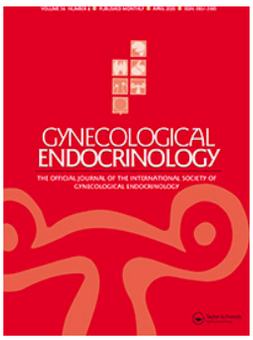

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

Role of vitamin K_2 in bone metabolism: a point of view and a short reappraisal of the literature

A. Capozzi, G. Scambia, S. Migliaccio & S. Lello

To cite this article: A. Capozzi, G. Scambia, S. Migliaccio & S. Lello (2020) Role of vitamin K_2 in bone metabolism: a point of view and a short reappraisal of the literature, Gynecological Endocrinology, 36:4, 285-288, DOI: 10.1080/09513590.2019.1689554

To link to this article: https://doi.org/10.1080/09513590.2019.1689554

Published online: 12 Nov 2019.

GYNECOLOGICAL ENDOCRINOLOGY
2020, VOL. 36, NO. 4, 285–288
https://doi.org/10.1080/09513590.2019.1689554

Taylor & Francis
Taylor & Francis Group

BONE METABOLISM

Role of vitamin K_2 in bone metabolism: a point of view and a short reappraisal of the literature

A. Capozzi[a], G. Scambia[a], S. Migliaccio[b] and S. Lello[a]

[a]Department of Woman and Child Health, Policlinico Gemelli Foundation-IRCCS, Rome, Italy; [b]Department of Movement, Human and Health Sciences, Unit of Endocrinology, University of "Foro Italico" of Rome, Rome, Italy

ABSTRACT

Vitamin K_2 (vit K_2) belongs to a large group of fat-soluble compounds whose formulation is MK (menaquinone) (MK-2 to MK-14), that seem to be involved in different biological functions. In particular, vit K_2 has been recently recognized as efficacious and safe in treatment of bone loss, as it contributes to structural integrity of osteocalcin (OC), the major non-collagenous protein typically found in bone matrix. Several studies proved low vit K_2 intake is linked to bone loss and to increased fracture risk in both sexes. Nowadays, vit K_2 supplementation is considered a significant manner to enhance the association of calcium and vitamin D whose role on bone health is largely recognized. On the other hand, vit K_2 may be used alone or with other drugs to preserve bone quality/strength from skeletal degradation after menopause and/or in patients affected by secondary osteoporosis. In this paper, we review the most recent data about vit K_2 on skeleton.

ARTICLE HISTORY
Received 3 July 2019
Revised 26 October 2019
Accepted 3 November 2019
Published online 12 November 2019

KEYWORDS
Vitamin K_2; bone; osteoporosis; fracture; menaquinone

Introduction

Vitamin K2 (vit K2) includes different types of menaquinones (from menaquinone-4 – MK-4 – to menaquinone-13 – MK13), a group of chemicals characterized by a naphthoquinone ring and a side variable length chain. The chemical formulation of vit K2 is MK_n (MK-2 to MK-14) where 'n' stays for the number of chains of isoprenoid, which are mainly unsaturated; in contrast, forms of menaquinones, except for MK-4, which are produced by anaerobic bacteria present in the colon, have saturated prenyl units [1]. All types of vitamin K differ in their biological actions, due to discrepancies in enzyme affinity and tissue distribution. Vitamin K_1 is mainly stored in the liver; thus, it plays a pivotal role in synthesis of coagulation proteins, while vit K2 is extensively distributed in the human body [1]. In particular, vit K2 properties were largely investigated since this fat-soluble compound seems to be involved in different physiological processes [1]. Specifically, the role of vit K2 in maintenance of bone integrity assumed growing interest in bone biology and treatment of osteopenia/osteoporosis.

In this review, we summarize recent evidence about vit K2 impact on bone metabolism.

Vitamin K2 and bone tissue: state of the art

Many data regarding vit K2 action on bone tissue are now available. It is largely known how low levels of vitamin K might negatively impact on inner skeletal structure, producing an increased risk of osteopenia/osteoporosis in both sexes. In a prospective study, Feskanich et al. demonstrated that low consumption of vitamin K was associated with higher hip fracture risk at 10 years in women aged 38–63 years in the lowest quintile of intake (<109 μg/day). For instance, that risk seemed to be inversely related to lettuce consumption (RR: 0.55; 95% CI: 0.40, 0.78), as that food is particularly rich of vitamin K [2].

This observation was confirmed in following studies, suggesting that in elderly men and women vitamin K intake was associated with femoral fracture risk but not with bone mineral density (BMD) [3]. On the other side, the Hordaland Health Study conducted from 1997 to 2000 did not confirm relevant positive association between dietary intake of both vitamins K_1 or K2 and BMD. However, the authors pointed out how women with low intake of vitamin K_1 had higher risk of low BMD while vit K2 assumption seemed to less significantly affect BMD [4].

Macdonald et al. showed vitamin K dietary intake was directly associated with higher BMD and concomitant reduction of markers of bone turnover (BTMs) in a cohort of post-menopausal Scottish women aged 49–54 years [5].

Furthermore, low vitamin K consumption had been linked to bone turnover in adolescent girls aged 3–16 years. In fact, Kalkwarf et al. reported high plasma phylloquinone and low percentage undercarboxylated osteocalcin (ucOC) were associated with lower bone resorption and formation [6].

Given these data which still require further clarifications in largest population studies, the role of vitamin K in bone metabolism may be crucial and possible benefits of its supplementation becomes even more intriguing.

According to the latest evidence, vitamin K supplementation in addition to vitamin D and calcium seems to contribute to increase lumbar spine BMD in comparison to the standard combination of calcium and vitamin D alone [7]. In particular, vit K2 seemed to be more efficacious in improving bone quality, owing to its pharmacological features. In fact, as mentioned earlier, vit K2 is characterized by many long side chains that confer structural complexity and specificity to this compound [8].

CONTACT S. Lello lello.stefano@gmail.com Department of Woman and Child Health, Policlinico Gemelli Foundation-IRCCS, Rome, Italy

Vit K2 can be linked to the maximum gamma-carboxylation activity in comparison with other kind of vitamin K (such as vitamin K_1 and vitamin K3): this aspect is particularly important as it is essential in the maintenance of osteocalcin (OC) structure, the most important non-collagenic skeletal vitamin K-dependent (VKD) protein. In fact, the gamma-carboxylated OC (cOC) corresponds to the active OC that can effectively bind calcium to bone hydroxyapatite crystals [9]. Moreover, the presence of normal level of vit K2 ensures the key phenomenon of carboxylation of all other VKD proteins, including Periostin and Matrix Gla protein (MGP), producing their functional activation in different organs [10]. Besides, vit K2 was supposed to act through other peculiar mechanisms of action. Rank–RankL pathway plays a pivotal role in the regulation of osteoclastic activity and differentiation, stimulating bone resorption [11]; interestingly, vit K2 has been demonstrated to directly inhibit this pathway, thus reducing osteoclastogenesis [11]. On the other hand, it appears vit K2 might improve osteoblastogenesis ensuring bone formation, directly interacting with the steroid and xenobiotic receptor (SXR), a nuclear receptor of osteoblasts which can promote the accumulation of collagen into the bone. However, these observations need further investigations and characterizations [12].

As regards bone physiology, many authors showed circulating ucOC is an independent risk predictor of bone fragility fractures and the reduction of ucOC together with the augmentation of cOC may demonstrate the effects of vit K2 use even after few months of treatment [13]. Effects of vit K2 supplementation on bone structure are very interesting in the light of the most recent concept of osteopenia/osteoporosis as the consequences of progressive loss of both bone density and quality [10]. In fact, even if the importance of vit K2 needs to be contextualized taking into account the importance of all vitamins in general bone health, its key role in bone homeostasis seems to be much more defined in comparison with nutrients other than vitamin D and calcium [7]. Indeed, combined use of the latter standard supplements with vit K2 might enhance bone strength counteracting the effect of age- and menopause-related and/or secondary bone resorption alone or along with major anti-osteoporotic drugs [13].

Analysis of bone status assessed *in vivo* in ovariectomized rats treated with a bone health product (BHP) including calcium, vitamin D_2, and vit K2, showed vit K2 supplementation efficiently improved osteoblastic activity inhibiting osteoclastogenesis, as demonstrated by decreased blood concentrations of C-terminal telopeptide of type I collagen (CTX) compared to the control diet [14]. Furthermore, an other previously published study, pointed out vit K2 and 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), alone and in combination increased osteoblastogenesis in diabetic mice [15]. That common mechanism of action could represent an important strategy in prevention and/or treatment of bone loss often observed in diabetes. In fact, although diabetic patients usually have normal BMD, they are at higher fracture risk due to the possible deterioration of bone structure induced by advanced glycation endproducts (AGEs) [16]. In that manner, vit K2 – in accordance with its capability to preserve bone quality – may represent a novel therapeutic approach to the reduced bone strength of these patients with increased fragility fracture risk, whose consequences could strongly impact on their general health and quality of life which is often already compromised.

On the other hand, Kanellakis et al. confirmed the association of calcium 800 mg/die and 10 mcg vitamin D_3 (=400 UI) with 100 mcg vitamin K_1 or vit K2 as menaquinone-7 stronger ameliorated lumbar spine BMD compared to calcium and vitamin D alone. The usefulness of that combination should consist in the possibility to protect not only bone density but also bone quality, acting at different levels, obtaining an unique beneficial result: the maintenance of bone strength [7].

Vit K2 supplementation appeared also useful to sustain the activity of antiresorptive agents. Calcium ± vitamin D always strengthen bisphosphonates (BPs) effects on bone density: at the same time, their adjunct to all anti-osteoporotic drugs is strongly recommended by international guidelines [17]. Additional assumption of vit K2 may have a further promising role in bone homeostasis. For example, according to many studies, vit K2 contributes to both increase femoral BMD and reduce the incidence of vertebral fracture, if associated respectively to alendronate and etidronate [18,19]. However, data about other BPs remain controversial. For instance, even if patients reporting vertebral fractures during risedronate therapy showed higher ucOC in comparison with patients without, the superiority of additional therapy with vit K2 in respect to risedronate alone in reducing ucOC and fragility vertebral fracture risk was not confirmed [20].

Another study revealed concurrent treatment with risedronate (2.5 mg/day or 17.5 mg/week) and vit K2 (45 mg/day) of late post-menopausal osteoporotic women (>65 years) was not more efficacious as compared to monotherapy with risedronate to decrease fracture risk. While level of ucOC significantly decreased in subjects assuming both treatments, discontinuation rate of therapy was higher in the risedronate and vit K2 group than in the risedronate alone group (10.0% vs. 6.7%) [21]. That phenomenon may at least in part explain the final results. In fact, sometimes low adherence to different anti-osteoporotic treatments, probably due to a general scarce awareness of bone loss, can explain the recurring delay and/or reduction of expected benefits of different treatments [22].

Newsworthy data emerged from few studies concerning vit K2 with parathyroid hormone (PTH; recombinant human PTH (1-34), **t**eriparatide) therapy. Teriparatide is generally used in more severe cases of osteoporosis associated with ≥2 serious vertebral fractures and/or femoral fracture and/or in absence of positive evident effects in reducing fracture risk of other anti-osteoporotic drugs. Few but interesting data showed PTH plus vit K2 as MK-4 can improve osteoblastic activation and bone healing in animal models [23–25]. This observation could represent a new opportunity in the future of anti-osteoporotic therapy, although we need more powerful proofs in real clinical practice.

Limits and future implications

Even if the key role of vit K2 in bone health is assuming growing interest, there are still some points concerning its medical practical use which needs further characterization.

The assessment of vit K2 levels remains a matter of discussion in absence of a unique cutoff indicating its normal value. In fact, nowadays the only possibility to obtain some informations about vit K2 status is the calculation of the ratio ucOC/cOC. It may be considered an indirect parameter that can be weak to evaluate baseline condition of each patient in terms of bone quality but that can be more useful to estimate the effect of vit K2 after some weeks of supplementation [6,7]; therefore, the ratio ucOC/cOC assumed similar impact of BTMs in relation to bone evaluation, and its significant modification in the long term may

demonstrate a beneficial effects on bone quality due to vit K2 therapy.

In addition, the dose normally used in clinical studies producing beneficial effects on bone, corresponded to 45 mg/day of MK-4 or MK-7 while vit K2 is now available in different compound in association with vitamin D_3 and calcium at dosage of 45 mcg. That aspect could supposedly define a subtle risk of underdosing of this element in respect to the other two major nutrients (i.e. vitamin D and calcium). However, the choice of more appropriate pharmaceutical composition and the opportunity to improve tolerability reducing side effects may render that dose of vit K2 more suitable for assumption, ensuring to osteopenic/osteoporotic patients a complete supplementation. It must be noticed that the latest claim of the European Food Safety Authority (EFSA) declared adequate intake of vitamin K as phylloquinone may reach about 70 mcg/day for all adults including pregnant and lactating women [26].

Although many studies showed positive results about vit K2 use with regards to improvement of BMD and amelioration of bone quality, its protection from global fracture risk need to be confirmed in larger randomized controlled trials (RCTs). The most important evidence about fragility fracture reduction were reported in some meta-analysis which even if pointed out the capability of vit K2 to preserve bone metabolism of patients just affected by significant bone loss, remained methodologically controversial [27]. However, those studies properly did not confirm the advantages of vit K2 use in healthy subjects, while it appeared to reduce the risk of VFXs in osteoporostic patients, suggesting to avoid an important mistake in patient selection not only in future scientific insights but also in every-day clinical activity [28]. Moreover, those data are not surprising given that, although many authors found an inverse correlation between vitamin K_1 – the principal form of vitamin K in foods – and fracture risk [29], the same link between dietary vitamin K and risk of fragility fractures in overall population still remains to be elucidated.

Conclusions

The prospective of larger supplementation with vit K2 is to ensure the maintenance of skeletal inner integrity in order to preserve the whole strength of bone appeared promising. More data about vit K2 efficacy in preventing osteoporotic fragility fracture are necessary, though recent studies seem to corroborate the positive benefits of its use regarding moderate increase of BMD at major risk fracture sites, such as femur and vertebrae, and remarkable reduction of ucOC in favor of cOC, the most appropriate form of OC to guarantee an adequate bone structure. In this view, it is important to consider the reduction of fragility fracture risk exerted by vit K2 seems to be more significant in osteoporotic patients. This concept could be essential in individualization of treatment strategy.

Disclosure statement

The authors declare no conflict of interest concerning this paper.

ORCID

S. Lello http://orcid.org/0000-0002-1616-9105

References

[1] Akbari S, Rasouli-Ghahroudi AA. Vitamin K and bone metabolism: a review of the latest evidence in preclinical studies. Biomed Res Int. 2018;2018:1.

[2] Feskanich D, Weber P, Willett WC, et al. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr. 1999;69(1):74–79.

[3] Booth SL, Tucker KL, Chen H, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr. 2000;71(5):1201–1208.

[4] Apalset EM, Gjesdal CG, Eide GE, et al. Dietary vitamins K_1, K_2 and bone mineral density: the Hordaland Health Study. Arch Osteoporos. 2010;5(1–2):73.

[5] Macdonald HM, McGuigan FE, Lanham-New SA, et al. Vitamin K_1 intake is associated with higher bone mineral density and reduced bone resorption in early postmenopausal Scottish women: no evidence of gene-nutrient interaction with apolipoprotein E polymorphisms. Am J Clin Nutr. 2008;87(5):1513–1520.

[6] Kalkwarf HJ, Khoury JC, Bean J, et al. Vitamin K, bone turnover, and bone mass in girls. Am J Clin Nutr. 2004;80(4):1075–1080.

[7] Kanellakis S, Moschonis G, Tenta R, et al. Changes in parameters of bone metabolism in postmenopausal women following a 12-month intervention period using dairy products enriched with calcium, vitamin D, and phylloquinone (vitamin K(1)) or menaquinone-7 (vitamin K (2)): the Postmenopausal Health Study II. Calcif Tissue Int. 2012;90(4):251–262.

[8] Schwalfenberg GK. Vitamins K_1 and K_2: the emerging group of vitamins required for human health. J Nutr Metab. 2017;2017:1.

[9] Wen L, Chen J, Duan L, et al. Vitamin K-dependent proteins involved in bone and cardiovascular health. Mol Med Rep. 2018;18(1):3–15.

[10] Myneni VD, Mezey E. Regulation of bone remodeling by vitamin K_2. Oral Dis. 2017;23(8):1021–1028.

[11] Wu WJ, Kim MS, Ahn BY. The inhibitory effect of vitamin K on RANKL-induced osteoclast differentiation and bone resorption. Food Funct. 2015;6(10):3351–3358.

[12] Azuma K, Ouchi Y, Inoue S. Vitamin K: novel molecular mechanisms of action and its roles in osteoporosis. Geriatr Gerontol Int. 2014;14(1):1–7.

[13] Koshihara Y, Hoshi K. Vitamin K_2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. J Bone Miner Res. 1997;12(3):431–438.

[14] Boulier A, Schwarz J, Lespesailles E, et al. Combination of micellar casein with calcium and vitamins D_2 and K_2 improves bone status of ovariectomized mice. Osteoporos Int. 2016;27(10):3103–3112.

[15] Poon CC, Li RW, Seto SW, et al. In vitro vitamin K(2) and 1α,25-dihydroxyvitamin D(3) combination enhances osteoblasts anabolism of diabetic mice. Eur J Pharmacol. 2015;767:30–40.

[16] Napoli N, Chandran M, Pierroz DD, et al. IOF Bone and Diabetes Working Group. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol. 2017;13(4):208–219.

[17] Adami S, Bertoldo F, Brandi ML, Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro, et al. Guidelines for the diagnosis, prevention and treatment of osteoporosis. Reumatismo. 2009;61(4):260–284.

[18] Hirao M, Hashimoto J, Ando W, et al. Response of serum carboxylated and undercarboxylated osteocalcin to alendronate monotherapy and combined therapy with vitamin K_2 in postmenopausal women. J Bone Miner Metab. 2008;26(3):260–264.

[19] Iwamoto J, Takeda T, Ichimura S. Combined treatment with vitamin K_2 and bisphosphonate in postmenopausal women with osteoporosis. Yonsei Med J. 2003;44(5):751–756.

[20] Kasukawa Y, Miyakoshi N, Ebina T, et al. Effects of risedronate alone or combined with vitamin K_2 on serum undercarboxylated osteocalcin and osteocalcin levels in postmenopausal osteoporosis. J Bone Miner Metab. 2014;32(3):290–297.

[21] Tanaka S, Miyazaki T, Uemura Y, et al. Comparison of concurrent treatment with vitamin K_2 and risedronate compared with treatment with risedronate alone in patients with osteoporosis: Japanese Osteoporosis Intervention Trial-03. J Bone Miner Metab. 2017;35(4):385–395.

[22] Yeam CT, Chia S, Tan HCC, et al. A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int. 2018;29(12):2623–2637.

[23] Weng SJ, Yan DY, Chen L, et al. Combined treatment with vitamin K_2 and PTH enhanced bone formation in ovariectomized rats and increased differentiation of osteoblast in vitro. Chem Biol Interact. 2019;(18):30561–30561.

[24] Li H, Zhou Q, Bai BL, et al. Effects of combined human parathyroid hormone (1-34) and menaquinone-4 treatment on the interface of hydroxyapatite-coated titanium implants in the femur of osteoporotic rats. J Bone Miner Metab. 2018;36(6):691–699.

[25] Shimizu T, Takahata M, Kameda Y, et al. Vitamin K-dependent carboxylation of osteocalcin affects the efficacy of teriparatide (PTH(1-34)) for skeletal repair. Bone. 2014;64:95–101.

[26] Turck D, Bresson JL, Burlingame B, et al. and EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Dietary reference values for vitamin K2. EFSA J. 2017;15.

[27] Cockayne S, Adamson J, Lanham-New S, et al. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166(12):1256–1261.

[28] Huang ZB, Wan SL, Lu YJ, et al. Does vitamin K_2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: a meta-analysis of randomized controlled trials. Osteoporos Int. 2015;26(3):1175–1186.

[29] Hao G, Zhang B, Gu M, et al. Vitamin K intake and the risk of fractures: a meta-analysis. Medicine (Baltimore). 2017;96(17):e6725.