

Vitamin K Deficiency in Chronic Kidney Disease: Evidence Is Building Up

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Vitamin K has important biological actions, mediated by the activation of vitamin K-dependent proteins (VKDPs), such as blood coagulation factors and other proteins involved in bone metabolism and in the inhibition of vascular calcifications. Table 1 summarizes the physiological function of the main VKDPs and the consequences of vitamin K deficiency in patients with chronic kidney disease (CKD) and normal renal function.

Vitamin K deficiency may result in the following: (a) anticoagulation with warfarin, a well-known inhibitor of vitamin K 2,3-epoxide reductase, vitamin K recycling (VKOR), an enzyme that recycles oxidized vitamin K to its reduced form; (b) inadequate dietary intake of vitamin K.

There are 2 main forms of vitamin K: K₁ or phylloquinone, found in green vegetables, and K₂ or menaquinones (MK-n), found in specific food (such as natto, in Japan) or derived from the metabolic activity of intestinal bacteria. MK-4 is the unique menaquinone produced by systemic conversion of phylloquinone to vitamin K₂ through the action of prenyltransferase domain-containing protein 1 (UBIAD1) [1].

In this issue of the AJN, McCabe et al. [2] highlight, in a rat model of adenine-induced renal failure, how CKD can negatively affect vitamin K metabolism, generating a decreased expression of VKOR and utilization (γ -glutamyl carboxylase, *Ggcx*) enzymes in thoracic aorta. In addition, the uremic status was associated with a decrease in the kidney level of the phylloquinone to MK-4 bioconversion enzyme, UBIAD1. Thus, this study

adds an important piece of understanding to the framework of the deranged vitamin K metabolism in CKD.

A reduced GGCX activity in the kidneys and in the aorta (but not in the liver) of uremic animals was previously found by Kaesler et al. [3], indicating that uremia per se affects the vitamin K system. In addition, supplementation of phylloquinone or menaquinone (MK-4) at pharmacological doses restored the abnormal vitamin K cycle activity and slowed the progression of vascular calcification [3].

Additional evidence is now available from studies in humans. An observational, prospective study of 167 CKD patients (stages 3–5) highlighted that patients with the CG/GG genotype of vitamin K epoxide reductase complex subunit 1 (the enzyme target of warfarin) had a higher risk of coronary artery calcification progression and poorer survival [4]. Taken together, these findings are consistent with the higher prevalence of vascular calcifications in hemodialysis patients, as well as with the observation of warfarin-associated increased calcifications in patients with CKD [5].

A reduced dietary intake may be an important additional cause of vitamin K deficiency in CKD patients, as indicated by previous studies, in part due to the dietary limitations imposed by the uremic status. Recently, we confirmed a low vitamin K₁ intake in hemodialysis patients on a Mediterranean diet, compared to control subjects with normal renal function [6]. Participants completed a food journal of 7 consecutive days for the estima-

Table 1. Consequences of vitamin K deficiency in the general population and in CKD patients

VKDPs	Physiologic function	Vitamin K deficiency in the general population	Vitamin K deficiency in CKD patients
Coagulation factors X, IX, VII and II	Part of the coagulation cascade	Bleeding (or controlled, warfarin-induced anticoagulation)	Bleeding Warfarin accumulates in CKD patients
MGP	Inhibition of osteogenic factors, and consequently vascular and soft tissue calcification	Vascular calcifications Mortality	Vascular calcifications Mortality
BGP, osteocalcin	Involved in bone mineralization	Bone fragility Vascular calcifications Abnormal glucose metabolism Mortality	Bone fragility Vascular calcifications
GAS6: expressed in endothelial cells, vascular smooth muscle cells and bone marrow	Mediated by TAM receptor activation – Effects on primary hemostasis and coagulation – Anti-inflammatory or pro-inflammatory effect, depending on cell type – Apoptosis of vascular smooth muscle cells	Unknown consequences (putative: effects on hemostasis, inflammation, and cancer growth)	Unknown consequences
Protein S (40% sequence identity with GAS6)	– Co-factor for protein C – Direct inhibitor of coagulation factors	Protein S deficiencies are associated with thrombosis, usually venous thromboembolism	Involved in calciphylaxis
GRP	– Regulation of extracellular calcium metabolism – Inhibitor of vascular and valvular calcification – Novel anti-inflammatory agent, with potential beneficial effects on osteoarthritis progression	Unknown consequences	Unknown consequences
PIVKA-II	– Abnormal form of the coagulation protein, prothrombin (factor II) – Used as a marker of hepatocellular carcinoma	Detected in people with vitamin K deficiency	Bleeding

MGP = Matrix gla protein; BGP = bone gla protein; GAS6 = growth arrest-specific 6; GRP = gla rich protein; PIVKA-II = protein induced by vitamin K antagonist-II; TAM = TAM receptors (Tyro3, Axl, and Mer).

tion of dietary intakes of macro- and micronutrients (minerals and vitamins). When considering the adequate vitamin K₁ intake recommended in the literature, it was noted that there was a remarkable prevalence of reduced intake, which was approximately 70–90% less than normal. We found an average total daily vitamin K₁ intake of 72 µg/day compared to 129 µg/day in healthy controls. However, when normalized per 1,000 kcal energy intake, dietary vitamin K₁ was 47 µg in dialysis patients compared to 89 µg in controls [6]. Thus, CKD patients appear to be exposed to the negative effects of vitamin K deficiency for at least 2 reasons, that is, a reduced dietary intake and a reduced expression and activity of the VKOR enzymes. In addition, an increased prevalence of atrial fibrillation often requires starting warfarin treatment, with further inhibition of both hepatic and extra-hepatic VKDPs activity.

Therefore, assessing the vitamin K status could be potentially important in CKD patients, especially if studies on vitamin K supplementation will prove a positive effect on bone and vascular disorders [7]. Up to now, vitamin K administration to hemodialysis patients at pharmacological doses was tested with surrogate biomarkers indicating the vitamin K status, such as dephosphorylated undercarboxylated matrix Gla protein. Such studies highlighted an improvement of VKDPs function, proportional to the increase in dose [8, 9]. More relevant outcomes such as bone disease, including fractures, vascular calcifications, cardiovascular morbidity and mortality are warranted. Indeed, studies evaluating the progression of vascular calcifications with vitamin K at pharmacological doses are currently in progress in CKD patients. The VitaVasK study in Europe (ClinicalTrials.gov identifier: NCT01742273) investigates the effects of phylloquinone

(5 mg thrice weekly for 18 months) on the progression of thoracic aortic and coronary artery calcification. In Canada, the placebo-controlled iPACK HD study (ClinicalTrials.gov identifier: NCT01528800) also evaluates the progression of coronary artery calcifications but with a higher dose of phylloquinone and a shorter follow-up, 10 mg thrice weekly for 12 months.

In the process of establishing a physiopathological role of deranged vitamin K metabolism in CKD patients and the possibility of treatment of such abnormalities with an adequate cost–benefit ratio, several pieces of the puzzle are already in place. The experimental evidence provided by McCabe et al. [2] is a further step in the direction of establishing the uremic status as an independent risk factor of vitamin K deficiency and the deranged vitamin K metabolism in CKD as a therapeutic target.

Future studies should be implemented, addressing several undefined areas. First, more information is needed on the assessment of vitamin K status, possibly distinguishing phylloquinone and menaquinones, through

standardized methods measuring undercarboxylated VKDPs and/or serum vitamin K levels. An effort should be made in determining the utility of vitamin K determination at the research and clinical level. Second, better characterization of vitamin K₂ content in food is required, as the current available information is mainly related to vitamin K₁. Dietary sources of vitamin K should be known both to the public and healthcare personnel. Third, more randomized placebo-controlled studies in CKD patients using phylloquinone, menaquinones or a combination of different vitamers should address the safety of vitamin K administration at high doses and relevant clinical outcomes, such as vascular calcifications, bone fractures, cardiovascular morbidity and mortality. Such studies should also assess the doses of vitamin K with the better cost–and risk–benefit ratio.

Disclosure Statement

The authors have no conflict of interest to report.

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