Kidney Medicine

Testing Vitamin D Analogues for Vascular Calcification in Patients With CKD

Madhuri Ramakrishnan and Daniel W. Coyne

Calcitriol and its analogues are commonly used in patients with secondary hyperparathyroidism (SHPT) due to chronic kidney disease (CKD) because these agents suppress parathyroid hormone (PTH) in a dose-dependent fashion.[1-3] Observational studies suggest that their use is associated with improved survival,[4,5] and some preclinical studies have shown beneficial effects on a number of systems, including reduced progression of vascular calcification, as potential mediators of this survival benefit.[5-7] Vascular calcification is exceedingly common in individuals with CKD and inversely correlates with kidney function. Coronary artery calcification (CAC) is a subset of vascular calcification, and studies report its presence in ~60% of non–dialysis-dependent patients with CKD, with a slightly higher prevalence in patients receiving maintenance dialysis.[8] Both vascular calcification and CAC are strongly associated with cardiovascular events and death in the CKD and non-CKD populations.[8]

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In this issue of *Kidney Medicine*, Anis et al[9] report results of a 48-week, randomized, double-blind, single-center trial comparing the effects of calcitriol and paricalcitol on CAC progression in 44 patients with CKD stage 3 or 4. All patients had SHPT and a baseline CAC score greater than zero.[9] The investigators hypothesized that paricalcitol would lead to slower progression of CAC compared with calcitriol.

In contrast to their hypothesis, the primary end point, the difference in the percent change in the CAC Agatston unit score, favored use of calcitriol over paricalcitol (21% vs 48.3%; $P = 0.03$).[9] Three other assessments of CAC progression were reported by Anis et al, including absolute change in CAC score, square root difference in CAC volume, and proportion of patients showing >15% progression in CAC score. None of these outcomes were significantly different between the treatment groups. The investigators also examined progression in aortic and mitral valve calcification and aortic calcification scores. Although both treatment arms experienced progression, there were no significant differences between treatment arms. Just 1 (2.3%) patient developed hypercalcemia.[9]

Based on the primary end point, we could conclude that paricalcitol causes more CAC progression than calcitriol. However, there are reasons to doubt that paricalcitol is definitively worse than calcitriol given the lack of differences between arms when multiple other assessments of CAC and vascular calcification progression are examined. However, more importantly, neither calcitriol nor paricalcitol halted the progression of CAC or other types of vascular calcification, and both CAC and vascular calcification progression in this trial appear greater than that observed in other studies. As noted by the authors, the relatively high rate of CAC and vascular calcification progression they observed likely reflects the requirement for the presence of CAC at baseline, the high prevalence of participants with diabetes, a high proportion of men enrolled in the trial, and lower estimated glomerular filtration rates than previous studies.[9] The lack of a placebo group in this trial is particularly frustrating because we are left wondering whether use of active vitamin D products slowed vascular calcification progression, was ineffective, or even hastened vascular calcification progression.

Endogenous calcitriol levels progressively decline beginning in stage 3 CKD.[10] Lower calcitriol levels strongly correlate with higher mortality rates among CKD and incident hemodialysis patients.[4,11] Given that the high mortality rate in patients with CKD and dialysis patients is driven by excessive cardiovascular events, numerous animal studies have examined whether use of calcitriol or its analogues mitigates cardiovascular disease. Although some of these studies indicate that these agents slow the progression of vascular calcification, others have shown that high doses may promote vascular calcification if they induce or exacerbate hyperphosphatemia.[5] Some but not all of these studies show that paricalcitol, which has been shown to have less calcemic and phosphatemic effects in animals, is more protective against vascular calcification than calcitriol or doxercalciferol.[5]

Animal models also suggest a pathologic role of calcitriol deficiency in left ventricular hypertrophy (LVH). A 1α-hydroxylase knock-out mouse develops hypertension, LVH, and heart failure and is rescued by calcitriol treatment, but not by normalization of serum calcium and phosphate levels or supplemental vitamin D.[6] The Dahl salt-sensitive rat model of hypertension develops LVH on a high-salt diet, whereas both hypertension and LVH are ameliorated by treatment with paricalcitol.[7]

In studies of humans, calcitriol and its analogues suppress PTH in a dose-dependent manner compared with placebo or nutritional vitamin D. Early studies in the 1980s demonstrated a high frequency of hypercalcemia with calcitriol[1] but did not report on calcium supplement use, which may explain the results. Several later trials reported a low incidence of hypercalcemia, at ≤4%, with minimal change in mean serum calcium levels and usually no change in serum phosphorus levels relative to placebo.[2,3,12,13]

Several trials comparing calcitriol with its analogues have been performed in the dialysis population.[5] Although some of these trials have noted small differences between

calcitriol and its analogues in suppression of PTH, changes in serum calcium levels, and changes in serum phosphorus levels, these differences are of unclear clinical significance. Few head-to-head trials are available in the CKD population. One trial comparing paracalcitol and calcitriol in patients with CKD stages 3-4 showed a slightly more rapid suppression of PTH with paracalcitol, but no significant difference in serum calcium or phosphorus levels between these agents.[14] The incidence of hypercalcemia was 4% during 24 weeks.[14] Thus, head-to-head trials have failed to demonstrate clear superiority of any particular analogue for the treatment of SHPT.

Whereas these CKD stages 3-4 trials established the efficacy of calcitriol and its analogues in improving PTH and alkaline phosphatase levels, with minimal effects on serum calcium and phosphorus levels, the impact of these agents on bone morphology and bone turnover are less well studied. Although early trials with calcitriol showed improved bone histology or radiologic changes,[1,13] trials have not examined patient-level outcomes such as fracture reduction or parathyroidectomy rates.

Similarly, although the association of vascular calcification and cardiovascular disease with CKD is established, evidence to date fails to prove that the management of metabolic bone disease using calcitriol, calcitriol analogues, or even calcimimetics results in improved clinical outcomes. Randomized controlled trials examining cardiovascular surrogate end points are limited. The effect of calcitriol on flow-mediated vasodilatation, a measure of vascular function, has been examined in patients with CKD, but the results are mixed.[15,16] Two trials examined the effect of paricalcitol on left ventricular structure and function, and both used higher doses than those used to suppress PTH in clinical practice on the theory that this would lead to greater cardiovascular benefit. The Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity (PRIMO)[17] trial and the OPERA trial[18] demonstrated no significant difference in left ventricular mass index compared with placebo, though a post hoc analysis of the PRIMO data found a decrease in left atrial volume index with paricalcitol.[19] Both trials reported a high incidence of hypercalcemia with paricalcitol: 22.6% in the PRIMO trial and 44.3% in the OPERA trial.

The PRIMO and OPERA trials included patients with normal PTH values and used high doses of paricalcitol. In the OPERA trial, the paricalcitol dose was sufficient to suppress PTH by >70% according to the investigators. The paricalcitol dose was reduced only if hypercalcemia developed, despite marked PTH suppression. Because oversuppression of PTH can induce adynamic bone and consequent hypercalcemia, this management choice likely accounts for the high incidence of hypercalcemia observed in those trials. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines use the high incidence of hypercalcemia in these trials and the lack of LVH regression as the justification for suggesting that calcitriol and its analogues should not be used in patients with stages 3-5 nondialysis CKD.[20]

In contrast, trials using calcitriol or its analogues to treat SHPT routinely adjust the dose to maintain a stable lower PTH level, generally 30% to 60% below pretreatment levels, and report hypercalcemia rates ≤ 4%.[3,12,14] Anis et al used a relatively low starting dose of calcitriol and paricalcitol, titrated the dose based on degree of PTH suppression, and observed only 1 (2.3%) case of hypercalcemia during 48 weeks of treatment.[9] The KDIGO guideline also considers suppression of PTH a biochemical marker despite the long-known trial evidence that PTH suppression improves bone histomorphology.[1,13,20]

It remains to be proven whether treatment of SHPT with calcitriol, paricalcitol, or other active D analogues alters cardiovascular outcomes for better or for worse. The results from Anis et al demonstrate no advantage of paricalcitol over calcitriol. Calcitriol and its analogues are approved for the treatment of SHPT, and it is our view that suppression of PTH to avoid further parathyroid gland hyperplasia and severe hyperparathyroidism is a clinically important end point. This requires proper monitoring and dose adjustment to avoid oversuppression of PTH, which will eventually lead to hypercalcemia and subsequent adverse events. Consequently, in our practice, we routinely use calcitriol or its analogues in patients with CKD with PTH levels persistently >120 pg/mL to suppress PTH by 40% to 60%, with close monitoring of serum calcium and phosphorus levels. Others may choose not to use calcitriol or its analogues in patients with CKD stages 3-4 out of concern for possible progression of vascular calcification or development of hypercalcemia. Given the lack of definitive benefit and proven safety of these agents, that also seems reasonable.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Madhuri Ramakrishnan, MD, and Daniel W. Coyne, MD.

Authors' Affiliation: Division of Nephrology, Department of Medicine, Washington University, St. Louis, MO.

Address for Correspondence: Daniel W. Coyne, MD, Washington University, Division of Nephrology, 660 S Euclid Ave, CB 8126, St. Louis, MO 63110. E-mail: dcoyne@wustl.edu

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