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Editorial

Vitamin D Therapy in Kidney Disease: More Vitamin D Is Necessary

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The question of whether patients with kidney failure receiving dialysis should receive nutritional vitamin D (vitamin D_3 or vitamin D_2) therapy has been debated hotly over the past decade. Patients with kidney failure have a high prevalence of vitamin D insufficiency and deficiency, that is, serum 25-hydroxyvitamin D (25[OH]D) levels of 20 to 29 and <20 ng/mL, respectively. These serum 25(OH)D concentrations have been associated with elevated plasma parathyroid hormone (PTH) concentrations, decreased bone mineral density,[1] and increased mortality.[2,3] Multiple factors contribute to low vitamin D status in patients with kidney failure, including increased catabolism of circulating 25(OH)D, reduced conversion of circulating 25(OH)D to the more active vitamin D metabolite (1,25-dihydroxyvitamin D [$1,25(OH)_2D$]), urinary losses of vitamin D–binding protein, decreased dietary intake of vitamin D–enriched foods (eg, dairy products due to dietary restriction of phosphorus), and decreased outdoor activity. Low vitamin D status leads to secondary hyperparathyroidism, which when untreated can result in parathyroid hyperplasia and the development of tertiary hyperparathyroidism. When tertiary hyperparathyroidism develops, parathyroidectomy or therapy with calcimimetic drugs is required to manage hypercalcemia.

The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative)[4] and KDIGO (Kidney Disease: Improving Global Outcomes)[5] guidelines recognize that vitamin D insufficiency and deficiency should be avoided in patients with dialysis-dependent kidney failure; both recommend that vitamin D status be assessed by measuring serum 25(OH)D and that levels be repleted if vitamin D is found to be insufficient or deficient. The NKF-KDOQI guideline recommends 3 different vitamin D dosing regimens using ergocalciferol (vitamin D_2) for patients with chronic kidney disease (CKD) stages 3 to 4, ranging from 50,000 IU weekly to 50,000 IU monthly for 6 months based on serum 25(OH)D concentrations, with the aim of reaching a target serum 25(OH)D level > 30 ng/mL. (The guideline does not provide vitamin D dosing recommendations for CKD stage 5.) Given the long circulating half-life of 25(OH)D in blood, vitamin D repletion therapy can be administered at weekly or even monthly intervals.[6] However, targeted repletion protocols have not been defined.

In this issue of *AJKD*, Massart et al[7] report a 2-part study examining 2 protocols of vitamin D repletion in 55 hemodialysis patients. The objectives of the study, conducted at a pair of sites in Belgium, were bipartite: to test the safety and efficacy of a cholecalciferol (vitamin D_3) repletion protocol in hemodialysis patients and evaluate the suitability of basing a cholecalciferol dosing regimen on the NKF-KDOQI guideline, which was designed for treatment using ergocalciferol. In the first part of the study, Massart et al[7] randomly assigned participants to either cholecalciferol, 25,000 IU, or a matching placebo once weekly for 13 weeks. The second part of their study was open label; all participants received cholecalciferol therapy for 26 weeks according to the NKF-KDOQI guideline dosing regimen (serum 25[OH]D was measured at the halfway point and the cholecalciferol dose was adjusted if necessary).

In the randomized controlled trial portion of the study, Massart et al[7] demonstrated that a weekly bolus dose of cholecalciferol, 25,000 IU, for 13 weeks effectively increased serum 25(OH)D concentrations to >20 ng/mL in >95% of participants. However, only 61.5% reached the NKF-KDOQI target of 30 ng/mL.[7] Furthermore, participants who received cholecalciferol had significantly improved serum $1,25(OH)_2D$ concentrations, with >50% obtaining normal values (compared with only ~10% in the control group). Unfortunately, there was no benefit of cholecalciferol therapy on plasma PTH concentrations. Improvement in serum 25(OH)D levels was achieved without increases in serum calcium or phosphorus concentrations or aortic calcification scores. Therefore, the authors demonstrated that a weekly cholecalciferol regimen could safely and effectively improve vitamin D status in hemodialysis patients, though the dose was not sufficient for all patients to reach the NKF-KDOQI target.

The open-label portion of the study demonstrated that dosing cholecalciferol in accordance with the NKF-KDOQI guideline (the regimen is shown in the first figure in Massart et al[7]) increased serum 25(OH)D concentrations; however, only ~40% of patients

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Table 1. Selected Oral Cholecalciferol Pulse Dosing Studies in Patients With Kidney Failure Requiring Hemodialysis

Study	No. Randomly Assigned to Vitamin D_3	Equivalent Vitamin D_3 Dose (IU/wk)	Duration (wk)	Total Dose (IU)	Baseline Serum 25(OH)D (ng/mL)	Final Serum 25(OH)D (ng/mL)	Vitamin D Sufficient (%)
Armas et al[8] (2012)	20	10,333	15	154,995	13.3	36.9	NR
Delanaye et al[9] (2013)	16	12,500	52	650,000	12	33	75
Tokmak et al[10] (2008)	64	20,000	36	720,000	6.6	31.8	57
Jean et al[11] (2009)	107	25,000	64	1,600,000	12.8	42.3	91
Massart et al[7] (2014)	26	25,000	13	325,000	17.1	35.2	61.5
Marckmann et al[12] (2012)	13	40,000	8	320,000	8.3	54	100
Wasse et al[13] (2012)	25	200,000	3	600,000	14.3	52.4	91

Note: Mean values reported except for Armas et al[8] and Delanaye et al,[9] which reported median values.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; NR, not reported.

reached the NKF-KDOQI target. Because >60% of patients in the randomized controlled trial stage of the study reached the NKF-KDOQI target, Massart et al[7] deemed the 25,000-IU/wk regimen to be more effective in correcting vitamin D insufficiency in hemodialysis patients than the cholecalciferol-adapted NKF-KDOQI–recommended regimen.

The study by Massart et al[7] provides important information regarding correcting vitamin D status in hemodialysis patients. Recently completed clinical trials of pulse dosing of vitamin D_3 in patients treated with hemodialysis are summarized in Table 1.[7-13] Studies using 40,000 to 200,000 IU of cholecalciferol weekly were successful in the correction of 25(OH)D status in ≥90% of participants.[12,13] According to a 2012 systematic review of vitamin D therapy in patients with CKD,[14] a minimum daily dose of 2,000 IU of vitamin D_3 (equivalent to 14,000 IU/wk) likely is required to achieve serum 25(OH)D concentrations > 30 ng/mL.[14] The studies summarized in Table 1 generally are consistent with this, suggesting that at least 1,500 to 2,000 IU daily (or its equivalent weekly dose [10,000-14,000 IU]) of vitamin D is necessary to reach serum 25(OH)D concentrations > 30 ng/mL. However, because Massart et al[7] provided the equivalent of 3,500 IU of vitamin D_3 daily, this latest study implies that even more vitamin D may be required to increase serum 25(OH)D levels to >30 ng/mL.

In contrast to previous studies,[15] Massart et al[7] demonstrated that vitamin D_3 therapy did not lower PTH levels. The published literature suggests that when serum 25(OH)D concentrations are increased to >30 ng/mL, there may be additional benefits that include increasing serum $1,25(OH)_2D$ levels and lowering PTH concentrations. The observation that nearly 40% of patients in the Massart et al[7] study failed to reach this 25(OH)D concentration potentially explains why a PTH-lowering effect was not seen.

This study adds to the growing literature on the formulation and dosing protocol of vitamin D for hemodialysis patients, showing that even the equivalent of 3,500 IU of vitamin D_3 daily may not be adequate to increase serum 25(OH)D above the NKF-KDOQI target. The formulation of vitamin D should be cholecalciferol, especially when adequate serum 25(OH)D concentrations are not achieved with ergocalciferol.[16,17] Establishing an effective vitamin D dosing regimen that consistently increases serum 25(OH)D levels to the NKF-KDOQI target (>30 ng/mL) is an important step in the clinical care of hemodialysis patients. When an effective regimen is established, future research should evaluate whether optimizing vitamin D status is associated with improved patient outcomes.

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