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$(OH)_2$D], 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$(OH)_2D_3$], an abundant intermediate of 25$(OH)D_3$ clearance, have been described in CKD (2,3). The ratio of 24,25$(OH)_2D_3$ to its substrate, 25$(OH)D_3$, reflects activity of CYP24A1, the primary enzyme involved in 25(OH)D and 1,25$(OH)_2$D clearance (1). Because CYP24A1 is potently induced by 1,25$(OH)_2$D, the 24,25$(OH)_2D_3$-to-25$(OH)D_3$ ratio may help ascertain tissue-level 1,25$(OH)_2$D activity (1).

Vitamin D supplements (cholecalciferol and ergocalciferol) and vitamin D receptor agonists (calcitriol [1,25$(OH)_2D_3$] 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 $\geq$45 ml/min per 1.73 m^2) 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 m^2; 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$(OH)_2D_3$ to 25$(OH)D_3$ 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$(OH)_2D_3$ concentration and the ratio of 24,25$(OH)_2D_3$ to its immediate precursor, 25$(OH)D_3$. For cholecalciferol, serum 25$(OH)D_3$ increased substantially, but the change in 24,25$(OH)_2D_3$ was more than proportional to the change in 25$(OH)D_3$, suggesting both increased delivery of 25$(OH)D_3$ to CYP24A1 and perhaps, increased CYP24A1 activity. Notably, in prior studies of cholecalciferol or ergocalciferol alone, the 24,25$(OH)_2D_3$-to-25$(OH)D_3$ ratio increased with supplementation, regardless of whether 25$(OH)D_3$ increased or decreased (2,3). For calcitriol, 24,25$(OH)_2D_3$ and its ratio to 25$(OH)D_3$ increased without significant change in 25$(OH)D_3$, more

Table 1. Changes in markers of mineral metabolism with calcitriol and cholecalciferol administration

Metabolite	Baseline Concentration, Mean (SD)		6-mo Change from Baseline, Estimate (95% CI)			
	Cholecalciferol	Calcitriol	Cholecalciferol	Calcitriol	Difference, Cholecalciferol − Calcitriol	*P* Value for Difference
Total 25(OH)D, ng/ml	22.7 (7.6)	21.9 (7.8)	11.7 (9.9 to 13.6)	−0.8 (−2.7 to 1.0)	12.6 (9.9 to 15.2)	<0.001
$25(OH)D_3$	20.2 (8.7)	18.6 (8.6)	12.8 (11.0 to 14.6)	0.1 (−1.7 to 1.9)	12.7 (10.2 to 15.3)	<0.001
$25(OH)D_2$	2.5 (4.6)	3.2 (5.2)	−1.2 (−1.9 to −0.4)	−1.0 (−1.7 to −0.2)	−0.2 (−1.3 to 0.9)	0.74
$24,25(OH)_2D_3$, ng/ml	1.6 (1.2)	1.4 (1.0)	1.4 (1.2 to 1.7)	0.4 (0.1 to 0.6)	1.1 (0.7 to 1.4)	<0.001
Total $1,25(OH)_2D$, pg/ml	28.9 (10.9)	29.7 (11.2)	−0.6 (−3.6 to 2.4)	0.5 (−2.5 to 3.5)	−1.1 (−5.3 to 3.1)	0.62
$1,25(OH)_2D_3$	26.0 (12.2)	25.5 (11.4)	1.1 (−1.8 to 4.1)	3.1 (0.1 to 6.1)	−2.0 (−6.2 to 2.2)	0.35
$1,25(OH)_2D_2$	2.9 (5.1)	4.2 (8.1)	−1.8 (−3.2 to −0.4)	−2.6 (−4.0 to −1.2)	0.9 (−1.1 to 2.9)	0.39
$24,25(OH)_2D_3$-to-$25(OH)D_3$ ratio, pg/ng	73 (37)	71 (37)	17 (11 to 23)	21 (14 to 27)	−4 (−13 to 5)	0.43
$1,25(OH)_2D_3$-to-$25(OH)D_3$ ratio, pg/ng	1.4 (0.7)	1.6 (0.8)	−0.5 (−0.8 to −0.3)	0.2 (0.0 to 0.5)	−0.8 (−1.1 to −0.4)	<0.001
VDBG, μg/ml	257 (45)	255 (45)	−4 (−15 to 6)	−9 (−19 to 2)	4 (−11 to 20)	0.56
PTH, pg/ml	140 (167)	106 (65)	−23 (−53 to 7)	−27 (−57 to 3)	4 (−38 to 47)	0.84
iFGF-23, pg/ml	121 (99)	100 (60)	58 (−36 to 151)	176 (82 to 270)	−118 (−251 to 15)	0.08

Entries show baseline mean and SD for each marker by treatment group, the modeled difference in marker value comparing end of study with baseline marker value with 95% CIs, the modeled difference in marker change between cholecalciferol and calcitriol treatment groups, and the corresponding *P* value for the difference in change. All modeled estimates are derived from a linear mixed model with random intercepts and fixed effects of treatment group, time, and the treatment by time interaction. All randomized participants with any available vitamin D metabolites (n=128) were included in analysis. For the cholecalciferol group, measurements from n=62 and n=58 participants at baseline and 6 months, respectively, were included; for the calcitriol group, measurements from n=63 and n=56 participants at baseline and 6 months, respectively, were included. 95% CI, 95% confidence interval; 25(OH)D, 25-hydroxyvitamin D; $25(OH)D_3$, 25-hydroxyvitamin D_3; $25(OH)D_2$, 25-hydroxyvitamin D_2; $24,25(OH)_2D_3$, 24,25-dihydroxyvitamin D_3; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; $1,25(OH)_2D_2$, 1,25-dihydroxyvitamin D_2; VDBG, vitamin D binding globulin; PTH, parathyroid hormone; iFGF-23, intact fibroblast growth factor 23.

strongly suggesting CYP24A1 induction. Neither cholecalciferol nor calcitriol significantly changed circulating $1,25(OH)_2D$ concentration. This is consistent with prior trials that have reported little or no change in $1,25(OH)_2D$ with vitamin D supplements. Findings did not differ by stage of CKD.

Our findings suggest that circulating $1,25(OH)_2D$ concentration is carefully defended, even when low at baseline due to CKD. Mechanisms of defense could include induction of CYP24A1 and suppression of CYP27B1, the enzyme responsible for generation of $1,25(OH)_2D$ from 25(OH)D. In our study, cholecalciferol reduced the ratio of $1,25(OH)_2D_3$ to $25(OH)D_3$, and calcitriol reduced circulating $1,25(OH)_2D_2$, providing possible evidence of reduced CYP27B1 activity. Decreased PTH and increased FGF-23 could promote CYP24A1 activity and suppress CYP27B1 activity, but correlations of changes in PTH and FGF-23 with changes in vitamin D metabolites were weak.

In conclusion, cholecalciferol and calcitriol each resulted in significant changes in circulating markers of CKD-MBD. These changes maintained constant circulating $1,25(OH)_2D$ concentrations, partly through apparent induction of CYP24A1-mediated vitamin D clearance.

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Disclosures

None.

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