Vitamin Supplement Use in Patients With CKD: Worth the Pill Burden?

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All vitamins play essential roles in various aspects of body function and systems. Patients with chronic kidney disease (CKD), including those receiving dialysis, may be at increased risk of developing vitamin deficiencies due to anorexia, poor dietary intake, protein energy wasting, restricted diet, dialysis loss, or inadequate sun exposure for vitamin D. However, clinical manifestations of most vitamin deficiencies are usually subtle or undetected in this population. Testing for circulating levels is not undertaken for most vitamins except folate, B_{12}, and 25-hydroxyvitamin D because assays may not be available or may be costly to perform and do not always correlate with body stores. The last systematic review through 2016 was performed for the Kidney Disease Outcome Quality Initiative (KDOQI) 2020 Nutrition Guideline update, so this article summarizes the more recent evidence. We review the use of vitamins supplementation in the CKD population. To date there have been no randomized trials to support the benefits of any vitamin supplementation for kidney, cardiovascular, or patient-centered outcomes. The decision to supplement water-soluble vitamins should be individualized, taking account the patient's dietary intake, nutritional status, risk of vitamins deficiency/insufficiency, CKD stage, comorbid status, and dialysis loss. Nutritional vitamin D deficiency should be corrected, but the supplementation dose and formulation need to be personalized, taking into consideration the degree of 25-hydroxyvitamin D deficiency, parathyroid hormone levels, CKD stage, and local formulation. Routine supplementation of vitamins A and E is not supported due to potential toxicity. Although more trial data are required to elucidate the roles of vitamin supplementation, all patients with CKD should undergo periodic assessment of dietary intake and aim to receive various vitamins through natural food sources and a healthy eating pattern that includes vitamin-dense foods.

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Introduction

According to the Institute of Medicine, the human body needs at least 13 vitamins to function properly.[1] Having a healthy diet with vitamin-dense foods is essential to optimize the intake of different essential vitamins and meet the recommended dietary allowances (RDA), defined as the intake levels adequate to meet the known nutrient needs of healthy persons on the basis of scientific knowledge. Patients with chronic kidney disease (CKD), including those requiring maintenance dialysis, are at risk of vitamin deficiencies, with the risk increasing with worsening CKD severity.[2,3] With advanced CKD, patients may have poor appetite, anorexia, inflammation, protein-energy wasting (PEW), or altered taste, all of which may reduce dietary intake or variety; patients are often educated to restrict intake of fruits, vegetables, whole grains, dairy products, beans, and fermented foods, which frequently constitute a healthy dietary pattern, because these are rich in potassium and phosphorus. Patients receiving peritoneal dialysis may have abdominal fullness with peritoneal dialysis fluid, which may limit their food intake. Water-soluble vitamins are also lost during dialysis treatment.[4,5] This raises the questions of whether patients with CKD should receive vitamin supplementation routinely, who should receive vitamin supplementation, and which vitamins to supplement. Table 1 presents an overview of clinical manifestations of vitamin deficiencies, and Table 2 presents sources of various vitamins in food.

Systematic reviews in the general population have shown no helpful or harmful outcomes for those who take multivitamins, vitamin D, calcium, and vitamin C.[6] Similar conclusions were drawn in the Kidney Disease Outcome Quality Initiatives (KDOQI) nutrition guidelines in CKD 2020.[4] Folate and other B vitamins (B_6 and B_{12}) are associated with a reduction in the risk of stroke, largely due to data from a Chinese study.[7] Niacin and antioxidants were proven harmful and are associated with an increased risk of death when taken with statins.[6]

We provide an updated review of the use of vitamins A, B, C, D, E, and K and multivitamins in CKD. We searched PubMed and Medline for clinical trials, systematic reviews, and meta-analyses of clinical trials published since the last KDOQI nutrition guidelines evidence review, spanning December 2016 to 2023 using as search terms the name of the specific vitamin and "chronic kidney disease." The review was limited to adults with CKD, and our search strategy excluded vitamin K antagonists. Supplementation with minerals and trace elements is beyond the scope of the review. Only English language manuscripts were included. Table 3 provides a summary of different vitamins in the context of CKD, including likelihood of deficiency, specific considerations, supplementation, and risk of toxicity.

Vitamin A

Vitamin A, a class of retinoids essential for health, includes retinol and retinyl-esters, which are necessary for

Table 1. Clinical Manifestations of Vitamin Deficiencies

Vitamin	Clinical Manifestation of Deficiency
Vitamin A (retinol)	Dry skin, dry eyes, night blindness, poor wound healing, delayed growth, throat and chest infections
Vitamin B_1 (thiamine)	Refractory lactic acidosis, peripheral polyneuropathy (dry beriberi), congestive heart failure (wet beriberi) or Wernicke's encephalopathy (WE)[12,17,21,136]
Vitamin B_2 (riboflavin)	Nonspecific symptoms including weakness, sore throat, angular stomatitis, mucositis, cheilosis, glossitis, dermatitis, and anemia[12,22]
Vitamin B_3 (niacin)	Pigmented skin rash on sun exposure, bright red tongue, fatigue, vomiting, diarrhea, constipation, circulatory problems, depression, headache, memory loss, and in severe cases hallucinations
Vitamin B_5 (pantothenic acid)	Gastrointestinal disturbance, muscle cramps, paresthesia, ataxia, depression, and hypoglycemia;[22] nonspecific symptoms (fatigue, insomnia, depression, etc)[22,45,46]
Vitamin B_6 (pyridoxine)	Malaise, fatigue, weakness, dizziness, cardiovascular complications, lower limb numbness and burning paresthesia, gastrointestinal disturbance (anorexia, vomiting), and neurologic symptoms (depression, irritability, confusions, seizures)
Vitamin B_7 (biotin)	Hair loss, red rash around body openings, conjunctivitis, ketoacidosis and aciduria, seizures, skin infection, brittle nails, neurological findings (eg, depression, lethargy, hallucinations, and paresthesias of the extremities)
Vitamin B_9 (folate, folic acid)	Megaloblastic anemia[12] and erythropoietin hyporesponsiveness[49]
Vitamin B_{12} (cobalamin)	Megaloblastic anemia, hyperhomocysteinemia, cognitive impairment, neuropsychiatric disorders, peripheral neuropathy, and subacute combined degeneration of spinal cord
Vitamin C (ascorbic acid)	Fatigue, depression, and connective tissue defects (eg, gingivitis, petechiae, rash, internal bleeding, impaired wound healing), and scurvy (severe)
Vitamin D (cholecalciferol)	Fatigue, bone pain, muscle pain and weakness, low energy
Vitamin E (α-tocopherol)	Distal extremities numbness and paresthesias, loss of body movement control, muscle weakness, visual problems, and weakened immune system
Vitamin K_1 (phylloquinone), Vitamin K_2 (menaquinone)	Bleeding complications, may accelerate vascular calcification

nocturnal vision, immune function, reproduction, cell differentiation, kidney development; more recently, roles have been identified in glucose metabolism, obesity, and bone mineralization.[8] It is metabolized through the lymphatic system and is stored as retinol in the liver and to a lesser extent in adipose tissue.[9] Vitamin A status is tightly regulated, with retinol binding protein 4 (RBP4) as the key transporter of retinol to target tissues for conversion into its active form, all-trans retinoic acid (atRA). Elevated retinol and RBP4 are evident in CKD independent of dietary intake,[10] and vitamin A deficiency is rare, evident only with prolonged exceptionally poor diets.[11] Elevated circulating retinol, retinoic acid, and RBP4 levels may be due to increased hepatic synthesis. Vitamin A clearance is not reduced with estimated glomerular filtration rate (eGFR) decline.[10] Excess vitamin A may contribute to increased fracture risk, atherosclerosis, cardiovascular disease, and diabetes in people with CKD.[10] Because vitamin A is typically elevated in CKD, supplementation is not recommended, and even low doses may cause toxicity.[9]

Vitamin B_1 (Thiamine)

Thiamine is involved in carbohydrate and branched chain amino acid metabolism.[12] Thiamine deficiency is diagnosed by blood levels or by measuring erythrocyte transketolase activity.[12] Limited data suggest that thiamine deficiency may be observed in up to 25% of patients with CKD stage 5, and levels further decrease after initiation of dialysis,[13] which is attributed to low thiamine intake[14] and intradialytic losses.[15,16] Other factors include decreased bioavailability, poor nutrition intake, long-term diuretic therapy, malabsorption, and production of the thiamine antagonist oxythiamine by microbiota.[17-20] Kidney transplantation may not restore this deficiency, at least within 6 months after transplant.[13] Most of the manifestations mimic uremic complications, making an early diagnosis of thiamine deficiency difficult in advanced CKD.[21]

Because most studies have lacked quantitative thiamine assessments, it is not possible to precisely determine the daily needs of patients with advanced CKD. The RDA for thiamine and other vitamins generally follows that of the general population. KDOQI guidelines recommend periodic assessment of dietary intake of specific vitamins, especially water-soluble ones, in patients with CKD stages 3-5D. In patients with CKD stage 5D who have sustained periods of inadequate intake and PEW, supplementation of all water-soluble vitamins including thiamine is recommended.[4]

Vitamin B_2 (Riboflavin)

Riboflavin is important in fat, carbohydrate, and protein metabolism[22] and has anti-inflammatory effects.[23] Riboflavin is involved in homocysteine metabolism, and suboptimal supply increases the risk of hyperhomocysteinemia.[24] Tissue riboflavin status is determined by erythrocyte glutathione reductase activation coefficient (EGR-AC), and levels

Table 2. Natural Food Sources of Vitamins

Vitamin	Natural Food Sources
Vitamin A (retinol)	Animal-sourced foods such as oily fish, liver, cheese, and butter; β-carotene (pro-vitamin A) in plants food such as carrots, turnips, kale, winter squash, collards, mango, papaya, and apricots can be converted to retinol by human body
Vitamin B_1 (thiamine)	Peas, some fresh fruits (such as bananas and oranges), nuts, wholegrain breads, some fortified breakfast cereals
Vitamin B_2 (riboflavin)	Milk and dairy products, whole grains, legumes, lean meat, and fish[12]
Vitamin B_3 (niacin)	Many foodstuffs, particularly fresh vegetables, milk, meat, fish, and eggs[12,22]
Vitamin B_5 (pantothenic acid)	Pantothenic acid found in nearly all food sources[12]
Vitamin B_6 (pyridoxine)	Meat, yeast, legumes, nuts, avocados, and bananas[12,22]
Vitamin B_7 (biotin)	Yeast, tomato, liver, soybeans, rice, bran, and egg yolks
Vitamin B_9 (folate)	Green leafy vegetables, whole grains, yeast, and liver[12]
Vitamin B_{12} (cobalamin)	Animal and dairy products[12]
Vitamin C (ascorbic acid)	Citrus fruits, fruits and vegetables, potatoes
Vitamin D (cholecalciferol)	Oily fish, liver, egg yolk; mushrooms exposed to UV-B light contain some vitamin D_2; vitamin D–fortified foods such as milk, yogurt, breakfast cereals, bread, orange juice, some fat spreads
Vitamin E (α-tocopherol)	Seeds (including sunflower seeds), nuts (almonds, peanuts, and hazelnuts), and vegetable oils (rapeseed oil, sunflower oil, safflower oil), wheatgerm, peanut butter
Vitamin K_1 (phylloquinone)	–Leafy green vegetables including kale, spinach, cabbage, broccoli, and oils and margarine–
Vitamin K_2 (menaquinone)	Fermented products including cheese, fermented soybean product natto, animal products, with highest levels in eggs and chicken and ham, butter, cream, sour cream, and cheese[119,137]

greater than 1.3 suggest riboflavin deficiency.[12] Riboflavin deficiency is rare but occurs with severe PEW, typically in association with deficiencies of other vitamins. Around 40% of predialysis patients were reported to have suboptimal riboflavin intake.[25] Hemodialysis does not impact blood riboflavin concentrations.[15] KDOQI guidelines recommend that supplementation of riboflavin along with other water-soluble vitamins may be considered in patients with CKD stage 5D who experience sustained periods of inadequate dietary intake.[4]

Vitamin B3 (Niacin)

Niacin is crucial in the synthesis of carbohydrates, proteins, and fatty acids.[12] Chemically, niacin is known as nicotinic acid and its amide as nicotinamide.[22,26] Niacin status is assessed by urinary excretion of its metabolites N1-methyl-nicotinamide and N1-methyl-2-pyridone-5-carboxamide.[27] Niacin deficiency is thought to be extremely uncommon in CKD patients. Niacin supplementation may reduce oxidative stress and improve endothelial dysfunction, inflammation, and dyslipidemia.[28-31] Nicotinamide reduces intestinal phosphate absorption[30,32,33] and enhances urinary phosphate excretion.[30,32] Niacin (500-2,000 mg/day) and its derivatives (nicotinamide and nicotinic acid) may improve hyperphosphatemia, lipid profile, and kidney function in patients with CKD but has potential adverse effects such as flushing, nausea, and vomiting.[32,34-39] Extended-release niacin added to simvastatin improves lipid profile but has no benefits on cardiovascular outcomes in patients with CKD and established coronary heart disease.[40]

Vitamin B_5 (Pantothenic Acid)

Pantothenic acid, a precursor for coenzyme A, is involved in metabolism of proteins, carbohydrates, fats, and steroid hormones.[12,22,41,42] Mammalian cells do not synthesize pantothenic acid and require it to be generated by intestinal microbiome or from diet.[42] Deficiency states are exceedingly rare, largely as a component of severe PEW with combined vitamin deficiencies.[12,22] Data about pantothenic acid in CKD are scarce, and levels are reported to be normal in CKD.[12] There are no specific recommendations for pantothenic acid in CKD, apart from general considerations of supplementation in patients with inadequate intake.[4]

Vitamin B_6 (Pyridoxine)

Pyridoxine represents a family of related compounds including pyridoxine, pyridoxal, pyridoxamine, and their phosphates.[22] All are converted to active form pyridoxal 5-phosphate (PLP),[12] which is the most reliable indicator of body stores.[43] Pyridoxine is a cofactor for many enzymes involved in red blood cell synthesis, amino acid metabolism, histamine synthesis, and gene expression. PLP is a component of enzymes that metabolize homocysteine to cysteine, and its deficiency leads to hyperhomocysteinemia.[12,22,44] The etiology of pyridoxine deficiency includes decreased intake, impaired absorption, altered metabolism, drug interaction, increased degradation, and loss through dialysis.[45] Deficiency is often subtle and underrecognized.

Pyridoxine has a low molecular weight, higher dialyzer clearance, and lower body stores than other B group vitamins.[46] Although PLP levels in earlier stages of CKD are

Table 3. Summary of Vitamin Deficiencies, CKD-related Causes of Deficiencies, Assays, Supplementation Guidelines, and Risk of Toxicity in CKD

Vitamin	Deficiency	CKD-relevant Issues	Methods of Analysis	Supplementation Recommendations and Supporting Data	Risk of Toxicity
Vitamin A (retinol)	Rare	Elevated plasma concentration common in CKD and not associated with dietary intake	HPLC for plasma measurement	No data available, supplementation not recommended except with exclusive parenteral nutrition > 2 weeks' duration or with confirmed deficiency	Potential for toxicity in CKD so individual treatment for deficiency only; monitor levels periodically if taking multivitamin supplement containing vitamin A
Vitamin B_1 (thiamine)	25% in stage 5 CKD, more frequent in maintenance dialysis patients	Dietary restrictions, decreased bioavailability, malnutrition, long-term diuretic therapy; significant dialysis-related loss	Whole blood or serum levels; erythrocyte transketolase activity	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Unknown
Vitamin B_2 (riboflavin)	Uncommon	Suboptimal intake; severe malnutrition; no significant removal by HD	Erythrocyte glutathione reductase activation coefficient	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Unknown
Vitamin B_3 (niacin)	Extremely uncommon	Suboptimal intake	Urinary excretion of niacin metabolites[a]	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Gastrointestinal symptoms, elevated transaminases, myopathy
Vitamin B_5 (pantothenic acid)	Extremely uncommon	Severe malnutrition	Whole blood or plasma levels	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Unlikely
Vitamin B_6 (pyridoxine)	Often subtle	Levels normal in early stages of CKD, some decrease in maintenance dialysis patients; higher hemodialyzer clearance than other B group of vitamins, resin-based phosphate binders adsorb B_6; erythropoietin increases B_6 requirement	Plasma pyridoxal 5-phosphate levels	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Peripheral neuropathy
Vitamin B_7 (biotin)	Unlikely	None	Plasma or urine levels	During sustained periods of inadequate intake and PEW, along with all water-soluble vitamins	Unknown
Vitamin B_9 (folate)	10% of maintenance HD patients, much less in PD patients	Consistent favorable effects on homocysteine levels; no favorable effects on cardiovascular or kidney outcomes	Serum levels; erythrocyte folate level better indication of tissue stores	Recommended in deficiency/insufficiency states; recommended in HD patients in the form of a multivitamin beginning at least 3 mo before pregnancy, during pregnancy, and 4-6 weeks postpartum or as long as breastfeeding continues	Low

(Continued)

Table 3 (Cont'd). Summary of Vitamin Deficiencies, CKD-related Causes of Deficiencies, Assays, Supplementation Guidelines, and Risk of Toxicity in CKD

Vitamin	Deficiency	CKD-relevant Issues	Methods of Analysis	Supplementation Recommendations and Supporting Data	Risk of Toxicity
Vitamin B_{12} (cobalamin)	Uncommon	No significant removal by HD or PD	Serum levels; serum methylmalonic acid and homocysteine levels (better indicate functional status)	Recommended in deficiency/ insufficiency states; specific assessment in patients receiving folate supplementation	Cyanide toxicity
Vitamin C (ascorbic acid)	Unknown but shown to be lower in CKD compared with the general population	Lost during dialysis treatment	Markers of oxidative stress: paraoxonase activity, MDA; serum levels; ADMA	Reduction of oxidative stress; decrease central blood pressure in patients with CKD 3-5; reduction in circulating ADMA	Caution in patients with history of oxalate stones
Vitamin D (cholecalciferol)	High prevalence of vitamin D deficiency or insufficiency in CKD population	25(OH)D deficiency may occur due to reduced dietary intake, reduced sun exposure with sedentary lifestyle and few outdoor hours. Patients with nephrotic range proteinuria had increased renal loss of vitamin D–binding proteins, the main carrier protein for 25(OH)D, reduced renal tubular reabsorption of 25(OH)D, decreased 25(OH)D synthesis with worsening kidney function, and defective photoproduction of cholecalciferol despite normal skin content of 7-dehydrocholesterol. Increasing age, female gender, body adiposity, and diabetes were also correlated with more 25(OH) D deficiency in CKD.	Circulating 25(OH)D levels as marker of status	• PKDOQI nutrition guidelines suggest nutritional vitamin D be supplemented in patients with CKD 1-5D to correct 25(OH)D deficiency/ insufficiency. • 25(OH)D levels < 15 ng/mL should be supplemented regardless of PTH levels; patients with 25(OH)D levels between 15 and 20 ng/mL may not require treatment if no evidence of counter-regulatory hormone activity.	Caution in patients with renal stones or high plasma calcium
Vitamin E (α-tocopherol)	Data equivocal	Potentially impaired metabolism in CKD	Plasma level using HPLC	Mixed results in trials of supplementation across CKD stages	Potential for toxicity in CKD
Vitamin K_1 (phylloquinone), vitamin K_2 (menaquinone)	50% deficiency in CKD; almost 100% of CKD stage 5 patients functionally deficient	Low dietary intake of K-rich foods, as leafy green vegetables and dairy foods may be limited in some people with CKD.	Functional deficiency measured indirectly by higher levels of dp-ucMGP; direct measurement of vitamin K difficult due to low concentration and lipophilic nature	No benefit of K_1 supplementation has been demonstrated; K_2 supplementation reduced functional deficiency but did not improve vascular stiffness or aortic calcification scores.	No known risk of toxicity of K_2 or K_3; supplementation likely safe but no established benefit for vascular or bone biomarkers in CKD

Abbreviations: ADMA, asymmetric dimethylarginine; CKD, chronic kidney disease; dp-ucMGP: dephysphorylated undercarboxylated matric Gla protein; HD, hemodialysis; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; PD, peritoneal dialysis; PEW, protein energy wasting.
[a]*N*1-methyl-nicotinamide and *N*1-methyl-2-pyridone-5-carboxamide.

normal compared with healthy controls, patients on maintenance dialysis have relatively lower levels.[13] Low-dose supplementation (10 mg after dialysis) does not seem to increase the levels adequately.[47] Notably, resin-based phosphate binders adsorb pyridoxine, and erythropoietin increases requirements, which could exacerbate relative deficiency.[45,48] Supplementation of pyridoxine as a component of all water-soluble vitamins may be considered in patients with CKD stage 5D who have sustained periods of inadequate food intake.[4]

Vitamin B_7 (Biotin)

Biotin acts as a carrier of carbon dioxide and plays a role in carboxylase enzymes involved in gluconeogenesis and fatty acid metabolism.[12,22] Biotin is mostly produced by alimentary tract bacteria.[12] The RDA of biotin is not established, but the estimated adequate intake is 30 μg/day.[27] Based on available data, biotin deficiency is not likely to occur in CKD, and there is no specific recommendation other than considerations for the general population.[4]

Vitamin B_9 (Folate, Folic Acid)

Folate is derived from polyglutamates in food that are converted into monoglutamates in the bowel.[49] Folate serves as an antioxidant at mitochondrial level, ameliorates mitochondrial oxidative decay, and improves endothelial function.[50,51] Erythrocyte folate concentration, rather than serum folate, is a better indicator of tissue folate stores.[49] Folate stores are low, so a deficiency can occur within 21-28 days of severe dietary deficiency.[12] Folate deficiency leads to mitochondrial dysfunction, membrane depolarization, increased reactive oxygen species production, and premature cell death.[50]

Although folate intake is reported to be suboptimal in over half of predialysis patients, its deficiency is observed in only 10% of hemodialysis patients and is much less in peritoneal dialysis patients.[12,25] Folate, along with pyridoxine and cobalamin, is involved in homocysteine metabolism, and its relative deficiency could lead to hyperhomocysteinemia.[12] Multiple randomized controlled trials (RCTs) have investigated whether homocysteine reduction by vitamin B supplementation improves cardiovascular outcomes (Table 4). Despite consistent favorable effects of folate supplementation, with or without other B group vitamins, on homocysteine levels, no significant effects on cardiovascular or kidney outcomes were observed in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial. In the FAVORIT trial, high-dose folic acid, vitamin B_6, and B_{12} supplementation decreased homocysteine levels but did not improve cardiovascular outcome or survival compared with low-dose B_6 and B_{12} supplementation without folic acid in stable kidney transplant recipients.[52] Accordingly, folic acid supplementation is recommended for deficiency/insufficiency states but not for hyperhomocysteinemia in CKD patients regardless of the stage of their disease.[4]

Women receiving dialysis are at moderate risk for low folate status and hence neural tube defects or other folic-acid sensitive congenital anomalies in pregnancy. Canadian guidelines for women receiving dialysis recommend folic acid intake of 1.0 mg daily in the form of a multivitamin (containing vitamin B_{12}) beginning at least 3 months before pregnancy and through the first trimester then continuing with a multivitamin daily with 0.4-1.0 mg folic acid for the remainder of pregnancy and for 4-6 weeks postpartum or as long as breastfeeding continues.[53]

Vitamin B_{12} (Cobalamin)

Cobalamin is an essential cofactor for β oxidation of fatty acids, DNA synthesis, and red blood cell production.[54] Methylcobalamin, an active cobalamin metabolite, is involved in homocysteine metabolism.[49] In CKD, downstream metabolites of cobalamin such as methylmalonic acid and homocysteine, rather than serum vitamin B_{12} levels, are more accurate indicators of functional status.[51,55] Deficiency is due to inadequate dietary intake or vegan diet, malabsorption, advanced age, atrophic gastritis, proton pump inhibition, autoimmune diseases, and gastrectomy. Body stores of cobalamin (2-5 mg) are much higher than daily utilization (2-5 μg/day) and thus body stores are depleted over the long term (eg, span of years).[12] Macrocytosis may be masked with folate supplementation, delaying recognition of vitamin B_{12} deficiency and neurologic sequela.[12]

In most patients with CKD stages 1-5, vitamin B_{12} levels are reported to be normal.[56] Specific assessment of vitamin B_{12} status is recommended in patients receiving folate supplementation.[4] Importantly, vitamin B_{12} is supplemented with cyanocobalamin, the metabolism of which generates cyanide. Supplementation should be considered in deficiency/insufficiency states based on clinical signs and symptoms. High replacement doses may be toxic due to reduced cyanide clearance.[49,51]

Vitamin C (Ascorbic Acid)

Ascorbic acid is a powerful antioxidant and is able to combat oxidants before they cause oxidative damage.[57] Ascorbic acid is involved in the synthesis of collagen,[58] carnitine,[59] tyrosine, and other neurotransmitters[60] and possibly microsomal metabolism.[61] It exhibits pro-oxidant activity under certain pathological conditions.[62] High-dose ascorbic acid may increase serum oxalate levels,[63] possibly resulting in tissue and vascular damage.[12]

Patients in all CKD stages, including those receiving dialysis, may have low vitamin C levels compared with healthy controls.[5,12,64-70] Vitamin C deficiencies are more prevalent with longer duration of hemodialysis, are more common in dialysis than nondialysis requiring CKD, and

Table 4. Randomized Controlled Trials of Folic Acid Alone or in Combination With Other B Group Vitamins in CKD Patients

Study	Aim	Sample Characteristics	N	Study Design	Intervention	Duration	Outcome
Zoungas et al[138]	Whether high-dose folic acid slows the progression of atherosclerosis and reduces CV events in patients with CKD	Patients with CKD	315	RCT	Folic acid (15 mg/d) vs placebo	3.6 y	• Folic acid decreased Hcy by 19% • No difference in atheroma progression, CV morbidity and mortality
Jamison et al[139]	Whether high doses of folic acid and B vitamins reduce mortality and CV events in patients with CKD	Patients with advanced CKD (GFR ≤ 30 mL/min) or end-stage renal disease	2,056	RCT	Capsule of folic acid (40 mg/d), vitamin B_6 (100 mg/d), vitamin B_{12} (2 mg/d) vs placebo	3.2 y	• Vitamin B therapy decreased Hcy • No difference in all-cause mortality, CV events, or need to start dialysis
Mann et al[140]	Whether patients with moderate CKD benefit from vitamin B treatment	Patients with CKD (GFR < 60 mL/min) and at high CV risk	619	• RCT • Post hoc analysis of HOPE-2 trial	Folic acid (2.5 mg/d), vitamin B_6 (50 mg/d), and vitamin B_{12} (1 mg/d) vs placebo	5 y	• Hcy decreased in treatment group • No benefits of treatment on mortality due to CV disease, stroke, or total mortality
House et al[141]	Whether combined folic acid, vitamin B_6, and vitamin B_{12} slows progression of diabetic nephropathy and prevents vascular complications	• T1DM or T2DM and diabetic nephropathy • 63.9% with at least stage 3 CKD	238	RCT	Single tablet of folic acid (2.5 mg/d), vitamin B_6 (25 mg/d), and vitamin B_{12} (1 mg/d) vs placebo	31.9 mo	• Vitamin B therapy decreased Hcy • Vitamin B group had more rapid decline in GFR and higher rates of cerebrovascular and CV events
Xu et al[142]	Whether treatment with enalapril and folic acid is more effective in slowing renal function decline than enalapril alone across a spectrum of renal function at baseline from normal to moderate CKD	Patients with HTN and GFR ≥ 30 mL/min/1.73 m^2	15,104	• RCT • Renal substudy of CSPTT trial	Single tablet of enalapril (10 mg/d), folic acid (0.8 mg/d) vs enalapril only (10 mg)	4.4 y	• Enalapril and folic acid group had a greater drop in Hcy • Enalapril and folic acid reduced risk of CKD progression by 21% and slowed rate of GFR decline by 10% • Patients with baseline CKD benefited most from folic acid therapy
Li et al[143]	Modifying effect of vitamin B_{12} levels on association between folic acid treatment and CKD progression	Patients with HTN and baseline CKD	1,374	• RCT • Post hoc analysis of renal substudy of the CSPPT	Single tablet of enalapril (10 mg/d) and folic acid (0.8 mg/d) vs enalapril only (10 mg)	4.4 y	In patients with higher baseline vitamin B_{12} levels, enalapril plus folic acid treatment decreased odds of CKD progression by 83%

(Continued)

Table 4 (Cont'd). Randomized Controlled Trials of Folic Acid Alone or in Combination With Other B Group Vitamins in CKD Patients

Study	Aim	Sample Characteristics	N	Study Design	Intervention	Duration	Outcome
Bostom et al[52]	Whether decreasing Hcy levels with high doses of combined folic acid, vitamin B_6, and vitamin B_{12} reduce CV outcomes compared with treatment with low-dose combination of vitamins B_6 and B_{12} devoid of folic acid	Stable RTRs (GFR ≥ 30 mL/min) with HHcy	4,110	RCT	High-dose folic acid (5 mg/d), vitamin B_6 (50 mg/d), vitamin B_{12} (1.0 mg/d) vs low dose of vitamin B_6 (1.4 mg/d) and vitamin B_{12} (2.0 μg/d), no folic acid	4.0 y	• Early termination • High-dose supplementation decreased Hcy levels • High-dose supplementation did not reduce dialysis-dependent kidney failure, CV, or all-cause mortality

Abbreviations: CKD, chronic kidney disease; CSPPT, China Stroke Primary Prevention Trial; CV, cardiovascular; GFR, glomerular filtration rate; Hcy, homocysteine; Hhcy, hyperhomocysteinemia; HOPE, Heart Outcomes Prevention Evaluation Trial; HTN, hypertension; RCT, randomized controlled trial; RTR, renal transplant recipients; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

may relate to cumulative loss of vitamin C during dialysis.[71-73] KDOQI 2020 guidelines recommend that vitamin C supplementation should be considered in patients with CKD stages 1-5D who are at risk of deficiency, but treatment should be individualized.[74]

In hemodialysis patients, vitamin C supplementation had no demonstrable effects on nutrition markers, including albumin, transferrin, and normalized protein catabolic rate.[4] Parenteral ascorbic acid supplementation (500 mg) may reduce oxidative stress in hemodialysis patients as demonstrated by increased paraoxonase activity and decreased malondialdehyde (MDA),[70] a byproduct of lipid peroxidation and a marker of oxidative stress, with an inverse relationship observed between vitamin C and MDA.[69,70] Vitamin C supplementation may reduce circulating asymmetric dimethylarginine[68] and decrease central blood pressure in patients with CKD stages 3-5.[68,69,71-73] Although vitamin C supplementation improves serum vitamin C levels for vitamin C–deficient hemodialysis patients,[73] adequately powered RCTs to evaluate kidney, cardiovascular, and patients-centered outcomes have been lacking. The decision to supplement vitamin C should be individualized, taking account the CKD stage, dialysis modality, dietary intake, nutrition status, and comorbid conditions; the supplementation dose should be guided by the RDA. Finally, supplementation should be undertaken with caution in patients who have a history of oxalate stones.[4]

Vitamin D

Vitamin D plays an important regulatory role in mineral homeostasis and skeletal health. Over 80% of vitamin D is acquired through the skin from sunlight-induced synthesis of pre-vitamin D_3 from 7-dehydocholesterol, which is rapidly converted to D_3. D_2 and D_3 function as prohormones and are transported to the liver by vitamin D–binding protein and metabolized to 25-hydroxy (OH) D. 25(OH)D is further metabolized to active form $1,25(OH)_2D$ by renal 1α-hydroxylase. Renal production of $1,25(OH)_2D$ is tightly regulated by plasma parathyroid hormone (PTH), serum calcium, phosphorus, and fibroblast growth factor 23 (FGF-23) levels.[74]

25(OH)D deficiency/insufficiency is common in CKD patients,[74-76] and its prevalence increases with increasing CKD severity and in dialysis patients.[75,77,78] There is currently no consensus on optimal 25(OH)D levels for CKD.[79-82] The Kidney Disease Improving Global Outcomes (KDIGO) 2017 guidelines recommend its evaluation when PTH progressively increases at CKD stage 3 or above.[83] The National Kidney Foundation (NKF) suggested adequate 25(OH)D levels as >20 ng/mL without evidence of counterregulatory hormone activity.[84] 25(OH)D deficiency has been correlated with different adverse health outcomes including secondary hyperparathyroidism, decreased bone mineral density, progression of CKD,[85,86] adverse cardiovascular outcomes, and mortality[86-91] in CKD and dialysis patients.

Table 5. Randomized Controlled Trials of Nutrition Vitamin D Supplementation on Kidney Outcomes, Cardiovascular Surrogate and Hard Outcomes in CKD

Study	Study Design	Study Population	Sample Size	Vitamin D Formulation and Dosages	Duration	Study Outcome	Findings
Levin et al[93]	RCT	CKD 3b-4	119	Oral calcifediol 5,000 IU 3 time/wk vs oral calcitriol 0.5 μg 3 times/wk vs placebo	6 mo	Primary: change in PWV	PWV ↓ in calcifediol group but remained unchanged in calcitriol group and ↑ in placebo group
Kumar et al[94]	RCT	Nondiabetic CKD 3-4 and with 25(OH)D ≤ 20 ng/mL, age 18-70 y	120	Oral cholecalciferol 300,000 IU given at wk 0 and wk 8 or matching placebo	16 wk	Primary: change brachial artery FMD at 16 wk. Secondary: change in PWV and circulating biomarkers.	Sig ↑ in FMD with cholecalciferol but no change in FMD with placebo, sig between group differences. Sig improvement in PWV and ↓ IL-6.
Lu et al[100]	Systematic review of RCTs	CKD 3-5/5D, kidney transplant excluded	17 RCTs with 1,819 patients with CKD 3-5/5D	Intervention: nutritional vitamin D and active vitamin D versus non-vitamin D	Varied duration for different trials	Primary: all-cause mortality, CV mortality	Vitamin D supplementation did not reduce all-cause and CV mortality.
Dou et al[96]	Meta-analysis of RCTs	CKD 3-5, eGFR < 60 mL/min per 1.73 m^2	7 RCTs of 233 CKD patients for PWV end point; 320 CKD patients for FMD end point	Intervention: vitamin D versus placebo	Varied duration for different trials	Primary: flow mediated dilatation or PWV	Overall: no change in FMD with vitamin D therapy. Subgroup analysis: cholecalciferol supplementation improved FMD compared with placebo.
De Boer et al[98]	RCTs 2 × 2 factorial design	T2DM	1,312	Intervention: vitamin D_3 (2,000 IU/d) and/or omega-3 fatty acids vs placebo	5 y	Primary: change in GFR from baseline to year 5	No significant change in eGFR at 5 y.
Limonte et al[99]	RCTs 2 × 2	T2DM	1,312	Intervention: vitamin D_3 (2,000 IU/d) and/or omega-3 fatty acids versus placebo	5 y	Prespecified secondary end points: inflammatory and cardiac biomarkers.	Vitamin D_3 supplementation did not reduce serum IL-6, hs-CRP and NT-pro-BNP.
Banerjee et al[97]	Placebo-controlled RCT	Adults with nondiabetic CKD 3-4 with circulating vitamin D < 75 nmol/L, receiving ACEI or ARB and with high-normal LV mass	48	Interventions: cholecalciferol supplementation vs placebo	52 wk	Primary: change in LV mass index over 52 wk. Secondary: change in LV volumes, LV EF, RV volumes, and LA volumes.	Vitamin D supplementation does not reduce LV mass index. No change in LV volumes, LV EF, RV volumes and LA volumes.

(Continued)

Table 5 (Cont'd). Randomized Controlled Trials of Nutrition Vitamin D Supplementation on Kidney Outcomes, Cardiovascular Surrogate and Hard Outcomes in CKD

Study	Study Design	Study Population	Sample Size	Vitamin D Formulation and Dosages	Duration	Study Outcome	Findings
Morrone et al[109]	Phase 3, multicenter, randomized, open-label trial	Adults with kidney failure on hemodialysis treatment with vitamin D insufficiency [defined as 25(OH)D < 30 ng/mL]	284	Intervention: oral calcifediol versus standard care	24 mo	Primary: composite of all-cause death and major CV events. Secondary: CV death, non-CV death, nonfatal myocardial infarction, non-fatal stroke	Vitamin D supplementation did not reduce all-cause death and did not improve CV outcomes in hemodialysis patients with 25(OH)D insufficiency.
Yeung et al[101]	Systematic review of RCTs (trials <3 mo excluded)	Adults with CKD 3,4, 5/5D, kidney transplant excluded	128 trials involving 11,270 patients (84 trials in 7,242 dialysis patients and 44 trials in 4,028 CKD 3-5 patients)	Interventions included: nutrition vitamin D vs placebo or no treatment, different vitamin D compound	Varied duration for different trials	Primary: all-cause death, CV death, fracture. Secondary: MACE.	Little or no effect of nutrition vitamin D on all-cause death, CV mortality, fractures, and MACE. No evidence that type of vitamin D or length of follow up modified treatment effect.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FMD, flow mediated dilatation; GFR, glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; LA, left atrial; LV, left ventricular; MACE, major adverse cardiovascular events; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; PWV, pulse wave velocity; RCT, randomized controlled trial; RV, right ventricular; Sig, significant; T2DM, type 2 diabetes mellitus.

The KDOQI 2020 nutrition guidelines reviewed that 25(OH)D supplementation is effective in increasing 25(OH)D concentrations in CKD stages 1-4, hemodialysis, and PD patients. However, different formulations, dosages, and duration were used,[4] and baseline 25(OH)D status varied, making it difficult to compare across studies. A meta-analysis of 14 trials showed that nutritional vitamin D might be more effective in preventing further increases in PTH rather than reducing it.[92] Several RCTs and a meta-analysis of 4 RCTs suggested that nutritional vitamin D supplementation may improve vascular function and arterial stiffness in CKD[93-96] but did not improve cardiac structure and function[97]; in individuals with type 2 diabetes, no changes were found in eGFR, albuminuria, inflammatory markers, or cardiac biomarkers.[98,99] A meta-analysis of 17 RCTs including 1,819 patients showed no cardiovascular outcome benefit with nutritional or activated vitamin D.[100] Another meta-analysis of 128 studies with 11,270 participants showed that nutritional and active vitamin D did not reduce risk of all-cause death in people with CKD stages 3-5D and had uncertain effects on fractures, cardiovascular outcomes, and kidney outcomes compared with placebo[101] (Table 5).

The NKF suggested that 25(OH)D levels < 15 ng/mL should be supplemented regardless of PTH levels, and individuals with 25(OH)D levels between 15 and 20 ng/mL may not require treatment if there is no evidence of counterregulatory hormone activity.[84] KDIGO[83] and the KDOQI nutrition guidelines suggested that nutritional vitamin D be supplemented in patients with CKD stages 1-5D to correct 25(OH)D deficiency/insufficiency. In adults with CKD and nephrotic range proteinuria, it is reasonable to consider supplementation of cholecalciferol, ergocalciferol, or other safe and effective 25(OH)D precursors.[4] The choice of formulations or supplementation dosages would depend on local availability and degree of deficiency.

Extended-release calcifediol increases serum 25(OH)D levels without up-regulating FGF-23 and vitamin D catabolism, and it is 3.2-fold more potent than cholecalciferol.[102-105] Several RCTs showed that oral extended-release calcifediol effectively controlled secondary hyperparathyroidism; 42%-69% of patients achieved ≥30% reduction in PTH while correcting 25(OH)D deficiency without causing hypercalcemia or hyperphosphatemia.[106-108] However, it did not improve survival and cardiovascular outcomes in hemodialysis patients with vitamin D insufficiency over 24 months of treatment, but the trial had few events.[109]

Vitamin E

Vitamin E is mostly in the form of α-tocopherol in humans. It is an essential redox regulator, exhibits major antioxidative effects in cell membranes, and is a potent suppressor of low-density lipoprotein lipid oxidation.[110] It is transported by lipoproteins, so its plasma concentration

is affected by blood lipids. Vitamin E may have both pro- and antiatherogenic effects. Vitamin E intake in individuals with CKD may be lower than the RDA, although deficiency is rare, and vitamin E is not removed with dialysis.[9]

No new trials have been published on vitamin E use in CKD since the KDOQI guidelines review, which was conducted through 2016. A recent meta-analysis of trials suggested that vitamin E supplementation may reduce circulating markers of endothelial dysfunction and inflammation, including intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and C-reactive protein, but not interleukin 6 in hemodialysis patients,[111] which warrants further investigation. Previous randomized studies did not unequivocally demonstrate a reduction in cardiovascular events with vitamin E supplementation.[112-114] Routine supplementation of vitamin E is not recommended in CKD.

Vitamin K

Vitamin K is present as phylloquinone (vitamin K_1), menaquinone (vitamin K_2), and the synthetic analogue menadione (vitamin K_3). Phylloquinone acts as the catalyst for clotting protein activation in the liver, and menaquinone is involved in bone metabolism and vascular calcification. There are 17 vitamin K–dependent proteins that regulate bone metabolism, blood coagulation, and arterial calcification.[115] Direct measurement of vitamin K levels is difficult, and deficiency of vitamin K is usually detected by functional assay.[116] Vitamin K deficiency is very common in CKD, worsens as CKD progresses, and is associated with low dietary intake of vitamin K in hemodialysis patients.[117,118] Anticoagulants, phosphate binders, antibiotics, proton pump inhibitors, and calcimimetics may reduce vitamin K and interfere with its actions.[115,119-121]

Vitamin K deficiency has been suggested to accelerate vascular calcification, and increasing vitamin K levels may inhibit this process.[120] Matrix Gla protein (MGP), an inhibitor of vascular calcification, requires vitamin K_2–dependent activation of glutamate to γ-carboxyglutamate.[117] MGP "mops up" unbound calcium, phosphorus, and hydroxyapatite crystals circulating in blood and forms neutralized inactive compounds important for bone formation, preventing calcified deposits in arteries.[115] MGP also removes calcium and extracellular matrix from blood vessel walls. Vitamin K deficiency leads to increased dephosphorylated uncarboxylated MGP (dp-ucMGP), a marker of vitamin K insufficiency.[115] Because dp-ucMGP cannot bind to calcium, phosphorus, or hydroxyapatite, inhibition of vascular calcification is blunted.

In patients with kidney failure, subclinical vitamin K deficiency is common[122] and has been associated with vascular stiffness, vascular calcification, and mortality.[123] In the Prevention of Renal and Vascular End-Stage Disease study (PREVEND), 50% of patients with CKD had functional vitamin K deficiency, which was associated with an increased risk of all-cause and cardiovascular mortality.[124]

There have been 7 RCTs of vitamin K_2 or K_3 supplementation in CKD, dialysis, and kidney transplant recipients[125-131] published since the KDOQI 2020 guidelines.[4] Six studies used vitamin K_2 as menaquinone-7 (MK-7) at doses of 90-400 μg/day, and 1 study used vitamin K_3 as menadiol phosphate at 5 mg 3 times a week, and the duration of supplementation ranged from 270 to 720 days. All studies demonstrated reductions in dp-ucMGP or ucMGP, indicating an improvement in vitamin K status. All except 1 study showed no benefit on vascular outcomes including pulse wave velocity (PWV) or aortic calcification. A secondary analysis in 1 study observed a reduction in PWV in hemodialysis patients with diabetes after 24 weeks of treatment with MK-7 at 375 mg daily compared with control.[131] These studies were mostly of small samples and relatively high dropout rates. The lack of benefits of vitamin K_2 supplementation on vascular end points may partly be due to altered uptake and transport of vitamin K_2 in uremia, independent of dietary intake or supplementation.[132] The optimal dose of menaquinone remains to be elucidated.

The Inhibit Progression of Coronary Artery Calcification With Vitamin K_1 in Hemodialysis Patients (iPACK-HD) study did not observe any improvement in coronary artery calcification despite an 86% reduction in dp-ucMGP with vitamin K_1 supplementation (10 mg 3 times per week for 12 months).[133] Several other trials are ongoing including the Treatment to Reduce Vascular Calcification in Hemodialysis Patients Using Vitamin K (TReVasc-HDK) trial (NCT02870829), a study using menatetrenone (vitamin $K_{2\text{-}4}$) in dialysis (UMIN000011490) and the Vitamin K2 in Peritoneal Dialysis (VIKIPEDIA) study (NCT04900610).[134] Overall, the data have suggested that vitamin K supplementation reduces deficiency but does not benefit cardiovascular outcomes in CKD.

Multivitamins

No new data have been published on multivitamins since the KDOQI guidelines. A previous meta-analysis did not support routine multivitamins supplementation in hemodialysis.[135] Decisions for or against multivitamin supplementation should be based on clinical judgment and individualized assessment of dietary intake, nutrition status, likelihood of insufficiency/deficiency of the vitamins contained in the formulation, and consideration of pill burden.

Conclusions

The latest evidence does not support routine vitamin supplementation in the CKD population. Decisions on supplementation should be individualized by considering a patient's dietary intake, nutritional status, risk of deficiency/insufficiency, and comorbid status. All patients

with CKD should receive periodic assessment of dietary intake of vitamins and be encouraged to obtain vitamins through natural food sources from a healthy dietary pattern containing a variety of nutritional foods.

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