Patients with chronic kidney disease (CKD) often experience a decline in their nutrient intake starting at early stages of CKD. This reduction in intake can affect both energy-producing nutrients, such as carbohydrates, proteins, and fats, as well as vitamins, minerals, and trace elements. Knowledge of the burden and bioactivity of vitamins and their effect on the health of the patients with CKD is very incomplete. However, without sufficient data, the use of nutritional supplements to prevent inadequate intake may result in either excessive or insufficient intake of micronutrients for people with CKD. The purpose of this article is to briefly summarize the current knowledge regarding vitamin requirements for people with stages 3, 4, or 5 CKD who are not receiving dialysis.

**Overview**

Measures of protein–energy wasting are strongly correlated with mortality in end-stage renal disease (ESRD).1 The findings that body fat, skeletal muscle mass, and body mass index (BMI), including very large BMIs, have independent and direct associations with survival in chronic kidney disease (CKD) patients2–4 suggest that reduced nutritional status, besides inflammation, may be both a predictor and a cause of death in these individuals. Although there are many observational studies describing the nutritional status of patients on maintenance dialysis and those with CKD who are not receiving maintenance dialysis, these investigations generally address nutritional contributions from proteins, energy, fats, macrominerals such as sodium, chloride, and potassium, vitamin D, and iron.2–6 Several reviews of the nutritional status and requirements for vitamins in patients on maintenance dialysis have been published in the past several years.5,6 To the authors’ knowledge, no such review currently exists for patients who have stages 3–5 CKD and who are not at ESRD or awaiting renal transplantation. This review discusses the literature concerning nutritional status and requirements for vitamins in patients with CKD stages 3 (glomerular filtration rate [GFR], <60 mL/min/1.73 m²), 4 (GFR, <29 months/min/1.73 m²), and 5 (GFR, <15 months/min/1.73 m²), who are not receiving renal replacement therapy.

Vitamin deficiencies are common in people with advanced renal failure who do not take nutritional supplements.7 The causes for such vitamin deficiencies have been reviewed and include low dietary intake that may be because of anorexia, or the impaired ability to buy, prepare, or ingest foods that are high in nutrient content. Dietary prescription may limit foods which are high in vitamins, particularly water-soluble vitamins, because of their high potassium or phosphorus content.7 Also, some medicines may interfere with the metabolism or actions of certain vitamins including vitamin B6, folate, and possibly riboflavin.8 Seasonal variations may predispose to deficiency of
some vitamins because of reduced access to fresh fruits and vegetables, to dietary protein restrictions, and to sunlight. Superimposed illnesses may contribute to low intake, impaired digestion, absorption or actions of some vitamins, or may require the use of medicines that interfere with the actions of vitamins.

Our knowledge of the body concentration, function, metabolic effects, and clinical response to reduced intake and low serum concentrations on these nutrients in nondialyzed patients with stages 3–5 CKD is incomplete. Whether there is altered nutrient metabolism in stages 3–5 CKD, as there can be in patients suffering from ESRD and those on dialysis, is unclear. Data from the National Health and Examination Survey and the Modification of Diet in Renal Disease Study show that the daily ingestion of nutrients begins to decline in as early as stage 3 CKD. This reduction in intake may affect energy producing nutrients (carbohydrates, protein, and fat), macrominerals, vitamins, and trace elements. The Dialysis Outcome Practice Patterns Study reported that patients on maintenance hemodialysis taking water-soluble vitamin supplements had a 16% lower mortality than similar patients not taking such preparations. This latter analysis was adjusted for age, gender, race, comorbidity, hemoglobin, serum albumin, BMI, and other potential confounders. Whether such supplements may increase survival in people with stages 3–5 CKD is unknown.

Although the optimal intake of macrominerals, iron, and vitamin D nutrition has received substantial attention, less is written or known concerning recommended allowances or body burden of vitamins and trace elements in stage 3–5 CKD. Possible adverse consequences of excessive vitamin intake by patients with CKD are an important concern, because vitamin supplements are commonly taken in the United States. Approximately one-half of elderly prescription medication users are reported to take dietary supplements, predominantly multivitamins. It is likely that some CKD patients take excessive and hazardous amounts of certain supplemental vitamins as well as inadequate quantities of other vitamins. This review summarizes the previously published data concerning the function, food sources, and evidence for inadequate or excessive intake of vitamins in people with stage 3–5 CKD who are not receiving dialysis therapy and do not have a functioning kidney transplant.

**Definition of Terms Concerning Nutritional Adequacy**

Traditionally, the adequacy of the body content and functional activity of vitamins are determined by measuring dietary intake, the corresponding biochemical values of these compounds—usually measured in serum or plasma or red blood cells, occasionally in urine, and in enzyme activities, and other biological processes or clinical manifestations of deficiency or excess. For example, the effects of certain vitamin intakes on hemoglobin production or plasma and urinary oxalate levels may be indicators of deficiency or excess. The recommended amount of a specific nutrient which is considered to support health is referred to as the dietary reference intake (DRI).

Hence, the DRIs can be standards by which the adequacy of nutrient intake could be assessed. They allow clinicians to compare the quantity of a given nutrient in a patient’s diet with an established standard. The DRIs for nutrients are generally determined by considering several other established standards regarding nutrient intake. These include the estimated average requirement (EAR) for the nutrient, the recommended daily allowance (RDA), and the adequate intake (AI) of the nutrient in question. Initially, wherever sufficient data are available, an EAR is established for a specific nutrient. The EAR is the amount of nutrient needed by one-half of the healthy population to support normal biological and physiological processes. In the Dietary Reference Guidelines, it should be noted that the terms, “healthy population” and “general population” are often conflated. The RDA is statistically derived from the EAR; it is calculated to be 2 standard deviations (SD) more than the EAR. Thus, RDA values are the average daily requirement for practically the entire general population (97% to 98%) to support biochemical and physiological processes. Data to establish the EARs are obtained, where possible, from clinical trials; however, there are insufficient data to determine these values for some nutrients. When there are insufficient data, an AI is established instead. AI is defined as the average amount of a nutrient that a group of healthy people consume. It is assumed that because these latter individuals are healthy, their intake of the nutrient in question should be adequate. Finally, the tolerable upper intake level is the maximum daily amount of a nutrient that seems to be safe for most healthy people and above
which there is an increased risk of adverse health effects.

These terms and values are in reference to healthy people and represent oral intakes; they do not necessarily reflect the values for the intakes of people with CKD, especially if their nutrients are not taken orally. Thus, the DRIs can be used as general benchmarks, but extrapolating these benchmarks to patients with CKD or other morbid conditions should be done with caution. The focus of this article is to describe what is currently reported in the published data regarding vitamin status and requirements for nontransplanted adult patients with CKD stages 3-5 who do not require dialysis treatment. DRI values for the general population will be shown for adults aged 50 to 70 years. This age range was selected because it is similar to the ages of a large proportion of adults with CKD.

**Water-Soluble Vitamins**

**Vitamin B1-Thiamin**

**Action**

Thiamin is a hydrophilic B vitamin involved with many metabolic functions. Thiamin serves as a cofactor for oxidative decarboxylation reactions. These include the conversion of pyruvate to acetyl coenzyme A (CoA) in the pyruvate dehydrogenase complex, the conversion of α-ketoglutarate to succinyl CoA in the α-ketoglutarate dehydrogenase complex, and the conversion of leucine, isoleucine, and valine to isovaleryl CoA, α-methylbutyryl CoA, and isobutyryl CoA in the branched chain α-ketoacid dehydrogenase complex. Additionally, thiamin is a cofactor in the transketolase reactions of the nonoxidative phase of the pentose pathway which leads to the production of ribose-5-phosphate and nicotinamide adenine dinucleotide phosphate. The DRI for thiamin (age, 50 to 70 years) is 1.2 mg/day and 1.1 mg/day for normal men and women, respectively.\(^{17}\)

**Food Sources**

The following food items are rich in thiamin: pork, oat bran, whole grains, and enriched grains.\(^{18}\)

**Evidence for Altered Requirements**

Dietary intake and nutritional status for thiamin in patients with CKD (n = 14) was assessed by Frank et al.\(^6\) Patients with stages 4 and 5 CKDs consumed an average of 1.26 mg of thiamin/day from the foods in their diet. Their mean plasma thiamin concentration was 64.2 nmol/L, and their ETK-AC (erythrocyte transketolase activity coefficients, an indicator of thiamin adequacy) was 1.18 ± 0.19 (SD) (an ETK-AC indicating no deficiency is <1.20). ETK-AC has been regarded as a good functional indicator of thiamin status.\(^8\)

Thus, according to the data generated by Frank et al.,\(^6\) a substantial proportion of patients with stages 4 and 5 CKD had ETK-AC values >1.20, indicating a thiamin-deficient status. These data are presented as mean ± SD, and the medians were not provided in this study. Thus, it is somewhat difficult to compare these results by Frank et al.\(^6\) with those by Weber and Kewitz\(^9\) in 91 generally healthy hospital employees that indicate what are presumably normal or healthy thiamin values. These latter investigators found the normal plasma thiamin concentrations to have a skewed distribution and presented their data as a median and range. The volunteers had a median plasma thiamin concentration of 11.6 nmol/L and a range of 6.6 to 43 nmol/L. Contrary to the ETK-AC findings, the patients with CKD appear to have increased concentrations of plasma thiamin when compared with the normal volunteers. The mean plasma thiamin values of these patients were higher than the upper range value of the healthy volunteers. It should be noted that plasma thiamin concentrations are not considered to be a reliable indicator of nutritional adequacy for thiamin.\(^{18}\) Although the data do not indicate that all patients have a deficiency of thiamin, there are data that indicate the risk for insufficient or deficient concentrations in patients with CKD. Whether the DRI level of intake is sufficient for patients with CKD is also unknown. However, a daily supplement at the DRI to augment dietary intake seems prudent to prevent possible deficiencies.

**Vitamin B2-Riboflavin**

**Action**

Riboflavin is a hydrophilic B vitamin with phosphorescent properties. It is necessary for oxidation–reduction reactions. When phosphorylated by adenosine triphosphate, riboflavin is converted to flavin mononucleotide (FMN). This molecule can then be complexed with various apoenzymes to form several flavoproteins. Most of the FMN is converted to flavin adenine
dinucleotide (FAD) by FAD synthetase. Hence, FAD is the predominant flavoenzyme in the body. The enzymes with which FMN and FAD are associated include oxygenases, monooxygenases, dehydrogenases, oxidoreductases, and electron transferases. This wide range of enzyme activities is based on the fact that the molecules can transition well between oxidized, single electron reduced semiquinoid, and double electron reduced hydroquinoid states. Normally, the DRI for riboflavin is 1.1 mg/day for women and 1.3 mg/day for men.

Food Sources

The following foods are rich sources of riboflavin: liver, duck, milk, eggs, mushrooms, spinach, chicken, and enriched grains.

Evidence for Altered Requirements

Porrini et al. studied patients with advanced CKD who were not undergoing dialysis using the \( \alpha \)-erythrocyte glutathione reductase (\( \alpha \)-EGR) stimulation index to assess riboflavin status. In this study, 8% of patients were found to have elevated \( \alpha \)-EGR, thus indicating riboflavin deficiency. When the prescribed protein intake of these patients was intentionally reduced to 1.0 g protein/kg/day or 0.6 g protein/kg/day, from the patients’ usual intake, according to the research protocol, the prevalence of elevated \( \alpha \)-EGR increased from 8% to 25% and 41%, respectively. The increased prevalence of elevated \( \alpha \)-EGR was attributed to the fact that riboflavin is particularly abundant in foods containing animal proteins (see earlier in the text). Indeed, several works have recommended riboflavin supplements for patients with CKD, especially when they ingest very low-protein diets (i.e., \(<0.6 \text{ g protein/kg/day})\).

Niacin-Vitamin B3

Action

Niacin is another hydrophilic B vitamin that is ingested as either nicotinamide from animal sources or nicotinic acid from plant sources. Niacin becomes active in human beings when it is converted to either nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate. These molecules are necessary cofactors for many oxidation-reduction reactions. A few notable processes involving niacin activity are the citric acid cycle, electron transport chain, and \( \beta \)-oxidation of lipids. Niacin also prevents and is the therapeutic agent for pellagra, which is a condition caused by niacin deficiency and often referred to by “the D’s”: dermatitis, diarrhea, dementia, and death. Pellagra is associated with the chronic intake of low riboflavin diets, alcoholism, food faddism, and when untreated maize is a primary staple of the diet. It has been shown that diets prescribed for patients with CKD are often not well accepted and may lead to poor intake. The DRI for healthy individuals is 14 mg/day for women and 16 mg/day for men.

Food Sources

Niacin is unusual in that it has an amino acid precursor, tryptophan; some of the tryptophan in the body is routinely converted to niacin. Niacin becomes active in human beings when it is converted to either nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate. These molecules are necessary cofactors for many oxidation-reduction reactions. A few notable processes involving niacin activity are the citric acid cycle, electron transport chain, and \( \beta \)-oxidation of lipids. Niacin also prevents and is the therapeutic agent for pellagra, which is a condition caused by niacin deficiency and often referred to by “the D’s”: dermatitis, diarrhea, dementia, and death. Pellagra is associated with the chronic intake of low riboflavin diets, alcoholism, food faddism, and when untreated maize is a primary staple of the diet. It has been shown that diets prescribed for patients with CKD are often not well accepted and may lead to poor intake. The DRI for healthy individuals is 14 mg/day for women and 16 mg/day for men.

Evidence for Altered Requirements

It is possible that patients with CKD who are prescribed with low-protein diets (such as 0.6 g protein/kg/day) with phosphorus restriction (such as 800 mg/day) may be at risk for niacin deficiency because of the low niacin content of plant food; thus, their dietary niacin intake may be quite low. However, the authors are unaware of any clinical trials that have examined the niacin intake of patients with CKD and whether that amount is sufficient to maintain adequate niacin status.

Recently, a novel use for niacin has been discovered. The niacin metabolite, nicotinamide, has been successfully used to reduce serum phosphorus concentrations in patients on hemodialysis who have been using megadoses of niacin, 500 to 1500 mg/day, given twice daily. The mechanisms of action involve the inhibition of the sodium/phosphorus type IIb cotransporter (NaPi-2b) and type IIa cotransporter (NaPi-2a), which are the major transporters of inorganic phosphorus in the intestinal brush border and in the proximal renal-tubular epithelial cells of the kidneys, respectively. Therefore, it is likely that in nondialyzed patients with stages 3-5 CKD, the action of nicotinamide on the NaPi-2a and NaPi-2b cotransporters will inhibit
both renal-tubular phosphorus reabsorption and phosphorus absorption in the intestinal brush border, thereby increasing renal phosphorus excretion in urine and feces. At present, the authors are unaware of published studies on the effects of niacin supplementation on urinary phosphorus excretion in CKD patients who are not receiving dialysis. The use of nicotinamide is associated with many side effects; most relevant are flushing, thrombocytopenia, hepatotoxicity (especially with sustained release doses), gastrointestinal symptoms such as diarrhea, vomiting, and constipation, and increased serum uric acid concentrations. The increased serum uric acid may be of concern as hyperuricemia has been associated with both hypertension and more rapid progression of renal failure. At this time, there does not seem to be data to warrant supplementation with nicin. However, CKD patients with chronically suboptimal dietary intake may benefit from a supplement at the DRI level to prevent deficiency.

Vitamin B-6—Pyridoxine

Action

Vitamin B6 exists in vivo as 6 compounds. These are pyridoxal, pyridoxine, pyridoxamine, and the 5' phosphates of these 3 compounds. Pyridoxal-5-phosphate (PLP) is a cofactor for many enzymes, particularly those involving amino acid metabolism and which include aminotransferases, decarboxylases, racemases, and dehydratases. Notably, PLP is necessary for (6)-aminolevulinate synthase to initiate heme synthesis. The DRI for pyridoxine (age, 50 to 70 years old) in men is 1.7 mg/day and in women is 1.5 mg/day.

Food Sources

The following food sources are rich in vitamin B6: liver, fish, meat, poultry, plums, bananas, plantains, barley, sweet potatoes, potatoes, and enriched grains.

Evidence for Altered Requirements

Koppel et al. conducted both dietary and biochemical assessments of pyridoxine status on patients with different stages of CKD. In a cross-sectional analysis, the amount of vitamin B6 consumed in foods declined as GFR decreased, from 2.2 ± 0.8 (SD) mg/day in 6 patients with stages 3 and 4 CKD (serum creatinine from 2.1 to 3.5 mg/dL) to 1.2 ± 0.5 mg/day in 7 nondialyzed patients with stages 4 and 5 CKD. The mean intake of vitamin B6 for patients with severe CKD was significantly lower than the DRI for their age cohort. These declining intakes were reflected in the stimulation index of erythrocyte glutamic pyruvic transaminase (EGPT) activity. EGPT activity and the EGPT index are measurements of adequacy of body pyridoxine levels. An EGPT index >1.25 is an indicator of vitamin B6 deficiency. The mean EGPT stimulation index increased (indicating vitamin B6 deficiency) inversely with the stage of CKD, in which patients with higher GFR levels (stages 3 and 4 CKD) had a mean EGPT index of 1.23 ± 0.09 (SD); CKD patients with lower GFR levels (stages 4 and 5 CKD) had a mean index of 1.30 ± 0.11. These were all significantly higher than the normal control values of 1.16 ± 0.06.

Podda et al. found significantly lower serum PLP concentrations, 37.3 ± 51.7 versus 79.3 ± 65.6 pmol/mL, in patients with the nephrotic syndrome as compared with healthy controls. The serum B6 values correlated with the magnitude of their proteinuria (r = 0.41, P < .001). These studies provide evidence that there are suboptimal levels of serum vitamin B6 in many patients with CKD.

Many medicines and other compounds can interfere with the actions or metabolism of vitamin B6 and may increase the likelihood that they will develop B6 deficiency. This is especially likely to occur in patients with CKD, because their vitamin B6 intake is often low, they may have increased dietary needs for B6, and it is likely that they may be prescribed some of these medicines. These interfering compounds include isoniazid, thyroxine, iproniazid, theophylline, hydralazine, caffeine, penicillamine, ethanol, and oral contraceptives. The data presented in this study suggest that patients at stage 3 or worse CKD are at an increased risk for deficient concentrations of vitamin B6 and therefore should be supplemented adequately. It has been recommended by both the European Society of Parenteral and Enteral Nutrition and Caring for Australians with Renal Insufficiency guidelines that vitamin B6 should be supplemented daily at a dose of 5 mg.

Folic Acid

Action

Folic acid is a pteroylmonoglutamic acid. It transfers single-carbon or methyl groups mainly
as the tetrahydrofolate, thereby providing methyl groups for pyrimidine and purine synthesis. Folate is also necessary for histidine catabolism, the conversion between serine and glycine, and the conversion of homocysteine to methionine, in addition to other processes. Deficiency of folic acid results in megaloblastic anemia. The DRI for both healthy men and women is 400 μg/day.17

**Food Sources**

The following food sources are rich in folic acid: legumes, orange juice, spinach and other leafy greens, broccoli, beets, artichokes, papaya, and enriched grains.18

**Evidence for Altered Requirements**

The causes for folic acid deficiency have been discussed earlier in the text (see Overview). As indicated earlier, low folate intake can be an important contributor to folate deficiency in patients with CKD. The primary source of dietary folate is fresh green vegetables which, because of their high potassium content, are frequently restricted in the diet of these patients. Medicines that interfere with folic acid and might lead to deficiency, particularly in people with low folate intakes, include barbiturates, primidone, cycloserine, pyrimethamine, diphenylhydantoin, triamterene, methotrexate, trimethoprim, nysoline, pantamidine, salicylasulfapyridine, and ethanol. Said et al.33 reported that radiolabeled 5-methyltetrahydrofolate absorption is reduced in the intestinal tract in azotemic rats. This does not seem to be confirmed in human beings.34 A possibly dialyzable compound or compounds in the azotemic rats may be responsible for the impaired absorption.33 Anions found in uremic sera may impair folate transport across membranes.35

In patients with advanced CKD (such as stages 4 and 5 before dialysis), the metabolism of folic acid appears to be altered, although the cause and timing of the alteration is not well defined. Hannisdal et al.36 compared the serum concentrations of folate and folic acid metabolites between healthy volunteers and nondialized patients with stages 3-5 CKD. Folate metabolites were analyzed by liquid chromatography–tandem mass spectrometry. The samples from patients with CKD had 22 to 30 times higher concentrations of folate metabolites than in sera from healthy volunteers. These elevated serum metabolite levels may reflect impaired excretion rather than altered metabolism of folic acid.

The optimal or safe daily intake for folate for patients with CKD before dialysis is unknown. Considering that there is currently no evidence for impaired folate activity or metabolism for nondialyzed people with stages 3-5 CKD, the daily intake for these individuals may be similar to that of people who do not have CKD.

**Cyanocobalamin—B-12**

**Action**

B12 is critical in 2 major reactions. It acts as a coenzyme in the reaction that converts homocysteine to methionine and for the reaction that converts L-methylmalonyl-coA to succinyl-coA.8 B12 has the following two metabolically active forms: (1) coenzyme 12 and (2) methylcobalamin. B12 is unique in its process for absorption in which it requires an intrinsic factor for absorption by the brush border of the ileum.5 The DRI for B12 is 2.4 μg/day for both men and women aged ≥51 years.17

**Food Sources**

The following food sources are naturally rich in B12: liver, beef, chicken, eggs, trout, and salmon. Fortified foods, such as breakfast cereal, are also a good source of B12.18

**Evidence for Altered Requirements**

In healthy adults, there is a 3- to 6-year body supply of B12.8 Therefore, if a healthy person consumed insufficient quantities of B12 for a short period (<3 years), they would not have insufficient B12 levels. However, there are no data on the body storage amounts in patients with CKD. A paucity of data has suggested that patients with CKD receiving hemodialysis respond favorably and quickly when supplemented with B12, even when the plasma values indicate normal ranges.37 This may be related to the fact that plasma B12 is not a sensitive indicator of B12 status. Methylmalonic acid and homocysteine are more sensitive indicators of B12 status. Additionally, B12 is found in high protein foods. Thus, patients who consume low amounts or remain on very low-protein diets for extended period, for example >3 years, with no B12 supplementation, may have insufficient B12 levels. Currently, the data
on B12 are limited and what is available does not indicate that patients with CKD are routinely deficient. However, it is prudent to have patients on low (0.6 g/day) or very low (0.3 g/day) protein diets receive a supplement with the DRI for B12.

**Homocysteine**

Serum total homocysteine appears to be increased to approximately 1.5 to 2 times the upper limit of normal in most of the patients with stage 5 CKD. This is of particular concern because in the general population elevated serum homocysteine concentrations are associated with an increased incidence of adverse cardiovascular events and mortality. This relationship is less clear in patients with CKD, because hyperhomocysteinemia has been associated with both increased and reduced mortality in these individuals, probably because of the interaction of serum homocysteine levels with protein-energy wasting. Several clinical trials have tested treatment of the patients with stages 4 and 5 CKD with large doses of folic acid, pyridoxine HCl, and often vitamin B6 to reduce elevated plasma homocysteine levels. A post hoc analysis of the Modification of Diet in Renal Disease Study indicates that serum homocysteine is increased in many patients with both stages 3 and 4 CKD and that the elevated serum levels appear to be influenced by the intake and blood levels of serum folate, vitamin B12, and possibly vitamin B6, and also by the GFR level. This analysis indicated that prescription of a daily multivitamin that provided 1 mg folic acid, 10 mg pyridoxine HCl, and 6 μg vitamin B12, which, essentially doubled the estimated daily folate and vitamin B12 intake, was associated with a 7% to 10% decrease in serum homocysteine concentrations.

Conversely, Nanayakkara et al. conducted a secondary analysis of a randomized clinical trial in patients with stages 2-4 CKD who were not taking a vitamin supplement. The researchers used a step-wise intervention with pravastatin 40 mg/day, at baseline; vitamin E 300 mg/day, initiated after 6 months; and finally, the B vitamins pyridoxine HCl 100 mg/day, folic acid 5 mg/day, and B12 1 mg/day after another 6 months. The primary outcome of this study was asymmetric dimethylarginine, which inhibits the endothelium-dependent nitric oxide-mediated response. Increased asymmetric dimethylarginine is associated with greater cardiovascular risk. At the conclusion of this trial, there was no difference between the treatment group and the control group with regard to serum asymmetric dimethylarginine levels. The serum homocysteine concentrations were not reported; however, when the asymmetric dimethylarginine results were stratified by baseline homocysteine, a significant decrease in serum asymmetric dimethylarginine was observed in the patients in the highest stratum of serum homocysteine as compared with the individuals receiving placebo. Mann et al. also found that lowering serum homocysteine with folic acid, B6, and B12 in patients with CKD did not reduce cardiovascular risk.

Another marker that has received attention in cardiovascular disease and homocysteine is S-adenosylhomocysteine (SAH). This molecule is the result of the conversion of S-adenosylmethionine, a universal donor for a large variety of acceptor compounds, into SAH via transmethylation. In a study with CKD patients and healthy controls by Valli et al., SAH was significantly elevated in patients with cardiovascular disease compared with those without (683 [201 to 3,057 nmol/L] vs. 485 [259 to 2,620 nmol/L, median [range], P < .001). Furthermore, in a multinomial logistic regression analysis, SAH was a significant predictor of cardiovascular disease ($r^2 = 0.31$).

Perhaps the largest clinical trial with the longest follow-up concerning vitamins to lower homocysteine (Hcy) concentrations and improve clinical outcome was the Homocysteinemia in Kidney and End Stage Renal Disease (HOST) study. This was a randomized, double-blind, placebo-controlled trial conducted in 2,056 Veterans Administration patients with stages 4 and 5 CKD who were either nondialyzed (n = 1,305) or were on maintenance hemodialysis (n = 751). All patients were hyperhomocysteinemic (Hcy, >15 umol/L), and they were randomized to receive daily treatment with 40 mg folic acid, 100 mg pyridoxine HCl, and 2 mg vitamin B12, or with placebo. Patients were treated for a mean of 4.5 years. Serum homocysteine levels decreased by 25.8% in the vitamin group ($P < .001$) as compared with the placebo group; however, there were no significant differences between the treatment group and the control group with regard to mortality, myocardial infarction, or amputations.

In a recently published study, patients with 238 diabetic nephropathy and nephrotic syndrome,
stage 3 or earlier, were randomized to treatment with either placebo or a combination of folic acid 2.5 mg/day, pyridoxine HCl 25 mg/day, and vitamin B12 1 mg/day, for a mean of 31.9 months. Patients randomized to vitamin treatment had a significantly faster reduction in GFR (−16.5 ± 1.7, mean change at 36 months) compared with patients receiving placebo (−10.7 ± 1.7, P = .045). The patients taking the vitamins were significantly more likely to have a myocardial infarction, stroke, revascularization, or all-cause mortality.

Thus, there currently does not seem to be any clinical advantage to the routine use of megavitamin therapy to lower the moderately elevated serum homocysteine levels in typical patients with CKD. It should be noted that genetic causes of severe hyperhomocysteinemia occur uncommonly and can be associated with ESRD. Patients with this condition are at increased risk for serious thromboembolic events, which can involve the major renal blood vessels. These individuals can respond to large doses of pyridoxine HCl or folic acid, depending on the genetic defect, and they should be treated accordingly.

Pantothenic Acid

Actions

Pantothenic acid is derived from pantothenate and is used in the synthesis of CoA. Coenzyme is critical for many metabolic processes such as fatty acid oxidation, transport of proteins, and the formation of acetyl CoA, a key molecule in energy metabolism. There is inadequate information to determine an RDA for pantothenic acid; however, the AI is set at 5 mg/day for men and women aged >51 years.

Food Sources

Although pantothenic acid appears to be ubiquitous in the food supply, the following foods are rich sources: beef, poultry, whole grains, potatoes, tomatoes, and broccoli.

Evidence for Altered Requirements

There are currently no reports in the published data demonstrating pantothenic acid deficiency in patients with CKD. There are a few reports of lower dietary intake by patients with CKD who are on low-protein diets. However, in validation studies plasma concentrations do not correlate well with whole blood pantothenic acid levels or dietary intake; therefore, these findings may not accurately reflect body stores. Given the ubiquitous nature of pantothenic acid in the general food supply and the lack of evidence for insufficiency or deficiency in patients with CKD, at this time intake beyond the AI is not warranted.

Vitamin C

Actions

Vitamin C, or ascorbic acid, is a hydrophilic, 6-carbon lactone that is capable of inhibiting the oxidation of other compounds by donating a maximum of 2 electrons and, in the process, undergoes oxidation. When 1 electron is donated, the ascorbic acid becomes a free radical known as semidehydroascorbic acid. After receiving a second electron, semidehydroascorbic acid is converted to dehydroascorbic acid. This process scavenges free radicals in the body, after oxidation of which, the threat of cellular damage is reduced. The DRI for vitamin C is 75 mg/day for women and 90 mg/day for men.

Food Sources

The following food sources are rich in vitamin C: citrus fruits, berries, papaya, peppers, mangos, pineapple, broccoli, cauliflower, melons, greens, tomatoes, and tubers.

Evidence for Altered Requirements

The causes of low vitamin intake and deficiency have been discussed earlier in the text. Vitamin C intake is particularly likely to be low in patients with CKD because of the potassium restriction. The authors are unaware of studies of vitamin C levels or requirements in nondialyzed patients with CKD.

Oxalate is a metabolite of ascorbic acid. Urine oxalate and, in renal failure patients, serum oxalate may increase when individuals ingest supplemental ascorbic acid. Thus, high doses of vitamin C traditionally are not recommended for patients with advanced CKD because of the possible increased risk for hyperoxalosis. However, in a recent study of people without CKD who were at increased risk for oxalate formation, 500 mg/day of vitamin C did not increase 24-hour urinary oxalate excretion. Because of these concerns, for nondialyzed
patients with CKD, the CARI guidelines recommend no more than 60 mg/day of vitamin C and the ESPEN guidelines recommend supplementation with 30 to 60 mg/day of vitamin C for the patients with CKD.31,50

Fat-soluble Vitamins

Vitamin A

Action

Vitamin A is a set of fat-soluble compounds classified as retinoids. Human beings ingest preformed vitamin A (retinyl esters) or carotenoids, which are vitamin A precursors. Retinyl esters can go through conversions to form retinol (the alcohol form of the retinoids), which can be subsequently converted to retinal (the aldehyde form) and then to retinoic acid (the acid form). Retinal and retinoic acid (the acid form) are required for various reactions in the eye to support vision. Retinoic acid also promotes embryonic development, and retinoids are necessary for normal immune function.

The carotenoids are β-carotene, α-carotene, and β-cryptoxanthin,51 with β-carotene being the most common form. It can be converted to retinol; however, it has only approximately 50% of the activity of retinyl esters.

Vitamin A is transported in blood bound to retinol-binding protein (RBP). RBP associates with 2 other proteins to form a trimolecular complex, called transthyretin. The current RDA for healthy men and women aged >51 years is 900 and 700 μg retinol activity equivalents/day, respectively, and the upper intake level is 3,000 μg retinol activity equivalents/day.52

Food Sources

The following food sources are rich in vitamin A: liver, fish liver oils, dairy products, butter, and eggs. β-carotene is found in red and yellow colored fruits and vegetables such as cantaloupe, carrots, sweet potatoes, winter squash, and dark green leafy vegetables such as spinach.18

Evidence for Altered Requirements

Serum vitamin A concentrations are often increased in patients with advanced CKD. Potential mechanisms include decreased catabolism of RBPs. Frey et al.53 showed that isoforms of RBP 4 (the main transporter or retinol in blood) is increased in CKD, and this may partly explain the elevated plasma concentrations in CKD patients. The National Health and Examination Survey III data demonstrated an association between elevated serum creatinine and elevated serum vitamin A concentrations54; this correlation was consistent across ethnicities and persisted after adjustment for confounding factors. This finding reinforces earlier studies that described elevated vitamin A levels in nondialyzed patients with CKD, ESRD patients, and kidney transplant recipients.55–57

Because serum vitamin A concentrations begin to increase with the increase in serum creatinine,53 there would seem to be no need to provide supplemental vitamin for patients with CKD, except in unusual conditions. This is consistent with the current recommendations against the need for supplemental vitamin A in CKD unless the patient is commonly ingesting less than the RDA for vitamin A.31 In this latter circumstance, supplemental vitamin A up to the RDA can be given.5

Vitamin E

Action

Vitamin E is a lipophilic molecule that typically resides in cell membranes. It acts as an anti-oxidant because it remains highly stable even after it scavenges free radicals. Vitamin E exists in 4 forms, α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol; however, only α-tocopherol has an established RDA. These forms differ by the level of methylation. The DRI for vitamin E (α-tocopherol) is 15 mg/day for both healthy men and women.48

Food Sources

The following food sources are rich in vitamin E: vegetable oils, unprocessed grains, nuts, fruits, vegetables, and meat.18

Evidence for Altered Requirements

The role of oxidative stress as a pathologic agent in several disease states has become increasingly apparent, and vitamin E has concurrently been considered as a potential treatment for this condition. Plasma vitamin E levels in patients with CKD do not appear to be different from healthy controls,58,59 even when dietary intake of vitamin E is reduced.59

The vitamin E metabolite, carboxyethyl-
hydroxychromans (CEHC), significantly increases in serum with declining renal function; this increase in serum CEHC has been observed with creatinine clearances of 45 mL/min (stage 3). Galli et al.\(^59\) suggest that the accumulation of this metabolite (CEHC) could interfere with the functions of vitamin E in patients with uremic CKD.

The results of clinical trials evaluating the effectiveness of vitamin E for the prevention of cardiovascular disease in people with CKD have been mixed. Mann et al.\(^60\) examined outcomes in patients with mild-moderate kidney failure (serum creatinine, 1.4 to 2.3 mg/dL; approximately stage 3 CKD) and increased risk for cardiovascular events who were given 400 IU/day of vitamin E as part of the Heart Outcomes Prevention Evaluation (HOPE) trial. Consistent with studies in such patients who did not have CKD, there was no cardiovascular benefit to taking this dose of vitamin E. Moreover, the long-term use of this dose (400 IU/day or 363 mg/day) of supplemental vitamin E in individuals with or without CKD who were at high risk for adverse cardiovascular events in the HOPE trial resulted in an increased incidence of heart failure, heart failure-related hospitalizations, and all-cause mortality (hazard ratio, 1.13; 95% confidence intervals, 1.01 to 1.26, \(P = .4\)).\(^38,39\) This increased risk was associated with vitamin E intakes as low as 150 IU/day (136 mg/day).\(^61,62\)

These studies, taken together, suggest that among people at high risk for cardiovascular events, supplemental vitamin E may not be indicated in the general population or in nondialysis CKD patients. At present, we recommend that nondialyzed patients with stages 2–5 CKD receive the normal DRI for vitamin E of 15 IU/day.

**Vitamin K**

**Action**

Vitamin K participates in the posttranslational carboxylation of specific glutamic acid (Gla) residues in proteins (such as blood clotting proteins and osteocalcin), enabling the protein to bind to calcium and interact with other compounds. This is a necessary step for such processes involving calcium interactions as blood clotting and bone mineralization. The dietary form of vitamin K is phylloquinone, which is absorbed in the jejunum and ileum and is primarily stored in the liver. Bacteria in the gut also produce vitamin K in the form of menaquinones which are absorbed from the distal bowel and stored in the liver. If vitamin K deficiency occurs, body proteins may be undercarboxylated. Carboxylation status of proteins, such as osteocalcin, can be measured and used to diagnose vitamin K deficiency. The normal AI for vitamin K is 90 µg/day for women and 120 µg/day for men.\(^52\)

**Food Sources**

The following food sources are rich in vitamin K: green vegetables, cabbage, and plant oils.\(^18\)

**Evidence for Deficiency**

Till date, there is little evidence that the reference intake for patients with CKD differs from the DRI for normal individuals. However, a decrease in dietary intake of vitamin K (phyloquinones), and/or a reduction in vitamin K production by gut bacteria can lower vitamin K levels. Antibiotics that suppress gut flora, and hence bacterial production of vitamin K, may increase the risk of vitamin K deficiency and impaired blood clotting. This is especially likely to happen if the patient is also not eating or taking vitamin supplements and therefore has a low vitamin K intake. In one study of hospitalized patients with extended prothrombin times, one-third of the patients had CKD and were not receiving dialysis.\(^63\)

A recent study in 172 patients with stages 3–5 CKD found that depending on the vitamin K indicator used, 6% to 97% of patients were vitamin K deficient. When serum phylloquinone was used as a measure, 6% deficiency was found in this population. However, when the more accurate marker, percent undercarboxylated osteocalcin, was measured 60% of the patients were found to be deficient in vitamin K. Finally, when Proteins Induced by Vitamin k Absence-II (PIVKA-II), a less used but a potentially very accurate marker was measured, 97% of the patients were found to be deficient.\(^64\)

These considerations suggest that men and women with CKD should ingest a minimum of 90 µg/day and 120 µg/day of vitamin K, respectively. When such individuals receive oral or parenteral antibiotics that may suppress...
gastrointestinal bacteria for extended period, they may be considered for vitamin K supplements; this is particularly the case if they have prolonged prothrombin times.

**Vitamin D**

**Action**

Vitamin D is found as 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol (calcitriol) in the body. Vitamin D is important in bone formation, immune function, vascular and nervous systems, and reproduction.65

**Food Sources**

Cholecalciferol or D3 is formed in the skin through sunlight exposure or is absorbed from ingested foods which are high in the vitamin; whereas ergocalciferol or D2 is synthetically manufactured from yeast. The amount of sun exposure needed for an individual to reach their daily requirement of D3 varies by the amount of melanin in the skin, whether sun screen is used, the season of the year, and their location in relationship to the equator. Foods containing high amounts of vitamin D are often high in fat because vitamin D is a fat-soluble vitamin. Thus, vitamin D in fortified milk may be better absorbed in milk with fat, such as ≥1%, verses skim milk which contains little to no fat. Other foods high in vitamin D are fatty fish, such as salmon or sardines, and eggs.18

**Evidence for Altered Requirements**

The use of 1,25-dihydroxycholecalciferol (calcitriol) and its analogues for people with CKD has been scientifically investigated and discussed extensively,66–68 however; space does not allow us to review this important subject. Emerging evidence, not yet definitive, also indicates that supplemental calcitriol precursors, such as ergocalciferol or cholecalciferol, may benefit patients with CKD.69 Because of the new and nondefinitive nature of the evidence regarding the nutritional needs for these latter compounds, they will be discussed in more detail.

Recent studies show that low serum 25-hydroxycholecalciferol levels are associated with adverse outcomes in CKD and incident MD patients.70,71 Mehrotra et al.72 found that patients with CKD, regardless of CKD stage or underlying cardiovascular disease, who had serum 25-hydroxycholecalciferol levels <15 ng/mL, were at increased risk of all-cause mortality (hazard ratio, 1.56 [95% confidence intervals, 1.12 to 2.18]). Furthermore, low serum 25-hydroxycholecalciferol levels or deficient intake is associated with increased risk of cardiovascular disease, cancer, and mortality in the general population.73,74 It has been suggested that serum 25-hydroxycholecalciferol levels of <15 ng/mL indicate deficiency, serum levels of 15 to 30 ng/mL indicate insufficiency, and levels ≥30 ng/mL are adequate.

The fact that extra-renal 1-alpha-hydroxylase is widely distributed may help to explain the potential positive benefits of ergocalciferol and cholecalciferol.75 Receptors for these latter compounds and for calcitriol are widely distributed in various cell types, which is consistent with the findings that the benefits of vitamin D extend far beyond bone health. Cell receptors for 25-hydroxycholecalciferol are also widely distributed, which may provide further support that this latter compound has beneficial effects that are independent from calcitriol.69,72

The accumulating evidence indicating benefits to the importance of nutritional vitamin D was reflected in the recent Kidney Disease: Improving Global Outcomes (KDIGO) recommendations for bone and mineral metabolism, which suggest serially measuring serum 25-hydroxycholecalciferol levels in stages 3-5 CKD; if serum levels are low, supplements of this compound should be given.76

Clinically, it may be suggested that patients with stages 3-5 CKD should be routinely prescribed cholecalciferol or ergocalciferol without ascertaining whether serum levels are decreased.77 The rational for this is that (1) a high prevalence of deficient serum 25-hydroxycholecalciferol levels in patients with CKD, (2) the expensive costs of routinely measuring serum 25-hydroxycholecalciferol, and (3) the safety of taking this compound. This proposal may be particularly relevant because patients with CKD might develop low serum 25-hydroxycholecalciferol levels some months after a normal serum value is obtained.

Against this suggestion, a recent meta-analysis by Palmer et al. reported that, “vitamin D is of unproven efficacy in CKD except for its effects on some biochemical indexes.”78 This meta-analysis has been criticized for combining the results of many discordant studies into single sets of...
analyses. However, there is a consensus that more randomized controlled clinical trials are necessary before definitive answers will be available concerning vitamin D supplementation.

Despite the accumulating evidence for the potential benefits of taking cholecalciferol or ergocalciferol, most renal vitamin preparations do not contain vitamin D. If vitamin D is to be prescribed, there is no consensus as to the compound and the dose that should be used. Holick et al. have recently reported that in otherwise normal vitamin D deficient individuals, 1,000 IU/day of ergocalciferol resulted in the same serum 25-hydroxycholecalciferol levels as did 1,000 IU/day of cholecalciferol.

Some multivitamins provide approximately 400 IU of vitamin D for a daily dose; however, that dose is not evidence-based, it is possible that closer to 800 IU to 1,000 IU of cholecalciferol or ergocalciferol /d may be a more adequate dosage for many patients with CKD, perhaps particularly for those aged >60 years. Although 50,000 IU of ergocalciferol, given once a month, has been recommended for these patients, some data suggest that this dose of vitamin D may not be converted to adequate amounts of 25-hydroxyvitamin D in all CKD patients. This concern should be added to the consideration that this once-monthly dosage of vitamin D is decidedly unphysiological. Until more evidence is available, given the high prevalence of low serum 25-hydroxycholecalciferol levels in patients with CKD, the epidemiological association of low serum levels with adverse outcomes, and the apparent safety of a cholecalciferol supplement of 800 to 1,000 IU per day, it could be argued that a routine supplement of this dose of the vitamin is clinically indicated for these individuals. At present, there is no clear evidence that equivalent doses of ergocalciferol are not equally safe and effective.

Conclusion

In conclusion, knowledge of vitamin and trace element needs for patients with CKD remains incomplete. The data reviewed in this article suggest that it is not unlikely that patients with stages 3-5 CKD may be at risk for deficiency of vitamins. The risk of excess and toxicity and toxicity of some vitamins also exists. Much research will be necessary before the nutritional needs for these essential nutrients in CKD are well defined.

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