The development of chronic kidney disease (CKD) is accompanied by a progressive decrease in the ability to produce 1,25-dihydroxyvitamin D. Pharmacological replacement with active vitamin D therefore has been a cornerstone of secondary hyperparathyroidism therapy in the end-stage renal disease population treated by long-term dialysis. Recent evidence suggests that extrarenal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D may have significant biological roles beyond those traditionally ascribed to vitamin D. Furthermore, low 25-hydroxyvitamin D levels are common in patients with all stages of CKD. This article focuses on the role of nutritional vitamin D replacement in CKD and aims to review vitamin D biology and summarize the existing literature regarding nutritional vitamin D replacement in these populations. Based on the current state of the evidence, we provide suggestions for clinical practice and address areas of uncertainty that need further research.

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INDEX WORDS: Cholecalciferol; chronic kidney disease; end-stage renal disease; ergocalciferol; vitamin D.

CASE PRESENTATION

Case 1
A 55-year-old African American man with stage 4 chronic kidney disease (CKD) from type 2 diabetes mellitus has the following laboratory data: parathyroid hormone (PTH), 160 pg/mL (160 ng/L); serum calcium, 8.8 mg/dL (2.20 mmol/L); serum phosphorus, 3.9 mg/dL (1.26 mmol/L); and serum 25-hydroxyvitamin D (25[OH]D), 15 ng/mL (37.44 nmol/L). Should he be started on nutritional vitamin D therapy?

Case 2
A 65-year-old white woman has end-stage renal disease (ESRD) requiring thrice-weekly in-center maintenance hemodialysis therapy. Review of her laboratory data shows the following values: PTH, 200 pg/mL (200 ng/L); serum calcium, 8.8 mg/dL (2.20 mmol/L); and serum phosphorus, 3.9 mg/dL (1.26 mmol/L). Serum 25(OH)D level is 15 ng/mL (37.44 nmol/L). She currently is receiving paricalcitol, 2 μg, with each hemodialysis treatment. Should she be started on nutritional vitamin D therapy?

INTRODUCTION

The first scientific descriptions of rickets were made in the mid-17th century. However, it was not until the 20th century that a low level of vitamin D, a nutritional fat-soluble component, was identified as a causative factor for rickets through the independent experiments of Edward Mellanby and Elmer McCol- lum. A few years prior to this discovery, scientists Alfred F. Hess and Lester J. Unger had shown that exposing children with rickets to sunlight could cure the disease. The exact chemical linking this nutritional fat-soluble component and sunlight subsequently was identified as ergosterol in 1927 through pioneering work by Nobel Laureate Adolf Windaus. Through a series of experiments in 1930s, Windaus identified the chemical structure of vitamin D produced in the skin—cholecalciferol. He also described the structure of its parent molecule, 7-dehydrocholes- terol. In 1931, Askew et al identified the chemical structure of vitamin D found in irradiated foods (ergocalciferol). In the years to come, 25(OH)D and 1,25-dihydroxyvitamin D (1,25[OH]2D) were isolated, vitamin D receptor (VDR) was identified, and the role of vitamin D in bone mineral metabolism was outlined. The enzyme responsible for conversion of 25(OH)D to 1,25(OH)2D was identified in the kidneys and it was shown that as kidney function deteriorates, production of 1,25(OH)2D decreases.

With the availability of active vitamin D analogues in the 1980s and 1990s, data supporting their role in the management of secondary hyperparathyroidism, and survival benefits seen in prospective observational studies, they have become widely used therapy in long-term dialysis patients. Circulating 1,25(OH)2D generated from the kidney appears to drive most endocrine functions of vitamin D, such as...
its effects on calcium transport and mineral metabolism. Additional tissues, including prostate, breast, colon, testes, myocardium, pancreas, and components of the immune system, also express 1α-hydroxylase, and VDR is expressed ubiquitously.14-21 Local production of 1,25(OH)2D from 25(OH)D likely is necessary for additional autocrine or paracrine functions.22 In these scenarios, adequate circulating levels of 25(OH)D (derived from sun exposure or nutritional sources), rather than 1,25(OH)2D, may be essential. Furthermore, benefits from active vitamin D analogues seen in prospective cohort studies of patients with CKD and long-term dialysis patients have not been shown consistently in randomized controlled trials,23,24 and low 25(OH)D levels are highly prevalent in these populations.13,25-27 Given the relatively low cost of nutritional vitamin D and the potential benefit in conjunction with active analogues, it is important to evaluate the role of these supplements. Clinical practice guidelines provided by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) recommend measuring 25(OH)D in patients with stages 3 and 4 CKD with accompanied secondary hyperparathyroidism, and if levels are <30 ng/mL, administering nutritional vitamin D prior to considering an active vitamin D analogue.28 The KDIGO (Kidney Disease: Improving Global Outcomes) guideline includes similar suggestions.29 However, for patients requiring dialysis, no specific recommendation is made regarding the role of nutritional vitamin D replacement. In addition, these guidelines have been criticized as being opinion based24 and derived largely from observational data,30 and there is a tremendous amount of confusion regarding nutritional vitamin D replacement in patients with CKD and those with ESRD treated by long-term dialysis.

In this review, we summarize vitamin D biology, discuss the existing literature regarding nutritional vitamin D replacement in these populations, provide clinical recommendations, and address areas of uncertainty that need further research.

**VITAMIN D TERMINOLOGY**

The terminology related to vitamin D has been confusing and inconsistent.31 This is due in part to the fact that various forms of vitamin D exist (Table 1; Fig 1).32 For this review, we have applied the following terminology: ergocalciferol and cholecalciferol are referred to as nutritional vitamin D analogues seen in prospective cohort studies of patients with CKD and long-term dialysis patients have not been shown consistently in randomized controlled trials,23,24 and low 25(OH)D levels are highly prevalent in these populations.13,25-27 Given the relatively low cost of nutritional vitamin D and the potential benefit in conjunction with active analogues, it is important to evaluate the role of these supplements. Clinical practice guidelines provided by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) recommend measuring 25(OH)D in patients with stages 3 and 4 CKD with accompanied secondary hyperparathyroidism, and if levels are <30 ng/mL, administering nutritional vitamin D prior to considering an active vitamin D analogue.28 The KDIGO (Kidney Disease: Improving Global Outcomes) guideline includes similar suggestions.29 However, for patients requiring dialysis, no specific recommendation is made regarding the role of nutritional vitamin D replacement. In addition, these guidelines have been criticized as being opinion based24 and derived largely from observational data,30 and there is a tremendous amount of confusion regarding nutritional vitamin D replacement in patients with CKD and those with ESRD treated by long-term dialysis.

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the exception that the bond between carbon atoms 9 and 10 is broken.

A wide range of criteria are used to define vitamin D deficiency, and unfortunately, there is no consensus on this issue.33-36 Many clinicians define serum 25(OH)D levels <20 ng/mL as deficient, 20-29.9 ng/mL as insufficient, and ≥30 ng/mL as sufficient (Table 2). There also is controversy regarding the upper limit of normal, with different cutoffs of 50-150 ng/mL proposed by different experts.33,35 A recent Institute of Medicine report considers 20 ng/mL as a “sufficient” level of vitamin D status for bone health.37 However, it is important to consider that the optimal vitamin D level may vary per the disease outcome considered. Levels >10 ng/mL are optimal for the prevention of rickets and osteomalacia, whereas to maximally prevent secondary hyperparathyroidism or osteoporosis, levels >30 ng/mL may be needed.38,39

**VITAMIN D METABOLISM**

Key steps in the metabolism are shown in Fig 2.40 In healthy individuals, 7-dehydrocholesterol in the skin is exposed to UV rays (wavelength, 285-310 nm) in sunlight, leading to its conversion to previtamin D.41 Previtamin D then isomerizes in a temperature-dependent manner to form cholecalciferol. Stamp et al42 reported that brief casual exposure of ~20% of body surface area to sunlight is equivalent to ingesting 200 IU (5 μg) of cholecalciferol. Repeated total-body exposure sufficient to cause mild erythema can increase plasma 25(OH)D level as much as long-term ingestion of 10,000 IU (250 μg) of cholecalciferol per day.41,42 Cutaneous production of cholecalciferol thus is highly efficient. However, many individuals lack the necessary exposure to UV light to maintain adequate stores. In individuals who are elderly, have higher melanin levels, have low baseline UV exposure, or are uremic, cutaneous production of cholecalciferol is reduced.19,43,44 In these cases, cutaneous production can be supplemented with dietary sources of vitamin D, including both plant (ergocalciferol) and animal (cholecalciferol) forms. These dietary forms are incorporated into chylomicrons and are transported through the lymphatic system into venous circulation. Both the dietary form and vitamin D produced in the skin can be stored in and released from fat cells. Most of the stored form of vitamin D in adipose tissue is cholecalciferol.45 Vitamin D is transported to the liver, where it undergoes hydroxylation of the 25th position by cytochrome P450 enzymes to become 25(OH)D, also known as calcidiol.19 CYP2R1 has been described as the key enzyme for this process; however, CYP2D11 and CYP2D25 are also believed to be involved.46,47 Hepatic production of 25(OH)D is inhibited by 1,25(OH)2D.48 Although the exact steps in this inhibition process have not been worked out, data support transcriptional regulation of the involved cytochrome P450 hydroxylases.49

25(OH)D is a major circulating form of vitamin D and is the best measure of vitamin D status because it has a long half-life (2-3 weeks vs 4 hours for 1,25(OH)2D), reproducible assay, high concentrations (100 times compared to 1,25(OH)2D), and lack of

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**Table 2. Commonly Used Definitions of 25(OH)D Levels**

<table>
<thead>
<tr>
<th>Definition</th>
<th>25(OH)D Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30-80 ng/mL</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>20-30 ng/mL</td>
</tr>
<tr>
<td>Deficiency</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Toxic</td>
<td>&gt;80 ng/mL</td>
</tr>
</tbody>
</table>

**Note:** Conversion for units: Serum 25(OH)D from ng/mL to nmol/L, ×2.496.

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.
fluctuations induced by PTH in response to subtle changes in serum calcium levels.50 Almost all 25(OH)D is bound to vitamin D–binding protein, with only 0.003% of the metabolite circulating in the free form.51 This complex is filtered by the glomerulus and taken up by the epithelial cell of the proximal convoluted tubule. This uptake is mediated by multiligand endocytic receptors, megalin and cubulin.52,53 The 25(OH)D–vitamin D–binding protein complex then is degraded in proximal tubule lysosomes, releasing 25(OH)D, which then translocates to mitochondria.54 In the mitochondria, 25(OH)D is converted to 1,25(OH)2D by the cytochrome P450 enzyme 1α-hydroxylase (CYP27B1) and returned to the circulation as the active form of vitamin D.55 Although initial studies identified 1α-hydroxylase in proximal tubular cells, this enzyme is also found in other parts of the nephron, including the distal tubules and collecting duct.56 In states of vitamin D deficiency, the distal nephron is a major site of 1α-hydroxylase expression.57 Another mitochondrial enzyme, 24α-hydroxylase (CYP24A1), is responsible for catabolism of 25(OH)D and 1,25(OH)2D into inactive 24,25-dihydroxyvitamin D [24,25(OH)2D].19,33

The 1α-hydroxylase enzyme is present in multiple extrarenal sites, including the pancreas, brain, lymph nodes, heart, gastrointestinal tract, adrenal glands, and prostate; 1,25(OH)2D may be made locally in these tissues if adequate substrate 25(OH)D is available.19,20,33,47,58 Actions of 1,25(OH)2D are mediated by binding to VDR, an intracellular class II steroid hormone receptor that is expressed universally in all nucleated cells.19,33,59 It has been reported that this receptor directly or indirectly controls the function of more than 200 genes.39,59

In the gastrointestinal tract, active vitamin D promotes enteroctyte differentiation and is capable of increasing calcium and phosphorus absorption.33,60 In bone, active vitamin D can stimulate osteoclast activity through an increase in RANKL (receptor activator of nuclear factor-κB ligand) expression, leading to release of calcium into the circulation.33,61 Vitamin D, along with PTH, can further stimulate calcium absorption from the distal tubule in the kidney.50 Active vitamin D in turn suppresses the release of PTH. In addition to effects on bone metabolism, active vitamin D may regulate other cellular functions. Central roles of active vitamin D have been described in the maintenance of muscle function,62,63 blood pressure and cardiovascular health,63-66 glucose control,67 both innate and acquired immune systems,68-72 and brain function73,74 and in the prevention of certain cancers.21,75,76 Through VDR, active vitamin D regulates processes such as cellular proliferation, differentiation, apoptosis, and angiogenesis in different tissues.21

Renal cytochrome P450 enzyme 1α-hydroxylase (CYP27B1) is tightly regulated by PTH, serum calcium and phosphorus, and fibroblast growth factor 23 (FGF-23).47 Low serum calcium, low serum phosphorus, and high PTH levels stimulate this enzyme to increase the synthesis of active vitamin D, which in turn suppresses PTH production. FGF-23 has been shown to inhibit production of active vitamin D by inhibiting 1α-hydroxylase (CYP27B1) expression and simultaneously increasing 24α-hydroxylase (CYP24A1) expression, leading to production of inactive metabolites of vitamin D.77 Active vitamin D also increases 24α-hydroxylase (CYP24A1) expression to convert 1,25(OH)2D and 25(OH)D to inactive forms.78 However, PTH decreases 24α-hydroxylase (CYP24A1) enzyme activity.

**VITAMIN D METABOLISM IN CKD**

**Calcidiol Deficiency**

Serum 25(OH)D levels begin to decrease in stage 2 CKD,79,80 and vitamin D deficiency is prevalent in all subsequent stages of CKD,25,81-84 including ESRD treated by long-term dialysis.26,85 Multiple factors have been reported to be responsible for this (Box 1). Patients with CKD are likely to have reduced sun exposure,86,87 and uremic patients have impaired skin synthesis of endogenous vitamin D in response to UV light.53,88 Hyperpigmentation, frequently seen in patients with advanced kidney disease, may impair the dermal synthesis of endogenous vitamin D.25,89 Furthermore, intake of foods rich in vitamin D (e.g., dairy products) is decreased in patients with CKD, and uremia may impair gastrointestinal vitamin D absorption.90-94 Proteinuria may be accompanied by high urinary loss of vitamin D–binding protein, leading to increased renal loss of all vitamin D metabolites.81,90,95,96 Patients on peritoneal dialysis therapy may lose 25(OH)D and vitamin D–binding protein in peritoneal dialysis fluid.97,98 Although not well supported, a possibility also has been raised that CKD may impair hepatic conversion of cholecalciferol to calcidiol.25

**Calcitriol Deficiency**

In individuals without kidney disease, renal 1α-hydroxylase is regulated by 1,25(OH)2D and is less dependent on the available substrate.35 As CKD advances, renal 1α-hydroxylase becomes progressively more substrate dependent, and less availability of substrate for reasons outlined earlier will lead to lower 1,25(OH)2D production.27,35,81,94,100,101 This reduced availability of substrate 25(OH)D is accompanied
A decrease in glomerular filtration rate will lead to reduced filtration of the 25(OH)D–vitamin D–binding protein complex that will further limit delivery and uptake of this complex by the receptors megalin and cubulin in renal tubular cells.\textsuperscript{54,112,113} CKD also is associated with decreased expression of megalin.\textsuperscript{114} Furthermore, secondary hyperparathyroidism associated with low vitamin D levels depletes vitamin D body stores by promoting 24,25-dihydroxy hydroxylases. Elevated FGF-23 levels also induce 24-hydroxylase, which degrades 1,25(OH)\textsubscript{2}D.\textsuperscript{105}

The effects of CKD on extrarenal 1α-hydroxylase are unclear.\textsuperscript{24,115} Experimental and clinical data have shown that administration of nutritional vitamin D even in anephric individuals is associated with significant increases in 1,25(OH)\textsubscript{2}D levels. This suggests that extrarenal production of active vitamin D can be induced by nutritional vitamin D supplements in patients with advanced CKD.\textsuperscript{16,115} Effects of FGF-23 on nonrenal 1α-hydroxylase are unclear; however, speculation that nonrenal 1α-hydroxylase is regulated differently than the renal 1α-hydroxylase and the well-established fact that vitamin D has several autocrine/paracrine functions opens the door for the possibility that nutritional vitamin D, even in patients with CKD and long-term dialysis patients, may help correct adverse consequences of vitamin D insufficiency and deficiency.

**Vitamin D Resistance**

In advanced CKD, there is progressive loss of VDR in the parathyroid gland, leading to vitamin D resistance.\textsuperscript{116} In addition, low levels of active vitamin D further lead to impairment in the binding of active vitamin D to VDR, as well as in the binding of the vitamin D–VDR complex to the vitamin D response element.\textsuperscript{117,118} Thus, CKD is characterized by both low vitamin D levels and vitamin D resistance.

**VITAMIN D STATUS AND OUTCOMES**

**Evidence in Populations Without CKD**

Multiple ecologic, cross-sectional, and longitudinal observational studies have reported a significant inverse association between serum 25(OH)D levels and cardiovascular outcomes in populations without established CKD.\textsuperscript{119-123} These studies have been conducted in different populations, including elderly patients,\textsuperscript{124} male health care professionals,\textsuperscript{125} patients referred for cardiac angiography,\textsuperscript{126,127} and general populations.\textsuperscript{128,129} Results from these studies have reported up to 2-3 higher magnitudes of cardiovascular outcomes in patients with vitamin D deficiency when comparisons are made between the highest and lowest levels of serum 25(OH)D. However, as noted in a recent meta-analysis by Pittas et al,\textsuperscript{54} these observations have not been uniformly confirmed in longitudinal observational studies and randomized controlled trials. Pittas et al\textsuperscript{54} summarized data regard-
ing the association between vitamin D status and cardiometabolic outcomes from 13 longitudinal observational studies and 18 trials. Studies involving patients with CKD were excluded. Outcomes included incident hypertension, incident type 2 diabetes, and incident cardiovascular events, such as myocardial infarction, stroke, and cardiovascular-related death, in generally healthy adults. The review authors concluded that the association between vitamin D status and cardiometabolic outcomes is uncertain. They observed a higher risk of incident hypertension in cohorts with low serum 25(OH)D levels (relative risk, 1.8; 95% confidence interval [CI], 1.3-2.4); however, supplementation with nutritional vitamin D did not have statistically significant reductions in systolic and diastolic blood pressures. Similarly, although lower 25(OH)D levels were associated with incident diabetes and incident cardiovascular disease, supplementation with nutritional vitamin D did not reduce the risk of incident diabetes or cardiovascular disease. Heterogeneity in the definition of outcomes and types of assessments precluded meta-analysis for the outcomes of diabetes and cardiovascular disease.

There is a paucity of clinical data regarding whether nutritional vitamin D supplementation improves non-cardiometabolic outcomes such as infections. A study by Fabri et al. has recently shown in vitro experiments a vitamin D–dependent pathway that is involved in acquired T-cell immune response mediated by interferon γ against Mycobacterium tuberculosis. In vitamin D–sufficient sera, interferon γ induced this antimicrobial pathway in human macrophages. In vitamin D–deficient sera, this induction was not achieved, but supplementation with cholecalciferol restored the pathway, outlining a key role of nutritional vitamin D in immunity against infections such as tuberculosis. However, further clinical trials will be needed to confirm whether supplementation with nutritional vitamin D is associated with a decrease in infectious complications. A recent review from the Institute of Medicine on this topic, although controversial, has highlighted this lack of definitive data for the health benefits of vitamin D supplementation beyond bone health in the general population.

**Evidence in CKD Populations**

Despite key alterations in vitamin D metabolism in patients with decreased kidney function, a similar story can be told when it comes to clinical data regarding associations between vitamin D status and outcomes. The prevalence of vitamin D deficiency in the general population has been described to range from 20%-50%, with race, age, sunlight exposure, and comorbid conditions such as diabetes mellitus and obesity accounting for wide variation in prevalence rates. Vitamin D deficiency is reported to have an even higher prevalence in the CKD population, with estimates as high as 70%-80% in some studies.

Wolf et al. performed a cross-sectional analysis of 825 consecutive incident hemodialysis patients from 569 unique centers in the United States. They observed that in this prospective cohort, 78% of patients were vitamin D deficient (serum 25(OH)D <30 ng/mL) and 18% were severely deficient (serum 25(OH)D <10 ng/mL). In the same cohort, Bhan et al. have identified hypoalbuminemia and winter season (for hemodialysis therapy initiation) as clinical measures that are almost universally associated with vitamin D deficiency. LaClair et al. performed a cross-sectional study analyzing serum 25(OH)D levels in patients with stages 3 and 4 CKD (not yet on dialysis therapy) derived from 12 diverse geographic areas from the United States. They defined vitamin D deficiency as 25(OH)D level <10 ng/mL, and insufficiency, as 10-30 ng/mL. In this cohort, only 29% and 17% of patients with stage 3 and stage 4 CKD had adequate vitamin D status, respectively. Even in patients with milder CKD, low vitamin D values commonly are reported, and vitamin D deficiency has been described to begin even before abnormalities in serum calcium, phosphorus, or PTH levels become detectable.

In cross-sectional studies, vitamin D deficiency has been described to be associated independently with albuminuria in adults participating in the Third National Health and Nutrition Examination Survey and also in other studies. Vitamin D deficiency also has been identified as a contributor to racial disparity in albuminuria. A number of studies have reported on the association between 25(OH)D levels and mortality in CKD populations. A meta-analysis by Pilz et al. showed improving survival with increasing 25(OH)D levels in CKD populations requiring and not requiring dialysis treatments. In this analysis, an increase of 10 ng/mL in serum 25(OH)D level was associated with a 14% reduction in mortality risk (relative risk, 0.86; 95% CI, 0.82-0.91). Although the review is limited by potential publication bias and other limitations that are inherent to the included observational studies, it provides strong support for measuring 25(OH)D to identify high-risk subgroups within the CKD population.

Studies of the association between 25(OH)D levels and other important outcomes, such as cardiovascular events, coronary artery calcification, CKD progression, early GFR loss, and bone fractures in CKD, are summarized in Table 3. Recently, Drechsler et al. reported an analysis of data from the NECOSAD (Nederland Cooperative Study on the
Table 3. Studies Evaluating Associations Between Low Serum 25(OH)D Levels and Clinical Outcomes in CKD and Long-term Dialysis Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>No.</th>
<th>Follow-up (y)</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrus et al,148</td>
<td>Cross-sectional</td>
<td>ESRD patients on maintenance HD</td>
<td>144</td>
<td>NA</td>
<td>25(OH)D &lt; 8 ng/mL independently associated with 11.2 times odds of bone fracture</td>
</tr>
<tr>
<td>de Boer et al,137</td>
<td>Cross-sectional</td>
<td>Civilian noninstitutionalized adults participating in NHANES III in US</td>
<td>15,068</td>
<td>NA</td>
<td>With decreasing quartiles of 25(OH)D concentration, stepwise increase in albuminuria prevalence observed: 8.9%, 11.5%, 13.7%, and 15.8% (P &lt; 0.001)</td>
</tr>
<tr>
<td>de Boer et al,150</td>
<td>Prospective cohort</td>
<td>Community-dwelling adult residents aged 45-84 y from MESA</td>
<td>1,370 (394 with CKD, 976 without CKD)</td>
<td>3</td>
<td>Each 10-ng/mL lower 25(OH)D concentration independently associated with 23% increased risk of developing coronary artery calcification</td>
</tr>
<tr>
<td>de Boer et al,149</td>
<td>Prospective cohort</td>
<td>Older adults with predominantly normal baseline kidney function from Cardiovascular Health Study</td>
<td>1,705</td>
<td>4</td>
<td>Each 10-ng/mL lower 25(OH)D concentration independently associated with 25% greater risk of rapid GFR loss</td>
</tr>
<tr>
<td>Drechsler et al,147</td>
<td>Prospective cohort</td>
<td>Incident ESRD (both HD and PD patients)</td>
<td>762</td>
<td>Short term, 0.5; long term, 3</td>
<td>Compared with patients with 25(OH)D levels &gt; 10 ng/mL, those with ≤ 10 ng/mL independently associated with higher short- (HR, 2.0; 95% CI, 1.0-3.8) and longer term all-cause mortality (HR, 1.5; 95% CI, 1.0-2.1), and independently associated with short- (HR, 2.7; 95% CI, 1.1-6.5) and longer term cardiovascular mortality (HR, 1.7; 95% CI, 1.1-2.7)</td>
</tr>
<tr>
<td>London et al,146</td>
<td>Cross-sectional</td>
<td>ESRD patients on maintenance HD</td>
<td>52</td>
<td>NA</td>
<td>Low 25(OH)D levels associated with atherosclerosis and endothelial dysfunction (negative correlation with aortic pulse wave velocity [P &lt; 0.001], positive correlation with brachial artery distensibility [P &lt; 0.01] and flow-mediated dilatation [P &lt; 0.001])</td>
</tr>
<tr>
<td>Mehrotra et al,142</td>
<td>Prospective cohort</td>
<td>Civilian noninstitutionalized adults with CKD participating in NHANES III in US</td>
<td>3,011</td>
<td>9</td>
<td>25(OH)D levels &lt; 15 ng/mL independently associated with 56% increase in all-cause mortality with serum 25(OH)D levels &gt; 30 ng/mL as reference; 25(OH)D levels 15-30 ng/mL independently associated with 17% increase in all-cause mortality with serum 25(OH)D levels &gt; 30 ng/mL as reference</td>
</tr>
</tbody>
</table>

(Continued)
Adequacy of Dialysis) cohort and further explored the association between 25(OH)D levels and short- (6 months) and long-term (36 months) mortality in incident maintenance dialysis patients who were alive at 1 year after dialysis therapy initiation. The cohort used in this analysis was composed of 762 adult hemodialysis and peritoneal dialysis patients recruited over 13 years from 37 dialysis centers in the Netherlands. Even for those who had survived their first year on dialysis therapy, subsequent mortality rates were high (7% at 6 months and 30% at 36 months), and cardiovascular causes were responsible for >50% of these deaths. In analyses adjusted for possible confounders, including bone mineral metabolism parameters and seasonal variation in vitamin D levels, the authors reported higher cardiovascular mortality in patients with 25(OH)D levels <10 ng/mL compared with patients with 25(OH)D levels >10 ng/mL; adjusted hazard ratios were 2.72 (1.05-7.05; \( P = 0.04 \)) and 1.61 (1.00-2.57; \( P = 0.048 \)) for the 6-month and 3-year follow-up, respectively. In stratified analyses, patients with high PTH levels and 25(OH)D levels <10 ng/mL experienced more than a 3-fold higher risk of cardiovascular death compared with patients with high PTH levels and 25(OH)D levels >10 ng/mL. No association was seen between vitamin D deficiency and noncardiovascular mortality, but few patients died of noncardiovascular causes. These results not only confirmed the previously reported associations between 25(OH)D levels and short-term clinical outcomes in dialysis patients, but also suggest that 25(OH)D level measured at 1 year after dialysis therapy initiation predicts long-term (3-year) cardiovascular mortality. These associations (both short and long term) were particularly prominent in a subgroup of patients with high PTH levels, raising the possibility that the patient population with severe underlying bone and mineral disorders is particularly more susceptible to adverse effects of low 25(OH)D levels. Studies such as that by Drechsler et al are important for understanding the implications of low vitamin D levels in this patient population.

### Table 3 (Cont’d). Studies Evaluating Associations Between Low Serum 25(OH)D Levels and Clinical Outcomes in CKD and Long-term Dialysis Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>No.</th>
<th>Follow-up (y)</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melamed et al, 2009</td>
<td>Prospective cohort</td>
<td>Civilian noninstitutionalized adults with baseline eGFR &gt;15 mL/min/1.73 m² participating in NHANES III in US</td>
<td>13,328</td>
<td>9.1</td>
<td>Patients with 25(OH)D levels &lt;15 ng/mL had independent 2.6-fold higher risk of ESRD than those with levels ≥15 ng/mL</td>
</tr>
<tr>
<td>Navaneethan et al, 2011</td>
<td>Prospective cohort</td>
<td>CKD stages 3-4</td>
<td>12,763</td>
<td>1.2 (median)</td>
<td>33% increase in all-cause mortality in patients with 25(OH)D levels &lt;15 ng/mL compared with those with ≥30 ng/mL</td>
</tr>
<tr>
<td>Ravani et al, 2009</td>
<td>Prospective cohort</td>
<td>CKD stages 2-5 without imminent need for dialysis commencement</td>
<td>168</td>
<td>4 (median)</td>
<td>Each 10-ng/mL decrease in 25(OH)D concentration independently associated with 42% greater risk of development of ESRD and 28% greater risk of mortality</td>
</tr>
<tr>
<td>Wolf et al, 2007</td>
<td>Nested case-control</td>
<td>Incident ESRD patients on HD</td>
<td>1,000</td>
<td>0.25</td>
<td>Patients with 25(OH)D levels &lt;10 ng/mL had independent 60% higher risk of all-cause mortality compared with those with levels ≥30 ng/mL</td>
</tr>
<tr>
<td>Wang et al, 2008</td>
<td>Prospective cohort</td>
<td>ESRD patients on maintenance PD</td>
<td>230</td>
<td>3</td>
<td>Every 1-unit increase in log-transformed 25(OH)D level associated with 44% decrease in hazard of fatal or nonfatal cardiovascular events</td>
</tr>
</tbody>
</table>

Note: Conversions for serum 25(OH)D in ng/mL to nmol/L, \( \times 2.496 \).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not applicable; NHANES III, Third National Health and Nutrition Examination Survey; PD, peritoneal dialysis.
because they expand our existent knowledge about implications of 25(OH)D deficiency in dialysis patients and also provide some clues toward which patient cohorts are likely to benefit the most from maintaining normal 25(OH)D levels (eg, patients with severe underlying bone mineral metabolism disorders, as indicated by elevated PTH levels).152

**NUTRITIONAL VITAMIN D REPLACEMENT IN CKD**

The data presented here provide a convincing case for the association between serum 25(OH)D levels and clinical outcomes. Although definitive conclusions regarding causality cannot be made from such observational data, a natural question is whether supplementing nutritional vitamin D will provide clinical benefits and whether there may be adverse effects of such supplementation.

The CKD and long-term dialysis populations, with higher rates of vitamin D deficiency, cardiovascular events, and infections compared with the general population, represent ideal groups to evaluate the efficacy and safety of nutritional vitamin D supplements. Reports of the use of vitamin D compounds in the setting of kidney disease appeared as early as the 1950s. In 1957, Stanbury153 reviewed the then-available literature on this topic and reported that “Vitamin D steroids should not be given to patients in whom the predominant osseous lesion is renal osteitis fibrosa; even with full metabolic control, this would be little more than a hazardous therapeutic experiment.”153 Subsequent case reports noted that the dose of cholecalciferol required to correct biochemical and bone abnormalities of renal osteodystrophy was in the magnitude of 100,000-300,000 IU/d, doses that carried a significant risk of hypercalcemia.154 This led to testing whether calcitriol can achieve the same biochemical and bone histology corrections with a better adverse-effect profile.

Berl et al155 conducted a double-blind controlled trial in patients on long-term dialysis therapy (n = 31) comparing oral calcitriol (0.5-1.5 µg/d) with cholecalciferol (400-1,200 IU/d) for 12 weeks. They concluded that effects of PTH lowering and improvements in bone histology that were seen with calcitriol were not observed in the cholecalciferol group.155 Although 5 of 15 patients in the calcitriol group developed hypercalcemia, the authors noted that hypercalcemia was of shorter duration and also was easily reversible upon reducing the dose of calcitriol. Malluche et al156 evaluated the effects of cholecalciferol on bone histology in patients with CKD with creatinine clearance of 30-80 mL/min/1.73 m² (n = 36). They noted that intestinal absorption of calcium increased and was normalized in all patients. However, in 17 patients who underwent bone histology studies, cholecalciferol in doses that normalized intestinal absorption of calcium did not restore bone histology to normal after 18 months of therapy (17 patients). These early trials reporting the inferiority of nutritional vitamin D compound in patients with kidney disease and the subsequent availability of vitamin D compounds with fewer calcemic effects contributed to a lack of enthusiasm to study nutritional vitamin D supplements in patients with CKD and long-term dialysis patients for more than 2 decades. However, modern understanding of the biology of vitamin D as described earlier in this review has led to re-emergence of interest in this topic and a number of recent observational studies and randomized controlled trials have been conducted to evaluate this further (Tables 4 and 5).157-172 As reviewed in these tables and also previously reported,24,30 to date there are no well-designed randomized controlled trials or large observational cohort studies that evaluate whether administration of nutritional vitamin D in patients with CKD improves patient-centered clinical outcomes, such as overall mortality, cardiovascular disease, or infection.

A recent systematic review and meta-analysis by Kandula et al130 on this topic identified 17 observational cohort studies and 5 randomized controlled trials, noting that most studies conducted on this topic are of low to moderate quality. They noted a statistically significant increase in serum 25(OH)D levels (mean difference, 24.1 [95% CI, 19.6-28.6] ng/mL), along with a decrease in PTH levels (mean difference, −41.7 [95% CI, −55.8 to −27.7] pg/mL) in observational studies. In randomized controlled trials, there was a significant increase in serum 25(OH)D levels (mean difference, 14 [95% CI, 5.6-22.4] ng/mL) and an associated decrease in PTH levels (mean difference, −31.5 [95% CI, −57 to −6.1] pg/mL). A low incidence of hypercalcemia (up to 3%) and hyperphosphatemia (up to 7%) was reported with nutritional vitamin D supplementation. Both hypercalcemia and hyperphosphatemia resolved when vitamin D therapy and/or phosphate binders were withheld. However, none of the studies reported outcomes related to cardiovascular disease, bone disease, or mortality. This emphasizes the need for well-designed randomized controlled trials on this topic.

The clinical trial registry ClinicalTrials.gov lists several studies in both non–dialysis-dependent patients with CKD and long-term dialysis populations designed to assess biochemical and clinical outcomes. Although none of these studies is powered to detect differences in mortality or cardiovascular events, these studies will further enrich our understanding of vitamin D pathobiology by addressing the role of nutritional vitamin D on outcomes such as immune function (hCAP18 Levels and Vitamin D Deficiency in
Table 4. Observational Cohort Studies Evaluating Nutritional Vitamin D Replacement in CKD and Long-term Dialysis Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No.</th>
<th>Intervention</th>
<th>Duration (mo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Aly et al, 2007</td>
<td>CKD stage 3 or 4 with serum 25(OH)D &lt;30 ng/mL and increased plasma iPTH; patients with history of active vitamin D sterol use excluded</td>
<td>66</td>
<td>Ergocalciferol, 50,000 IU, 1×/wk for 12 wk, 1×/mo thereafter</td>
<td>6</td>
<td>Increase in 25(OH)D from 16.6 ± 0.7 to 27.2 ± 1.8 ng/mL (P &lt; 0.05); decrease in plasma iPTH from 231 ± 26 to 192 ± 25 pg/mL (P &lt; 0.05)</td>
</tr>
<tr>
<td>Blair et al, 2008</td>
<td>Maintenance HD patients with 25(OH)D &lt;40 ng/mL</td>
<td>318</td>
<td>Ergocalciferol, 50,000 IU/wk</td>
<td>6</td>
<td>Increase in 25(OH)D from baseline (18.4 ± 9.0 ng/mL) to 6 mo (42.0 ± 24.7 ng/mL) (P &lt; 0.0005); PTH showed nonsignificant downward trend; glycosylated Hb decreased from 6.9% ± 1.9% at baseline to 6.4% ± 1.5% at 6 mo (P &lt; 0.0005); Hb increased from 12.1 ± 1.6 g/dL to 12.3 ± 1.4 g/dL (P &lt; 0.0005)</td>
</tr>
<tr>
<td>Bouchard et al, 2008</td>
<td>Maintenance PD patients</td>
<td>27</td>
<td>Ergocalciferol, 41,440 IU/wk</td>
<td>1</td>
<td>Increase in 25(OH)D from 12.3.8 to 17.1 ± 5.2 ng/mL (P &lt; 0.001), but levels remained insufficient in all but 1 patient; no significant decrease in iPTH</td>
</tr>
<tr>
<td>Bucharels et al, 2011</td>
<td>Maintenance HD patients with iPTH &lt;300 pg/mL and 25(OH)D &lt;30 ng/mL</td>
<td>30</td>
<td>Cholecalciferol, 50,000 IU/wk for 3 mo and 20,000 IU/wk for next 3 mo</td>
<td>6</td>
<td>Increase in 25(OH)D from 18.1 ± 6.6 to 40.4 ± 10.4 ng/mL (P &lt; 0.001); no significant decrease in iPTH; significant reduction in LVMI</td>
</tr>
<tr>
<td>Deville et al, 2006</td>
<td>CKD stages 3-5; patients on dialysis excluded</td>
<td>85</td>
<td>Ergocalciferol in doses ranging from 800 IU/d to 100,000 IU/wk</td>
<td>3</td>
<td>Increase in serum 25(OH)D from 17.4 to 42.3 ng/mL (P &lt; 0.001); decrease in iPTH from 18.7 to 15.8 pmol/L (P &lt; 0.01)</td>
</tr>
<tr>
<td>Jean et al, 2009</td>
<td>Maintenance HD patients with 25(OH)D &lt;30 ng/mL</td>
<td>107</td>
<td>Cholecalciferol 100,000 IU/mo</td>
<td>15</td>
<td>Increase in serum 25(OH)D from 12.8 ± 5.2 to 42.48 ± 10.8 ng/mL (P &lt; 0.001); decrease in iPTH from 295 to 190 pg/mL (P &lt; 0.001)</td>
</tr>
<tr>
<td>Kim et al, 2011</td>
<td>Diabetic nephropathy (urine ACR &gt;30 mg/mmol) patients with 25(OH)D &lt;32 ng/mL</td>
<td>49</td>
<td>25(OH)D &lt;16 ng/mL: cholecalciferol, 40,000 IU/wk, for 2 mo then same dose/mo; 25(OH)D 16-32 ng/mL: cholecalciferol, 40,000 IU/mo</td>
<td>4</td>
<td>Increase in serum 25(OH)D across all GFR categories; decrease in urine ACR from 16 to 12 mg/mmol (P &lt; 0.05)</td>
</tr>
<tr>
<td>Matias et al, 2010</td>
<td>Maintenance HD patients with 25(OH)D &lt;30 ng/mL</td>
<td>158</td>
<td>25(OH)D &lt;15 ng/mL: cholecalciferol, 50,000 IU/wk; 25(OH)D of 16-30 ng/mL: cholecalciferol, 10,000 IU/wk; 25(OH)D &gt;30 ng/mL: 2,700 IU of cholecalciferol 3×/wk</td>
<td>12</td>
<td>Increase in serum 25(OH)D from 8.9 ± 4.8 to 16.9 ± 4.8 ng/mL (P &lt; 0.001); decrease in iPTH from 233 to 208 pg/mL (P &lt; 0.001); decrease in paricalcitol and sevelamer use; decrease in darbepoetin use; brain natriuretic peptide levels and LVMI significantly reduced at end of supplementation</td>
</tr>
</tbody>
</table>

(Continued)
Chronic Kidney Disease, registration number NCT01026363; DIVINE: Dialysis Infection and Vitamin D in New England, registration number NCT00892099; The Role of Vitamin D in Immune Function in Patients With Chronic Kidney Disease Stages 3 and 4, registration number NCT00749736), left ventricular mass (Vitamin D Supplementation and Cardiac Hypertrophy in Chronic Kidney Disease, registration number NCT01323712), insulin resistance (Study of Vitamin D3 Supplementation in Patients With Chronic Kidney Disease [VitaD-CKD1], registration number NCT00749736), and proteinuria (Effects of Vitamin D on Renal Blood Flow, Proteinuria and Inflammation in Patients With Chronic Kidney Disease, registration number NCT01426724). These studies also will provide valuable information to design future well-powered studies to address hard end points such as mortality. Future trials also should compare whether combining nutritional vitamin D with active vitamin D therapy results in better outcomes than active vitamin D or nutritional vitamin D therapy alone.

Despite the lack of evidence for clinical outcomes to support the use of nutritional vitamin D compounds, KDOQI28,173 and KDIGO29 guidelines suggest treatment with nutritional vitamin D supplements for patients with stages 3 and 4 CKD with accompanied secondary hyperparathyroidism if 25(OH)D level is <30 ng/mL. The recommended dose depends on the 25(OH)D level; 50,000 units of ergocalciferol once a week for 4 weeks followed by the same dose once a month for 6 months if level is 15-30 ng/mL. Serum calcium and phosphorus should be monitored every 3 months. The need for continuing therapy with ergocalciferol is to be re-evaluated annually. These guidelines have been based on extrapolation of data from the general population and also have been largely opinion based rather than evidence based. However, because (1) there is reasonable evidence to support the safety of nutritional vitamin D supplements at the recommended doses and with suggested monitoring schedule in these guidelines, (2) there is evidence that nutritional vitamin D administration in patients with CKD is associated with decreases in PTH levels, and (3) there is biological evidence to support that these supplements may have extrarenal actions, it is reasonable to adopt the present guidelines in clinical practice. In humans, cholecalciferol is more effective than ergocalciferol in increasing 25(OH)D levels and dose determinations should take into account these potency differences, as well as the availability of the nutritional forms.174 Future trials to address effects of nutritional vitamin D on patient-centered outcomes and trials comparing nutritional vitamin D with active vitamin D preparations are

### Table 4 (Cont’d). Observational Cohort Studies Evaluating Nutritional Vitamin D Replacement in CKD and Long-term Dialysis Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No.</th>
<th>Intervention</th>
<th>Duration (mo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al,165</td>
<td>Maintenance PD patients with 25(OH)D &lt;15 ng/mL</td>
<td>23</td>
<td>Ergocalciferol, 50,000 IU/wk</td>
<td>1</td>
<td>Increase in serum 25(OH)D from &lt;7 to 30 ng/mL (P &lt; 0.001); no significant decrease in iPTH; decrease in reports of muscle weakness and bone pain</td>
</tr>
<tr>
<td>Tokmak et al,166</td>
<td>Maintenance HD patients</td>
<td>64</td>
<td>Cholecalciferol, 20,000 IU/wk</td>
<td>9</td>
<td>Increase in serum 25(OH)D from 6.7 ± 3.8 to 31.9 ± 10.9 ng/mL (P &lt; 0.001); no significant decrease in iPTH</td>
</tr>
<tr>
<td>Zisman et al,167</td>
<td>CKD stages 3-4 with 25(OH)D &lt;30 ng/mL</td>
<td>52</td>
<td>Ergocalciferol per KDOQI guidelines</td>
<td>12</td>
<td>CKD stage 3: increase in serum 25(OH)D from 20.3 ± 1.3 to 31.6 ± 2.2 ng/mL (P &lt; 0.0001); decrease in iPTH from 154.1 to 130.5 pg/mL (P = 0.041); CKD stage 4: increase in serum 25(OH)D from 18.8 ± 1.3 to 35.4 ± 1.9 ng/mL (P &lt; 0.0001); no significant decrease in iPTH</td>
</tr>
</tbody>
</table>

Note: Conversion factors for units: serum 25(OH)D in ng/mL to nmol/L, ×2.496; hemoglobin in g/dL to g/L, ×10. No conversion is necessary for serum PTH in pg/mL to ng/L.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ACR, albumin-creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; iPTH, intact parathyroid hormone; KDOQI, Kidney Disease Outcomes Quality Initiative; LVMI, left ventricular mass index; PD, peritoneal dialysis.
urgently needed. Until data from such trials become available, we suggest the following approach for patients with CKD and long-term dialysis patients. The strengths and limitations of these recommendations are summarized in Box 2.

1. Measure serum 25(OH)D annually.
2. Patients with levels <30 ng/mL should receive oral ergocalciferol, 50,000 IU (or cholecalciferol, 10,000 IU), weekly for 8 weeks, followed by repeated serum 25(OH)D measurement.
3. If serum 25(OH)D level remains <30 ng/mL, repeat another 8-week course of ergocalciferol, 50,000 IU (or cholecalciferol, 15,000 IU), weekly. Because the 25(OH)D test is not inexpensive and 16 weeks of ergocalciferol treatment at 50,000 IU/wk (or cholecalciferol, 15,000 IU/wk) is an adequate dose to correct the deficiency, we do not suggest rechecking the level at 16 weeks.

4. Patients with levels ≥30 ng/mL are to be continued on a maintenance dose of oral ergocalciferol at 50,000 IU once per month (or cholecalciferol, 15,000 IU/mo). Oral cholecalciferol at 1,000-2,000 IU/d can be used as an alternative maintenance dose.

5. Nutritional vitamin D supplements should be withheld if serum 25(OH)D level is >100 ng/mL or serum calcium level is >10.5 mg/dL.

CONCLUSIONS

Both calcidiol and calcitriol deficiency are common in patients with CKD and long-term dialysis patients. There is ample evidence to support the claim that extrarenal conversion of 25(OH)D to 1,25(OH)₂D has significant biological roles beyond those traditionally ascribed to vitamin D. However, clinical data that address nutritional vitamin D therapy in patients with CKD and long-term dialysis patients have been fo-
When the level is 8-week course of 50,000 IU/wk of ergocalciferol. If serum 25(OH)D level remains 50,000 U/wk for 8 weeks. If serum 25(OH)D level is reasonable to initiate therapy with ergocalciferol at the KDIGO and KDOQI guidelines, it will be reasonable to consider therapy in this scenario will have beneficial clinical effects, and further research is needed in this area.

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