the product of animal and human intestinal bacteria from the conversion of other forms of vitamin K and may be also present in fermented food such as beef liver, butter and natto [4]. All subgroups of vitamin K take their name from the German word "koagulation", as it seemed to be principally involved in blood clotting. Afterwards, lots of data reported vitamin K was linked to bone metabolism, cardiovascular health and cell growth regulation, due to its pluripotent activity [4].

General mechanism of action

All different side chains of isoprenoid units of vitamin K are used by a specific enzyme called gamma-glutamate carboxylase to functionally activate Vitamin K-dependent proteins (VDK) [5]. They include significant proteins involved in blood coagulation - like factors II (prothrombin), VII, IX, and X, protein C, and protein S- , in bone formation - Osteocalcin (OC) and Periostin, and in inhibition of soft tissue calcification - Matrix GLA protein (MGP) [5]. The carboxylation of all these factors is essential to guarantee their structural integrity and tissutal activity; so, vitamin K intake need to be sufficient to ensure this phenomenon [6]. Vit K2 has the most potent gamma-carboxylation activity, probably owing to the lenght and complexity of its side chains corresponding to different menaquinones (from Menaquinone-4 -MK-4- to Menaquinone-13 -MK13) [6]. For example, vitamin K2 as MK-4 seem to be less active then MK-7 which provides the highest vitamin K2 activity because of its longer half-life [7]. Being fat-soluble, all forms of vitamin K are normally absorbed as mixed micelle in bowel of individuals with a regular pancreatic and bilious function; however, its lipophilicity does not ensure an effective storage in the body and its reserve should be rapidly depleted without a regular dietary intake because of its rapid metabolism[8].

Vitamin K and bone health

The role of vitamin K in bone metabolism is strictly related to osteocalcin (OC), the main non collagenic protein of bone [9]. OC need to be always converted in its carboxylated form to become efficacious: fully carboxylated OC (cOC) can be found within hydroxyapatite, strongly binding calcium to consolidate calcification of hydroxyapatite crystals [9,10]. This process should be exerted in presence of sufficient level of vitamin K because hydroxyapatite-binding properties of OC strongly decreases if the undercarboxylated form (ucOC) is predominant [11]. Moreover, recent evidence demonstrated vitamin K may bind a specific nuclear receptor called Steroid and Xenobiotic Receptor (SXR) expressed by osteoblasts, the essential cells for bone formation, and implicated in matrix deposition [12]. Other authors reported vitamin K, especially vitamin K2, may reduce osteoclastogenesis, inhibiting Rank-L activity [13]. In fact, the link between Rank-L and Rank is a specific mechanism of regulation of osteoclastic differentiation and function particularly crucial to activate bone resorption [14]. All the mechanisms proposed to clarify vitamin K activity on bone, were supposed to be reciprocally involved in modulating bone quality in vitamin K deficiency.

Many studies recognized a significant link between vitamin K status and risk of bone loss [15]; in fact, lower level of vitamin K was reported in patients affected by osteoporosis. Circulating undercarb oxylated osteocalcin (ucOC) was considered an independent risk predictor of bone fractures by different authors [16] . Low consumption of vitamin K seem to be associated with higher femoral fracture risk [17] , increased bone turnover [18] and lower Bone Mineral Density (BMD) in both sexes [19,20]. On the other hand, vitamin K requirement for carboxylation of OC is not met by usual dietary intake but carboxylation readily responds to phytonadione or menaquinone supplementation [6,7]. In particular, vitamin K2 demonstrated to be more powerful on bone than vitamin K1, probably due to its greater bioavailability [8]. Results from some randomized controlled trials (RCTs) showed monotherapy with Menatetrenone - the brand name of a synthetic vitamin K2 chemically identical to MK-4- produced significant reduction of ucOC in association with modest increase of lumbar and distal radius BMD and reduction of fracture risk [21]. In all the principal studies, Menatetrenone dose corresponded to 45 mg/day, offering a good tolerability profile, except for few gastrointestinal side effects, like diarrhea and temporary abdominal pain, reported in some cases [22]. An important metanalysis published in 2006 studying the consequences of treatment with vitamin K2 on bone health, showed a significant reduction of all major fragility fractures (vertebral, non vertebral, hip) after supplementation [23]. An other one written by Huang ZB et al. confirmed these data [24]. These authors included 19 randomized controlled trials involving a total of 6759 participants. Interestingly, they showed vitamin K2 supplementation may improve vertebral BMD and prevent all major osteoporotic fractures in postmenopausal women with osteoporosis. Likewise, the subgroup analysis of participants without osteoporosis found no significant difference between treatment group and placebo with respect to vertebral, femoral and forearm BMD and global fracture incidence. It may be concluded vitamin K2 can sustain bone integrity, especially in patients affected by bone loss, efficiently reducing their risk of fragility fracture. However, the benefits of vitamin K2 addition remain uncertain in healthy subjects.

The direct beneficial effects of vitamin K2 on fracture risk remains a matter of controversy. The most important evidence about vitamin K2 bone benefits mainly concern bone quality [25]. In an interesting manner, Knapen et al. observed 325 postmenopausal women receiving either placebo or 45 mg/day of vitamin K2 as menatetrenone during 3 years [25]. At the end of the study, authors pointed out MK-4 supplementation can ameliorate bone strength, acting on bone geometry and structure, regardless of bone density. In particular, mean change from baseline of Femoral Neck Width (FNW) and lumbar Bone Mineral Content, was greater than that obtained with placebo after 3 years [25]. Although neither group did report significant modifications referring BMD, as probably expected by the use of a single supplement, the impact of vitamin K2 use on bone structure remained significative. In fact, according to its mechanism of action, vitamin K2 should improve bone health, ensuring structural integrity other than providing a certain rapid achievement of bone density [26].

Vitamin K2 action on bone metabolism may streghten calcium and vitamin D supplementation effects in postmenopausal women, as indicated by an important evaluation performed in The Post-Menopausal Health Study II [27]. The authors analyzed 173 women divided in 4 groups: the control placebo group only taking calcium 800 mg/die (CG); Group 1 treated with Calcium 800 mg/die + 10 mcg (=400 UI) (CaD); Group 2 with Calcium + Vitamin D3 + 100 mcg Vit K1 (CaDK1); Group 3 Calcium + Vitamin D3 + 100 mcg Vit K2 as MK-7 (CaDK2). At the end of the study after 12 months, significant increases in total-body BMD were observed in all intervention groups compared to CG ($P<0.05$), while significant increases in lumbar spine BMD were observed only for CaDK1 and CaDK2 compared to CG ($P<0.05$). The positive intervention effect in these two study groups was also reflected in the suppression of the bone remodeling process, indicated by the reduction of the urinary bone resorption marker Pyridinoline (Pyr) in CaDK2 and deoxypyridinoline (D-Pyr) in both CaDK1 and CaDK2, leading to significantly lower follow-up levels in these two groups compared to CaD and CG ($P = 0.047$) [27]. These indices are two cross-links of collagen molecules that are present in the extracellular matrix and specifically released during bone matrix degradation: therefore, their urinary excretion might be a sensitive marker of bone turnover [27]. According to these findings, it is conceivable Vitamin K may potentiate beneficial effects on bone of usual recommended supplementation with calcium and vitamin D, acting at both different level, such as bone density and bone quality, even if the predominant impact remains on structural characteristics, as shown by the most important evidences [27,28]. Interestingly, a randomised, placebo-controlled, double-blinded clinical trial about 148 postmenopausal women with osteopenia, all supplemented with calcium and vitamin D but partly taking 375 µg of MK-7 for 12 months, revealed vitamin K2 use prevented age-related deterioration of trabecular bone microarchitecture measured by high-resolution peripheral quantitative computed tomography (HRpQCT) and biochemical bone turnover markers at tibia [29]. In particular, reduction of trabecular numbers and augmentation of trabecular spacing seemed to be more expressed in placebo group than treatment group, suggesting the use of vitamin K2 preserves trabecular structure slowing bone quality loss, even in patients with initial bone impairment [29]. However, longer-term studies need to prove these results.

In clinical practice, vitamin K2 is frequently used in combination with bisphosphonates (Bps), the best known antiresorptive agents which are analogues of inorganic pyrophosphate [30]. Iwamoto et al. showed etidronate associated with vitamin K2 had a more significant beneficial effects on radial BMD than each treatment alone assessed after 24 months [31]. Besides, that combined therapy resulted in significant reduction of vertebral fracture incidence compared to calcium or etidronate or vitamin K2 assumption alone [31]. Other findings suggested vitamin K2 associated with alendronate enhanced the decrease in serum ucOC concentrations and significantly increased femoral neck BMD [30]. Kasukawa et al. [32] studied the effects of risedronate together with vitamin K2 on serum ucOC and OC levels in postmenopausal women affected by osteoporosis, enrolling 101 women aged > 60 years randomly, stratified into two groups respectively treated with risedronate alone (R group n = 51) and with risedronate and vitamin K2 (R + K group n = 50). Although vertebral fracture incidence did not significantly differ between the groups at 6 and 12 months, ucOC levels assessed at 6 months in patients with incident vertebral fractures were significantly higher than in patients without, when using risedronate alone ($p < 0.05$), according to the lack of a possible precocious protective role of vitamin k2 supplementation that cannot be available in the R group [32].

On the other hand, the more recent Japanese Osteoporosis Intervention Trial-03 [33] excluded concurrent treatment with vitamin K2 (45 mg/day) and risedronate (2.5 mg/day or 17.5 mg/week) is effective compared with monotherapy with risedronate in terms of fracture prevention. However, uoOC concentration decreased from 5.81 ± 3.93 ng/mL to 2.59 ± 1.52 ng/mL at 6 months in the risedronate and vitamin K2 group, whereas the change in the risedronate alone group was minimal (from 5.96 ± 4.36 ng/mL to 4.05 ± 3.40 ng/mL at 6 months) ($p < 0.01$) [33]. These data suggested K2 has synergistic effect with other bone treatments on preventing the deterioration of bone architecture, particularly at vertebral level, where trabecular weakness may be more rapidly induced by estrogen deficiency in postmenopause [34]. However, we need further investigations to strenghten these concepts.

Vitamin K and cardiovascular system

The relationship between cardiovascular health and vitamin K is mainly sustained by the role of Matrix Gla Protein (MGP) [35,36]. MGP is a VKD protein mostly working in extracellular matrix of soft tissues (vascular, heart, lung, kidney, cartilage) to down-regulate calcium deposition [37]. In fact, carboxylated MGP inhibits vascular calcification by directly binding calcium ions and sequestring them, decreasing their incorporation into the extracellular matrix [37]. The exceeding clinical paradigm on the impact on blood vessels of MGP is the typical abnormal calcification of cartilage and arteries of Keutel Syndrome, caused in humans by an inactivating MGP gene mutation [38]. On the other hand, many studies demonstrated anticoagulant treatment is associated with an increased number of vascular and cartilagineous calcifications, aside from non-traumatic bone fractures [39]. Therefore, it was supposed the lack vitamin K should negatively affect not only bone integrity through the reduction of efficacious carboxylated OC (cOC) but also vascular walls by the detrimental structural modification of MGP [40]. In animal models, increased Vit K2 intake has been associated with decreased arterial calcium deposition and ability to reverse vascular calcification [41] Furthermore, low Vit K status may worsen vascular calcifications [42,43]. In two different randomised, double-blind controlled trials, supplemental Vit K has been shown to significantly delay both the development of Coronary artery calcification (CAC) [44] and the deterioration of arterial elasticity [45]. Kyla Shea et al. showed in 229 healthy patients of both sexes with preexisting CAC, 500 mcg/die phylloquinone supplementation for 3 years, slows the progression of CAC, independent of its effect on total MGP concentrations [46]. In these context, clear mechanisms by which vitamin K conferred a protective role on blood vessels need to be still elucidated. In an other study [47], 181 postmenopausal women were given either a placebo or a supplement containing vitamin D plus minerals (MD-group), or the same supplement with vitamin K1 (MDK-group). Elastic properties of the common carotid artery in the MDK-group remained unchanged over 3 years, but decreased in the MD- and placebo-group, suggesting vitamin K1 supplementation may substantially improve the elastic properties of the arterial vessel wall [47].

Interestingly, these data pointed out the meaningful "bone-vascular cross-talk" which seemed to be crucial to explain the strong association between bone loss and cardiovascular disease [37]. Growing interest about this link led to recognize multiple common risk factors (such as age, smoking, alcohol consumption, physical activity and menopause) and different molecules, (for example bone morphogenetic proteins, osteoprotegerin, receptor activator of nuclear factor kB ligand, parathyroid hormone, phosphate, oxidized lipids and vitamins D) implicated in both conditions [48]. In particular, Vitamin K may play a pivotal role in both cardiovascular and bone homeostasis, regulating "calcium paradox" phenomenon [49]: optimal level and activity of carboxylated form of MGP should prevent the deposition of calcium in the vessel wall with the simultaneous reduction of calcium deposition in the bone, contributing to bone and cardiovascular protection.

Vitamin K and tumor growth

Among different VKD proteins, the Growth arrest specific-6 gene (Gas-6), became relevant, especially owing to its anti-oncogenic potential [50]. Gas-6 generally contributes to anticalcificant activity of

MGP, inhibiting apoptosis of the vascular smooth muscle cells (VSMC) of the vessel wall which provides the major number of initial structured foci of calcification [51]. Moreover, it seem to directly delay proliferation, survival and migration of tumoral cells, by binding to its receptors Tyro3, Axl and Mer (TAM) [51]. Lots researchears are studying the anti-proliferative effects in several cancer cell lines of other VKD proteins which may exert their positive regulatory effect on different signaling pathways via transcription factors and protein kinases [51,52]. In particular, some authors demonstrated Vitamin K2 supplementation had beneficial effects on chemoprevention of hepatocellular carcinoma (HCC) recurrence after curative ablation therapy and surgical resection of the liver [53]. Vitamin K therapy may have a synergistic action with other antitumoral agents, reducing serum des-γ-carboxy prothrombin (DCP) levels, identified as a tumor growth and angiogenesis factor in HCC [54]. However, large randomized control trial (RCT) remain fundamental to confirm the advantage of vitamin K2 assumption in this setting. At present, according to the possible role of many VKD proteins on tumor biology, the coadministration of vitamin K with anti-tumoral agents may offer to these patients a chance not only to strenghten their anti-neoplastic therapies but also to better preserve their bone quality and strenght which should be impaired by the same anti-cancer drugs [55].

Conclusion

According to its biochemical characteristics and well-known action at different levels, Vitamin K can be considered a pluripotent substance. Low intake of vitamin K is strongly associated with bone fragility and cardiovascular risk. In particular, vitamin K2 assumption, especially as MK-7, seem to be a valid option to potentiate the beneficial effects of calcium and vitamin D supplementation on bone strenght. Positive results of vitamin K2 in combination with BSPs have been also clearly demonstrated in different studies. Although further investigations and RCTs are necessary, increasing future higlights may confirm the role of vitamin K2 in cardiovascular health and tumor prevention.

The authors declaire that there is no conflict of interest regarding the publication of this article

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