ORIGINAL RESEARCH

Vitamin Needs and Treatment for Chronic Kidney Disease Patients

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This paper summarizes the biochemistry, metabolism, and dietary needs of vitamins in patients with chronic kidney disease (CKD) and kidney transplant recipients. Evidence indicates that the dietary intake, in vivo synthesis, urinary excretion or metabolism of different vitamins may be substantially altered in kidney failure. There are discrepancies in vitamin status assessment depending on whether the assay is functional or measuring the blood vitamin level. Whether vitamin supplements should be routinely prescribed for patients with CKD is controversial. Because low dietary intake and compounds that interfere with vitamin activity are not uncommon in patients with CKD, and water-soluble vitamin supplements appear safe and not costly, the authors recommend that supplements of the water-soluble vitamins should be routinely offered to these individuals. More research is needed to assess vitamin nutrition and function and to determine the daily vitamin needs for all patients with CKD.

THIS REVIEW WILL discuss vitamin biochemistry and metabolism and clinical manifestations of vitamin deficiency or excess, particularly as it is related to chronic kidney disease (CKD) and will comment on the current recommendations regarding vitamin supplementation. We will suggest needed research for vitamins in patients with nondialysis CKD, in chronic dialysis and post-transplantation patients. Interference between medicines or other compounds and vitamins will not be addressed because of space limitations and is reviewed elsewhere.[1]

Vitamins in CKD

Vitamin A

Retinol is the main vitamin A compound. Vitamin A is essential for vision, epithelial function, and embryonic and fetal development. It plays a regulatory role in cellular and humoral immune processes and has antioxidant properties. However, large scale clinical trials do not demonstrate a benefit of large doses of retinol and carotenoids for the prevention of cancer or cardiovascular disease.[2] In plasma, retinol is bound to apo-retinol binding protein (RBP-4) and is transported by prealbumin (also called transthyretin) to tissues containing the RBP cell-surface receptor. The vitamin A complex is not cleared by hemodialysis; whether it is found in peritoneal dialysate effluent is controversial. Serum vitamin A is commonly increased in patients with advanced CKD, maintenance hemodialysis (MHD), and on chronic peritoneal dialysis (CPD) even though vitamin A intake is usually decreased.[3] The mechanism for this increase in blood has been attributed to decreased catabolism of RBP-4. Recently, among nine assessed vitamins in 759 CKD patients with a broad range or renal function, plasma vitamin A levels were found to be significantly and inversely correlated with the glomerular filtration rate.[4] There is no obvious toxicity that has been associated with the typical increase in plasma vitamin A levels found in advanced patients with CKD and chronic dialysis therapy. However, hypercalcemia may be associated with high plasma retinol levels. The lower quartiles of plasma retinol levels, even if still above normal values, are associated with increased mortality in MHD patients and renal transplant recipients.[5] However, adding plasma transthyretin to these models abolishes the relationship between plasma retinol quartiles and mortality. This suggests that this association maybe more of a reflection of the nutritional or inflammatory status of the patient than a direct effect of plasma retinol on patient survival.

Vitamin D

Vitamin D is a steroid hormone that is found as two compounds in food: ergocalciferol (vitamin D2) found in plant sources and cholecalciferol (vitamin D3) from animal sources and which is also synthesized in the skin. Both forms of vitamin D are transported to target tissues by vitamin D–binding protein (VDBP). The most active natural form of vitamin D is calcitriol (1,25-dihydrocholecalciferol, also referred to as 1,25(OH)D3). Cholecalciferol is

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hydroxylated in the 25-position in the liver to form 25(OH)D3 and then in the 1-position in the kidney to form calcitriol. Because of the central role of the kidney in the 1-hydroxylation of vitamin D, there is a high risk of vitamin D deficiency as people develop advanced CKD unless they receive vitamin D supplements. Serum calcitriol levels decline progressively as the glomerular filtration rate (GFR) falls.[4] Calcitriol may also decrease as GFR decreases due to low serum levels of its precursor 25(OH)D3 and increased serum levels of fibroblast growth factor-23 (FGF-23), which suppresses 1-hydroxylation of 25(OH)D3,[6,7] and to low dietary vitamin D intake.[3] Vitamin D deficiency is associated with many adverse effects in patients with nondialyzed CKD and requiring chronic dialysis therapy. These include secondary hyperparathyroidism, bone fractures,[8,9] muscle weakness, falls,[10] arterial stiffness,[11] and increased mortality.[12] Kandula et al[13] reported, in a meta-analysis, that supplementation with ergocalciferol or cholecalciferol in patients with nondialyzed CKD increases serum 25(OH)D levels and decreases serum PTH without significantly increasing serum calcium or phosphorus. Vitamin D supplements (cholecalciferol 100,000 U/month or calcifediol 10–50 μg/day) given to patients with advanced CKD decrease the frequency of very high serum PTH values.[9] In MHD patients, dialyzer membranes that have a high molecular weight cut-off or that are highly adsorptive may increase the risk of vitamin D deficiency.[14]

Vitamin E

Vitamin E is a fat-soluble vitamin; the main active compound is α-tocopherol. The main sources of vitamin E are vegetable oils, such as corn, soybean, wheat germ, and sunflower oil. Tocopherol is transported in plasma by lipoproteins. Vitamin E is the main antioxidant in biological membranes and protects phospholipid membranes from oxidative stress. A genetic deficit of the α Tocopherol Transfer Protein (TTPA) engenders a severe neurologic disorder which occurs between the ages of 5 to 15 years and is called AVED (Ataxia with Vitamin E Deficiency). Epidemiological studies indicate a reduced risk of coronary heart disease in men and women who have higher intakes of vitamin E (>60 IU per day) from foods.[15,16] The mechanism for this protective effect is attributed to decreased oxidation of LDL cholesterol. However, as with vitamin A, large-scale clinical trials have not demonstrated a benefit of vitamin E supplementation for prevention of cardiovascular disease or cancer.[2] Reports on the vitamin E status of patients with CKD are conflicting. A majority of patients with nondialyzed advanced CKD, or under MHD and CPD therapy have low dietary vitamin E intakes. But plasma levels are usually within the normal range.[3] The Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease (SPACE) study, which showed a lower incidence of cardiovascular events in MHD patients receiving vitamin E therapy, has not been confirmed.[17] Moreover, in the long-term follow-up of the Heart Outcomes Prevention Evaluation - The Ongoing Outcomes (HOPE-TOO) study in the general population, individuals who received 400 IU/day (268 mg) of α-tocopherol for 7 years developed an unexpectedly higher incidence of heart failure compared to the placebo group (relative risk (RR), 1.21; 95% confidence interval (CI), 1.00-1.47; p = .045).[18] There are no studies concerning the effects of vitamin E coated hemodialysis membranes on morbidity or mortality in MHD patients. Vitamin E may be effective for preventing radiocontrast-induced nephropathy.[19]

Vitamin K

Phylloquinone (K1, found in leafy vegetables) and menaquinones (K2, present in fermented food) are the main sources of vitamin K. Vitamin K is a coenzyme for the post-translational carboxylation of glutamate residues on proteins called “gla-proteins”. These proteins play important roles for normal blood coagulation (the “K” in vitamin K is for coagulation), bone metabolism, calcium deposition in tissues, and renal tubular function. Coumarin derivatives block the recycling of vitamin K, interfering with vitamin K epoxide reductase (VKOR) mainly produced by the liver. Osteocalcin and Matrix Gla Protein (MGP) are vitamin K–dependent proteins essential for normal bone homeostasis. The usual amount of vitamin K that patients with CKD ingest is not clear. However, prescribed diets for patients with nondialyzed CKD and chronic dialysis patients that restrict leafy vegetables (to reduce potassium intake) and cheese (to reduce phosphate intake) may favor low vitamin K intakes.[20] Subclinical vitamin K deficiency with low MGP, as indicated by increased plasma proteins induced by vitamin K absence (PIVAK-2) and elevated serum uncarboxylated (uc)-MGP levels, is frequent in patients with CKD and is worsened when these patients are given such vitamin K antagonists (VKA) as warfarin compounds. However, measurements in clinical laboratories of plasma PIVAK-2 and uc-MGP are not routinely available. This potential deficiency of vitamin K may increase the risk of arterial calcification for patients with CKD . At present, clinical trials have not yet demonstrated that taking vitamin K supplements by patients with advanced CKD will correct their high levels of serum dephosphorylated-uncarboxylated MGP (dp-ucMGP), reduce the risk of arterial calcification, or decrease adverse vascular events.[21]

Thiamine (Vitamin B1)

Vitamin B1 or thiamine plays a central role in the energy biochemistry of the body. It has a key role in energy metabolism and neurotransmitter synthesis.[22] Thiamine deficiency leads to beriberi which can be manifested primarily by heart failure (wet beriberi) or neurological disorders (dry beriberi). Thiamine is bound to albumin in plasma, limiting its clearance by dialysis. Dietary thiamine

intake is often below the recommended dietary allowances (RDA)[23] in most patients with advanced CKD, or under MHD and CPD therapy.[3] An important issue in examining vitamin nutrition in kidney failure patients is that a discrepancy may exist between the measured serum or plasma concentrations of a vitamin and the presence of impaired functional tests. This appears to be the case for thiamine. The erythrocyte transketolase activity (EKTA) and the ETKA stimulation index, which are indicators of vitamin B1 inadequacy,[24] may be impaired due to competitive inhibition of EKTA by oxythiamine and possibly other compounds that accumulate in uremia,[25] even though plasma levels may be normal. In patients with advanced CKD, and under MHD and CPD therapy or in kidney transplant recipients who develop unusual and unexplained neurological symptoms, thiamine deficiency should be considered.[26] Treatment of acutely and severely ill patients with a combination of vitamin C (ascorbic acid), thiamine, and glucocorticosteroids (ATS), which has been used to prevent or limit the severity of AKI and to decrease mortality, is controversial.[27] A randomized control trial is currently being conducted to assess the effect of folic acid and thiamine therapy on cognition of MHD patients.[28]

Vitamin B6 (Pyridoxine)

Three vitamers, pyridoxine, pyridoxal and pyridoxamine, carry out the functions of vitamin B6 after they first undergo phosphorylation in the liver. They are coenzymes for more than 140 enzymatic reactions, especially for those involving amino acid and lipid metabolism. Dietary vitamin B6 intake is often below the RDA in patients with advanced CKD and in chronic dialysis patients.[3] Four decades ago, Kopple et al[29] assessed vitamin B6 adequacy in CKD using a standard functional enzymatic test: in vitro activity of erythrocyte glutamic pyruvic transaminase (EGPT) assayed in the basal state and after addition of pyridoxal-L-phosphate (PLP; i.e., the EGPT stimulation index). They reported a high prevalence of vitamin B6 deficiency in advanced CKD and chronic dialysis patients who were not receiving vitamin B6 supplements. This was confirmed by other studies. Dose response trials in these patients, using the EGPT stimulation index, indicated that the quantity of pyridoxine HCl necessary to correct vitamin B6 deficiency is substantially greater than the RDA for vitamin B6 for normal adults. The EGPT stimulation index became normal in 30 MHD patients given 10 mg/day and in eight CPD and six nondialyzed CKD patients taking 5 mg of pyridoxine hydrochloride.[29] This amounts to about 3 to 7 times the RDA for vitamin B6 healthy adults (Table 1). However, Wang et al, using high pressure liquid chromatography (HPLC), recently reported high serum levels of vitamin B6 in a large cohort of hospitalized patients with nondialyzed CKD stage 4 and 5.[4] These apparent contradictory findings suggest that there may also be inhibitors of vitamin B6 that may increase the amount of pyridoxine necessary to maintain normal vitamin B6 activity in advanced CKD and chronic dialysis patients. Vitamin B6 deficiency may engender inflammation, immune dysfunction, increased oxalate generation and polyneuropathy, although these manifestations are either subtle or not detectable in patients with CKD.

Vitamin C (Ascorbic Acid)

Ascorbic acid is the active agent that prevents and corrects scurvy. Ascorbic acid is present in fresh fruits and vegetables. This small compound (176 Da) circulates unbound in plasma and is easily cleared by hemodialysis. Epidemiological data do not clearly indicate whether the prevalence of vitamin C deficiency is much increased in patients with nondialyzed CKD, whereas vitamin C deficiency is not uncommon in MHD patients who are not taking vitamin C supplements.[33] However, scurvy is rarely diagnosed in MHD patients. Low vitamin C intake, which is at least partly due to the need for patients with CKD to eat potassium-restricted diets,[3] and losses of ascorbic acid during the dialysis procedure, appear to be major contributors to the high prevalence of vitamin C deficiency in these individuals. Treatment of acutely and severely ill patients with ascorbic acid or a combination of ascorbic acid, thiamine, and glucocorticosteroids (i.e., ATS) to prevent or limit the severity of AKI and to decrease mortality remains controversial.[34] Vitamin C may be effective for preventing contrast-induced nephropathy.[35] Supraphysiologic doses of vitamin C have been proposed for CKD and chronic dialysis patients. However, large daily doses of vitamin C increase the risk of hyperoxaluria and therefore should also be avoided in CKD, chronic dialysis, and AKI patients.[36] More research is necessary to determine whether ascorbic acid has clinically apparent anti-inflammatory and antioxidant effects and will improve endothelial dysfunction in patients with CKD and patients under chronic dialysis therapy.

Folate (Vitamin B9)

Folate is a general term that is commonly used for a group of water-soluble compounds that have a pteroylglutamic acid core. Folate serves as a methyl donor and plays an essential role in the synthesis of nucleotides, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and certain amino acids. Folate is found in foods in reduced form, usually as tetrahydrofolate (yeast, liver, meats, green vegetables, and fruits). Folic acid (pteroylglutamic acid) is a synthetic folate that is seldom found in nature but is quite stable and is therefore commonly used as a folate supplement and a food fortificant. Folate deficiency causes megaloblastic anemia. Dietary folate intake is frequently below the RDA in patients with nondialyzed advanced CKD, under MHD and CPD therapy, and in kidney transplant recipients.[3] The common prescription of potassium-restricted diets probably contributes to the low folate intake. Whether there is a high prevalence of folate deficiency in advanced

Table 1. Recommendations/suggestions for Daily Vitamin Intake (From US RDA in Healthy Adults) and for Supplementation [EBPG, KDOQI and Authors' Suggestions] for CKD, MHD, CPD, and Post-transplant Patients

	Dietary Reference Intake[23,30]	European Best Practice Guidelines (EBPG) (2007)*[,31]	K-DOQI guidelines (2020)*[,32]	Authors' suggestions
	RDA in healthy normal adult subjects Daily Intake	MHD,CPD patients Daily Intake	ND-CKD, MHD, CPD, and post-transplant patients Daily Intake	ND-CKD, MHD, CPD, and post-transplant patients Daily Intake
Vitamin A	700-900 RE	Do not supplement	None; Do not supplement	None; Do not supplement
Vitamin D2&D3	600-800 IU	Not addressed	up to serum level ≥30 ng/ml†	up to serum level ≥30 ng/ml†
Vitamin E	22.5 IU	400-800 IU	Do not supplement	Do not supplement
Vitamin K	80-120 μg	Do not supplement	No supplement needed if anticoagulation or medicines interfering with Vit K	Do not supplement‡
Vitamin B1	1.1-1.2 mg	1.1-1 .2 mg	According to guidance§	1.1-1.2 mg
Riboflavin	1.1-1.3 mg	1.1-1.3 mg	According to guidance§	1.1-1.3 mg
Vitamin B6	1.3-1.7 mg	10 mg‖	According to guidance§	5/10 mg‖
Vitamin C	75-90 mg	75-90 mg	75-90 mg	75-90 mg
Folic acid	400 μg	1 mg	If clinical signs and symptoms	1mg
Vitamin B12	2.4 μg	2.4 μg		2.4 μg
Niacin	14-16 mg	14-16 mg	According to guidance§	14-16 mg
Biotin¶	30 μg‖	30 μg	According to guidance§	30 μg
Pantothenic acid	5 mg	5 mg	According to guidance§	5 mg

EBPG, European Best Practice Guidelines for Nutrition; RDA, Recommended Dietary Allowances (see definition in the text); RE, Retinol Equivalent

*Year the guidelines were published.

†Cholecalciferol or ergocalciferol.

‡Vitamin K, 10 mg/day, if patient has low food vitamin K intake and combined with prolonged antibiotic therapy.

§Multivitamin supplements according to vitamin intake assessment in all CKD patients or in case of prolonged low dietary intake in dialysis patients.

‖Dose refers to pyridoxine hydrochloride, which is the pharmacologically available source of vitamin B6 and which is contains about 82% free pyridoxine. The daily requirement for pyridoxine HCl is about 5 mg per day for nondialyzed CKD and CPD patients and 10 mg per day for MHD patients.[29]

¶Adequate Intake (AI) rather than Recommended Dietary Allowances (RDA). AI is considered to be the average intake of a nutrient by apparently normal, healthy people.

CKD and chronic dialysis patients who do not take folate supplements is not clearly established, in part because functional studies to assess for folate deficiency are lacking. Routine folic acid supplementation is not currently recommended for anemia management of patients with advanced CKD receiving erythropoiesis-stimulating agents.[37] Increased plasma homocysteine is very common in advanced CKD and chronic dialysis patients and has been associated with adverse clinical outcomes in some but not all studies. Folic acid supplements or the combination of folic acid, vitamin B6, and vitamin B12 supplements will reduce elevated plasma homocysteine to near-normal or normal levels, but this does not improve clinical outcomes in patients with advanced CKD, receiving chronic dialysis or living with a kidney transplant.[38] It is important to recognize that this discussion refers to the mild plasma homocysteine elevation that occurs commonly in advanced CKD and chronic dialysis patients where the plasma homocysteine levels are not increased by more than about 50 percent above the upper range of normal. It does not refer to genetic hyperhomocysteinemia where plasma homocysteine levels are markedly higher. A low dose of folic acid (0.8 mg/day) in combination with the angiotensin converting enzyme inhibitor enalapril, 10 mg/day, has been associated with a reduction in the rate of GFR decline in Chinese patients with nondialyzed CKD.[39]

Vitamin B12

Cobalamin is the antipernicious anemia factor (Biermer's disease). Patients with advanced CKD and patients under chronic dialysis are usually reported to have normal serum vitamin B12 levels without clinical manifestations of vitamin B12 deficiency, even though studies commonly describe low dietary vitamin B12 intakes in these patients.[3] Cobalamin C deficiency due to mutation of the MMACHC gene can cause AKI from thrombotic microangiopathy.[40] Losses of vitamin B12 during the dialysis procedure are very low because of the large size of the

cyanocobalamin-transcobalamin complex (>40 kDa). One observational study has reported increased mortality in MHD patients who have high serum vitamin B12 levels; this finding remains to be confirmed.[41]

Niacin (Vitamin B3)

Niacin is a generic term that includes both nicotinic acid and nicotinamide. Tryptophan is a precursor of niacin, and intake of tryptophan can provide the entire RDA for niacin. Niacin is recognized as the antipellagra agent, a condition that occurs in maize-eating populations and is characterized by diarrhea, dermatitis, and dementia. Niacin is present in meat, fish, legumes, coffee, and tea, which constitute the main dietary sources. Niacin is converted in vivo to nicotinamide adenine dinucleotide (NAD) and NAD phosphate. NAD and NAD phosphate act as coenzymes for many enzymatic reactions involving carbohydrate, fatty acid, amino acid, and steroid metabolism. In patients with advanced CKD and for patients under chronic dialysis therapy, niacin intake is often reported to be below the RDA, but blood and red cell levels of niacin are usually normal. Clinical syndromes of niacin deficiency (e.g., pellagra) have not been reported in advanced CKD or chronic dialysis patients. Large pharmacological doses of niacin can inhibit intestinal phosphate absorption by acting on the Na-Pi cotransporter in the intestinal tract, and thereby reduce serum phosphorus levels. But side effects such as flushing, gastrointestinal symptoms, hepatotoxicity, hyperuricemia, and thrombocytopenia are frequent. At present, the use of niacin to reduce serum phosphorus levels has not gained wide acceptance.[42] Niacin can increase serum HDL and lower serum triglycerides. However, in patients with stage 3 CKD in the AIM-HIGH trial, adding a pharmacological dose of niacin to simvastatin did not change cardiovascular outcomes and was associated with increased overall mortality.[43] More research is needed to assess whether the effects of niacin on serum lipids may improve cardiovascular outcomes in patients with advanced CKD, under chronic dialysis patients and in kidney transplant recipients.

Riboflavin (Vitamin B2)

Riboflavin is present in many plant and animal products. Its active forms are flavin mononucleotide and flavin adenine dinucleotide. They are necessary for the actions of flavoproteins that are involved in oxidant status, apoptosis, and DNA repair. Dietary riboflavin intake is frequently reported to be below the RDA in patients with advanced CKD and MHD and CPD therapy. Data regarding blood riboflavin (vitamin B2) levels in CKD and chronic dialysis patients are conflicting. This may be partly due to discrepancies between the direct of measurements of plasma riboflavin concentrations and functional tests (e.g., the erythrocyte glutathione reductase (EGR) stimulation index). No clinical syndromes related to riboflavin deficiency have been described in patients with advanced CKD or under chronic dialysis therapy or in renal transplant recipients.

Biotin (Vitamin B8)

Biotin is found in such foods as liver, egg yolk, soybean, yeast, cereals, legumes, and nuts. It acts as a "CO_2 carrier", being the coenzyme for carboxylases, needed for carbohydrate, fatty acid, and amino acid metabolism. Plasma, red blood cell, and white cell biotin concentrations are usually reported to be normal in patients with advanced CKD and chronic dialysis treatment. No data are currently available regarding the dietary biotin intake of CKD or chronic dialysis patients, and no specific diseases related to increased or decreased body biotin levels have been reported in these individuals. Biotin supplements can cause very high plasma biotin levels which may interfere with laboratory tests that use biotinylated antibodies; for example, for measurement of thyroid stimulating hormone, thyroxin (T4), and parathyroid hormone (PTH).[44]

Pantothenic Acid (Vitamin B5)

Pantothenic acid is required for the formation of coenzyme A (CoA) and acyl carrier proteins. It is ubiquitous and present in large amounts in many foods. It is involved in the synthesis of fatty acids, cholesterol, steroid hormones, δ-aminolevulinic acid, amino acids, and some neurotransmitters. The nutritional status of pantothenic acid in advanced CKD and chronic dialysis patients is controversial. Dietary pantothenic acid intake of these patients is probably often below the RDA, and normal, elevated and low blood levels have each been reported in these individuals. No specific syndromes related to low body pantothenic acid have been reported in patients with CKD. In the PROGREDIR study, pantothenic acid intake was found to be positively related to the coronary artery calcification score in patients with non-dialyzed CKD.[45]

Vitamin Needs in CKD

Our recommendations and those of various panels of experts for vitamin supplementation in patients with CKD, and under MHD and CPD therapy are summarized in Table 1. The RDA for normal adults have been developed by the Food and Nutrition Board, Institute of Medicine of the National Academies and are listed for a standard comparison. In the last decades, most organizations or individual authors who offered recommendations regarding vitamin intake indicated that there was no need for additional intake of vitamins A, E, and K. Recommendations regarding vitamin K intake may change if clinical trials show that vitamin K reduces vascular calcification or atherosclerosis or improves bone health. It is our view that there is a need for increased intake of pyridoxine (vitamin B6) and, often, for supplements of vitamin D and calcitriol to prevent or correct plasma 25(OH)D or $1,25(OH)_2D$ deficiency. Different strategies have been well-summarized for vitamin D supplementation,[32] It has been recommended that patients need

a 25(OH)D intake that is sufficient to attain serum 25(OH)D levels at the higher ranges of normal, up to about 50–75 ng/mL, to better prevent or correct high PTH levels and reduce bone fragility.[32,46] Routine supplements providing the RDA of the water-soluble vitamins are controversial, but in our opinion, are usually needed. One cohort study from DOPPS displayed a better nutritional status and a 16% survival advantage in chronic dialysis patients receiving supplements of vitamins B6, B12, and C, and folic acid.[47] Randomized controlled trials with hard clinical outcomes are lacking to support these recommendations.

The recent K-DOQI guidelines[32] make a number of recommendations that are summarized in Table 2. First, recent data have clearly shown that a significant percentage of patients with advanced CKD, MHD, and CPD therapy and kidney transplant recipients have a vitamin intake below the daily requirement.[3,46–49] Furthermore, these individuals not infrequently develop intercurrent illnesses during which intake of foods, including vitamins, may fall. This course of events, by itself, provides a rationale for routine supplements of most water-soluble vitamins for these patients. Second the K-DOQI guidelines excluded the literature published before 1985. In recent years, direct measurement of blood levels of vitamins has become rather common, especially with the widespread availability of HPLC. In previous years, functional tests for nutritional adequacy of vitamins were commonly employed, such as the EGPT stimulation index for vitamin B6[29] or the erythrocyte transketolase activity (ETKA) stimulation index for thiamine.[50] However, as indicated above, functional tests may indicate vitamin deficiency when blood levels indicate normal or high levels of the vitamin.[4,51] Data indicate that there may be inhibitors of thiamine such as oxythiamine, pyridoxine, folate, and vitamin B12 in kidney failure patients. The intracellular transport of folate is inhibited in vitro by uremic serum.[52] The intracellular uptake of vitamin B12 by blood mononuclear cells in patients with nondialyzed CKD has been found impaired.[51] Descombes et al[50] reported in MHD patients who were not receiving thiamine or pyridoxine supplements that blood thiamine levels were measured as normal, whereas the red blood cell transketolase activity (ETKA) was low or marginal in 51% of the patients. In this same group of patients, there was more consistency between the glutamate oxalo-acetate transaminase and pyridoxal-5-phosphate measurements; both were found to be low or marginal in 89% and 92% of the patients, respectively. These data underscore the need to rethink whether the functional status or body content of a vitamin in kidney disease

Table 2. The Recent K-DOQI Clinical Practice Guidelines for Nutrition in CKD (2020 Update): Recommendations for Vitamin Supplementation in Adults With CKD1-5D and Post-kidney Transplantation

Statement For General Guidance
Dietary vitamin intake in CKD3-5D or post-transplantation (OPINION)
Counseling by dietitian for diet meeting RDA micronutrient requirements
Vitamin Assessment and Supplementation CKD3-5D or post-transplantation (OPINION)
Dietitian and physician close collaboration
Periodic assessment of vitamin intake
Consider multivitamin supplementation for individuals with inadequate vitamin intake
Vitamin supplementation, dialysis (OPINION)
In adults with CKD 5D who exhibit inadequate dietary intake for sustained periods of time, it is reasonable to consider supplementation with multivitamins, including all the water-soluble vitamins to prevent or treat vitamin deficiencies (OPINION).
Folic acid supplementation for Hyperhomocysteinemia in adults with CKD 3-5D or post-transplantation
No reduction in adverse cardiovascular outcomes is demonstrated with routine supplement of folic acid with or without B complex (1A)
Folic acid supplementation for folic acid deficiency and insufficiency in adults CKD 1-5D or post-transplantation
Prescribe folate, vitamin B12, and/or B complex supplement to correct for folate or vitamin B12 deficiency/insufficiency based on clinical signs and symptoms (CKD 1-5D (2B); Post-transplantation (Opinion))
Vitamin C supplementation in adults with CKD 1-5D or post-transplantation
Consider supplementation in patients who are at risk of vitamin C deficiency to meet the recommended intake of at least 90 mg/d for men and 75 mg/d for women (OPINION).
Vitamin D supplementation for vitamin D deficiency and insufficiency in adults with CKD 1-5D or post-transplantation
Prescribe vitamin D supplementation in the form of cholecalciferol or ergocalciferol to correct 25-hydroxyvitamin D (25(OH)D) deficiency/insufficiency (CKD 1-5D (2C); Post-transplantation (Opinion))
Vitamin D supplementation in CKD1-5 adults with nephrotic-range proteinuria
Consider vitamin D supplementation in the form of cholecalciferol or ergocalciferol or other safe and effective 25(OH)D precursors (Opinion)
Vitamins A and E supplementation and toxicity
Do not routinely supplement CKD 5D patients with vitamin A or E because of the potential for vitamin A toxicity. However, if supplementation is warranted, care should be taken to avoid excessive doses, and patients should be monitored for toxicity (OPINION).
Anticoagulant medication and vitamin K supplementation in adults with CKD 1-5D or post-transplantation
Do not prescribe vitamin K supplement to patients receiving anticoagulant medicines known to inhibit vitamin K activity (e.g., warfarin compounds)

and kidney failure patients should be assessed by blood levels, by functional tests or by some other method. If functional tests give a more accurate indication of the body content of a given vitamin, then which test of vitamin function is most valuable? Third, there are many medicines and other compounds taken by CKD and chronic dialysis patient that may interfere with vitamin uptake or metabolism. Fourth, multivitamin pills have been designed specifically according to the needs of patients with CKD and chronic dialysis therapy. However, according to the DOPPS, their prescription is very unevenly distributed in the world because of varying degrees of availability, the cost and the different vitamin compositions of the supplements. Additionally, many nephrologists are not convinced that their CKD and chronic dialysis patients may benefit from vitamin supplements.[53] The United States is the country with the highest proportion of chronic dialysis patients, 70%, who are prescribed multivitamins,[53] whereas less than 5% of chronic dialysis patients may be prescribed vitamins in other countries. On the other hand, the new K-DOQI guidelines do not recommend routine supplementation of multivitamins, and this may lead to a reduction in the number of advanced CKD and chronic dialysis who are prescribed multivitamins. It may be helpful to examine whether there are changes in the prescription of vitamin supplements in the United States and other countries as a result of these new guidelines. It would also be of interest to evaluate the proportion of patients with vitamin intakes documented to be below the RDA who are not prescribed vitamins, and whether there are nutritional and clinical effects of withholding such supplementation.

The Future of Vitamin Use in CKD

There is a need for more research to explore the effects of uremia on vitamin metabolism and the nutritional needs for vitamins in patients with CKD and chronic dialysis therapy. For instance, the role of vitamin metabolites that might inhibit the action of a vitamin, such as the effects of oxythiamine, on thiamine function, need further investigation. This is essential in the era of precision medicine. Randomized control trials will be necessary to assess the effects of one vitamin or multivitamins in patients with CKD on adverse cardiovascular events and cardiovascular and total mortality as well as other outcomes. The results of the DOPPS study may help to estimate the numbers of patients needed for such trials.[53] A specific randomized trial investigating the effects of vitamin C supplementation MHD patients might be justified because of the observations of Deicher et al that low plasma vitamin C is associated with increased cardiovascular and total mortality in MHD patients.[54] The recent SARS-CoV2 pandemic, the high mortality it has engendered in virtually all CKD patient categories and the rapid development of vaccines have increased interest in the immune response in these patients. Since many vitamins have a role in the immune function, it may be profitable to study the interactions between immune processes and vitamins. The potential effects of vitamins A and K on prevention and treatment of bone mineral disorders in kidney failure requires more investigation. Recent data on the relationship between plasma vitamin A and survival indicate a need for more research to understand this relationship and potentially to change the current recommendation for no vitamin A supplements in chronic dialysis patients.[5] The increasing use of dialysis convective therapies and more permeable membranes require more research on the effects of these powerful dialysis techniques on micronutrient losses during hemodialysis. It would be helpful to develop more effective digital tools for assessing food intake, so that vitamin supplementation may be more precisely tailored for the needs of patients with CKD and under chronic dialysis therapy.

Conclusions

At present, in the absence of new information concerning vitamin needs that may allow more precise prescription of vitamin intake for individual nondialyzed patients with CKD, patients undergoing chronic dialysis therapy and kidney transplant patients, it would seem reasonable to provide these patients with a daily intake of the RDA for all of the water-soluble vitamins plus pyridoxine HCl 5 mg per day nondialyzed CKD and CPD patients and 10 mg per day for MHD patients. This should increase the likelihood that each water-soluble vitamin is taken in adequate amounts. There is often a need for vitamin D supplements for these patients. Supplemental vitamin E and K are usually not needed, and vitamin A supplements are usually contraindicated. These amounts of the water-soluble vitamins should be safe, and the cost of this treatment should not be very expensive.

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