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Vitamin K role in mineral and bone disorder of chronic kidney disease

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1. INTRODUCTION

In December, 1944, Henrik Dam and Edward Adelbert Doisy were awarded the Nobel Prize for Physiology or Medicine for their discovery and characterization of vitamin K. Firstly, Dam had discovered in 1929 that a fat-soluble compound present in the diet had antihemorrhagic properties.\(^1\) Ten years later, the compound’s chemical structure was determined by Doisy.\(^2\) Although Dam named this compound “vitamin K” (due to the first letter of the Danish and German word Koagulation), its precise role over coagulation was only clarified more than 30 years later, when the vitamin K-dependent coagulation factor prothrombin was isolated.\(^3\)

In subsequent years, it became clear that vitamin K has a role in gamma (γ) carboxylation reactions in which glutamic acid (Glu) residues present in some proteins are converted to γ-carboxyglutamic acid (Gla) residues by the enzyme γ-glutamyl carboxylase. These reactions promote the activation of so-called vitamin K-dependent proteins involved in a spectrum of functions related to blood coagulation (prothrombin, factors VII, IX and X, and proteins S, C and Z), the modulation of apoptosis (growth arrest-specific protein-6 [Gas6]), and the control of mineralization in bone (osteocalcin [OC]) and vessels (matrix Gla protein [MGP]).\(^4\text{-}^8\)

Given the deep involvement of vitamin K-dependent proteins in important pathophysiological processes, it is speculated a great potential for discovering new mechanisms and therapies involving them. For example, Gas6 (molecular weight of 75 kDa) is not only involved in apoptosis but also in many physiological activities ranging from cellular proliferation, cellular migration and cellular homeostasis. Leukocytes, endothelial cells and vascular smooth muscle cells express Gas6 gene, and its role in cancer therapy and vascular calcification has been investigated.\(^9\text{-}^{12}\)

Researchers have recently focused on understanding vitamin K’s role in chronic kidney disease (CKD).\(^{13}\text{-}^{18}\) From the early stages of CKD onwards, patients develop mineral and bone disorders (CKD-MBD). These constitute a major, life-threatening complication characterized by soft tissue calcification, osteodystrophy, abnormal mineral homeostasis, and hormonal imbalances.\(^19\) As part of the management of CKD, dietary restrictions on potassium and phosphate translate into a low intake of green leafy vegetables, dairy products and meat – all if which are rich in vitamin K. These
restrictions contribute to the low serum vitamin K levels measured in patients with CKD.\textsuperscript{13-15} There is evidence of an elevated risk of vascular calcification and calciphylaxis associated with the use of vitamin K antagonists in patients with CKD.\textsuperscript{16,17} Lastly, data from animal studies shows that uremia per se impairs vitamin K metabolism by modifying the expression of genes whose products are involved in vitamin K recycling.\textsuperscript{18}

For all the above-mentioned reasons, CKD may lead to the expression of a unique clinical condition related to vitamin K deficiency. Although no specific treatments are currently available for reducing vascular calcification and increasing bone volume and mineralization,\textsuperscript{19} vitamin K modulation has emerged as a possible therapeutic option.\textsuperscript{20,21} A body of scientific evidence has highlighted vitamin K’s important functions in bone and vessels, which are greatly affected during the course of CKD. The purpose of the present review is to shed light on the impact of vitamin K deficiency on patients with CKD-MBD.

2. CHEMICAL STRUCTURE, METABOLISM AND ACTIONS OF VITAMIN K

The term “vitamin K” refers to a group of fat-soluble molecules with similar chemical structures (1,4-naphthoquinones with a side chain composed of a varying number of isoprenoid residues). The natural forms of vitamin K are K1 (phylloquinone) and K2 (menaquinones). There are 17 types of menaquinone, depending on the side chain’ length and degree of saturation of carbon (Figure 1).\textsuperscript{7,20,21}

In humans, the main dietary sources of vitamin K are foods rich in vitamin K1, such as vegetable oils, green vegetables (e.g. kale, spinach, Swiss chard, Brussels sprouts, parsley, watercress, and broccoli), and animal livers. Bacteria present in intestinal microbiota or in fermented foods [e.g. cheese, curds, and Japanese soybean “natto”) can synthesize vitamin K2, however, little is known about the bioavailability of vitamin K2 from the gut.\textsuperscript{7,21,22} For example, propionibacterium present in Swiss emmental cheeses, produce menaquinone-9. The genera Bacteroides synthesise predominantly long chain forms menaquinones-10 and 11, and in minor concentrations menaquinones-7, 8, 9 and 12.\textsuperscript{23,24}
Menaquinone-4 (one of the different forms of vitamin K2) can be endogenously produced from phylloquinone in some tissues. Tissues like brain, kidney, pancreas and salivary gland are rich in menaquinone-4, probably due to local biosynthesis. Some preclinical studies were able to demonstrate the conversion in the kidney HEK-293 kidney cell line and by primary cultures of mouse cerebral hemispheres.

It is estimated that the daily intake of vitamin K in the Western diet is between 80 and 210 µg per day, while the recommended daily allowance for total vitamin K is 1 µg/kg/day. However, it seems that this recommended daily allowance is not sufficient for the proper carboxylation of extra-hepatic Gla-proteins (e.g., OC and MGP) - especially when vitamin K metabolism is impaired, as in the setting of CKD.

After the digestion of food, vitamin K is emulsified by bile salts, absorbed by enterocytes (via chylomicron receptors), incorporated to triacylglycerol-rich lipoproteins which contains apolipoprotein-A and apolipoprotein-B48, and secreted into the lymphatic system and the blood. Subsequently, all vitamin K variants, in special vitamin K1 and menaquinone-7, are absorbed by the liver. In the liver chylomicrons enter hepatocytes by endocytosis, and apolipoprotein-B100 is added before to return to circulation. In the circulation after additions and removals of apolipoprotein particles the different vitamin K molecules are transported by LDL cholesterol particles and captured by target cells and tissues via LDL receptors, like arteries, cartilage and bone.

Vitamin K’s main physiologic role is to act as cofactor for the enzyme γ-glutamyl carboxylase in the gamma-carboxylation reactions that add carboxyl groups to Glu residues in proteins. Gamma-glutamyl carboxylase oxidizes vitamin K into vitamin K epoxide, removes a proton from the Glu residue, and then adds CO₂. The newly carboxylated residues in such proteins are referred to as Gla domains. This process transforms inactive (uncarboxylated) proteins into active (carboxylated) proteins, and enables them to bind calcium. Adequate calcium binding is a critical physiologic step in bone mineralization and in countering vascular calcification (Figure 2).
Vitamin K reserves in the body are limited, and vitamin K is efficiently recycled through a series of redox reactions. A factor that can impair the recycling system is the use of a vitamin K antagonist (e.g. warfarin) that inhibits vitamin K epoxide reductase and quinone reductase. Furthermore, there is evidence to suggest that uremia disturbs vitamin K recycling in some tissues by alters the mRNA expression of vitamin K oxidoreductase (VKOR) and γ-glutamyl carboxylase. Impaired vitamin K recycling in uremia can be ameliorated - at least in part - by vitamin K supplementation. Lastly, oxidative catabolism vitamin K takes place in the liver and mainly generates glucuronide metabolites excreted in the bile and urine.

3. CLINICAL ASPECTS OF VITAMIN K DEFICIENCY

3.1. Laboratory evaluation of vitamin K status

The different forms of vitamin K and levels of uncarboxylated/carboxylated vitamin K-dependent proteins can be assayed in the plasma, serum and tissues by using Enzyme-Linked Immunosorbent Assay (ELISA), high performance liquid chromatography (HPLC), and mass spectrometry.

However, the analysis of vitamin K status is complex, and the results are not always easy to interpret. At present, the optimal levels of serum vitamins K and carboxylated/uncarboxylated vitamin K-dependent proteins have not been defined. No single analyte is considered to be a gold-standard marker of vitamin K status, however, measurement of activated vitamin K-dependent proteins seems to give attractive functional information compared to a random sample for evaluation of vitamin K1 or K2 levels.

3.1.1. Evaluation of vitamin K1 and K2 levels

The direct measurement of different forms of vitamin K is influenced by several factors, such as vitamin K1’s short half-life, the intake of specific nutrients (especially for vitamin K2), low circulating levels (compared with other lipophilic vitamins), the dietary and serum levels of triglycerides, and inter-individual variability among healthy subjects and among patients with chronic diseases (including CKD). Regarding to
vitamin K2, menaquinone-7 is often below the detection limit and menaquinone-4 is the only demonstrable menaquinone in subjects under a normal Western diet, but still about analytical influence of triglycerides.\textsuperscript{42}

Despite the difficulty in interpreting plasma levels of vitamin K1, values ranging from 0.029 to 2.65 nmol/L have been reported in the literature.\textsuperscript{14,41} Most studies have used HPLC with a C-18 reverse-phase column and fluorometric detection after post-column zinc reduction; this has become the “gold standard” measurement. Although this HPLC technique is sensitive and specific, it is also time-consuming, expensive, not widely available, and requires external validation.\textsuperscript{40,41,43}

3.1.2. Evaluation of vitamin K-dependent proteins

The measurement of uncarboxylated or carboxylated vitamin K-dependent proteins has been used to reflect the functional status related to a specific tissue, either as a deficiency (i.e., high levels of uncarboxylated proteins) or sufficiency (i.e., sufficient levels of bioactive carboxylated proteins).

In this respect, dephosphorylated-uncarboxylated-MGP (dp-ucMGP) and phosphorylated-carboxylated-MGP (p-cMGP) are biomarkers of vascular calcification and cardiovascular outcomes.\textsuperscript{21} There are other two different MGP molecules in the circulation: dephosphorylated carboxylated MGP (dp-cMGP) and phosphorylated uncarboxylated MGP (p-ucMGP). However, the generation of active form (p-cMGP) occur only by combination of two post-transcriptional steps: one phosphorylation of 3 serine residues (on 5) and a carboxylation of 5 glutamate residues (on 9).\textsuperscript{7,44} Phosphorylated or carboxylated MGP species have a high affinity for calcium mooting the interpretation of their serum levels. Then, only dp-ucMGP is used to evaluate vitamin K status.\textsuperscript{21} Schlieper et al. and Westenfeld et al., suggest a median level nearby 500 pmol/L in healthy subjects.\textsuperscript{45,46}

Others vitamin K-dependent proteins such as uncarboxylated-OC, carboxylated-OC, and total OC are used to evaluate bone mineralization, and protein induced in vitamin K absence (PIVKA) and the prothrombin time are markers of the hepatic concentration of vitamin K.\textsuperscript{20,21,44,47}
The measured levels of uncarboxylated or carboxylated vitamin K-dependent proteins depend on the assay used, and thresholds for sufficiency or deficiency have not been determined. A recent review of Caluwé et al. presented a summary of studies evaluating vitamin K status through of vitamin K-dependent proteins measurements in CKD patients. There is a wide variation in the values of these molecules, which prevents us from specifying a reference range for each one of these molecules.

3.2. Vitamin K deficiency and its relationship with CKD-MBD

Many researchers have reported on vitamin K deficiency in patients with CKD undergoing conservative treatment, peritoneal dialysis, or hemodialysis. In addition to dietary restrictions, impaired vitamin K recycling, and a high requirement for vitamin K-dependent proteins in the inhibition of calcification, it has been suggested that drugs frequently prescribed to patients with CKD (such as statins, proton-pump inhibitors, and phosphate binders) can contribute to vitamin K deficiency (Figure 3).

Phosphate binders are of special interest in the context of CKD-MBD, due to their intrinsic ability to chelating other substances, and possibly vitamin K. Neradova et al. tested the in vitro ability of five different phosphate binders to alter the availability of vitamin K2 in the presence or absence of phosphate. They found that only sucroferric-oxyhydroxide and sevelamer carbonate did not bind vitamin K2, whereas calcium, magnesium and lanthanum-based phosphate binders bound vitamin K2 (with a variable influence of phosphate). In a clinical setting, Jansz et al., reported that sevelamer hydrochloride or carbonate were associated with high levels of dephosphorylated-uncarboxylated MGP (dp-ucMGP) - an indirect marker of vitamin K deficiency.

Regardless of the cause of vitamin K deficiency, the latter condition has been linked to cardiovascular disease, vascular calcification, calciphylaxis, altered bone metabolism (resulting in fractures), and mortality. All these complications are part of the spectrum CKD-MBD, and are discussed below in detail.
3.2.1. Vitamin K deficiency and altered bone metabolism

Mature OC secreted by osteoblasts is essential for bone mineralization. After vitamin K-dependent carboxylation, OC develops a high affinity for calcium ions and incorporates them into the hydroxyapatite crystals in bone matrix. Uncarboxylated OC (ucOC) can be released during osteoclastic resorption, and is thought to be responsible for functions related to energy metabolism. Indeed, ucOC has a role in glucose homeostasis by stimulating β cells to release insulin and fat cells to release adiponectin. These actions suggest that OC has a role in insulin resistance.

Plasma vitamin K and OC levels appear to reflect alterations in bone metabolism or a risk of bone fractures. The ucOC level, the total OC level and the ratio between the two (%ucOC) are frequently used to reflect vitamin K status linked to bone health. In a depletion-repletion study (using dietary intake to modulate vitamin K levels), it was suggested that a %ucOC cutoff >20% reflected vitamin K deficiency; however, this value was not consistently reproduced other studies with a similar methodology.

In clinical settings, %ucOC and vitamin K levels are associated with bone fractures. In a Japanese study involving 99 patients without CKD who presented hip fracture plasma concentrations of vitamin K1 and K2 (menaquinone-7) were significantly lower compared to a control group. Vitamin K1 levels were a significant and independent determinant of hip fracture risk.

In the study of Kohlmeier et al. involving 68 hemodialysis patients, high %ucOC was associated with the incidence of bone fractures. In the same study the authors observed that low serum vitamin K1 levels were associated with personal history of bone fractures. Of note, patients who never had bone fractures had approximately three times higher serum vitamin K1 levels. However, information about the bone fracture site as well as the nature (traumatic or pathological) is not described.

A study of patients with stage 3-5 CKD found that high serum ucOC levels were positively associated with phosphate and parathormone levels and negatively associated with 25-vitamin D levels - suggesting a relationship with bone remodeling.
VIKI study, total OC and ucOC levels were higher in patients with CKD than in healthy controls, and vitamin K1 deficiency was an independent predictor for vertebral fractures in prevalent hemodialysis patients (the median total OC level was 29% lower in patients with one or more vertebral fractures).\(^{55}\)

Despite the evidence from preclinical studies and observational clinical studies, the literature data on the effect of clinical vitamin K supplementation on bone mineral density are contradictory - probably as a result of differences in adherence, small sample sizes, the inclusion with low-risk patients (without CKD), and insufficient statistical power.\(^{21}\) It is noteworthy that in Sasaki at al.’s study of 20 steroid-treated patients with glomerulonephritis, supplementation with menaquinone-4 for a year prevented steroid-induced bone loss.\(^{65}\)

To the best of our knowledge, vitamin K supplementation and bone fractures in patients on dialysis have not been studied in a controlled, randomized clinical trial. We expect in the near future to have new data through the study iPACK-HD (NCT01528800), which is evaluating the impact of vitamin K1 supplementation to attenuate vascular calcification and the prevalence-incidence of thoracic-lumbar vertebral fractures in hemodialysis patients.\(^{66}\)

3.2.2. Vitamin K deficiency and vascular calcification

Vascular calcification is a complex process that involves many factors and results in negative outcomes in patients with CKD.\(^{67}\) Despite some encouraging preclinical results concerning the use of sodium pyrophosphate to prevent and treat vascular calcification,\(^{68}\) there are currently no specific treatments for this condition in the clinical setting and new treatments are urgently needed.

One clear example of the role of vitamin K in vascular calcification comes from studies of vitamin K antagonists. The administration of these antagonists can lead to vitamin K deficiency and vascular calcification in animal models and in humans.\(^{53,56,69}\) McCabe et al. found that vascular calcification was more intense in warfarin-treated rats with CKD than in healthy Sprague-Dawley rats.\(^{53}\) Matrix-Gla-protein-deficient mice develop soft tissue calcification, whereas MGP expression in the vessels prevents
calcification. The physiologic explanation is that vitamin K deficiency impairs the carboxylation of MGP - a small protein produced by vascular smooth muscle cells, chondrocytes and endothelial cells, that inhibits vascular calcification.21,43,47

Taken as a whole, these observations suggest that vitamin K supplementation might prevent the development of vascular calcification. On the vascular level, vitamin K deficiency might be indirectly expressed as the presence of high serum concentrations of dp-ucMGP. The latter protein is considered to be a surrogate marker for vitamin K status in vessels, and has been used when cardiovascular endpoints are studied.47 Three other forms of MGP can be found in the circulation: dp-MGP, p-ucMGP, and p-cMGP. At present, the optimal serum levels of the four MGP forms have not been determined.21

There are many reports of altered MGP levels and the latter’s positive association with vascular calcification or mortality.43,56 Liabeuf et al. reported that patients with CKD and serum dp-ucMGP levels above 559.5 pM (the median value observed in the cohort) presented higher calcification scores than patients with type II diabetes (3447 ± 7040 vs. 1609 ± 3983 Agatston units).43 Nigwekar et al. observed that hemodialysis patients with calciphylaxis presented with proportionally less cMGP and more ucMGP than peers without calciphylaxis.56

Recent data in patients with small intestinal bacterial overgrowth (SIBO) who also presented with a higher concentration of dp-ucMGP and low circulating levels of vitamin K2, carotid intima-media thickness and arterial calcifications were not different in them in comparison to the control. However, the vascular calcification has been evaluated in the last study by ultrasound which may underestimate the frequency of vascular calcification.72

Although the data are inconsistent, there is some evidence of a relationship between dp-ucMGP levels and mortality.45,73 In a study of 107 patients with stage 2-5 CKD, Schurgers et al. observed that the level of dp-ucMGP rose with the CKD stage and was associated with abdominal aorta calcification, but not mortality after adjustments.73

With view to treating patients in the future, vitamin K2 supplementation appears to attenuate calcification in vessels - probably via enhanced MGP carboxylation. Zaragatski et al. studied an animal model of vascular hemodynamic stress (through
creation of an arteriovenous fistula), and observed that vitamin K2 supplementation was associated with a relative reduction in calcified areas in both healthy and CKD female rats.74

In clinical settings, the Rotterdam study examined whether dietary intake of vitamin K1 and K2 were related to vascular calcification in 4,807 subjects with no history of myocardial infarction, which were followed by nearly ten years. The authors observed that high dietary intake of vitamin K2, but not vitamin K1, was associated with a reduction in the risk of severe aortic calcification, coronary heart disease mortality and all cause-mortality.75

Lastly, OC (under the influence of vitamin D) also seems to protect against vascular calcification.63 In the VIKI study, for example, the median total OC level was 36% lower in patients with vascular calcification than in those without.55

4. THERAPEUTICS ASPECTS OF VITAMIN K MODULATION IN CKD-MBD

The physiologic and clinical data presented above prompts one to speculate as to whether patients with CKD might benefit from vitamin K supplementation, with the goal of increasing the activity of vitamin K-dependent proteins, improving bone quality, and reducing vascular calcification and mortality rates. Most past or ongoing trials have tested vitamin K1 (ranging from 0.5 to 4.28 mg/d) or vitamin K2 (menaquinone-7, ranging from 180 to 2000 µg/d, or menaquinone-4, ranging from 15 to 45 mg/d).42,46,76-78

The earliest studies focused on the effects of vitamin K replacement on vitamin K status markers, namely, dp-ucMGP, PIVKA-II and ucOC.76,77 Westenfeld et al. tested different doses of menaquinone-7 (45, 135, or 360 µg/d) over 6 weeks in 53 hemodialysis patients; the researchers observed a dose- and time-dependent decrease in circulating levels of dp-uc-MGP, ucOC and PIVKA-II.46 Similarly, Caluwé et al. found that supplementation with menaquinone-7 (360, 720 or 1080 µg, thrice weekly) for 8 weeks dose-dependently reduced plasma dp-uc-MGP levels in 200 patients on chronic hemodialysis.42
A number of ongoing studies are expected to provide important clinical answers in the coming years. Most of these studies recruited hemodialysis patients and use common primary endpoints: the progression of thoracic aorta and coronary artery calcification, the progression of the coronary artery calcium score, cardiovascular events, and the progression of arterial stiffness.\textsuperscript{76}

One of the largest ongoing studies is the VitaVask Study (NCT01742273), a prospective, international, multicenter, randomized trial of the effects of vitamin K1 (5 mg thrice weekly) on the progression of vascular calcification in hemodialysis patients. The estimated study completion date is September 2019.\textsuperscript{78}

Another interesting ongoing project is the Danish study entitled \textit{Effect of Vitamin K2 (MK7) on Cardiovascular and Bone Disease in Dialysis Patients: A Prospective, Randomized Placebo-controlled Double Blind Trial} (NCT02976246). The estimated study completion date is August 2020. In an assessment of vitamin K2 supplementation (menaquinone-7, 360 \(\mu\)g/d) on patients on hemodialysis or peritoneal dialysis, the investigators are using a pulse wave velocity technique to examine the effects of on arterial stiffness, and dual-energy X-ray absorptiometry to assess bone mineral density in the distal radius.
5. **CONCLUSIONS**

CKD is a natural model for vitamin K deficiency, which is prevalent in these patients as a result of dietary restrictions, altered intestinal function, changes in the microbiota, and impaired vitamin K recycling. Vitamin K deficiency is related to the physiopathology of CKD-MBD, complication linked to elevated mortality rates. The literature data suggest that modulation of vitamin K status is possible and the present scientific knowledge leads us to speculate of whether patients with CKD might benefit from vitamin K supplementation.

At present, no single biomarker adequately reflects a patient’s vitamin K status. The degree of carboxylation of various vitamin K-dependent proteins is used as an indirect measure of this vitamin K status. Future research efforts must develop, improve and standardize methods for evaluating vitamin K status, including definitions of the optimal level of each compound in each patient subgroups (especially in CKD).

Lastly, the effects of vitamin K supplementation on clinical outcomes (such as bone fractures, cardiovascular events and mortality) merit further investigation in appropriately designed randomized clinical trials. In the near future, at least two ongoing studies (NCT01742273 and NCT02976246) are expected to deliver important results about vitamin K use in patients with CKD.
6. REFERENCES


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Figure Title / Legends

**Figure 1.** A) The molecular structures of vitamin K1 and two variants of vitamin K2. (B) Edward Adelbert Doisy, the American biochemist who determined the chemical structure of vitamin K.²

**Figure 2.** Schematic representation of the activation of vitamin K-dependent proteins by vitamin K and the enzyme γ-glutamyl carboxylase.

Vitamins K1 and K2 in the diet and produced by bacteria are cofactors for the enzyme γ-glutamyl carboxylase, which catalyzes the addition of carboxyl groups to Glu residues in specific proteins like osteocalcin, matrix Gla protein and prothrombin. This reaction causes activation of these proteins involved in bone mineralization, coagulation, and protection against vascular calcification. Vitamin K is then recycled via a series of redox reactions. Menaquinone-4 (a form of vitamin K2) can be generated from the endogenous conversion of phylloquinone. VSMCs: vascular smooth muscle cells; +: activation of vitamin K-dependent proteins.

**Figure 3.** Factors and potential negative consequences related to vitamin K deficiency in patients with CKD.

A number of factors have been implicated in vitamin K deficiency in patients with CKD, including impaired vitamin K recycling, dietary restrictions, altered intestinal function, changes in the microbiota, and drugs used in patients with CKD. Vitamin K deficiency is related to bone disorders and vascular calcification, which are frequently observed in patients with CKD.
CKD → Vitamin K recycling disturbances

Dietary restrictions

↓

Green leafy vegetables, broccoli, milk, meat

Altered intestinal function or microbiota

Drugs

Statins
Phosphate binders
Proton-pump inhibitors

Vitamin K

Bone disorders
Vascular calcification

Patient with CKD