Vitamin D Therapy in Chronic Kidney Disease and End Stage Renal Disease

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Summary
Vitamin D has garnered much research and debate about supplementation in recent years, not only as it pertains to patients with kidney disease but also to those in the general population. This review discusses observational and available clinical trial evidence about the effects of both calcitriol and vitamin D analogs (active) and ergocalciferol and cholecalciferol (nutritional) vitamin D in patients with CKD and ESRD.

Introduction
Vitamin D has garnered much research and debate about supplementation not only as it pertains to patients with kidney disease but also to the general population. Patients with kidney disease have reduced activity of the enzyme 1-α hydroxylase (CYP27B1) in the kidneys, which converts 25-hydroxyvitamin D (25(OH)D) to its more active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), and thus patients with kidney disease have traditionally been given vitamin D replacement with active, 1,25-dihydroxyvitamin D or a related analog. Although extrarenal 1-α hydroxylation has been appreciated for some time (1,2), the location and potential use of 1-α hydroxylation for autocrine and paracrine signaling has led nephrologists to consider replacing nutritional vitamin D, the inactive form, as well as active vitamin D in patients with kidney disease (Table 1). Interestingly, some vitamin D analogs, such as paricalcitol, actually lower 1,25(OH)2D levels, thus acting as vitamin D mimetics (3). This review outlines the available evidence for multiple outcomes associated with vitamin D in patients with kidney disease.

Vitamin D Physiology
Individuals obtain vitamin D either through consuming vitamin D–rich foods (oily fish, dairy products) or supplements, or through the skin’s exposure to ultraviolet B radiation producing vitamin D. This vitamin D, once it enters the body, is extracted by the liver and converted to 25-hydroxyvitamin D, which circulates in the blood stream and is used to evaluate an individual’s vitamin D nutritional status because of its relatively long t½ (2–3 weeks). The more active form of vitamin D, 1,25-dihydroxyvitamin D, has a t½ of only 8–12 hours and responds dynamically to changes in calcium and phosphate metabolism. 25(OH)D circulates in nanogram per milliliter concentrations, which are 1000-fold higher than concentrations of 1,25(OH)2D. Although 25(OH)D stimulates the vitamin D receptor (at 100- to 150-fold higher concentrations than 1,25(OH)2D in vitro (4,5), it is unclear whether it has effects in vivo.

Vitamin D and CKD: Metabolic Bone Disease
As kidney function worsens, low circulating 1,25-dihydroxyvitamin D levels, low calcium levels, and high serum phosphate levels lead to secondary hyperparathyroidism (SHPT). SHPT, identified by elevated parathyroid hormone (PTH) levels, is associated with both bone disease (renal osteodystrophy) and, in epidemiologic studies, poor outcomes in dialysis patients (6–8). Before the discovery of calcitriol, patients with ESRD were treated with high doses of nutritional vitamin D to treat SHPT (9). Unfortunately, most of the studies of its effects during that time are small and observational in nature. Once calcitriol was introduced and subjected to more rigorous, albeit small, randomized controlled trials, it quickly became the mainstay of therapy for SHPT (10–12). Two recent Cochrane reviews (13,14) confirm that in both dialysis and predialysis CKD patients (4 studies, 153 patients), calcitriol and vitamin D analogs decrease PTH (−196 pg/ml [95% CI, −298 to −94] in dialysis patients; −49 pg/ml [95% CI, −86 to −13] in predialysis patients) but increase serum phosphate and calcium levels. Not enough data exist from randomized clinical trials to draw conclusions about patient-level outcomes such as fractures, mortality, or need for dialysis in predialysis patients (13,14). Another meta-analysis of nutritional vitamin D compounds was recently performed and the authors found that in four randomized clinical trials (90 patients) including both dialysis and nondialysis CKD patients, PTH levels decreased significantly (−31.5 pg/ml [95% CI, −57 to −6.1]) (15). Similarly to the data about calcitriol and vitamin D analogs, there was no evidence regarding patient outcomes (15). Since the topic was last reviewed in the Clinical Journal of the American Society of Nephrology in 2009 (16), there have been several new published clinical trials of nutritional vitamin D in CKD, which are outlined in Table 2.
recently published, randomized, not-blinded study in 80 mostly white men showed that paricalcitol decreased PTH levels, whereas ergocalciferol did not (17). In summary, meta-analyses indicate that both nutritional and active vitamin D therapies have been shown to lower PTH levels, the primary indication for their use. The evidence is stronger, with larger, better designed, clinical trials for active vitamin D. Although the effect of vitamin D on PTH is clearly established, animal studies and observational studies in humans have suggested roles of vitamin D, both active and nutritional, in systems outside of bone and mineral metabolism. The remainder of this review focuses on these areas (Figure 1).

Effects of Vitamin D and Its Analogs in Animal Models

BP, Left Ventricular Hypertrophy, and Albuminuria

Complications of CKD in humans include hypertension, left ventricular hypertrophy and diastolic dysfunction, and albuminuria, and animal models suggest that vitamin D may play a role in these complications. One of the stronger pieces of evidence that vitamin D exerts an effect on the cardiovascular and renal systems comes from vitamin D receptor knockout mice. These mice develop elevated BP’s and left ventricular hypertrophy (18), which occurs due to a rise in renin consequent to loss of normal suppression of the renin-angiotensin system by vitamin D (19). In rats with spontaneous hypertension, treatment with vitamin D analogs ameliorates left ventricular hypertrophy and improves left ventricular diastolic measures (20). Active vitamin D, in various forms, decreases albuminuria in multiple animal models of kidney disease, including Heymann nephritis (21), murine MRL/l lupus nephritis (22), mercuric-chloride–induced nephritic syndrome (23), and subtotal nephrectomized rats (24). In the anti-Thy 1.1 model of GN, rats treated with 1,25(OH)2D3 had less albuminuria (25) and showed preserved slit-diaphragm protein morphology (26). Combination therapy with an angiotensin receptor blocker and a vitamin D analog abrogated the albuminuria in the streptozotocin-induced diabetic nephropathy model (27). Rats treated with 22-oxa-calcitriol, a vitamin D analog, had lower levels of TGF-β1 protein in the tubules and glomeruli compared with nontreated diseased rats (24,28). Thus, multiple animal models suggest a role for active vitamin D in cardiac structure and function, albuminuria, and kidney fibrosis.

Vascular Calcification and Infection

Vascular calcification and infection are other common complications of CKD in which vitamin D has been implicated. Interestingly, an early experimental model of atherosclerosis was the cholesterol- and vitamin D-fed rat, a model without superimposed kidney disease. These rats were given an extremely high dose of vitamin D2 (1.8 million U/kg) and developed aortic atherosclerosis (29). However, there is potentially an important difference in action depending on the dose of the vitamin D analog. For example, in a mouse model of kidney disease, low levels of vitamin D (paricalcitol or calcitriol) were protective against vascular calcification, whereas higher doses were associated with more calcification (30). Potentially, both lack of and too much vitamin D may lead to vascular calcification.

Vitamin D likely also plays a role in the innate immune response. Activation of the vitamin D receptor and the vitamin D 1-α hydroxylase gene leads to increased expression of cathelicidin, an antimicrobial peptide (31). Low levels of cathelicidin are associated with a higher risk of death from infectious disease in dialysis patients (32). In 60 participants without kidney disease, cathelicidin levels increased after vitamin D supplementation (33).

Observational Studies of Vitamin D

Low Vitamin D Levels in CKD and ESRD and Outcomes

Multiple observational studies have shown low levels of both 25(OH)D and 1,25(OH)2D in patients with CKD and ESRD (34,35). Many factors may account for low levels of 25(OH)D in kidney disease, including the loss of vitamin D binding protein in the urine (36), ineffective synthesis in the skin upon exposure to ultraviolet B radiation (37), and likely reduced nutritional intake and sun exposure.

Low 25(OH)D levels in patients with CKD and ESRD have been associated with a higher risk of all-cause mortality and a faster progression of kidney disease (34,38–40). In the general population, low 25(OH)D levels have also been associated with all-cause mortality, cardiovascular events, peripheral vascular disease, hypertension, congestive heart failure, and the later need for renal replacement therapy (41–46). Low 1,25(OH)2D levels have been associated with all-cause mortality (34,47). The studies of vitamin D levels are all potentially confounded by sicker patients having low vitamin D levels because of less sun exposure or poor nutrition. Therefore, randomized trials are required to test whether supplementation of vitamin D may affect outcomes.

Evaluation of Active Vitamin D Therapy and Outcomes

Multiple observational studies have shown an association between the use of active vitamin D therapy in patients on dialysis and with CKD and improved survival. These range from larger studies from databases of dialysis providers to smaller cohort studies (6,7,48–51). Active vitamin D therapy has also been associated with slower progression to ESRD (52). There are a few studies in the literature in which an association between activated vitamin D use and improved survival was not found (53,54). One of these studies showed a mortality benefit for vitamin D (combining both oral and intravenous vitamin D analogs) using traditional models and marginal structural models but not when using a more complicated modeling system called
<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Control Group</th>
<th>Randomized</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chandra et al. (67)</td>
<td>Double-blind, placebo-controlled, randomized controlled pilot study</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
<td>Among cholecalciferol-treated participants, serum 25(OH)D concentration increased on average from 17.3 ng/ml (95% CI, 11.8–25.2) at baseline to 49.4 ng/ml (95% CI, 33.9–72.0) at week 12. As-treated analysis indicated a trend toward lower PTH levels among cholecalciferol-treated participants ($P=0.07$)</td>
<td>Small study</td>
</tr>
<tr>
<td>Dogan et al. (66)</td>
<td>Randomized</td>
<td>40</td>
<td>Yes</td>
<td>Yes</td>
<td>Administration of depot oral cholecalciferol (300,000 IU vitamin D$_3$) resulted in a significant increase in calcidiol (6.8±3.5 to 17.8±21.4 ng/ml, $P&lt;0.001$), significant decrease in iPTH (368±274 to 279±179 pg/ml, $P&lt;0.001$). No statistically significant change in Ca, P, Ca × P, and urinary calcium creatinine rate was observed</td>
<td>Small study</td>
</tr>
<tr>
<td>Oksa et al. (68)</td>
<td>Randomized</td>
<td>87</td>
<td>No</td>
<td>Yes</td>
<td>Vitamin D insufficiency/deficiency in CKD significantly improved after the 12-mo cholecalciferol treatment, with more significant improvement with higher dose (20,000 IU/wk) being more effective and equally safe</td>
<td>Lack of a placebo control The inclusion of a subgroup of patients who received calcium carbonate for correction of metabolic acidosis is a potential confounder</td>
</tr>
<tr>
<td>Kovesdy et al. (17)</td>
<td>Randomized, not blinded</td>
<td>80</td>
<td>Active Randomized</td>
<td>80 CKD patients randomized to ergocalciferol versus paricalcitol. Paricalcitol group showed lower PTH levels than ergocalciferol group</td>
<td>Not blinded Differential initiation of phosphate binders in the two groups</td>
<td></td>
</tr>
</tbody>
</table>

95% CI, confidence interval; PTH, parathyroid hormone.
instrumental variable models (53). The other study did show an association with improved all-cause mortality but not with specific causes of mortality such as cardiovascular or infection (54), suggesting the possibility that perhaps all of these specific causes are influenced by vitamin D and thereby diluting the effect on any individual one. There are no published reports of associations between nutritional vitamin D supplementation and improved survival in kidney disease, and data are mixed in the general population (55,56).

Randomized Clinical Trials of Active Vitamin D Therapy in CKD

Albuminuria and BP

Several recent studies have highlighted the importance of vitamin D therapy in areas outside of traditional bone and mineral metabolism in humans. Several small, randomized clinical trials have evaluated the effect of active vitamin D therapy on albuminuria, a marker of kidney damage. A single-center study of 61 patients showed lower urine protein/creatinine ratios and lower PTH levels in patients randomized to paricalcitol compared with placebo (57). Another small single-center study of 24 patients randomized to two different doses of paricalcitol or placebo showed lower high-sensitivity C-reactive protein levels and lower rates of 24-hour albumin excretion in the paricalcitol group (58).

A large, placebo-controlled, double-blinded, randomized clinical trial of two different doses of paricalcitol in 281 participants with type 2 diabetes mellitus showed similar results (59). In this multicenter, multinational study, all patients had to have albuminuria and be taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at baseline. The study population in the trial had a mean age of 64 years, and 69% of participants were male, 72% were white, 14% were black, and the median urinary albumin excretion was approximately 700 mg per 24 hours. The results showed that there was a significant reduction in the urinary albumin/creatinine ratio in participants taking the 2-μg dose compared with placebo. This was associated with a lowering of estimated GFR (eGFR), as estimated from serum creatinine, which was also significant at the 1-μg dose. Twelve weeks after randomization, the eGFR was 2 ml/min per 1.73 m² lower in the participants receiving the 1-μg dose, whereas it was 4 ml/min per 1.73 m² lower in participants receiving the 2-μg dose. BP was also significantly lower in the participants randomized to the 2-μg dose by a mean of approximately 8 mmHg. Interestingly, a recent study showed that in a small group of patients with kidney disease, paricalcitol increased serum creatinine levels without affecting iothalamate GFR measurements (60). The multicenter paricalcitol study is important for several reasons. It shows a decrease in
albuminuria and eGFR in patients with type 2 diabetes with nephropathy in a nicely designed and executed randomized trial. It does not, however, answer the more important question of whether this decrease in albuminuria will translate to better clinical outcomes, such as less rapid progression to dialysis.

Other Outcomes
A small recent trial comparing doxercalciferol and cholecalciferol showed no difference in end-of-treatment PTH levels between active and nutritional vitamin D compounds (61). This study found no effect on BP or albuminuria. Another currently ongoing placebo-controlled randomized clinical trial is evaluating treatment of 227 stage 3 and 4 CKD patients with paricalcitol with change in left ventricular mass index as the primary outcome (62). This study, the PRIMO Study (NCT00497146), is also evaluating diastolic function and cardiovascular hospitalizations as secondary outcomes.

Interventional Studies of Nutritional Vitamin D in Patients with CKD and ESRD
The fact that the 1-α hydroxylase enzyme has been found in parts of the body outside the kidney suggests that there may be a role for nutritional vitamin D in patients with kidney disease. A recent study in hemodialysis patients showed that 1,25-dihydroxyvitamin D levels increased after supplementation with nutritional vitamin D, suggesting that even in ESRD there is enough extrarenal 1-α hydroxylase activity to influence serum levels (63). A cohort study of 158 hemodialysis patients who received cholecalciferol supplementation in a nonrandomized study showed higher 25(OH)D, 1,25-dihydroxyvitamin D, and albumin levels, while at the same time reducing serum calcium, PTH, brain natriuretic peptide, left ventricular mass index, and erythropoietin stimulating agent and active vitamin D doses (64). A study of seven hemodialysis patients who underwent cholecalciferol supplementation reported that after supplementation, there were lower levels of proinflammatory cytokines, IL-8, IL-6, and TNF and differences in circulating monocyte proteins (65). These studies are small and are not randomized clinical trials; however, their results suggest that nutritional vitamin D may be needed in patients with kidney disease. However, larger well designed trials are required.

Current Ongoing Studies of Nutritional Vitamin D
There are several current ongoing studies of nutritional vitamin D supplementation that are worth noting although their results are not yet available. One hundred and five dialysis patients, as part of the Dialysis Infection and Vitamin D in New England (DIVINE) study (NCT 00892099), are being randomized to high-dose ergocalciferol (50,000 IU/week), low-dose ergocalciferol (50,000 IU/week), or placebo for 12 weeks. Primary end points include cathelicidin, cytokine, and PTH levels over follow-up and the incidence of infections. Another randomized clinical trial is currently evaluating the effect of ergocalciferol supplementation versus placebo on albuminuria and 24 hour BP in patients with stage 3 and 4 CKD (NCT 01029002). The Vitamin D and

<p>| Table 3. Table of possible effects of vitamin D supplementation in patients with kidney disease |
|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nutritional or Active Vitamin D</th>
<th>Proposed Mechanism</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH suppression</td>
<td>A, maybe N</td>
<td>Direct suppression of parathyroid gland</td>
<td>A: RCT</td>
<td>13,14</td>
</tr>
<tr>
<td>Reduction of albuminuria</td>
<td>A, maybe N</td>
<td>Suppression of renin-angiotensin system</td>
<td>A: RCT</td>
<td>59</td>
</tr>
<tr>
<td>Reduced risk of infections</td>
<td>N</td>
<td>Increase in cathelicidin levels</td>
<td>Observational studies only</td>
<td>N: limited RCTs 61</td>
</tr>
<tr>
<td>Progression of kidney disease</td>
<td>A, maybe N</td>
<td>Suppression of renin-angiotensin system</td>
<td>A: Observational studies only</td>
<td>51,52</td>
</tr>
<tr>
<td>Cardiovascular effects (left ventricular hypertrophy and vascular calcification)</td>
<td>A</td>
<td>Suppression of renin-angiotensin system, possibly direct effects on myocytes</td>
<td>A: Observational studies only</td>
<td>32,33</td>
</tr>
<tr>
<td>Mortality</td>
<td>A</td>
<td>Likely multiple mechanisms</td>
<td>Observational studies only</td>
<td>6,7,48</td>
</tr>
<tr>
<td>PTH, parathyroid hormone; A, active; N, nutritional; RCT, randomized controlled trial.</td>
<td>362 Clinical Journal of the American Society of Nephrology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OmegA-3 trial (VITAL; NCT01169259) will test the role of 2000 IU/d of vitamin D and ω-3 fatty acids (in a 2 × 2 factorial design) in the primary prevention of cancer and cardiovascular disease among 20,000 men and women throughout the United States. A recent search of clinicaltrials.gov revealed over 1000 records of ongoing or completed clinical trials of vitamin D for various health outcomes.

Judging the Evidence and Unanswered Questions

Results from randomized clinical trials, conducted in a population similar to the patient and with clinically meaningful end points, comprise the gold standard for clinical decision making. Unfortunately, this level of evidence does not exist for vitamin D therapy in CKD. We know from clinical trials that both nutritional and active vitamin D decrease PTH levels, but we do not know whether that affects fracture rates or other adverse outcomes, including mortality. We know from clinical trials that paricalcitol decreases albuminuria, but we do not know if it decreases the risk of dialysis or progression of kidney disease. Without randomized clinical trials, causation cannot be inferred from observational designs. As other examples have shown, such as hormone therapy in women and statin use in dialysis patients, observational studies or even clinical trials in other populations may not inform the clinician of the correct treatment. Because well designed clinical trials are expensive, evidence from animal studies, observational studies, and small pilot randomized trials with surrogate outcomes are needed to evaluate which therapies have the most potential for success to be tested in definitive clinical trials. We have outlined above several ongoing clinical trials; however, even with the results of these studies, many questions remain unanswered. For example, do we need to measure 25(OH)D levels in all CKD patients, or can we replete knowing most are deficient? Can we combine nutritional and active vitamin D or does this put patients at increased risk?

Multiple observational studies suggest an important role of vitamin D in patients with CKD and ESRD and potentially in the general population. There are potentially different roles for nutritional and active vitamin D compounds (Table 3). Nutritional vitamin D may play more of a role in infections, whereas active vitamin D compounds may play more of a role in albuminuria and mortality. Both nutritional and active vitamin D eventually affect the same vitamin D receptor; however, nutritional vitamin D has to undergo additional activation in the body, potentially at sites distant from the kidney. Active vitamin D has been shown to decrease albuminuria, BP, and eGFR in patients with diabetic kidney disease. There are current ongoing studies to test these outcomes with nutritional vitamin D compounds as well. It is important to mention that there are very few data about combining therapy with both nutritional and active vitamin D compounds; thus, caution should be used in clinical practice because of worry about possible vitamin D intoxication, manifested by hypercalcemia and possibly vascular calcifications. Much further work is needed in this area.

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References


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