Editorial

Is Nutritional Vitamin D Supplementation Beneficial in Dialysis Patients?

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CKD leads to progressive derangement of vitamin D metabolism. Renal synthesis of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) is reduced, due to decreased activity of 1α-hydroxylase (CYP27B1), likely caused by the counter-regulatory effects of increasing levels of fibroblast growth factor-23 (FGF-23) (1,2). These changes cause widespread vitamin D endocrine dysfunction, and contribute to the development of secondary hyperparathyroidism (SHPT) and other abnormalities of CKD–mineral and bone disorder (CKD-MBD). The accepted treatment paradigm in CKD has focused on the administration of calcitriol or other active vitamin D analogs in order to treat an elevated parathyroid hormone (PTH) level. As a consequence, the measurement and treatment of vitamin D deficiency in CKD, as defined by low serum 25-hydroxyvitamin D (25[OH]D) levels, has largely been neglected.

The use of active vitamin D in CKD and dialysis patients has been supported by many large cohort studies reporting an associated reduction in mortality with this treatment (3,4). However, other studies have shown conflicting results, in particular data from the Dialysis Outcomes and Practice Patterns Study, which reported no mortality benefit after adequate adjustment for confounders (5). In addition, the advantages of calcitriol appear to decrease at higher doses, perhaps in part explained by associated increases in phosphorus and FGF-23 levels, which have also been independently associated with adverse outcomes in patients with CKD (6,7).

Low serum 25(OH)D levels are common in dialysis cohorts, with a reported prevalence approaching 80% in some studies (8). This is a reflection of the accumulated comorbidities in these patients as well as factors such as decreased sun exposure, reduced cutaneous synthesis, dietary restrictions, and urinary losses (9). Numerous studies have linked low serum 25(OH)D levels to morbidity and mortality in CKD cohorts (8,10). One meta-analysis reported increased mortality in dialysis and nondialysis patients with CKD with a relative risk of 0.86 per 10-ng/ml increase in 25(OH)D levels (11). Observational studies also suggest that PTH levels are inversely associated with 25(OH)D levels, even after adjustment for renal function (12). Coupled with increasing evidence of preserved autocrine/paracrine 1,25(OH)$_2$D synthetic pathways in CKD (13), these studies have reinvigorated interest in the treatment of low serum 25(OH)D levels in CKD with nutritional vitamin D compounds.

In a number of meta-analyses in dialysis and nondialysis CKD, nutritional vitamin D replacement was reported to successfully increment serum 25(OH)D levels and significantly reduce PTH, without clinically significant hypercalcemia or hyperphosphatemia (14,15). Despite abundant observational evidence supporting the use of nutritional vitamin D in dialysis cohorts, a clear causal relationship with outcomes has not been established. Both the variable practice patterns across the world and somewhat conservative guideline recommendations reflect not only the current ambivalence of the renal community, but also the lack of adequate prospective clinical trials. There are also ongoing concerns about the safety and effectiveness of nutritional vitamin D compounds in dialysis cohorts, especially when combined with active vitamin D compounds.

In this issue of *CJASN*, Bhan *et al.* report on the Dialysis Infection and Vitamin D in New England (DIVINE) study, a prospective multicenter, double-blinded, randomized placebo-controlled trial that compared two dosing regimens of ergocalciferol with placebo in a hemodialysis cohort (16). The aims of DIVINE were to assess the efficacy and safety of short-term nutritional vitamin D replacement, as reflected by changes in serum 25(OH)D levels and common markers of CKD-MBD. A total of 105 hemodialysis patients, within 2 months of starting dialysis, were enrolled and prescribed either 50,000 IU of oral ergocalciferol weekly ($n=36$) or monthly ($n=33$), or placebo ($n=36$). The primary end point was vitamin D sufficiency, defined as a serum 25(OH)D level of $\geq$32 ng/ml (80 nmol/L) at the end of the 12-week treatment period. At 12 weeks, vitamin D sufficiency was achieved in 91% (weekly dosing), 66% (monthly dosing), and 35% (placebo). The mean levels were also significantly higher in the weekly (49.8 ng/ml) and monthly (38.3 ng/ml) arms compared with placebo (27.3 ng/ml). Approximately 50% of patients in each arm received active vitamin D, and treatment was associated with a trend toward higher PTH values, likely as a result of bias due to treatment requirement. When the groups were reanalyzed based on the use of active vitamin D, no effect of ergocalciferol on PTH was observed. There was no significant difference between calcium and phosphate levels between the groups during the study

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period. However, in those patients not receiving active vitamin D therapy, the calcium level at 12 weeks was significantly higher in the weekly arm compared with placebo.

Interestingly, for a dialysis cohort, the mean 25(OH)D levels at baseline were somewhat higher than expected (>20 ng/ml) in all of the study arms. There was no difference in 1,25(OH)$_2$D levels between the groups at 12 weeks, nor within each group compared with baseline. The significant increase in serum FGF-23 at 12 weeks compared with baseline in all three groups was also unexpected, given the short study duration and absence of a significant change in phosphorus or 1,25(OH)$_2$D levels. Adverse outcomes were comparable across the three arms. The interpretation of secondary analyses including mortality was limited by the study size.

Bhan *et al.* should be commended on the DIVINE trial because it addresses many important questions in this field. First, the randomized controlled study design (the largest trial assessing nutritional vitamin D in dialysis to date) obviates much of the confounding associated with observational studies. Second, graded vitamin D replacement regimens and the concurrent use of active vitamin D allows for a realistic representation of real-world clinical practice. Third, it demonstrates the short-term safety of even high-dose ergocalciferol in dialysis patients with regard to hypercalcemia and others markers of CKD-MBD. Finally, the results of this trial enable more informed clinical decision-making and provide invaluable information for designing much needed future clinical studies.

The appropriately termed "pleiotropic" effects of vitamin D suggest that sufficiency remains difficult to define and measure. Total 25(OH)D levels are currently accepted as being the most reliable marker of long-term vitamin D status. However, it may be that the free or bioavailable fraction of vitamin D provides a more accurate reflection of the vitamin D that is being utilized for cellular processes. This measurement has shown stronger correlations with certain clinical outcomes than serum 25(OH)D levels in early studies, and may better account for the genetic polymorphisms that influence vitamin D binding protein and total 25(OH)D levels (17,18). Similarly, new-generation 1,25(OH)$_2$D assays may allow for more reliable measurements and provide an alternative approach to determining the effects of nutritional and active vitamin D therapies. The relationship between total 25(OH)D and 1,25(OH)$_2$D levels is generally more aligned in advanced CKD; therefore, the lack of increment in the 1,25(OH)$_2$D levels in this study was surprising. This was attributed to a lack of endocrine vitamin D synthesis; however, small studies in anephric patients suggest that there is compensatory activity of the paracrine/autocrine system, and vitamin D supplementation to supra-physiologic 25(OH)D levels can increment 1,25(OH)$_2$D levels (19).

The increasingly broad "optimal" recommended PTH reference range for hemodialysis patients is an acknowledgment that PTH remains a poor indicator of the underlying bone pathology. The temptation to use PTH as a surrogate marker of vitamin D sufficiency is equally problematic. The lack of effect of ergocalciferol on PTH in this cohort even after stratification by active vitamin D use is surprising. The possible use of cinacalcet (which was not reported) and the relatively high baseline 25(OH)D levels may in part explain these findings. Therefore, concluding that the potential effects of nutritional vitamin D on PTH suppression are not present in patients reaching ESRD may be a little premature. The concomitant and uniform rise in serum FGF-23 levels again highlights that we have a poor understanding of the changes occurring in bone in advanced CKD. This also raises concerns about the long-term safety of high-dose vitamin D administration, especially in light of general population data that suggest an increased fracture risk (20). Finally, it is possible that paracrine and autocrine 1,25(OH)$_2$D synthesis is not directly regulated by only PTH and FGF-23, but also by locally derived mediators. This again raises the question as to how accurately systemic measurement of 25(OH)D or 1,25(OH)$_2$D reflects local synthetic activity.

How does this study affect clinical practice? A single study is limited to its target population and the number of interventions and outcomes, which may limit generalizability. However, the compelling evidence demonstrated by the DIVINE trial, in terms of safety and efficacy of short-term ergocalciferol, should pave the way for larger clinical trials and a gradual shift in clinical practice. More data are needed about the long-term safety of vitamin D in CKD, especially high-dose regimens, and studies should be compared with more physiologic daily replacement protocols. The optimal serum 25(OH)D target level in CKD remains unknown, and despite recent attempts at uniformity, is still variably defined. It may be that free or bioavailable vitamin D levels may emerge as better markers of optimal vitamin D status. Finally, the complexity of CKD-MBD requires a multifaceted approach. The likely beneficial role of nutritional vitamin D in these patients will see its use in conjunction with active vitamin D compounds. Benefits are likely to extend beyond bone and mineral metabolism, and these require further study in larger clinical trials. The results from the DIVINE trial, however, offer one more reason for why nutritional vitamin D compounds should be more broadly considered in hemodialysis patients.

Disclosures
None.

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