Comparative Effects of Cholecalciferol and Calcitriol on Circulating Markers of CKD Mineral Bone Disorder
A Randomized Clinical Trial

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CKD mineral and bone disorder (CKD-MBD) is characterized by several inter-related abnormalities in circulating vitamin D metabolites and related regulatory hormones (1). Reduced kidney function leads to reduced circulating concentrations of 1,25-dihydroxyvitamin D [1,25(OH)2D], the active vitamin D hormone, and elevated concentrations of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23). Circulating concentrations of 25-hydroxyvitamin D [25(OH)D] are also often low due to reduced sun exposure, low dietary vitamin D intake, obesity, and urinary losses.

More recently, decreased circulating concentrations of 24,25-dihydroxyvitamin D [24,25(OH)2D], an abundant intermediate of 25(OH)D clearance, have been described in CKD (2,3). The ratio of 24,25(OH)2D to its substrate, 25(OH)D3, reflects activity of CYP24A1, the primary enzyme involved in 25(OH)D and 1,25(OH)2D clearance (1). Because CYP24A1 is potently induced by 1,25(OH)2D, the 24,25(OH)2D-to-25(OH)3D ratio may help ascertain tissue-level 1,25(OH)2D activity (1).

Vitamin D supplements (cholecalciferol and ergocalciferol) and vitamin D receptor agonists (calcitriol [1,25(OH)2D3] and its analogs) are commonly prescribed to treat CKD-MBD (1). However, few studies have compared the relative effects of cholecalciferol and calcitriol on the vitamin D metabolic system. We tested the effects of these common interventions on a comprehensive set of circulating CKD-MBD markers in a secondary analysis of a previously published clinical trial (NCT01384539), which was approved by the Colorado Multiple Institution Review Board. Briefly, 128 participants with moderate-severe CKD (53, 52, and 23 participants with eGFR <30, 30–44, and ≥45 ml/min per 1.73 m2) were randomized between October 2011 and March 2015 to receive either oral cholecalciferol (n=64; 4000 IU daily for 1 month and then 2000 IU daily for 5 months) or calcitriol (n=64; 0.25 μg daily for 1 month and then 0.5 μg daily for 5 months) for 6 months (4). For this analysis, we included all randomized participants, all of whom had mineral metabolism markers measured at least once. We analyzed the change in biomarker level with administration of cholecalciferol or calcitriol via linear mixed models with random intercepts and effects for treatment, time, and their interaction. All analyses used the R 3.4.2 computing environment (R Statistical Computing, Vienna, Austria).

Participants had a mean (SD) age of 58 (12) years old and a mean eGFR of 34 (11) ml/min per 1.73 m2; 67% were men, 25% were black, and 45% had diabetes. Characteristics were similar between treatment groups (4). Table 1 shows baseline values and modeled changes in marker concentrations by arm. The change in the ratio of 24,25(OH)2D3 to 25(OH)D3 was poorly correlated with the change in PTH (r=0.03) and the change in FGF-23 (r=0.09).

Our results provide a unique direct comparison of the short-term effects of a vitamin D supplement and a vitamin D receptor agonist, building on trials of individual interventions and extending those of prior comparative trials. From prior trials, it is clear that vitamin D supplements increase circulating 25(OH)D concentration and that both vitamin D supplements and vitamin D receptor agonists reduce PTH and increase FGF-23. In our study, effects on PTH were consistent with some prior studies (4) in direction and magnitude but not significant, probably due to modest sample size. Effects on FGF-23 were significant only for calcitriol, unlike in another study (4). We found no significant difference in change in PTH with cholecalciferol versus calcitriol, likely due to sample size, because prior studies including a direct comparison showed larger effects for vitamin D receptor agonists (5).

The most novel results of our study relate to circulating vitamin D metabolites. Cholecalciferol and calcitriol each significantly increased circulating 24,25(OH)2D3 concentration and the ratio of 24,25(OH)2D3 to its immediate precursor, 25(OH)D3. For cholecalciferol, serum 25(OH)D was increased substantially, but the change in 24,25(OH)2D3 was more than proportional to the change in 25(OH)D3, suggesting both increased delivery of 25(OH)D3 to CYP24A1 and perhaps, increased CYP24A1 activity. Notably, in prior studies of cholecalciferol or ergocalciferol alone, the 24,25(OH)2D3-to-25(OH)D3 ratio increased with supplementation, regardless of whether 25(OH)D3 increased or decreased (2,3). For calcitriol, 24,25(OH)2D3 and its ratio to 25(OH)D3 increased without significant change in 25(OH)D3, more
FGF-23 with changes in vitamin D metabolites were weak. Increased FGF-23 could promote CYP24A1 activity and suppression evidence for reduced CYP27B1 activity. Decreased PTH and calcitriol reduced circulating 1,25(OH)2D2, providing possible CYP24A1-mediated vitamin D clearance.

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**Disclosures**

None.

**References**


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