Vitamin D and Kidney Disease

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Abnormalities in vitamin D metabolism play a major role in the pathogenesis of secondary hyperparathyroidism in chronic kidney disease. The gradual and progressive decline in 1,25-dihydroxyvitamin D in the course of chronic kidney disease is the result of several mechanisms that limit the ability of the failing kidney to maintain the levels of 1,25-dihydroxyvitamin D despite increasing levels of parathyroid hormone. Recent observations have indicated that chronic kidney disease seems to be associated with a high incidence of nutritional vitamin D insufficiency or deficiency as manifested by decreased levels of 25-hydroxyvitamin D. This contributes to the inability to maintain the levels of 1,25-dihydroxyvitamin D; therefore, current practice guidelines suggest repleting vitamin D status by the administration of native vitamin D as a first step in the therapy of the abnormalities of bone and mineral metabolism in chronic kidney disease. The efficacy of this therapy is extremely variable, and active vitamin D sterols may be required, especially as kidney disease progresses. The importance of the abnormal vitamin D metabolism is being investigated vigorously in view of the observations that vitamin D may have important biologic actions in many tissues in addition to bone and parathyroid. Thus, observational data have suggested potential survival benefits of vitamin D sterol administration in this clinical setting, and experimental data have suggested a potential beneficial effect of vitamin D sterols on the progression of kidney disease. Further work is required to define the mechanisms involved and to examine the effects of vitamin D therapy on outcomes in randomized, controlled trials.

In recent years, it has been demonstrated that many tissues not only express the vitamin D receptor (VDR) but also may possess 1-hydroxylase and are therefore capable of the production of 1, 25-dihydroxyvitamin D, which may act locally. Such tissues include the prostate; the colon; the breast; macrophages; and cells of the vasculature, pancreas, and potentially other sites. The role of this extrarenal 1-hydroxylase, with the production of 1,25-dihydroxyvitamin D in these tissues, is not well understood, but a variety of in vitro studies indicate that this process may be involved in the regulation of cell growth and differentiation (1).

Mechanisms of Altered Vitamin D Metabolism in Kidney Disease

There seem to be several mechanisms involved in the decreased levels of 1,25-dihydroxyvitamin D that occur in the course of kidney disease (Figure 1). Thus, a decrease in renal mass will obviously limit the quantities of 1-hydroxylase that are available for production of the active vitamin D metabolite. A reduction in GFR may limit delivery of substrate to the 1-hydroxylase, which may also limit the ability of the kidney to produce 1,25-dihydroxyvitamin D. The importance of a declining GFR in limiting the ability of the kidney to produce 1 to
25-dihydroxyvitamin D was illustrated by the work of Nykaer et al. (2–6), who demonstrated that glomerular filtration of 25-hydroxyvitamin D, bound to vitamin D–binding protein, undergoes glomerular filtration and uptake into the proximal tubule cell by the receptor megalin and was the rate-limiting step in the delivery of 25-hydroxyvitamin D to the 1-α-hydroxylase enzyme. Accordingly, as GFR declines, there is a limitation of substrate delivery that can compromise the ability of the failing kidney to produce 1,25-dihydroxyvitamin D (7). This may be compounded by the decreased levels of 25-hydroxyvitamin D that seem to be common in patients with kidney disease (vide infra).

The recent discovery that fibroblast growth factor-23 (FGF-23), which increases in the course of kidney disease, can directly suppress 1-α-hydroxylase may be an additional contributing factor that limits the ability of the failing kidney to maintain levels of 1,25-dihydroxyvitamin D as kidney disease progresses. Shimada et al. (8) demonstrated that FGF-23 could decrease the levels of 1,25-dihydroxyvitamin D and decrease mRNA for 1-α-hydroxylase. Perwad et al. (9) also showed that FGF-23 induced a dosage-dependent decrease in 1-α-hydroxylase mRNA. In addition, the activity of 1-α-hydroxylase may be directly suppressed by phosphate retention and hyperphosphatemia (1). An additional factor that may be involved is the potential for N-terminally truncated PTH fragments or C-terminal PTH fragments to decrease activity of 1-α-hydroxylase (10).

**Vitamin D Deficiency in CKD**

Recent observations have demonstrated that kidney disease seems to be associated with a high incidence of vitamin D insufficiency or deficiency (11). Studies by Gonzalez et al. (12) demonstrated that 25-hydroxyvitamin D values are <30 ng/ml, believed to be the lower limit of normal, in the majority of patients with CKD. Patients who are severely proteinuric have the lowest values. These investigators have shown that virtually all of the secondary hyperparathyroidism that occurs in the course of CKD is associated with 25-hydroxyvitamin D values that are <30 ng/ml. It is interesting to note that in this patient group, there is a positive relationship between 25-hydroxyvitamin D levels and 1, 25-dihydroxyvitamin D levels, in contrast to what is seen in normal individuals. Thus, when 25-hydroxyvitamin D levels are increased by therapy, one would anticipate an increase in the levels in the 1,25-dihydroxyvitamin D. It is not clear whether this is a contribution of renal 1-α-hydroxylase or the 1-α-hydroxylase at extrarenal sites; however, because of the association of low levels of 25-hydroxyvitamin D with hyperparathyroidism in the course of CKD, it is recommended that in patients with CKD, if hyperparathyroidism is detected, then 25-hydroxyvitamin D should be measured, and if found to be <30 ng/ml, then the initial step in the therapy should be to try to correct this abnormality, as the first step in the control of hyperparathyroidism.

**Effects of Therapy with Ergocalciferol**

Zisman et al. (13) evaluated the current therapeutic guidelines to raise 25-hydroxyvitamin D by the administration of ergocalciferol. These investigators showed that in 52 patients with stages 3 and 4 CKD, the concentration of 25-hydroxyvitamin D could be raised slightly above 30 ng/ml, and such therapy was associated with a relatively small decrease in the levels of intact PTH, only in the patients with stage 3 CKD and not in those with stage 4 CKD. Chandra et al. (14) evaluated cholecalciferol therapy, 50,000 U/wk for 12 wk, in a randomized, controlled trial of stages 3 and 4 CKD and successfully raised the geometric mean value for 25-hydroxyvitamin D to almost 50 ng/ml and showed a 31% decrease in PTH in the treated group compared with 7% decrease in the placebo group, but this was NS because of high variability in PTH values.

Studies by Al-Aly et al. (15) were similar in design to the studies of Zisman et al. (13), although the conclusions are somewhat different and may shed light on the results of Chandra et al. (14). These investigators showed that only approximately 50% of patients with CKD successfully incremented the levels of 25-hydroxyvitamin D in response to the standard treatment regimens, whereas the remainder did not increase the levels of 25-hydroxyvitamin D. It is interesting that in patients who did increase their levels of 25-hydroxyvitamin D, PTH levels declined, whereas PTH levels did not change substantially in patients who did not respond. Similar findings were also demonstrated in patients with stage 4 CKD. Accordingly, additional studies need to be performed to understand the reasons that 25-hydroxyvitamin D levels were not successfully incremented in half of the patients, to assess the efficacy of this maneuver on the control of hyperparathyroidism.

This issue assumes particular importance in light of the observations that the administration of active vitamin D therapy to patients who are on dialysis seems to be associated with a survival advantage, compared with patients who did not receive any vitamin D (16). These observations are confirmed by other investigators, including Young et al. (17), using the Dialysis Outcomes and Practice Patterns Study (DOPPS) database,
and Kalantar-Zadeh et al. (18) in a different cohort of patients, raising the need to understand the mechanisms involved in this apparent survival benefit associated with vitamin D therapy. In these studies, it seems that this apparent survival benefit is seen regardless of calcium, phosphorus, or the levels of PTH, suggesting that this may be an effect of vitamin D that is independent of the effects of vitamin D on bone and mineral metabolism. These observations have also been further extended to vitamin D analogs; the analog paricalcitol has been shown to have an improved survival advantage over the native vitamin D sterol calcitriol (19). Similarly, 1-alpha-hydroxyvitamin D$_3$ has also been associated with an apparent improved survival advantage over the native hormone calcitriol (20). Again, in these studies, the apparent survival benefit seems to be independent of levels of calcium, phosphorus, or PTH. Accordingly, it seems important to understand the potential mechanisms involved in this apparent survival benefit, with the objective that this can be potentially exploited to improve survival in this patient group.

London et al. (21) evaluated 52 patients who were on hemodialysis in a cross-sectional study for possible relationships of aortic stiffness, brachial arterial distensibility, and arterial calcification scores with 25(OH)D$_3$ and 1,25(OH)$_2$D$_3$ serum levels. These investigators noted that these values were negatively correlated with aortic pulse wave velocity and positively correlated with brachial arterial distensibility and flow-mediated dilation. Whether vitamin D supplementation will improve arteriosclerosis and endothelial dysfunction in patients who are on hemodialysis needs to be further evaluated in the future (21).

Because there seems to be only a single VDR, it is difficult to understand how vitamin D analogs may differ from the effect of the native hormone, but this indeed seems to be the case. In studies in vitro in vascular smooth muscle cells, calcitriol seems to be a growth factor for vascular smooth muscle cells, whereas the analog, paricalcitol, is not (22). Furthermore, in studies in experimental animals in vivo, vitamin D sterols seem to have a different effect on vascular calcification, in that 1-alpha-hydroxyvitamin D$_3$ or calcitriol seems to be associated with greater vascular calcification than is seen with paricalcitol, despite equivalent suppression of PTH in these animal models (23). Similar studies have been reported by Wu-Wong et al. (24,25), and other investigators have shown similar results in studies of calcitriol, compared with 22-oxacalcitriol (26). Further studies are clearly needed to understand the potential mechanisms involved for these differential effects.

The pleiotropic effects of vitamin D beyond the control of parathyroid function or mineral metabolism may extend to other potential areas in the course of CKD. Thus, in the course of clinical studies with oral paricalcitol for control of hyperparathyroidism in CKD, it was noted that patients who received paricalcitol seemed to have a reduction in proteinuria, even patients who were treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (27). In those studies, Agarwal et al. (27) demonstrated that the antiproteinuric effect of oral paricalcitol in CKD was shown by a reduction in proteinuria in 29 (51%) of 57 in the paricalcitol group compared with 15 (25%) of 61 in the placebo group with a $P = 0.004$. This was regardless of age, gender, race, diabetes, hypertension, or use of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors.

These observations raise the possibility or the consideration that paricalcitol therapy may be associated with or may have the potential to alter the progression of CKD. Some evidence exists to support this possibility. Thus, whereas the role of the renin-angiotensin system (RAS) has been well described in the progression of kidney disease, the vitamin D system has been shown to be involved in the regulation of the RAS by Li et al. (28). In experimental circumstances, there is evidence that vitamin D therapy may favorably affect the progression of CKD. Thus, there are data to show that glomerulosclerosis may be decreased in a model of five-sixths nephrectomy (29). The involvement of the VDR in the suppression of the RAS and the reduction in glomerular growth, cell differentiation, and fibrosis is potentially crucial in the mechanism of CKD progression.

Similar effects have also been shown in models of glomerulonephritis, and in additional studies, effects on the widely known factors that have been identified to affect the progression of kidney disease, such as podocyte hypertrophy (30), expression of TGF-$eta$ (31,32), expression of monocyte chemoattractant protein-1 (33,34), and the invasion of the remnant kidneys with macrophage-like cells, all have been shown to be potentially modified by vitamin D therapy, such that there is potential for this to affect the progression of kidney disease (35). In addition, Zhang et al. (36) showed that diabetic VDR knockout mice developed more severe albuminuria and glomerulosclerosis and expressed more fibronectin and less nephrin compared with diabetic wild-type animals. In vitro, 1,25-dihydroxyvitamin D inhibited glucose-induced fibronectin production in mesangial cells and increased nephrin in podocytes. Thus, vitamin D has the potential to have a favorable impact in diabetic nephropathy. All of these experimental observations need to be addressed and tested in patients, and studies are in progress or in development to test this idea directly.

Vitamin D may also affect the myocardium directly and play a role in the regulation of myocyte hypertrophy (37). Bodyk et al. (38) showed that paricalcitol attenuates left ventricular abnormalities in Dahl salt-sensitive hypertensive rats. Thus, it is interesting to speculate that such effects of vitamin D on the RAS or on the heart may potentially have an impact on cardiovascular events that are a common cause of death in this patient group.

**Recommendations for Vitamin D Therapy in the Course of CKD**

A reasonable approach to the therapy of disorders of bone and mineral metabolism in CKD, on the basis of current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and clinical and experimental data, are proposed in Figure 2. Future guidelines may modify this approach as they become available and additional data are obtained, such as the forthcoming Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Disturbances in bone and mineral metabolism should be
26,27-hexafluorocalcitriol (46). 19-Nor-1,25-dihydroxyvitamin D2, respectively. Vitamin D analogs are the active calciferol (vitamin D3) with regard to the degree of response of the vitamin D prohormones 1-25(OH)2D3 and 1-25(OH)2D2 (44), 22-oxacalcitriol (45), and paricalcitol (43). In advanced kidney disease, the use of active vitamin D sterols is extremely effective in the control of hyperparathyroidism (Table 1). The vitamin D prohormones 1-α-hydroxyvitamin D3 and 1-α-hydroxyvitamin D2 undergo 25-hydroxylation in the liver and become 1 to 25-dihydroxyvitamin D3 and 1 to 25-dihydroxyvitamin D2, respectively. Vitamin D analogs are the active vitamin D molecules with side chain modification or A ring alterations that have been introduced with a goal of suppression of PTH while minimizing the effects on calcium and phosphorus levels. Three such analogs have been introduced: 19-nor-1,25-dihydroxyvitamin D2 (44), 22-oxacalcitriol (45), and 26,27-hexafluorocalcitriol (46). 19-Nor-1,25-dihydroxyvitamin D2 is widely used in the United States and has been effective with somewhat lesser toxicity than the native sterol calcitriol (47). The oral form can be used in stages 3 and 4 CKD (43). There are no comparative studies of the different vitamin D analogs with regard to safety and efficacy in patients with CKD.

Further studies are required regarding the importance of therapy with vitamin D sterols in the course of CKD in view of recent observations by Wolf et al. (48). These investigators examined the correlation of vitamin D levels and early mortality in a retrospective cohort cross-sectional analysis of 825 incident hemodialysis population. The team measured the blood level of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D at baseline, and 90-d mortality was evaluated. A total of 78% of the patient population was vitamin D deficient, and 18% were severely deficient, and low levels of 25-hydroxyvitamin D were associated with increased mortality (48). Intervention with active vitamin D seemed to be associated with improved outcome. These important results will need confirmation and extension by randomized, placebo-controlled trials, and additional studies will be needed to evaluate the effects of vitamin D sterols on the progression of kidney disease.

Table 1. Vitamin D sterols used in chronic kidney disease

<table>
<thead>
<tr>
<th>Native vitamin D</th>
<th>Ergocalciferol</th>
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<tbody>
<tr>
<td>vitamin D2</td>
<td>Cholecalciferol</td>
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<tr>
<td>vitamin D3</td>
<td></td>
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Vitamin D prohormones

| 1-α-(OH) D3       | Alfacalcidol |
| 1-α-(OH) D2       | Doxercalciferol |

Active vitamin D sterols

| 1-α-25-(OH)3 D3   | Calcitriol |
| 22-oxa-1, 25(OH)2 D3 | Maxicalcitol |
| 1,25(OH)2-26, 27-F6-D3 | Falecalcitriol |
| 19-Nor-1, 25(OH)2 D2 | Paricalcitol |

Dietary restriction of phosphorus may be used in early CKD to assist in the control of the developing hyperparathyroidism, although protein restriction should be modest to avoid malnutrition. Other measures that have been shown to be successful include calcium supplementation and the use of phosphate binders and the use of vitamin D sterols such as calcitriol (40), the vitamin D prohormones alfacalcidol (41) and doxercalciferol (42), and the vitamin D analog paricalcitol (43). In advanced kidney disease, the use of active vitamin D sterols is extremely effective in the control of hyperparathyroidism (Table 1). The vitamin D prohormones 1-α-hydroxyvitamin D3 and 1-α-hydroxyvitamin D2 undergo 25-hydroxylation in the liver and become 1 to 25-dihydroxyvitamin D3 and 1 to 25-dihydroxyvitamin D2, respectively. Vitamin D analogs are the active vitamin D molecules with side chain modification or A ring alterations that have been introduced with a goal of suppression of PTH while minimizing the effects on calcium and phosphorus levels. Three such analogs have been introduced: 19-nor-1,25-dihydroxyvitamin D2 (44), 22-oxacalcitriol (45), and 26,27-hexafluorocalcitriol (46). 19-Nor-1,25-dihydroxyvitamin D2 is widely used in the United States and has been effective with somewhat lesser toxicity than the native sterol calcitriol (47). The oral form can be used in stages 3 and 4 CKD (43). There are no comparative studies of the different vitamin D analogs with regard to safety and efficacy in patients with CKD.

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Conclusions

In-depth research in the past two decades has uncovered many of the potential mechanisms in which vitamin D is involved in the initiation and maintenance of the disturbances of bone and mineral metabolism in the CKD population. This has been reproduced in bench and bedside clinical observations. The currently available therapeutic strategies for vitamin D deficiency are important beyond the management and control of the complications of disturbed mineral metabolism. Further clinical research is needed to answer questions including such issues as the optimal time to screen for vitamin D deficiency irrespective of PTH levels; the effects of treatment of vitamin D deficiency and insufficiency, perhaps irrespective of PTH levels; potential differences between vitamin D2 and D3 sterols; and studies to define the optimal dosage, duration, goals, and outcomes of treatment of vitamin D deficiency.

Disclosures

None.
References


29. Schwarz U, Amann K, Orth SR, Simonaviciene A, Wessels S, Ritz E: Effect of 1,25 (OH)2 vitamin D3 on glomerulo-


