Dysbiosis in Patients with Chronic Kidney Disease

Current Nutrition Reports
https://doi.org/10.1007/s13668-022-00438-9

CARDIOVASCULAR DISEASE (JHY WU, SECTION EDITOR)

Dysbiosis in Patients with Chronic Kidney Disease: Let Us Talk About Vitamin K

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Accepted: 15 August 2022

Abstract

Purpose of Review This narrative review aimed to summarize the current evidence on the connection between dysbiosis and vitamin K deficiency in patients with chronic kidney disease (CKD). The presence of dysbiosis (perturbations in the composition of the microbiota) has been described in several non-communicable diseases, including chronic kidney disease, and it has been hypothesized that dysbiosis may cause vitamin K deficiency. Patients with CKD present both vitamin K deficiency and gut dysbiosis; however, the relationship between gut dysbiosis and vitamin K deficiency remains to be addressed.

Recent Findings Recently, few studies in animals have demonstrated that a dysbiotic environment is associated with low production of vitamin K by the gut microbiota.

Summary Vitamin K plays a vital role in blood coagulation as well as in the cardiovascular and bone systems. It serves as a cofactor for γ-glutamyl carboxylases and thus is essential for the post-translational modification and activation of vitamin K-dependent calcification regulators, such as osteocalcin, matrix Gla protein, Gla-rich protein, and proteins C and S. Additionally, vitamin K executes essential antioxidant and anti-inflammatory functions. Dietary intake is the main source of vitamin K; however, it also can be produced by gut microbiota. This review discusses the effects of uremia on the imbalance in gut microbiota, vitamin K-producing bacteria, and vitamin K deficiency in CKD patients, leading to a better understanding and raising hypothesis for future clinical studies.

Keywords Vitamin K · Chronic kidney disease · Gut dysbiosis · Nutrition

Introduction

Chronic kidney disease (CKD) is a growing worldwide public health problem, as it increases the risk of end-stage kidney disease (ESKD) and cardiovascular disease (CVD) [1]. Defined by the sustained presence of either kidney damage (albuminuria) or reduced kidney function (estimated

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This article is part of the Topical Collection on *Cardiovascular Disease*

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Published online: 23 September 2022

glomerular filtration rate [eGFR] < 60 ml/ min/1.73 m^2), CKD is believed to affect 10 to 15% of the population and is estimated to contribute to 5 to 10 million deaths annually [2]. Among many complications, the presence of dysbiosis, defined as perturbations in the composition of the microbiota, has been described [3, 4]. Multiple factors in CKD patients lead to alterations in gut microbiota composition, including the uremic milieu, low fiber diet, antibiotics, phosphate binder use, and oral iron supplementation [5, 6].

Gut microbes are known to provide many health benefits for the human body, including the production of vitamin K [7]. This fat-soluble vitamin serves as a cofactor for γ-glutamyl carboxylases (GGCXs). GGCX, and thus vitamin K, is essential in the post-translational modification and activation of vitamin K-dependent proteins (VKDPs) such as osteocalcin, matrix Gla protein, Gla-rich protein, and proteins C and S that are involved in regulating coagulation and calcification [8•]. Vitamin K is also an important antioxidant and anti-inflammatory factor [9]. Thus, an adequate plasma level of vitamin K is important to many vital functions of the body.

There are two naturally occurring forms of vitamin K, namely vitamin K1 (phylloquinone, PK), found in food sources such as green leafy vegetables, fruits, oils and dairy products, and vitamin K2 (menaquinone, MK), produced by fermentation or by the gut microbiota. Vitamin K3 (menadione) is of synthetic origin [10, 11, 12].

It has been shown consistently that patients with CKD have a subclinical vitamin K deficiency, which may occur due to poor appetite, dietary restriction, use of phosphate binders, or due to gut dysbiosis [7, 13, 14, 15]. In line with these observations, the number of studies on the association between gut dysbiosis and vitamin K deficiency is growing. The present review aims to summarize the current evidence on the connection between dysbiosis and vitamin K deficiency in CKD patients.

Vitamin K

All vitamin Ks are fat-soluble compounds and have a common structure: a 2-methyl-1,4-naphthoquinone ring and an aliphatic side chain with variable numbers of isoprenoid residues. The length and the degree of saturation of the side chain are responsible for the differences between the types of vitamin K [16•]. Vitamin K1 has a side chain consisting of four isoprenoid residues with three of them saturated, while vitamin K2 has one to 15 unsaturated residues in the side chain [10, 11]. Among the vitamin K2 subtypes, MK-11, MK-12, and MK-13 are the most commonly produced by commensal bacteria in humans [8•, 11].

The primary dietary sources of vitamin K1 are green leafy vegetables, while bacteria, including constituents of the gut microbiota, produce vitamin K2. Thus, vitamin K2 is mainly found in fermented food or animal-derived products (Table 1) [17, 18]. It is important to note that consumption of fermented foods (e.g., natto) has decreased in Japan with the introduction of a Western diet, which coincides with reduced vitamin K2 intake [19]. The recommended daily intake (RDI) of vitamin K is 120 µg/day for adult males and 90 µg/day for adult females [20], but discussions are ongoing as this recommendation takes into account only vitamin K1 [21].

Despite the similar structure of the two natural forms of vitamin K, the length of the isoprene side-chain impacts lipophilicity, thereby influencing their absorption, transport, and tissue distribution [22]. In the digestion process, both forms of vitamin K are emulsified by bile salts and the absorption occurs in the small intestine enterocytes [23, 24]. Vitamin K1 is reported to have an absorption rate of only 5–15% due to strong binding to the membranes of plant chloroplasts, thus hampering its bioavailability [11, 21, 25]. Some subtypes of vitamin K2, like MK-4, are absorbed poorly (10%) [26], whereas MK-7, -8, and -9 are absorbed nearly completely [27]. Another important factor influencing absorption is the food matrix, i.e., fat content of food that increases the absorption of vitamin K1 [28].

After absorption, vitamin K is transported in the circulation by triacylglycerol-rich lipoproteins to the liver [21]. Vitamin K1 is mainly retained in the liver, and from there utilized before it is metabolized. Vitamin K2 acts not only in the liver, but is also released into the circulation via LDL, and acts in extra-hepatic tissues, such as arteries, bone, and

Table 1 Food with highest content of vitamins K1 and K2

Foods		Vitamin K1 (µg/100 g)
Vegetables	Collards	706
	Turnip	568
	Broccoli	146
	Kale	724–1139
	Spinach	240–1220
	Lettuce	70–850
	Cabbage	46–584
Fruits	Dried prunes	51–68
	Kiwi	33–50
	Avocado	15–27
Nuts	Cashew	19–64
		Vitamin K2 (µg/100 g)
Cheeses	Roquefort	38
	Pecorino	93
	Brie	12
Fermented food	Natto (fermented soy)	108
	Sauerkraut	5

cartilage [16•, 21]. Due to differences in lipophilicity, long-chain MKs have better bioavailability, a longer half-life, and higher bioactivity than vitamin K1 [18]. Indeed, a study showed that MK-7 has a lifetime of 70 h, while vitamin K1 has a lifetime of 2 h [27]. In this context, it is suggested that MK-7, -8, and -9 have the highest proportion of extra-hepatic activity with 70%, followed by MK-4 with 25%, compared to vitamin K1 with only 5% [21].

Functions of Vitamin K

While the vital role of vitamin K in blood coagulation, as a cofactor of activating the vitamin K-dependent coagulant factors, has been recognized for a long time. More recently, it has also been recognized that vitamin K has also antioxidant and anti-inflammatory properties [22, 23].

Vitamin K and Coagulation

The discovery of vitamin K dates back to the work of Carl Peter Henrik Dam in the 1920s and 1930s. This Danish biochemist observed a bleeding tendency and lower blood prothrombin levels in chickens fed a fat-free feed [29, 30]. In contrast, supplementary feeding with green vegetables and liver led to normal coagulation. Dam presumed an undefined fat-soluble nutrient was responsible for the regulation of coagulation and gave this antihemorrhagic compound the name of coagulation vitamin. The new vitamin received the letter K, as the initial research was reported in a German journal, which referred to *Koagulations-vitamin*. The work on vitamin K continued in the 1930s, when the American biochemist Edward Albert Doisy isolated and identified the chemical naphthoquinone ring structure of vitamin K [31]. In 1943, Dam and Doisy were jointly awarded the Nobel Prize in Medicine for the discovery and elucidation of the chemical structure of vitamin K.

In the beginning, the role of vitamin K in coagulation was centered around the clinical observations where newborns developed bleedings, known as hemorrhagic disease of the newborn (HDN) or vitamin K deficiency bleeding (VKDB) [32, 33]. Giving vitamin K at birth and formula feeds with higher vitamin K content (than breast milk) can effectively prevent VKDB. Soon after that the relationship between vitamin K deficiency and decreased plasma prothrombin (factor II) activity was discovered, followed by the identification of more vitamin K-dependent coagulation factors, including factors VII, IX, and X and the anticoagulation proteins C, S, and Z [34].

Now we know that the main function of vitamin K is to act as a cofactor for GGCX in the carboxylation of VKDPs, modifying glutamic acid (Glu) residues into gamma-carboxyglutamate (Gla) residues [11, 16•, 22]. This conversion process of Glu into Gla is essential to the activity of VKDPs, and to maintain hemostasis [23, 35]. To become a GGCX cofactor, vitamin K-hydroquinone (KH2) is first reduced and next converted to vitamin K epoxide (KO). Subsequently, KO is recycled by the vitamin K epoxide reductase (VKOR) into vitamin K quinone again [35, 36]. Indeed, warfarin and other types of oral anticoagulants of the 4-hydroxycoumarin class inhibit vitamin K recycling by blocking VKOR activity [27]. Blocking VKOR results in impaired recycling and leads to low levels of vitamin K in tissues, resulting in undercarboxylated VKDPs (Fig. 1) [35]. Additionally, it has been suggested that an imbalance in the vitamin K forms leads to an alternative vitamin K cycle, which is known as noncanonical vitamin K cycle. In this cycle, the vitamin K-hydroquinone (KH2) is reduced to semiquinone (KH), also by the enzyme VKOR. In this step, this enzyme acts through the regulation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) activity preventing cell damage by reactive oxygen species (ROS). Moreover, this noncanonical vitamin K cycle avoids NADPH-dependent lipid peroxidation, characterizing an antioxidant effect [37]. Indeed, this alternative vitamin K cycle has been suggested to affect the cell and tissues redox-homeostasis [38].

The VKDPs group is comprised of coagulation factors II, VII, IX, and X, and the anti-coagulation proteins C, S, and Z. Extra-hepatic VKDPs consist of matrix Gla protein (MGP), osteocalcin (OC), and Gla-rich protein (GRP), which have beneficial functions in the bone and cardiovascular systems as they regulate bio-mineralization [22, 35]. Other extrahepatic Gla-proteins are growth arrest-specific protein 6 (Gas6), proline-rich Gla proteins (PRGP) 1 and 2, periostin (isoforms 1–4), periostin-like-factor (PLF), and transmembrane Gla proteins (TMG) 3 and 4, but their functions are not fully understood [39].

The biological function of coagulation factors depends on their binding to negatively charged phospholipid surfaces. The Gla-residues are essential in serving as a chelating site for (positively charged) calcium ions enabling phospholipid surface binding. Vitamin K-dependent protein C targets activated and phospholipid-bound factors V and VIII in the presence of calcium [40]. This anticoagulant process is enhanced by protein S, which acts as a cofactor, strengthening the binding of activated protein C to negatively charged phospholipids [41]. Indeed, for factor V this has been specified as a specific 20-fold enhancement of APC-mediated cleavage at Arg306 in FVa by protein S [42]. Protein Z is shown to have a prothrombotic and protective role in patients with thrombotic conditions, though the evidence for this is inconclusive [41, 43]. However, vitamin K-dependent control of the coagulation system is complex as it has also been revealed that factors II and IX, whose deficiencies are commonly associated with bleeding risk, have been linked to thrombosis in clinical and molecular studies [44, 45].

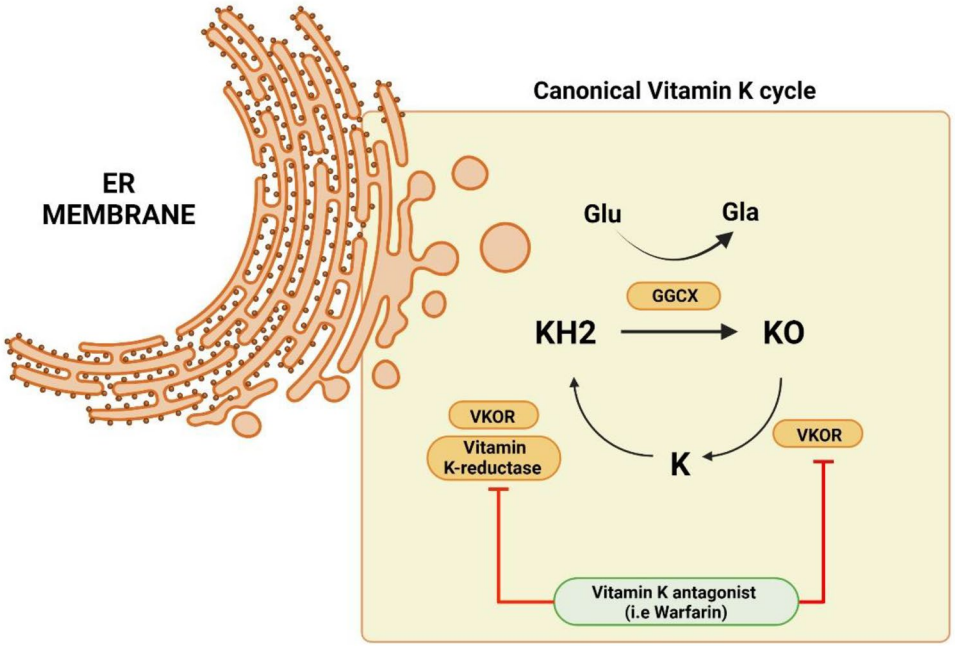

Fig. 1 Canonical vitamin K cycle. The carboxylation cycle of glutamate (Glu) residues into gamma-carboxyglutamate (Gla) through reduction and conversion of vitamin K to vitamin K epoxide (KO), and the recycle of vitamin K by the vitamin K epoxide reductase (VKOR). Image made with https://biorender.com/

Vitamin K and Calcification

Some VKDPs, such as matrix Gla protein (MGP), Gla-rich protein (GRP), periostin, protein S, growth arrest-specific 6 protein (Gas6), and osteocalcin, which has three Gla residues, are found in skeletal tissues. Osteocalcin is an important bone formation marker, since it binds to calcium crystals, thereby modulating the calcification processes [46]. MGP is an important vascular calcification inhibitor, which binds to hydroxyapatite and inhibits bone morphogenetic protein (BMP-2, a vascular calcification stimulator). There are several forms of circulating MGP such as phosphorylated uncarboxylated MGP (p-ucMGP), phosphorylated-carboxylated MGP (p-cMGP), dephosphorylated-uncarboxylated MGP (dp-ucMGP), and dephosphorylated-carboxylated MGP (dp-cMGP). The level of dp-ucMGP can be used as a marker of vascular vitamin K status [47].

Antioxidant and Anti-inflammatory Role of Vitamin K

Oxidative stress, resulting from the imbalance between the production of reactive oxygen species (ROS) and antioxidant activity, leads to macromolecular damage and subsequently chronic inflammation [48, 49]. Both these features have deleterious effects on cell function, contributing to aging and the development of non-communicable chronic diseases, such as diabetes mellitus, hypertension, CVD, and CKD [4, 50, 51].

Human studies have shown that dietary intake of vitamin K1 is beneficial for health, mainly because of the associated decrease in inflammation and insulin resistance markers. Thus, it can be considered a protective factor in chronic inflammatory diseases [52]. In randomized, double-blind, placebo-controlled trials with diabetic patients, the co-supplementation of vitamin D, vitamin K, and calcium decreased carotid intima-media thickness and insulin concentrations, improved β-cell function and insulin sensitivity, and increased the high-density cholesterol (HDL), high-sensitivity C-reactive protein (CRP) and MDA plasma levels [53, 54]. Indeed, vitamin K status, as measured by plasma vitamin K1 and vitamin K1 intake, is inversely associated with circulating inflammatory markers, such as intracellular adhesion molecule-1 (MCP-1), tumor necrosis factor (TNF), interleukin (IL)-6, and CRP [55, 56]. Vitamin K inhibits the nuclear translocation of nuclear factor kappa B (NF-κB), which may occur due to halted degradation of inhibitor of nuclear factor kappa B (IκB) and decreased inhibitor of nuclear factor kappa B kinase (IKK) activity [57]. This decreases the production of pro-inflammatory cytokines [11, 58, 59]. Studies (both in vitro and in vivo) have shown that vitamin K decreases the levels of IL-2, IL-6, IL-17A, IFN-γ, nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) expression through the inhibition of phosphor extracellular signal-regulated kinase (p-ERK) phosphorylation. This results in downregulation of NF-κB and p38 mitogen-activated protein kinase (MAPK) through the suppression of transcription factor AP-1, which leads to blocking of inflammatory pathways [50, 57, 60].

It is equally well-documented that vitamin K plays a vital role as an antioxidant [9, 61]. The antioxidant effects of vitamin K are related to its protective action against oxidative damage by an increase in nuclear factor erythroid 2–related factor 2 (Nrf2) expression with

consequential decrease in ROS mediated damage and increased synthesis of antioxidants, such as superoxide dismutase (SOD), glutathione peroxidase (GSH), and catalase (CAT) [11, 51]. Additionally, vitamin K prevents lipid peroxidation by downregulation of lipoxygenase 12 activity [62, 63, 64] and acts in the non-enzymatic antioxidant response, increasing serum glutathione (GSH) and vitamin C levels [64]. Finally, it has recently been shown that nicotine increases vascular smooth muscle cell calcification by inducing ROS production via α3 and α7 nicotinic acetylcholine receptors (nAChRs) and an increase in intracellular calcium and Nox-5 activation. Vitamin K reduced these effects [65].

While there are no studies in humans that aim to evaluate vitamin K alone as a modulator of inflammation and oxidative stress (Table 2), based on existing in vitro studies, however, as well as studies of vitamin K in combination with other factors, it could be speculated that such clinical trials would show an effect Fig. 2 summarizes the functions of vitamin K.

Additionally, inflammation and oxidative stress are associated with many chronic diseases, such as diabetes, cancer, obesity, CVD, and CKD that have gut dysbiosis as an additional complication. The connection between dysbiosis and vitamin K deficiency in these diseases has not been studied.

Role of Gut Microbiota in Vitamin K Synthesis

The intestinal tract possesses around four billion microorganisms such as bacteria, archaea, viruses and fungi, living in a complex interactive ecosystem. *Bacteroidetes* (15%) and *Firmicutes* (60%) are the most prevalent bacteria in a homeostasic milieu between all microorganisms that has a beneficial role for human health [73]. Many metabolites produced by gut bacteria are salutogenic, such as short chain fatty acids and vitamins, including vitamin K. Currently, it is known that a vast number of facultative and obligate anaerobes from the domains of Bacteria and Archaea produce MKs (Table 3) [8•, 74, 75].

However, aside from being useful vitamins for us, MKs are membrane lipid-soluble carriers of electrons in bacterial respiration resulting in ATP synthesis [10, 75, 76••]. Emerging evidence suggests that MKs synthesized by gut microbiota are used in their cytoplasmic membranes, reducing their bioavailability and resulting in a low vitamin K level in the systemic circulation [77]. To date, two pathways of bacterial synthesis of MKs have been described (Fig. 3). The first pathway involves MK synthesis from the shikimate pathway through O-succinylbenzoate and 2-demethylmenaquinone (DMK). The second pathway produces MKs through futalosine [75, 78, 79].

Dysbiosis and Vitamin K Status

Gut dysbiosis can be provoked by a range of biotic and abiotic factors, such as an unhealthy diet, illness, aging, and use of drugs including antibiotics [80]. These perturbations affect microbial metabolism and can lead to increased production of pro-inflammatory microbial metabolites. Dysbiosis can also reduce the levels of important molecules, such as short chain fatty acids and vitamins, including vitamin K, synthetized by symbionts [5, 81]. Indeed, mice treated with antibiotics presented a dysbiotic environment which provoked low production of vitamin K by the gut microbiota [82]. In obese mice, beneficial changes in gut microbiota induced by treatment with green tea polyphenols and tocotrienol were associated with increased numbers of vitamin K-producing bacteria [83]. In patients with Crohn's disease, vitamin K deficiency, evaluated by undercarboxylated osteocalcin (ucOC) levels, correlated with reduced gut microbiota diversity, suggesting a possible link between microbiota and vitamin K levels [84].

Dysbiosis also plays a role in disturbed coagulation. A study in the insulin-gastrin transgenic mouse model showed that treatment with antibiotic and dietary folate supplementation (to avoid DNA methylation and reduce gastric dysplasia) or with amino acid diets to eradicate H. pylori, provoked a reduction in Bacteroidales and Verrucomicrobiales (MK producers) and caused gastric hemorrhages. This was due to low levels of vitamin K in the diet and plasma, with a combination of an amino acid diet and antibiotics. As a result, vitamin K1 was used after antibiotic prescription, and anemia parameters were shown to recover in human subjects [85]. Indeed, it is well known that antibiotic use provokes an imbalance in gut microbiota, affecting not only the pathogenic, but also the salutogenic bacteria.

In short, only a few studies have reported on the relationship between gut dysbiosis, and vitamin K status and many questions remain unanswered. Does gut dysbiosis affect vitamin K synthesis? Can changes in the gut microbiota after antibiotic treatment affect blood coagulation [86]? Can changes in the gut microbiota of patients with CKD cause vitamin K deficiency? Can we impact gut microbiota in a way that favors vitamin K production? Studies investigating the role of dysbiosis on vitamin synthesis in these patients as well studies focusing on the profile of vitamin K-producing bacteria in CKD are needed.

Let Us Talk About Vitamin K in Patients with Chronic Kidney Disease

The uremic phenotype leads to many complications, including premature aging, persistent low-grade inflammation, oxidative stress, muscle wasting, osteoporosis, frailty,

Table 2 Studies involving vitamin K and its effects on inflammation and oxidative stress

References	Sample/design	Intervention	Results
In vitro			
Checker et al. [60]	CD4 T cells	1–10 μM of vitamin K3 for 4 h	↓ IL-2, IL-6, and IFN-γ cytokines levels ↑ GSH levels, ↑ phosphorylation of ERK ↓ NF-κB activation
Yu et al. [57]	Microglial cell line (BV2) exposed to rotenone	0.5–20 μM vitamin K2 for 24 h	↓ iNOS and COX-2 expression ↓ TNF-α and IL-1β production ↓ Nuclear translocation of NF-κB ↓ p38 activation, ROS production, and caspase-1 activation
Ramazani et al. [62]	PC12 cell lines treated with hydroxydopamine 6	5 μM of vitamin K2 for 24 h	↓ ROS generation ↓ Protein levels of pro-caspase-3, Bax ↑ GSH levels
Ambrozewicz et al. [63]	Human osteoblasts	Vitamins K1 and K2 at a concentration of 10 μM and/or vitamin D3 at concentration 1 nM for 4, 8, 12, 16, and 20 days	↓ ROS production ↑ GSH levels ↑ GSH-Px activity
Cirilli et al. [64]	Human umbilical vein endothelial cells treated with cigarette smoke extract	10 μM ubiquinol and vitamin K2 for 24 h	↓ Cytosolic and mitochondrial ROS ↓ Caspase 1 activation ↓ SA-β -galactosidase
Petsophonsakul et al. [65]	Human carotid artery lesion specimen	10 mM of vitamin K2 for 1 h	↓ Oxidative stress ↓ Extracellular vesicle secretion ↓ Calcification
In vivo			
Varsha et al. [66]	STZ-induced type 1 diabetic male Wistar rats	5 mg/kg of vitamin K1 twice a week for 3 months	↓ HbA1c, ↓ blood glucose ↑ Serum vitamin K1 levels ↑ Insulin secretion ↓ NF-kB and iNOS enzyme expression ↑ SOD, GSH, and CAT
Dihingia et al. [67]	T2D mice model with HFD	Vitamin K1 supplementation (1, 3, 5 μg/kg) for 2 months	↑ Glucose tolerance ↓ Body weight gain, fasting glucose, insulin, HbA1c, HOMA-IR ↓ NF-κB, ↓ MCP-1 and IL-6 ↑ PPARα
Dihingia et al. [68]	T2D mice model with HFD Monocytes in cell culture	Vitamin K1 supplementation (1, 3, 5 μg/kg) for 2 months Vitamin K1 supplementation (1, 5, or 10 nM)	↓ Body weight, glucose intolerance, fasting glucose, HbA1c, HOMA-IR ↓ MCP-1 and IL-6 Cell culture: ↓ NF-κB phosphorylation and MCP-1 secretion ↑ Nrf2 protein expression
Moghadam et al. [69]	Rat model of cerebral I/R	400 mg/kg of vitamin K2 — 2 h after cerebral I/R induction	↓ Bax/ Bcl2 ratio and GFAP mRNA expression ↓ IL-6, IL-1β, and TNF-α levels ↑ Level of SOD activity and GLT-1 mRNA expression
Dosumu et al. [70]	Wistar rats with hepatotoxicity induced by 7,12 dimethylbenz(A) anthracene	7.5 g/10 kg of vitamin K for 4 months	↑ Liver SOD ↑ GST, GSH and vitamin C serum levels ↓ NO and MDA in the liver ↓ GM-CSF and IL-17A expressions

Table 2 (continued)

References	Sample/design	Intervention	Results
In humans			
Shea et al. [55]	1381 participants from the Framingham Offspring Study (observational)	Vitamin K status measured by plasma vitamin K 1 and vitamin K1 intake	Negative association between CRP and vitamin K Negative association between inflammatory markers (CD40 ligand, intracellular adhesion molecule-1, IL-6, TNF) and vitamin K
Juanola-Falgarona et al. [52]	510 elderlies from PREDIMED centers (cross-sectional and longitudinal)	Dietary vitamin K1 intake estimated by food frequency questionnaires for 1 year	↓ Ghrelin, glucose-dependent insulinotropic peptide, glucagon-like peptide-1, IL-6, leptin, TNF, and visfatin plasma levels
Razavi et al. [71]	60 vitamin D-deficient women with polycystic ovary syndrome (RCT)	200 IU vitamin D, 90 µg vitamin K plus, 500 mg calcium supplements for 2 months	↑ Total antioxidant capacity ↓ Plasma MDA levels ↔ Glutathione levels, hs-CRP
Asemi et al. [53]	66 overweight T2D patients with coronary heart disease (RCT)	5 µg vitamin D, 90 µg vitamin K plus 500 mg Calcium supplements for 3 months	↑ HDL-cholesterol ↓ HOMA-IR ↓ MDA and CRP
Mazidi et al. [72]	17,689 participants from US National Health and Nutrition Examination Survey (cross-sectional)	Dietary intake (from 2001 to 2010)	Negative association between CRP and vitamin K

RCT randomized double-blind, placebo-controlled trial, *HbA1c* glycated hemoglobin, *HFD* high fat diet, *T2D* type 2 diabetic, *GM-CSF* granulocyte macrophage colony-stimulating factor, *IL* interleukin, *IFN-γ* gamma interferon, *GSH* glutathione, *ERK* extracellular signal-regulated kinase, *NF-κB* factor nuclear kappa B, *iNOS* induced nitric oxide synthase, *COX-2* cyclooxygenase-2, *TNF-α* tumor necrosis factor alpha, *ROS* reactive oxygen species, *Bax* member of the Bcl-2 family, *GSH-Px* glutathione peroxidase, *SOD* superoxide dismutase, *CAT* catalase, *HOMA-IR* homeostases model assessment-insulin resistance, *MCP-1* monocyte chemoattractant protein-1, *PPARα* peroxisome proliferator-activated receptor alpha, *Nrf2* erythroid nuclear factor 2 related to factor 2, *GFAP* glial fibrillary acidic protein, *GLT-1* glutamate transporter-1, *GST* glutathione S-transferase, *NO* nitric oxide, *MDA* malonaldehyde, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *hs-CRP* high-sensitivity C-reactive protein, *CRP* C-reactive protein

mitochondrial dysfunction, and increased risk of CVD, including accelerated vascular calcification [87, 88, 89].

The prevalence of vascular calcification in patients with CKD is high [90] and visible in all arteries, mainly coronary arteries [91]. Changes in mineral and bone metabolism play a vital role in the pathogenesis of vascular calcification in CKD [92]. An imbalance between inhibitors and promoters of vascular calcification results in ectopic mineralization. MGP, a VKDP, is an essential natural calcification inhibitor [93, 94]. Recently, a meta-analysis from observational studies showed that higher rates of CVD and death are associated with higher levels of inactive VKDPs [95]. However, few studies have been published on the role of vitamin K (mainly K2) deficiency on vascular calcification in CKD patients [96••]. Patients with CKD have a subclinical and functional vitamin K deficiency [15, 97, 98, 99, 100], which evolves with the progression of renal function [101, 102]. In a study including 172 subjects with stage 3–5 CKD, it was shown that vitamin K insufficiency was present in 6% of the subjects based on vitamin K1, in 60% based on uncarboxylated osteocalcin, and in 97% based on PIVKA-II (protein induced by vitamin K absence or antagonism factor-II). Additionally, in 493 CKD patients, a functional deficiency of vitamin K (measured by high plasma dp-ucMGP concentrations) was associated with an increased risk of mortality, independent of vascular calcification [100].

The etiology of vitamin K deficiency in CKD, especially in patients on hemodialysis, is multifactorial. Some of the causes are: inadequate intake of vitamin K, uremic inhibition of the vitamin K cycle and pharmacological impact on vitamin K metabolism [16•, 99, 103, 104]. Some of the typical features of the diet recommended for hemodialysis patients are control of potassium and phosphate intake, thus reducing consumption of green leafy vegetables and dairy products, two major sources of vitamins K1 and K2, respectively [98, 99, 105]. When evaluating the intake of vitamin K in patients undergoing hemodialysis through a food questionnaire, a lower intake of vitamin K [140 (30–546) µg/day] has been reported [15]. Uremia itself affect the vitamin K cycle. The uremic environment causes a reduction in GGCX activity in the kidneys and the aorta, promoting an increase in serum levels of the undercarboxylated MGP [106]. Additionally, the renal expression of VKORC1 is reduced in both mild and severe CKD [107].

Medications can also influence vitamin K levels in patients with CKD. Warfarin, an anticoagulant commonly used in CKD therapy due to cardiovascular complications, inhibits carboxylation of VKDPs. As a consequence, patients on warfarin have an increased risk of vascular calcification and all-cause mortality [108]. Indeed, a study with patients with coronary artery disease concluded that vitamin K antagonist treatment, e.g., warfarin, correlated with coronary artery plaque calcification [109].

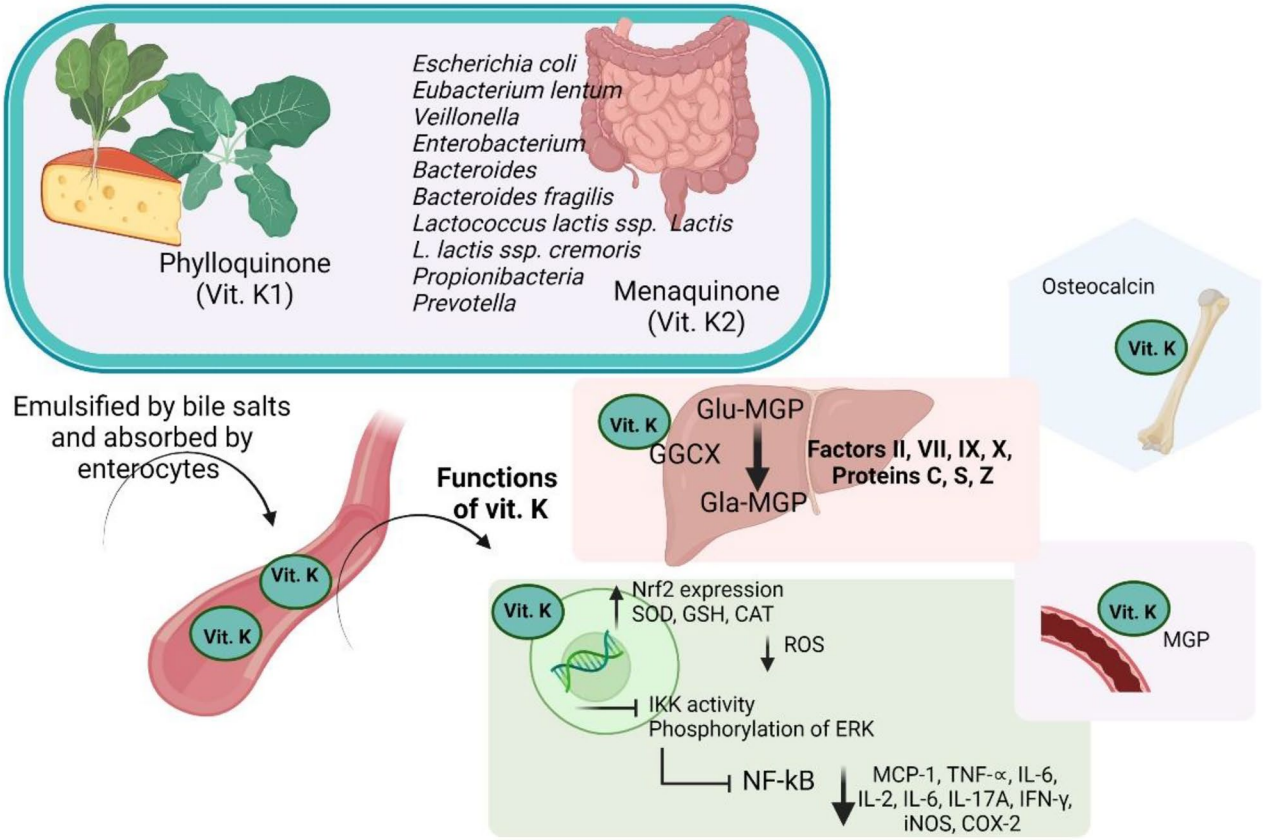

Fig. 2 Functions of vitamin K. Vitamin K from food or microbiota synthesis is absorbed by the enterocytes and transported in the blood by lipoproteins. In the liver, vitamin K acts as cofactor for the enzyme γ-glutamyl carboxylase (GGCX) modifying glutamic acid (Glu) into gamma-carboxyglutamate (Gla) on vitamin K-dependent proteins: coagulation factors II, VII, IX, and X, and the anticoagulant proteins C, S, and Z. Vitamin K can also activate nuclear factor erythroid 2–related factor 2 (Nrf2) expression and increase synthesis of superoxide dismutase (SOD), glutathione peroxidase (GSH), and catalase (CAT), which reduces reactive oxygen species (ROS). Vitamin K also inhibits inhibitor of nuclear factor kappa B kinase (IKK) activity or phosphorylation of extracellular signal-regulated kinase (ERK), blocking the activation of nuclear factor kappa B (NF-kB), reducing synthesis of pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), TNF-∝, IL-6, IL-2, IL-6, IL-17A, IFN-γ, nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Vitamin K is important to skeletal tissues and to inhibit vascular calcification through matrix Gla protein (MGP). Image made with https://biorender.com/

Table 3 Vitamin K-producing bacteria

Bacterial taxa	Menaquinone produced
Escherichia coli	MK-8
Eubacterium lentum	MK-6, MK7, MK-8, MK-10, and MK-11
Veillonella	
Enterobacterium	
Bacteroides	
Bacteroides fragilis	MK-10 to MK-12
Lactococcus lactis ssp. Lactis	MK-8 and MK-9
L. lactis ssp. cremoris	
Propionibacteria	MK-9
Prevotella	MK-5, MK-11, MK-13

Hyperphosphatemia is a common feature in CKD, often treated with intestinal phosphate binders some of which can bind vitamin K [104]. An in vitro study that tested vitamin K2 binding by five phosphate binders has shown that only sucroferric-oxyhydroxide and sevelamer carbonate did not bind vitamin K2. The authors attributed this finding to the low doses of sevelamer used [110]. Another study has observed that sevelamer, due to its binding to bile acids, can reduce the absorption of fat-soluble vitamins [111]. Fusaro et al. [112] have evaluated vitamin K levels in hemodialysis patients and found greater MK4 deficiency in patients treated with sevelamer [112]. Jansz et al. [113] have observed that in dialysis patients, the use of sevelamer monotherapy was associated with higher plasma levels of dp-ucMGP and worsening of vitamin K status [113]. Another study of 172 sevelamer users found higher plasma levels of dp-ucMGP compared to non-users [51].

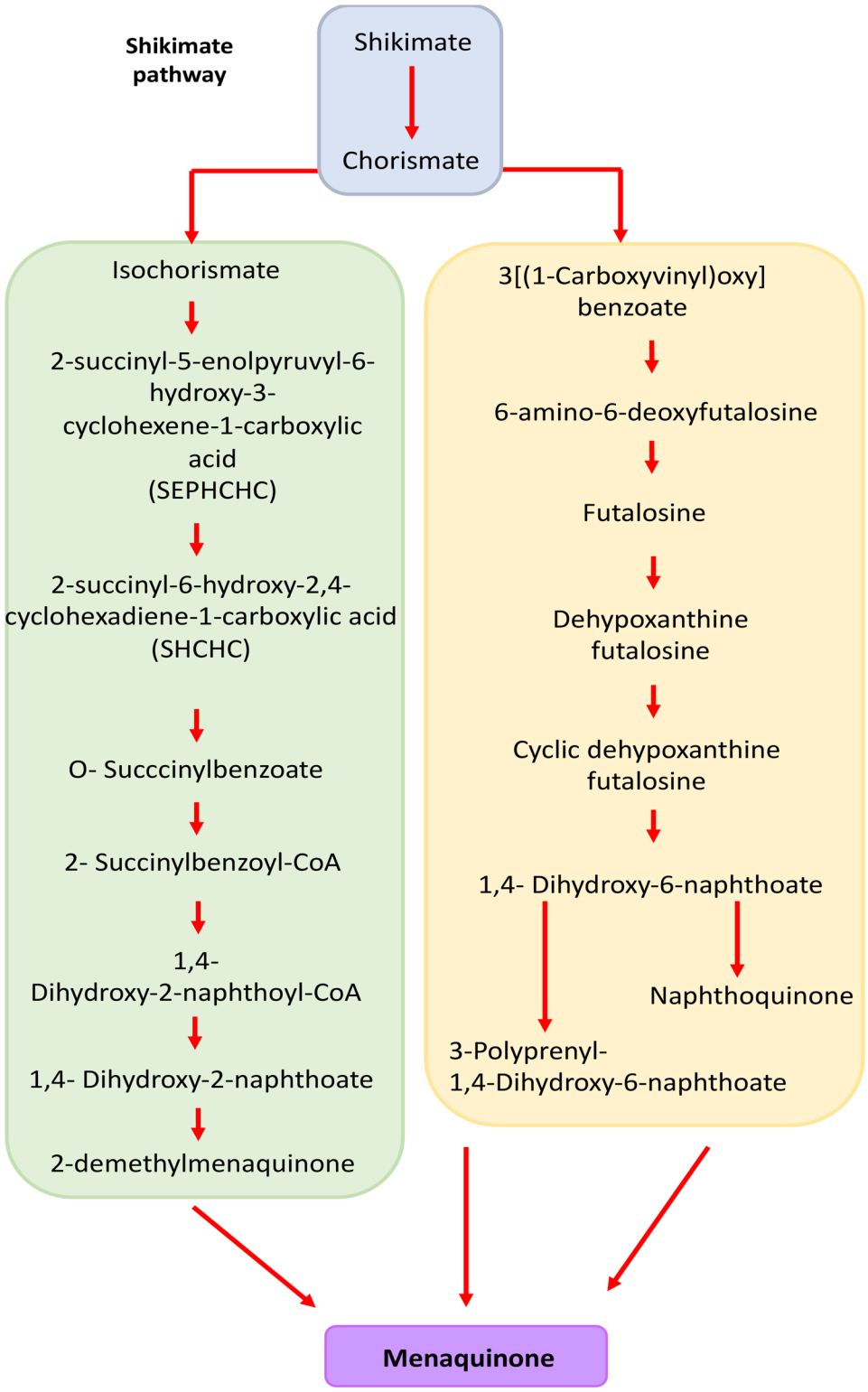

Fig. 3 Biochemical pathways utilized by gut bacteria to synthesize vitamin K

Due to dyslipidemia, statins are commonly prescribed in CKD. A study has shown that the addition of simvastatin along with menadione resulted in a significant inhibition of MK-4 production in vitro by vascular smooth muscle cells [114]. Lipophilic statins can inhibit the enzyme activity of UbiA prenyltransferase-domain containing protein 1 (UBIAD1) which plays an important role in MK-4 synthesis [115]. Other medications commonly used by CKD patients, such as proton pump inhibitors and antibiotics, can influence vitamin K levels through changes in the intestinal

Table 4 Studies investigating the effects of vitamin K in patients with CKD

References	Study Design	Sample	Intervention	Results
Schlieper et al. [117]	Pilot study, clinical trial	17 HD patients	135 µg daily vitamin K2 for 6 weeks	↓ dp-ucMGP
Westenfeld et al. [97]	Prospective randomized blinded intervention	53 HD patients	Vitamin K2 treatment at 45, 135, or 360 µg/d for 6 weeks	↓ dp-ucMGP, uncarboxylated osteocalcin, and uncarboxylated prothrombin
Caluwé et al. [105]	Prospective, randomized, single-blinded intervention	200 HD patients	360, 720, or 1080 µg of vitamin K2 thrice weekly for 8 weeks	Supplementation dose-dependently reduced dp-ucMGP
Kurnatowska et al. [119]	Prospective, randomized, double-blind	42 non-dialyzed CKD patients	90 µg vitamin K2 (menaquinone, MK-7) + 10 µg of vitamin D for 9 months	↓ Carotid intima-media thickness ↓ dp-ucMGP, OPG
Aoun et al. [120]	Prospective, pre-post intervention clinical trial	50 HD patients	360 µg daily vitamin K2 for 4 weeks	↓ dp-ucMGP
Oikonomaki et al. [121]	Prospective, randomized interventional	102 HD patients	200 µgr of vitamin K2 daily for 1 year	↓ Uncarboxylated MGP (uc-MGP) concentrations
Witham et al. [122]	Interventional, placebo-controlled, double-blind, randomized trial	159 non-dialyzed CKD patients	400 µg of oral vitamin K2 daily for 1 year	↔ Vascular stiffness or VC measures
De Vriese et al. [123]	Randomized, prospective, open-label interventional clinical trial	132 HD patients with atrial fibrillation treated with Vitamin K antagonists or qualifying for anticoagulation	10 mg rivaroxaban + 2000 mg vitamin K2 3x/week (after dialysis session) for 18 months	↓ dp-ucMGP ↔ VC progression
Levy-Schousboe et al. [124]	Double-blind, randomized, placebo-controlled trial	48 HD patients	360 µg daily vitamin K2 for 2 years	↓ dp-ucMGP plasma levels

CKD chronic kidney disease, *HD* hemodialysis, *VC* vascular calcification, *OPG* osteoprotegerin, *dp-ucMGP* desphosphorylated-uncarboxylated MGP, *MK-7* menaquinone-7

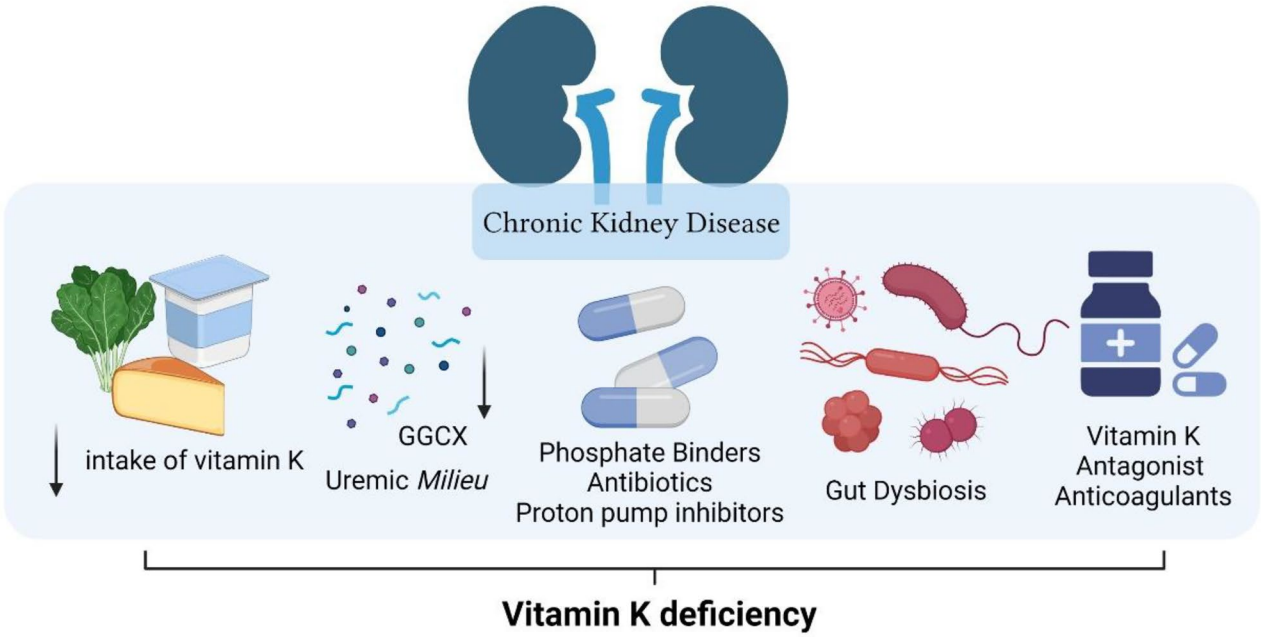

Fig. 4 Hypothesized reasons for vitamin K deficiency in patients with CKD. Reduced vitamin K intake (via green leafy vegetables and dairy products) and uremia cause a reduction in γ-glutamyl carboxylase (GGCX) levels and use of medications such as phosphate binders, antibiotics, proton pump inhibitors, and vitamin K antagonists. Additionally, gut dysbiosis leads to a reduced synthesis of vitamin K2. Image made with https://biorender.com/

microbiota. As gut dysbiosis is common in patients with CKD [116], they may have limited synthesis of MKs by anaerobic bacteria.

Another consequence of vitamin K deficiency, using dp-ucMGP as biomarker, is its association with increased bone fractures as well as CVD [117, 118]. Few clinical studies have explored the effects of vitamin K supplementation on cardiovascular calcification as well on vitamin K plasma levels in CKD (Table 4).

In non-dialyzed CKD patients the effects of vitamin K supplementation on carotid intima-media thickness are controversial [119, 122]. Other studies have evaluated vitamin K2 supplementation in patients undergoing hemodialysis and found no change in aortic calcification or coronary calcification, despite reduced circulating ucMGP levels [121, 123, 124]. Thus, whereas vitamin K supplementation has proven to be effective in reducing dp-ucMGP levels, it does not reduce vascular calcification in CKD. There are some hypotheses to explain this. Firstly, although vitamin K supplementation reduces dp-ucMGP levels, normal vitamin K levels are not reached [117]. Secondly, vascular calcification is a complex and multifactorial process due to an imbalance between calcification promoters (inflammation, aging, hypercalcemia, hyperphosphatemia, etc.) and inhibitors (vitamin K, klotho, magnesium, vitamin D, MGP, etc.) [125, 126]. In this complex scenario, a single isolated strategy is unlikely to arrest vascular calcification.

We have shown that many pathological aspects of CKD affect vitamin K levels and that CDK patients often present with gut dysbiosis. Therefore, we propose that an imbalanced gut microbiota may be related to vitamin K deficiency in CKD [127]. However, there have not yet been any clinical studies carried out in patients with CKD that have evaluated the dysbiosis–vitamin K axis (Fig. 4).

Conclusions

Gut microbiota play an important role in human health and gut dysbiosis is a prominent feature in CKD. We propose that changes in gut microbiota alter vitamin K production, leading to vitamin K deficiency. Thus, more attention should be paid to the gut microbiota balance in CKD patients and further studies should be carried out. Dietary interventions restoring gut microbiota balance and consequently vitamin K deficiency should be explored as a new nutritional strategy to improve the CKD patient's outcomes.

Author Contribution All authors contributed to the conception, drafting, and revision of the manuscript. All authors approved the final copy.

Funding Denise Mafra's research was supported by Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human oranimal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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