Role of Vitamin K in CKD: Is Its Supplementation Advisable in CKD Patients?

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Abstract

Background: Patients with CKD are at an increased risk of developing vascular calcification (VC) and bone complications which translate into a higher morbidity and mortality. The dephosphorylated and uncarboxylated matrix Gla protein (dp-ucMGP) is considered to be an indicator of vitamin K2 status and correlates with markers of VC. It is activated by γ-glutamyl carboxylase that converts inactive MGP into an active form, and vitamin K2 is a cofactor of this reaction. The active form of MGP is a known inhibitor of arterial wall calcification and plays an important role in bone turnover. Recent studies show poor vitamin K2 status in CKD patients. We aimed to review the literature for the association between vitamin K2 status and calcification and bone disease risk and the efficacy of vitamin K2 supplementation in CKD population.

Summary: Most CKD patients, including those on renal replacement therapy, have vitamin K2 deficiency. The dp-ucMGP level, a marker of vitamin K2 status, is decreased by vitamin K2 supplementation in CKD patients, but there is no unequivocal proof that it influences arterial calcification progression and bone complications.

Key Messages: CKD population are at risk of vitamin K deficiency. Supplementation of vitamin K2 is safe and improves the serum markers of its deficiency. There is lack of strong evidence that vitamin K2 supplementation slows progression of calcification or reduces the frequency of bone complications. More prospective studies are needed.

Introduction

Mineral disturbances lead to bone disorders and vascular calcification (VC) which are common complications in patients with CKD [1]. Cardiovascular (CV) events in CKD are the most often cause of morbidity and mortality in this population [2]. At the basis of their development lie many different triggering factors such as atherosclerosis and VC [3–5]. Patients with CKD are far more likely to die from a cardiovascular disease (CVD) than to progress to end-stage kidney disease [6]. As kidney function declines, phosphate retention occurs. Phosphate is a key signaling molecule mediating the conversion of vascular smooth muscle cells to osteoblast-like cells that produce bone matrix proteins that mediate arterial wall mineralization [7]. Abnormal circulating levels...
of calcium, phosphorus, parathyroid hormone, vitamin D, and fibroblast growth factor 23 may lead to the development of CKD-mineral bone disorder in CKD population [8–10]. Some studies present that hyperphosphatemia and elevated fibroblast growth factor 23 levels are associated with a higher aortic and coronary calcification scores in CKD [11, 12] and with increased mortality [13]. Also, protein Klotho deficiency, which is a typical phenomenon in CKD, may cause VC due to simplified entry of phosphorus into vascular smooth muscle cells, causing arteriosclerosis, bone disturbances, and CKD progression [14]. A possible role of sclerostin should be considered as well due to the involvement of the Wnt signaling in the development and progression of atherosclerosis [15]. However, the data on potential consequences of increased sclerostin levels in CKD patients are unequivocal [16–18]. And, as far as we know, there are no data proving any relationship between vitamin K and sclerostin.

There is a lot of ongoing intensive research on the ways whereby to inhibit VC and bone complications in CKD patients [19–22]. It has been suggested that vitamin K2 may play an important role both in pathogenesis and prevention of those complications. Vitamin K comprises a group of fat-soluble compounds that vary in length and degree of oxygenation of side chains. There are 2 forms of vitamin K: phylloquinone (K1) and menaquinone (K2). Menadione (vitamin K3) is a synthetic analog of vitamin K. The main sources of vitamin K1 are green vegetables such as spinach, broccoli, and brussels sprout [22]. Vitamin K2 is produced by intestinal bacteria and fermented products like cheese, butter, and a Japanese soybean product called natto are rich in this vitamin. Moreover, vitamin K2 can be found in egg yolk, poultry, and liver [22, 23]. Vitamin K is absorbed in the small intestine and packaged into chylomicrons secreted into the lymphatic system and passed via the thoracic duct to the blood system [24].

### Vitamin K in Calcification Process and Bone Metabolism

Both forms of vitamin K take part in essential metabolic processes: vitamin K1 is significantly active in the liver where it catalyzes the reaction of clotting protein activation, while vitamin K2 catalyzes protein carboxylation peripherally among others in blood vessel walls and bones. Smooth muscle cells and chondrocytes produce an inhibitor of VC called matrix Gla protein (MGP) [25–27]. MGP goes through 2 types of reactions in the posttransla-

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from 400 to 500 pmol/L in general population [19]; however, it is not clear what value should be considered as optimal. No biochemical parameter reflects the tissue bioavailability of vitamin K. dp-ucMGP concentration rises with the advance of CKD [29, 44].

The active form of MGP also inhibits the binding of bone morphogenetic protein-2 to its receptor, thus blocking its chondrogenesis, osteogenesis, and calcification function [29, 32]. The expression of MGP is 5-fold greater in the kidneys than bones [45], so it can be assumed that kidney insufficiency may lead to pathological expression of the protein signifying higher risk of calcification. Vitamin K2 is also a cofactor of osteocalcin (OC) γ-carboxylation. Uncarboxylated OC (ucOC) is an enzyme of bone metabolism, and its high concentration is an indirect indicator of vitamin K2 deficit [46, 47]. Holden et al. [48] examined 172 patients with CKD in stage 3–5 and observed that 6% had shortage of vitamin K1 with phylloquinone measured in blood plasma (<0.4 ng/mL) and as many as 60% had deficit of vitamin K2 when measured by ucOC level (>20% ucOC). Low serum OC level in hemodialyzed (HD) patients is connected with a higher risk of CV events [49]. Westenfeld et al. [19] showed that HD patients have 4.5-fold higher dp-ucMGP and 8.4-fold higher ucOC level than people with good kidney function. It is suggested that lack of vitamin K2 may lead to greater risk of atherosclerosis, calcification, and calciphylaxis and may augment vascular complications in CKD patients. Kohlmeier et al. [50] were the first to demonstrate independent correlation between low vitamin K level and higher bone break risk in HD patients. Similarly, Fusaro et al. [51] examined 387 HD patients where 50% had a broken spine, and a decreased phylloquinone level (<0.21 ng/mL) was its predictor. They also demonstrated that HD patients treated with warfarin for at least a year have a greater risk of spine fracture than those who do not take the VKA [39].

Vitamin K2 Deficiency in CKD Population

Dp-ucMGP level rises with the advance of CKD and is associated with albuminuria [52, 53]. Patients treated with renal replacement therapy (mainly dialyzed) are particularly vulnerable to vitamin K2 deficiency [54, 55]. It can be related to dietary limitations in CKD such as elimination of foods with high vitamin K2 content (meat, eggs, and cheese – foods with high content of phosphorus) [54, 55]. Vitamin K deficiency in CKD can be magnified by the uremic milieu which leads to gut dysbiosis, common in CKD population [56], with a consequent decrease in vitamin K2 production. Due to the fact that vitamin K2 resources depend on proper microbiome function, any abnormality there may also be a cause of vitamin K deficiency; however, it has not been well studied yet. The elevated vitamin K2 usage in metabolic processes such as VC inhibition and proper bone condition, the influence of the uremic toxins on the vitamin K2 cycle, and the decreased absorption due to phosphorate binder intake may be other causes of vitamin K deficiency [57, 58]. The VIKI study showed that treatment with sevelamer was connected with higher rate of menaquinone deficiency and aortic and iliac calcification [51]. Antibiotic therapy and widely used proton pomp inhibitors may also

Fig. 1. Pathophysiology of calcification in CKD and role of vitamin K in its process. CKD influences VC through calcium (Ca) and phosphorus (P) metabolism disturbances, high levels of FGF-23, PTH, low concentration of Klotho protein, and also disturbances in carboxylation of K-dependent proteins like MGP. Vitamin D deficiency and further hypocalcemia, together with hyperphosphatemia, stimulate FGF-23 and PTH secretion. These factors promote VC by higher deposition of hydroxyapatite in the extracellular matrix. High concentration of FGF-23 also may suppress renal 1α-hydroxylase expression, reducing its ability to activate vitamin D in kidney proximal tubules and subsequently impairing calcium absorption. α-Klotho protein, whose level is low in CKD, may cause VC due to simplified entry of phosphorus into vascular smooth muscle cells. Active MGP binds calcium and phosphorus ions and seems to have a high binding affinity to forming hydroxyapatite crystals, thus preventing their accumulation within the arterial wall, and furthermore stimulates the arterial macrophages to phagocytosis and apoptosis of the MGP-hydroxyapatite complex. The activity of MGP depends on γ-glutamyl carboxylase that converts inactive ucMGP to active cMGP, and vitamin K2 is a cofactor of this reaction. Deficiency of vitamin K2 leads to increase in the level of dp-ucMGP, which also rises with the deterioration of kidney function. VC, vascular calcification; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; MGP, matrix Gla protein; ucMGP, uncarboxylated MGP; cMGP, carboxylated MGP; dp-ucMGP, dephosphorylated and uncarboxylated MGP.
result in vitamin K deficiency [59]. Peritoneal dialysis (PD) patients may also have a deficit of vitamin K2 measured by dp-ucMGP concentration [60]. Qingdong Xu et al. [60] examined 158 PD patients, where the group with higher dp-ucMGP level (>1,093 pmol/L) was older, more frequently exhibited valve calcification, and also had a significantly higher risk of new CV events including brain stroke and a higher mortality rate. Jansz et al. [61] showed that KTx patients have significantly lower dp-ucMGP compared to the HD and PD ones. However, Keyzer et al. [20] found that 91% of KTx patients have vitamin K2 insufficiency, and higher level of dp-ucMGP is a risk factor of death in KTx patients. Some studies show as well that deficiency of both vitamin D and K, as compared to their better status, is linked with higher graft failure risk and mortality [62]. These observations should perhaps be further followed by randomized trials investigating whether vitamin K supplementation might lead to improved outcomes after KTx.

Calciphylaxis is a quite rare image of VC in CKD patients, affecting the skin and subcutaneous tissue in dialysis patients, and vitamin K2 deficiency may also play a role in its pathogenesis. Calciphylaxis in HD patients is associated with significant reduction of vitamin K2 level determined by cMGP level, necessary to inhibit VC [42, 63]. In the study by Nigwekar et al. [42, 63], HD patients with calciphylaxis had higher plasma levels of ucMGP and cMGP than HD subjects without this complication; however, relative cMGP was lower. Patients not taking warfarin had a similarly lower relative cMGP concentration. Each 0.1-unit reduction in cMGP concentration is associated with a >2-fold increase in calciphylaxis risk [42]. The authors concluded that vitamin K deficiency-mediated reduction in relative cMGP concentration may play a role in the pathogenesis of calciphylaxis, and vitamin K supplementation can prevent and/or treat calciphylaxis [42]. Its supplementation may have potential preventive or even therapeutic effect. It has been already tested in a few clinical trials, for example, in the clinical trial (NCT02278692), where dialysis patients received vitamin K1 in dose 10 mg orally 3 times a week after dialysis for 12 weeks; however, final results are still awaited.

**Efficacy of Vitamin K2 Supplementation in CKD Population**

Some studies suggest that high dietary menaquinone intake in general population has beneficial effect in case of CVD [64, 65] and together with supplementation with vitamin K for bone density and lower bone break risk [66–70]; however, the reports are not unequivocal. A Rotterdam study examined 4,800 patients and concluded that decreased amount of vitamin K2 in diet was bound with a higher risk of aortic calcification, CV incidence, and mortality in general population [67]. Slowing down of calcification progression is a potential beneficial effect of vitamin K2 supplementation [21]. On the other hand, Fulton et al. [71] showed no significant effect of vitamin K2 supplementation on vascular health in older people with vascular disease; however, that study had a few limitations, and one of them was that the patients received only 100 μg of vitamin K2. There are also some reports that supplementation of vitamin K2 may affect metabolic processes – it increases insulin sensitivity index [72, 73] and decreases fasting glucose and 2-h post-OGTT glucose [74]. On the other hand, there are also reports showing no effect on insulin resistance [75, 76].

Despite numerous studies, it has not been established what form, dosage, or duration of vitamin K2 supplementation is advisable, if at all, in general population and CKD patients. There are a few different chemical variants of vitamin K2, and their name is determined by the number of side chains. Menaquinone-4 (MK-4) and MK-7 forms are commercially used in supplementation. MK-7 has longer half-life and has more stable concentration in plasma achieved in the second week of supplementation [77]. It was shown that administration of phylloquinone has no influence on dp-ucMGP level, whereas an inversely proportional impact is observed for menaquinone [55]. Caluwe et al. [55] supplemented HD patients with 360, 720, and 1,080 μg of MK-7, 3 times a week for 8 weeks. They noticed a decrease in dp-ucMGP level by 17, 33, and 46%, respectively, and they suggest a possibility of a better effect with a higher dose of vitamin K2 [55], but the changes in VC were not investigated in their study. Brandenburg et al. [78] observed that HD patients supplemented with vitamin K1 had significantly lower dp-ucMGP level (by 45%) with slower progression of aortic valve calcification compared with patients without such supplementation. In a recently published study, HD patients were supplemented with MK-7 in a dose of 200 μg every day over 1 year. The authors did not observe any benefit of vitamin K2 supplementation on aortic calcification despite a decrease of serum level of ucMGP [79].

In the study by Kurnatowska et al. [80], non-HD patients with CKD stage 3–5 were supplemented with 10 μg of cholecalciferol with or without of 90 μg/day of
Safety of Vitamin K2 Supplementation

Nevertheless, vitamin K supplementation seems to be safe to administer. Regardless of the dose applied, adverse effects were insignificant – of gastrointestinal nature mainly – probably due to specific unpleasant scent of the preparation. No greater risk of thrombosis has been so far observed in patients on vitamin K2 supplementation [96]. Theuwissen et al. [97] examined 42 healthy men and women allocating them to 1 of 7 groups receiving placebo or vitamin K2 at a dose of 10, 20, 45, 90, 180, or 360 μg/day. With an increase of the dose, decreased dp-ucMGP concentration was noted, and the dose 90 μg/day proved to be clinically significant compared to the placebo group; no thrombogenic side effects were observed [97]. Theuwissen et al. [98] also studied the effect of simultaneous use of VKA and vitamin K2 supplementation in healthy people. The study showed that supplementation with vitamin K2 at dose 10 μg (lower than the commonly used dose of 45 μg) resulted in an increased sensitivity to the used anticoagulation in some participants; therefore, supplementation with vitamin K2 should be avoided in persons taking VKA [98]. De Vriese et al. [99] in their study divided patients into 3 groups using VKA, rivaroxaban, and rivaroxaban with supplementation of vitamin K2. They showed that dp-ucMGP level was significantly lower in the group receiving rivaroxaban and even more so in the group using rivaroxaban together with vitamin K2. However, no influence of vitamin K2 supplementation on progression of calcification was noted [99]. It seems that rivaroxaban is safe at the dose of 10 mg in HD patients, and the frequency of ischemic or hemorrhagic stroke did not differ between rivaroxaban alone and rivaroxaban with vitamin K2 groups, and hemorrhagic stroke was only reported in the VKA group [99]. Still, the findings should be confirmed by a larger study with more powerful statistical significance.

Conclusion

There are intensive ongoing studies focusing on the role of vitamin K, especially K2, in pathogenesis of CV and bone complications in patients in different CKD stages including patients treated with renal replacement therapy. The level of dp-ucMGP, an indirect marker of vitamin K2 deficiency, significantly decreases with vitamin K2 supplementation, but so far it has not been proven that such supplementation may slow progression of
calcification or reduce the frequency of bone complications. There is still want of randomized and prospective studies evaluating the clinical benefits of vitamin K2 supplementation in CKD patients.

**Conflict of Interest Statement**

The authors declare no conflicts of interest.

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