Vitamin K and bone metabolism in the elderly with normal and reduced kidney function

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Alternative title: Vitamin K and bone metabolism in subjects with normal and reduced kidney function
Abstract

Vitamin K plays a key role in the synthesis of several blood coagulation factors, but it is also involved in bone metabolism and vascular calcification. There are two forms of vitamin K: K1 and K2, which may behave differently. Oral anticoagulation with warfarin inhibits the vitamin K system. Although warfarin reduces ischemic stroke, there are concerns on hemorrhagic complications and, due to the impaired activity of other vitamin K dependent proteins such as osteocalcin (or BGP, bone Gla protein) and MGP (matrix Gla protein), on an increased burden of bone fractures and vascular calcifications. These in turn may be significant determinants of morbidity and mortality. The geriatric population, who is often affected by bone disorders frequently related to aging itself, could benefit from a supplementation of vitamin K, but further studies are necessary to prove actual benefits, both in CKD patients and in the general population. In patients at risk of vascular calcifications and fractures, in particular elderly patients affected by CKD, the possible beneficial role of vitamin K supplementation, as well as more a selected administration of vitamin K inhibitors for anticoagulation should be considered.

Key words

Chronic kidney disease
Menaquinone
Matrix Gla Protein
Bone Gla protein
Fractures
Introduction

Since its discovery in the 1930s, vitamin K was found to play a key role in the synthesis of several blood coagulation factors. However, it was subsequently recognized to be also involved in bone metabolism and vascular calcifications (1).

Bone disorders affecting elderly patients are very common. Osteoporosis, in particular, is characterized by reduced bone mineral density (BMD) and increased risk of fractures. Wedge, biconcave or crush fractures, depending on whether the reduction affects the anterior, central or posterior dimension of the vertebra, can be diagnosed (2,3). The association between vertebral fracture and vascular calcification is common in postmenopausal females and in patients affected by chronic kidney disease (CKD), with increased morbidity (4,5). Figure 1 illustrates an example of a patient affected by vertebral fractures and vascular calcifications.

In CKD patients the risk of bone disease is increased; in fact, the majority of patients with CKD from stage 3 to stage 5 is affected by “chronic kidney disease - mineral bone disorder” (CKD-MBD), a syndrome characterised by specific biochemical abnormalities, renal bone disorders with either high (secondary to hyperparathyroidism) or low (adynamic) bone turnover, and vascular calcifications (6).

Dietary intake of vitamin K is often insufficient. Moreover, some elderly patients are treated with anticoagulation therapy, which inhibits the recycling of vitamin K and consequently reduces its activity (Fig. 2). Low vitamin K intake is associated with bone disorders in the elderly population (7), and vitamin K deficiency has been linked to vascular calcifications (8). This article summarises how vitamin K may have an important role in bone metabolism in the elderly with normal and reduced kidney function.

Physiology of vitamin K

Vitamin K exists in two main natural forms: K1 (or Phylloquinone) and K2 (or Menaquinones, MKs). Vitamin K1 is found in green and leafy vegetables such as spinach, broccoli, lettuce, kale, and cabbage; vitamin K2 is contained mainly in cheese and fermented foods, such as natto (fermented soybean, common in Japan), or produced by the intestinal microflora through bacterial fermentation. The MKs are classified according to the length of their unsaturated side chains into 15 different types denominated as MK-n, when “n” defines the number of isoprenyl residues in the side chain. The most common MKs in humans are the short-chain MK-4, which is principally produced by systemic conversion of K1 to K2, and the long-chain vitamers, MK-7 through MK-10,
which are exclusively synthesized by bacteria in humans (9). Finally, vitamin K3 (menadione), is a synthetic form of vitamin K, which shares the same naphthoquinone ring with K1 and K2, but lacks a side chain.

Absorption of vitamin K takes place in the jejunum and ileum in the form of mixed micelle complexes with bile salts (10). The predominant dietary form of vitamin K in the Western Countries is vitamin K1, while the major form in Japan is vitamin K2, especially MK-7, which is the main component of “natto”.

The daily intake of vitamin K in a western diet ranges from 60 to 200 µg, about 90% of it being vitamin K1. However, only 10% of K1 is absorbed from food because of the tight binding to the chloroplast membranes in green vegetables. There are no exact data on the amount of vitamin K2 intake, but it is estimated about 10% of total vitamin K intake.

Vitamin K affects the coagulation system by regulating the introduction of a carboxyl group into the glutamic acid residue in four of the blood coagulation factors (II, VII, IX, X) to yield γ-glutamyl carboxyl (Gla) residues (11). In addition, extra-hepatic vitamin K-dependent proteins are osteocalcin (bone Gla-protein; BGP) and matrix Gla-protein (MGP) (12). These proteins are known to be involved in bone mineralization and inhibition of vascular calcifications, respectively. In case of vitamin K deficiency, these proteins are sub-optimally carboxylated and they are not able to bind calcium, so that the process of vascular calcification is enhanced. The amount of under-carboxylated osteocalcin (ucOC) is considered a sensitive marker of vitamin K status in humans (13).

There is no precise recommendation for daily intake of vitamin K. COMA (the UK Department of Health’s Committee on Medical Aspects of Food Policy) has suggested that a daily intake of 1 µg/kg body weight is probably adequate for blood clotting, but may be suboptimal for bone health (14).

Deficiency of vitamin K occurs when dietary intake is insufficient or when intestinal bacterial production of vitamin K2 is disrupted by prolonged treatment with antibiotics. Vitamin K deficiency may also occur in patients with fat malabsorption (table 1). There is also evidence suggesting that oestrogen levels in women may influence vitamin K status (15). Even if vitamin K is contraindicated in patients on anticoagulant therapy for its pro-coagulant effect, it has been observed that the stability of anticoagulant therapy was not significantly affected by vitamin K supplements at doses below 100 µg/day (16).

**Vitamin K and bone metabolism**
Bone disorders frequently affect elderly men and women, the most common being osteoporosis. Although it is accepted that vitamin K is an important cofactor for the post-translational activation of proteins involved in bone metabolism, the mechanisms underlying the role of vitamin K in the prevention of bone loss or risk of osteoporotic fractures are unknown (17). Many epidemiologic studies evaluated the association between vitamin K and bone metabolism, mostly in elderly men and women in USA, Europe or Japan.

The first evidence that vitamin K deficiency could be correlated with an increased risk of femoral neck fracture was found by Hart (18). Moreover, Feskanich reported that low intake of vitamin K1 was associated with increased risk of hip fracture in the Nurses’ Health Study (19). The Framingham Osteoporosis Study also showed a protective effect of vitamin K1 intake in men and women for hip fracture, but unexpectedly not for BMD (20). Other authors found an association between vitamin K and BMD, but results were often contrasting. Data from the Framingham Offspring Study reported that low dietary vitamin K1 intake was associated with low BMD at the spine and hip only in women, while low plasma vitamin K1 level was related to low BMD at the femoral neck only in a subgroup of men (21,22).

Only a limited number of interventional studies on the effects of vitamin K1 have been conducted, concluding that K1 alone improves osteocalcin carboxylation, but it has little effect on BMD when administered at a dose ranging from 250 mcg to 10 mg/day (23,24). A double-blind controlled trial showed that the group treated with vitamin K1 supplements had a significant decrease in the proportion of non-carboxylated BGP in contrast with the control group, although there was no difference in BMD change between the groups (25). The double-blind ECKO trial compared 5 mg of phylloquinone with placebo in Canadian women with osteopenia, but without osteoporosis (26).

This single center study was conducted to determine whether vitamin K1 supplementation, which increased serum vitamin K1 levels by 10-fold, could safely reduce bone loss, bone turnover, and fractures. It was designed as a 2-y randomized, placebo-controlled, double-blind trial, extended for up to an additional 2 y because of interest in long-term safety and fractures. Interestingly, there were no significant differences in changes in bone mineral density at any site between the two groups over the 2- to 4-y period. Although the study was not powered to examine fractures and their numbers were small (9 in the vitamin K1 group vs 20 in the control group), vitamin K1 treatment was associated with a significant reduction in the risk of clinical fractures versus placebo without an increase in adverse events, suggesting an effect of treatment on bone quality rather than on bone density (26).
Most studies on the beneficial effects of vitamin K2 were conducted in Japan. This is because natto, a major source of vitamin K2 in Japan, is consumed frequently and exclusively in Japan. One pack of natto contains about 20 μg of vitamin K1 and about 380 μg of vitamin K2, so that an accurate evaluation of natto associated K2 intake is possible, in contrast with vegetables. Kaneki et al. first suggested a possible beneficial effect of natto on bone health, finding an inverse association between natto intake and incidence of hip fracture (27). Using data from the Japanese Population-based Osteoporosis (JPOS) Cohort Study, Ikeda found a significant association between natto intake and the rate of change in BMD at the hip in postmenopausal women (28). A systematic review and meta-analysis of randomized controlled trials reported that vitamin K2 supplementation reduced the incidence of vertebral fracture by 60%, hip fracture by 77%, non-vertebral fractures by 81%, and reduced BMD loss (29).

In contrast with data regarding post-menopausal Japanese women, a study conducted in Caucasian women did not find an association between natto intake and bone loss (30). This may be related to dietary and genetic differences, but further studies are necessary to clarify the effects of vitamin K on bone. Some authors suggest that natto could protect bone independently of vitamin K, because it contains large amounts of isoflavones, which may decrease bone remodelling (31), and of calcium (90 mg for 100 mg of natto), which may to reduce bone loss (32).

In the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) Study (7), conducted in elderly Japanese men, subjects with greater intake of natto had significantly lower level of serum undercarboxylated osteocalcin (ucOC), and an association was found between greater intake of natto and significantly higher femoral neck BMD.

In a study on elderly Caucasian subjects observed for 2 years, dietary intake of vitamin K was significantly associated with higher BMD, while no significant associations were found between vitamin K intake and bone peripheral biochemical markers. High dietary vitamin K intake was associated with superior bone properties, even on the qualitative level. In fact, an increase in dietary vitamin K was significantly related not only to lower losses of BMD and smaller increases in the porosity and elasticity attributed to aging, which helps to explain the previously described protective effect of vitamin K intake against osteoporotic fractures (33).

Finally, in a retrospective cohort study of hospitalized patients with atrial fibrillation (34), Gage et al demonstrated that long-term use of warfarin was associated with osteoporotic fractures. Compared with patients who were not prescribed warfarin, the adjusted odds ratio of fracture was 1.25 in patients prescribed long-term (more than a year) warfarin therapy. In patients
prescribed warfarin for less than a year, the risk of osteoporotic fracture was not increased significantly. Interestingly, the association between osteoporotic fracture and long-term warfarin use was significant in men (OR, 1.63) but nonsignificant in women (OR, 1.05) despite the fact that on the overall population male sex was a factor conferring a reduced OR (0.54) for osteoporotic fractures (34).

The previous observations support the role of vitamin K in bone health. Warfarin may predispose to osteoporotic fractures by two mechanisms: directly, by inhibition of γ-carboxylation of osteocalcin (35) and other bone matrix proteins; indirectly, because patients treated with warfarin may limit their dietary intake of foods rich in vitamin K.

Table 2 summarizes the most relevant studies regarding the relationship between vitamin K and bone metabolism.

**Vitamin K and vascular calcifications: the role of warfarin**

Vitamin K deficiency has been linked to vascular calcifications, especially when related to the administration of warfarin. Warfarin is often administrated in elderly patients affected by atrial fibrillation, stroke, and hypercoagulable disorders. By blocking γ-carboxylation of vitamin K-dependent proteins (Fig. 2), it prevents not only the activation of clotting factors, but also of extrahepatic proteins, such as Matrix Gla Protein (MGP) and Growth Arrest Specific Gene 6 (Gas-6), which are carboxylated in vascular tissues. MGP prevents vascular calcification and Gas-6 affects vascular smooth muscle cell apoptosis and movement, also affecting mineralization of the vessel wall (36). In table 3, the so far recognized risks of pharmacological vitamin K inhibition, involving vitamin K dependent proteins, are summarized.

Animal experiments provide data useful for assessing mechanisms and pathogenetic pathways of disease. In experimental animals treated with warfarin, vascular calcifications appeared within two weeks (37). Spronk et al. studied warfarin-treated rats after a diet containing K1, MK-4, or both; despite their similar in vitro cofactor activity, the authors showed that MK-4, but not K1 inhibits warfarin-induced arterial calcification (38). These observations suggest that MK-4 is preferentially acting in the arterial vessel wall. In rats, hepatic accumulation of K1 is higher than MK-4, while higher MK-4 tissue concentrations were found in the arterial tissues, including aorta. This finding suggested the possibility of a conversion of K1 into MK-4 in vascular tissues. Moreover, Schurgers et al demonstrated a regression of warfarin-induced medial elastocalcinoses by high intake of vitamin K in rats (39).
In humans, observational data also suggest an association between the vitamin K system and vascular calcifications. Genetic variation in the carboxylation enzymes could explain individual sensitivity to the anticoagulant effect of warfarin, while polymorphisms in the peripheral carboxylation process may explain why some patients may have an increased risk of calcification [37]. Geleijnse et al reported a strong and inverse correlation between K2 intake and the risk of aortic arteriosclerosis, while no protective effect was observed for dietary K1 (40). In the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study, conducted in 564 healthy Dutch postmenopausal women, the prevalence of coronary artery calcification did not significantly differ across quartiles of phylloquinone intake, but on the other hand women in the highest quartile of menaquinone intake (mean ± SD = 48.5 ± 9.0 mg/day) had a significantly lower prevalence of coronary artery calcification (41). In another study involving U.S. military personnel with normal vitamin K1 intake (mean ± SD = 115 ± 79 mg/day), no association with coronary artery calcification was found (42). Low doses of warfarin may inhibit peripheral carboxylation without affecting hepatic carboxylation, suggesting that vascular vitamin K dependent proteins may be more sensitive to warfarin than hepatic clotting factors (43, 44).

Table 4 summarizes the most relevant observational studies regarding the relationship between vitamin K and vascular calcification. No intervention studies are available.

Vitamin K and Chronic Kidney Disease

CKD patients are usually affected by bone and mineral alterations that vary from fractures to extra-skeletal calcifications (6). Holden et al. measured vitamin D and K as dietary intake, plasma phylloquinone, proportion of serum under-carboxylated osteocalcin, proteins induced by vitamin K absence (PIVKA-II), vitamin K epoxide reductase single-nucleotide polymorphisms, apolipoprotein E genotype, and plasma 25-hydroxyvitamin D in subjects affected by CKD, stage 3 to 5. They concluded that a suboptimal vitamin K and D status is prevalent in CKD patients (45). These results suggested that further research is warranted in the CKD population to find a relationship between vitamin K and clinical outcomes, such as vascular calcifications or BMD loss, in order to evaluate potential benefits of vitamin K supplementation. In this respect, Krueger et al reviewed the role of vitamin K in CKD (46), indicating that the use of vitamin K antagonists might be risky, especially in CKD patients with a high background level of vascular calcification. Recent evidence also indicates that haemodialysis patients show sub-clinical vitamin K deficiency, assessed by circulating levels of vitamin K, under-carboxylated osteocalcin, and PIVKA-II. For
example, in a pilot trial vitamin K2 supplementation in 17 haemodialysis patients led to a decrease in plasma levels of dephosphorylated under-carboxylated MGP (47). Potentially due to the trapping in arterial calcifications, circulating under-carboxylated MGP is decreased in CKD patients (48). On the other hand, Pilkey et al reported data on vitamin K deficiency and elevated levels of under-carboxylated osteocalcin in dialysis patients (49). Due to its lipophilic properties and incorporation into lipoproteins, vitamin K is probably not removed by dialysis, as demonstrated for other fat soluble vitamins (50). Rather, vitamin K deficiency in CKD patients might be the consequence of inadequate intake, favoured by dietary requirements. In fact, a diet low in potassium and phosphorus also contains low levels of vitamin K1 and K2, respectively (51). Because vitamin K2 principally derives by a conversion of vitamin K1 and western diet itself is poor of vitamin K2, deficit of vitamin K2 may be frequent also in CKD patients.

In a recent randomized trial conducted in hemodialysis patients mostly with functional vitamin K deficiency, inactive MGP levels were decreased by daily vitamin K2 supplementation, suggesting the possible role of vitamin K supplementation in preventing and decreasing vascular calcifications (52). Another small study conducted in 21 patients treated with peritoneal dialysis (PD) also confirmed that a significant number of PD patients (23.8%) had sub-clinical vitamin K deficit (53). Malyszko et al (54) did not find any significant differences in vitamin K status between healthy volunteers versus patients affected by renal failure (grouped in patients on conservative treatment, on hemodialysis, on continuous ambulatory peritoneal dialysis, or kidney transplant patients versus control group). Table 5 summarizes the most relevant studies regarding vitamin K in chronic kidney disease.

Finally, the use of warfarin in CKD patients is largely discussed. The prevalence of warfarin use in hemodialysis patients is reported from 8% to 25%; a large group of them (up to 70%) take it for prevention of vascular access thrombosis, although prospective data to support this indication are lacking (55, 56). In a recent study, Limdi and colleagues examined the effect of decreased kidney function on warfarin dosing, demonstrating that lower doses are required in CKD patients versus healthy subjects (57). The absence of efficacy data opened questions about the risk/benefit ratio when using warfarin in CKD patients, particularly dialysis patients. Safety concerns include hemorrhagic complications, as well as vascular calcifications and fractures, as outlined in this article.

Conclusions
Vitamin K may be considered a safe drug, even if the therapeutic benefit and the daily intake are still unknown. In addition, vitamin K1 and K2 may behave differently. In addition to the vitamin K role in the coagulation system, great interest has been raised by vitamin K2 actions in promoting bone integrity and preventing vascular calcifications.

The geriatric population, who is often affected by bone disorders frequently related to aging itself, could benefit from a supplementation of vitamin K, but further studies are necessary to prove actual benefits, both in CKD patients and in the general population. In patients at risk of vascular calcifications and fractures, in particular elderly patients affected by CKD, the possible beneficial role of vitamin K supplementation, as well as more a selected administration of vitamin K inhibitors for anticoagulation should be considered. In particular, several open questions are related to vascular calcifications: is the combined risk of vascular calcification and bleeding too high in CKD patients starting warfarin? Will high-dose vitamin K supplementation be able to prevent or reverse vascular calcifications? Is the use of warfarin still justified? Are the alternative new oral anticoagulants safe in CKD, considering that they are also cleared by the kidneys and they have neither antidotes nor method of measuring the anticoagulant effect?

**Conflicts of interest statement**

Conflicts of interest: none
References


Figure legends

Figure 1.
Assessment of vascular calcifications and prevalent vertebral fractures with quantitative vertebral morphometry in a 54 year-old man in hemodialysis treatment for 44 months. Two vertebral fractures are present (arrows), affecting L1 (biconcave type, severe, with central height reduction of 46%) and T12 (wedge type, moderate, with anterior height reduction of 29%). In addition, aortic and iliac arteries calcifications are clearly visible (arrowheads). The patient had hyperphosphatemia and hypercalcemia with low PTH, which can be observed in cases of reduced bone turnover defining the condition of adynamic bone disease.

Figure 2.
Warfarin and the vitamin K cycle. Warfarin inhibits two key enzymes of the vitamin K system, quinone reductase and vitamin K-epoxide reductase, thus blocking the vitamin recycling and inactivating vitamin K dependent proteins. Reprinted with permission from reference 5 (Fusaro M, et al. J Endocrinol Invest. 2011; 34: 317-23.)
Table 1. Causes of Vitamin K malabsorption

Alcohol consumption
Drugs interfering with fat absorption
- salicylates
- anticonvulsants
- sulfamidics
- orlistat

Drugs modifying intestinal microflora
- antimicrobials

Bacterial or viral infectious

Congenital abnormalities (Neonatal Hemorrhagic Syndrome)

Defects of specific hydrolysis

Defects of ion transport (Cystic Fibrosis)

Pancreatic insufficiency (chronic pancreatitis)

Chronic liver failure

Impaired enterohepatic circulation (ischemia)

Bile duct obstruction

Surgery (intestinal resection or jejuno-ileal bypass)

Inflammatory enteropathy (amyloidosis, ulcerative colitis, Crohn’s disease, radiation enteritis)
Table 2. Vitamin K and bone metabolism. Summary of the most relevant studies.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Study description</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feskanich D (19)</td>
<td>1999</td>
<td>Prospective Study “Nurses’ Health Study” 72327 women, 38-73 year-old</td>
<td>Deficit of vitamin K1 increased the risk of hip fracture</td>
</tr>
<tr>
<td>Booth SL (20)</td>
<td>2000</td>
<td>“Framingham Osteoporosis Study” elderly 335 men and 553 women</td>
<td>Vitamin K intake had a protective effect in men and women for hip fracture, but not for BMD</td>
</tr>
<tr>
<td>Booth SL (21)</td>
<td>2003</td>
<td>Cross-sectional study Offspring Study 1112 men and 1479 women 29-86 years old</td>
<td>Low dietary vitamin K1 intake was associated with low BMD at the spine and hip in women, not in men. Low BMD at the femoral neck was observed in a subgroup of men</td>
</tr>
<tr>
<td>Ikeda Y (28)</td>
<td>2006</td>
<td>Cohort study JPOS (Japanese Population-based Osteoporosis Study: JPOS study) 944 women 20-79 year-old at baseline and at 3 year follow-up</td>
<td>Significant association between natto intake and the rates of changes in BMD at the femoral neck and at the distal third of the radius</td>
</tr>
<tr>
<td>Booth SL (25)</td>
<td>2008</td>
<td>Three year long randomised double-blind controlled trial in 452 men and women, 60-80 year-old</td>
<td>The group treated with vitamin K1 had a significant decrease in non-carboxylated BGP versus control group</td>
</tr>
<tr>
<td>Cheung AM (26)</td>
<td>2008</td>
<td>Single-center 2 to 4 year long randomized, placebo-controlled, double-blind trial (ECKO trial) in 440 postmenopausal women with osteopenia, randomized to either 5 mg of vitamin K1 or placebo daily</td>
<td>Vitamin K1 treatment was associated with a significant reduction in the risk of clinical fractures versus placebo group, despite no change in BMD</td>
</tr>
<tr>
<td>Fujita Y (7)</td>
<td>2012</td>
<td>Cross-sectional study FORMEN Study 1662 Japanese men ≥65 years</td>
<td>Intake of natto was related to lower level of serum undercarboxylated osteocalcin (ucOC) and to higher femoral neck BMD in elderly Japanese men</td>
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Table 3. Risks of pharmacological vitamin K inhibition, involving vitamin K dependent proteins.

<table>
<thead>
<tr>
<th>Affected organ / system</th>
<th>Vitamin K dependent proteins</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation</td>
<td>• Prothrombin (factor II)</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>• Factors VII, IX, X</td>
<td></td>
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<tr>
<td></td>
<td>• Protein C</td>
<td></td>
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<td></td>
<td>• Protein S</td>
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<tr>
<td></td>
<td>• Protein Z</td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td>• MGP</td>
<td>Vascular calcifications (BMP-2 involvement); vascular smooth muscle cell apoptosis</td>
</tr>
<tr>
<td></td>
<td>• Gas-6</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>• osteocalcin</td>
<td>Defective bone mineralization</td>
</tr>
<tr>
<td></td>
<td>• MGP</td>
<td>Fractures</td>
</tr>
<tr>
<td></td>
<td>• Periostin</td>
<td></td>
</tr>
<tr>
<td>Cell growth</td>
<td>• Gas-6</td>
<td>Unknown consequences (involved in cell adhesion, cell proliferation, and protection against apoptosis)</td>
</tr>
</tbody>
</table>

Abbreviations: MGP = Matrix Gla protein, BGP = Bone Gla protein, Gas = Growth Arrest Specific Gene
Table 4. Vitamin K and vascular calcification. Summary of the most relevant studies.

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<th>First Author</th>
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<tbody>
<tr>
<td>Phylloquinone</td>
<td></td>
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<tr>
<td>Geleijnce JM (40)</td>
<td>2004</td>
<td>A study of 4807 Dutch men and women (over 55 year-old, 62% female)</td>
<td>No association between phylloquinone intake and abdominal aortic calcification (AAC), while lower odds of AAC in highest tertile of menaquinone intake were found.</td>
</tr>
<tr>
<td>Villines TC (42)</td>
<td>2005</td>
<td>Cross-sectional study in 807 military personnel (18% female, 39–45 year-old)</td>
<td>No association between phylloquinone intake and coronary artery calcification (CAC)</td>
</tr>
<tr>
<td>Beulens JW (41)</td>
<td>2009</td>
<td>Cross-sectional study in 560 postmenopausal women.</td>
<td>No association between phylloquinone intake and CAC, but lower prevalence of CAC in highest quartile of menaquinone intake</td>
</tr>
</tbody>
</table>
Table 5. Vitamin K and chronic kidney disease. Summary of the most relevant studies.

<table>
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<tr>
<th>First Author</th>
<th>Year</th>
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<th>Conclusions</th>
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<tbody>
<tr>
<td>Małyszko J (54)</td>
<td>2002</td>
<td>A study of CKD patients (conservative treatment, hemodialysis, continuous ambulatory peritoneal dialysis and kidney transplant patients as control group)</td>
<td>No difference between vitamin K status in relation to bone metabolism in CKD patients and control group</td>
</tr>
<tr>
<td>Pilkey RM (49)</td>
<td>2007</td>
<td>A study of 142 hemodialysis patients, 62.6±14.8 year-old</td>
<td>A suboptimal vitamin K status was found: low phylloquinone concentrations and low undercarboxylated osteocalcin in 29% and 93% of subjects</td>
</tr>
<tr>
<td>Holden RM (53)</td>
<td>2008</td>
<td>21 patients treated with peritoneal dialysis</td>
<td>A subclinical K deficit was observed in 23.8% of patients</td>
</tr>
<tr>
<td>Westenfeld R (52)</td>
<td>2012</td>
<td>Interventional randomized non-placebo-controlled trial with 3 parallel groups (vitamin K2 treatment at 45, 135, or 360 μg/d for 6 weeks) 53 long-term hemodialysis patients versus 50 healthy individuals as control group</td>
<td>Vitamin K2 supplementation induced a dose- and time dependent decrease in circulating dephosphorylated-undecarboxylated MGP, undecarboxylated osteocalcin, and PIVKA-II levels (reduction of 77% in the groups receiving 135 μg and 93% in the group receiving 360 μg of vitamin K2)</td>
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