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Conventional thinking is that vitamin D therapy in end stage kidney disease (ESKD) is primarily for the management of secondary hyperparathyroidism. The relatively recent appreciation of the high prevalence of vitamin D deficiency and its potential associated comorbidities has resulted in a paradigm shift such that hyperparathyroidism is no longer the sole indication for the initiation of vitamin D treatment. In addition to the classic use of an active vitamin D compound, referred to as a vitamin D receptor activator (VDRA), therapy may now also involve repletion of 25 hydroxycholecalciferol (25-D). The K/DOQI guidelines recommend initiation of VDRA therapy in ESKD when the serum levels of intact PTH are greater than 300 pg/ml (1). In CKD stages 3 and 4, the recommendation is to first correct the 25-D deficiency and then to initiate VDRA if the PTH is greater that 70 pg/ml or 110 pg/ml, for CKD stages 3 and 4, respectively (1). Whether any type of vitamin D therapy is beneficial in CKD has created some controversy; in fact, a meta-analysis by Palmer et al. suggested that there was no benefit to vitamin therapy in patients with CKD (vide infra) (2).

This view of vitamin D therapy is rather narrow minded and ignores much data supporting an independent association of 25-D deficiency and various diseases in the general population (3) as well as an association with increased mortality in patients with ESKD (4). Furthermore, the administration of VDRAs in ESKD patients is associated with a survival advantage (5–8). In addition to the clinical observations, there is also a strong body of experimental evidence supporting nonclassical benefits of VDR activation. In reviewing these data, it is our opinion that the majority of CKD patients, including those with ESKD, would benefit from repletion of both 25-D and some clinically relevant dosage of a VDRA, independent of their effects on bone mineral metabolism.

VDRAs bind to the VDR to influence gene activation in not only the gut and parathyroid glands but numerous other tissues including the kidney, cardiac, and skeletal muscles, and pancreatic islet cells, to name a few (9–11). The absence of VDR activation results in high renin states with hypertension and cardiac hypertrophy in the VDR-null mouse (12). Similarly, such animals have reduced glucose-induced insulin secretion (13). VDR activation, in vitro, inhibits colon and prostate cancer cell lines, as well as leukemic cells (14,15). Clinical observational correlates include an association of both 25-D and 1,25 dihydroxycholecalciferol (1,25-D) deficiencies with hypertension, Type 1 diabetes, and colon and prostate cancers (16–19). In ESKD, both 25-D and 1,25-D deficiencies have been associated with arteriosclerosis and endothelial dysfunction (20).

There remains some controversy regarding the nonclassical benefits of activated vitamin D. High doses of activated vitamin D in animal studies increase vascular calcification of the aorta, carotid, hepatic, mesentery, renal, and femoral arteries (21). It is also recognized that VDRAs can cause hyperphosphatemia, an independent

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predictor of mortality in patients with ESKD. However, a recent study by Matthew et al. addresses this controversy (22). Utilizing a CKD stimulated atherosclerotic mouse model, they demonstrated a dose dependent response in aortic calcification with calcitriol and paricalcitol (22). At lower protective doses, VDR activation reduced aortic osteoblastic gene expression and hence vascular calcification. At higher doses, this effect was reversed with stimulation of aortic calcification.

The clinical evidence for the nonclassical benefits of VDRAs comes from a number of observational studies showing the association between increased survival and the administration of VDRAs in ESKD patients. Teng et al. first demonstrated in over 67,000 hemodialysis patients that patients on paricalcitol had a significant survival advantage as compared with patients receiving calcitriol (6). A subsequent study demonstrated a 20% survival advantage in patients receiving any parenteral VDRA compared with patients not receiving any form of vitamin D (5). These results were independent of parameters of bone mineral metabolism, including PTH, calcium, and phosphorous. Consistent with these studies, the observational data in cohorts of hemodialysis patients continue to support the survival benefit for use of VDRA as compared with no use of vitamin D.

The mortality benefit of 25-hydroxy vitamin D repletion with cholecalciferol or ergocalciferol in ESKD is lacking. However, its repletion is justified based on evidence of local 1-α hydroxylase activity in nonrenal target tissues. This indirectly may serve to amplify the nonclassical effects of VDR activation. Nutritional vitamin D repletion has been shown to lower PTH levels CKD patients and is relatively low in cost with an absence of toxicity. In the absence of appropriate controlled studies, it is our opinion that these data suggest that all ESKD patients should have 25-D levels measured and repleted if indicated.

However, as previously mentioned, the meta-analysis by Palmer et al. provides an opposing viewpoint for the use of vitamin D therapy in patients with CKD (2). Synthesizing 76 trials, the authors suggest that vitamin D compounds do not reduce the risk of death or vascular calcification, and that calcitriol, when compared with placebo, increased the risks of hypercalcemia and hyperphosphatemia while not consistently reducing PTH levels. Other VDRAs were associated with hypercalcemia (but not hyperphosphatemia) and also did not consistently reduce PTH. The authors conclude that vitamin D treatment for CKD patients remains of uncertain benefit.

Unfortunately this analysis excluded two notable studies. In one, a 220-patient, 24-week, placebo-controlled randomized trial, paricalcitol suppressed PTH by an average of 42%, and 90% of patients achieved at least a 30% suppression of PTH (23). In the second, a 266-patient, 32-week randomized controlled trial of calcitriol versus paricalcitol, PTH was suppressed by greater than 50% in 80% and 90% of patients, respectively (24). Instead, the authors included studies from the 1980s where PTH suppression was not the primary endpoint. For adverse outcomes such as hypercalcemia, the results were driven by a single study, which considered elevated calcium as acceptable and possibly necessary. Numerous placebo controlled studies demonstrated that the newer VDRAs do not result in significant hypercalcemia or hyperphosphatemia when compared with placebo. Thus, the conclusion that vitamin D is not useful in CKD cannot be ascertained from this study.

In summary, a number of trials provide evidence for the benefits of vitamin D supplementation in CKD for vitamin D deficiency. In stage 3 CKD it appears that vitamin D may have an effect in decreasing PTH (25). In ESKD, there are scarce data concerning the role of vitamin D on patient outcome. However, the use of selective VDRAs can reduce PTH without significantly affecting calcium and phosphate balance; they are also associated with decreased mortality. Adequately powered randomized controlled trials with direct head-to-head comparisons of vitamin D compounds are required to determine the impact on patient outcomes.

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