Randomized Trial Assessing the Effects of Ergocalciferol Administration on Circulating FGF23

Sherri-Ann M. Burnett-Bowie, Benjamin Z. Leder, Maria P. Henao, Chantel M. Baldwin, Douglas L. Hayden, and Joel S. Finkelstein

Summary

Background and objectives Fibroblast growth factor 23 is a phosphate- and vitamin D–regulating hormone. The objective of this study was to determine the effect of ergocalciferol administration on fibroblast growth factor 23 levels in healthy vitamin D–deficient subjects.

Design, setting, participants, & measurements In this 12-week trial conducted in a clinical research center, 18- to 45-year-old subjects (n=90) with 25-hydroxyvitamin D levels ≤20 ng/ml (by chemiluminescent immunoassay) were randomized to weekly ergocalciferol treatment of 50,000 international units or placebo, while consuming a self-selected diet. Changes in fibroblast growth factor 23, 25-hydroxyvitamin D (by liquid chromatography/tandem mass spectroscopy), 1,25-dihydroxyvitamin D, parathyroid hormone, and serum phosphate were measured.

Results Mean 25-hydroxyvitamin D (P<0.0001), 1,25-dihydroxyvitamin D (P=0.01), and fibroblast growth factor 23 (P=0.003) increased in the treatment versus placebo group. In the treatment group, 25-hydroxyvitamin D increased from 18.7±7 to 40±12 ng/ml at week 4 (P<0.0001) and remained stable at 43±12 ng/ml at week 12 (P<0.0001); 1,25-dihydroxyvitamin D increased from 42±17 to 52±18 pg/ml at week 4 (P<0.001) and then remained stable, and fibroblast growth factor 23 increased from 43±17 to 60±33 pg/ml at week 8 (P=0.001) and 74±42 pg/ml at week 12 (P<0.0001). Urinary phosphate excretion increased within the treatment group, but parathyroid hormone and serum phosphate were unchanged.

Conclusions Ergocalciferol administration increases circulating fibroblast growth factor 23. When measuring fibroblast growth factor 23, concurrent 25-hydroxyvitamin D measurements should be obtained, because vitamin D deficiency may lower circulating fibroblast growth factor 23 levels.


Introduction

Fibroblast growth factor 23 (FGF23) is a phosphate- and vitamin D–regulating hormone (1–6). FGF23 levels are elevated in patients with CKD and are independently associated with increased mortality in patients receiving hemodialysis (7,8). Additionally, elevated FGF23 levels are associated with increased cardiovascular mortality in individuals with stable coronary artery disease but normal renal function (9–11). Much is still unknown, however, about the physiologic regulation of FGF23.

1,25-Dihydroxyvitamin D [1,25(OH)2D], dietary phosphate, and circulating phosphate are key regulators of FGF23 (12–18). However, it is unknown if vitamin D (either ergocalciferol or cholecalciferol) affects FGF23 secretion. Given the increasingly common administration of vitamin D to people with normal renal function and people with CKD (19,20) and the association between FGF23 and mortality (7–9), knowledge of the effects of vitamin D on FGF23 may inform both clinical and investigative pursuits. We, thus, tested the hypothesis that weekly high-dose ergocalciferol would increase circulating FGF23 levels in subjects with normal renal function and low 25-hydroxyvitamin D (25OHD) levels.

Materials and Methods

Study Subjects

We recruited healthy, vitamin D–deficient volunteers through advertisements and mass mailings. To be eligible, subjects had to be 18–45 years old with a serum 25OHD level ≤20 ng/ml by chemiluminescent immunoassay (CLIA; CLIA was the available 25OHD assay at our institution at that time) (20). Subjects with disorders or using medications known to affect phosphate or vitamin D metabolism were excluded, as well as subjects with histories of nephrolithiasis, diabetes mellitus, malabsorption, recent ethanol abuse, or clinically significant disease. Subjects were required to have normal kidney, liver, and thyroid function; males had normal testosterone levels. Eligible females had regular menses (oral contraceptive use was allowed). Subjects self-identified as non-Hispanic or Hispanic and Asian,
black/African-American, white/Caucasian, multiple races, or other. The Human Research Committee of Partners Health Care System approved the study, and subjects provided written informed consent.

Of the 651 subjects screened by telephone, 419 subjects had screening blood tests, and 136 of those tests had 25OHD levels \( \leq 20 \text{ ng/ml} \); 130 subjects met the remaining inclusion criteria. Of these subjects, 92 subjects enrolled in the study, and 90 subjects completed the 12-week protocol. The season of recruitment was classified as winter (January, February, and March), spring (April, May, and June), summer (July, August, and September), or fall (October, November, and December).

**Study Protocol**

Subjects were randomized to receive either ergocalciferol at 50,000 international units (VIT-D) or matching placebo (PBO) weekly for 12 weeks. We used ergocalciferol, because it is available as a prescription in the United States. Randomization was stratified by sex and severity of vitamin D deficiency (25OHD \( \leq 10 \text{ versus} >10 \text{ ng/ml} \) by CLIA). Dietary calcium and vitamin D intakes were assessed at baseline and week 12. Daily calcium intake was maintained at 1000–1500 mg in both groups through diet and/or supplements. At study completion, PBO group subjects were treated with ergocalciferol at 50,000 international units daily for 7 days.

Fasting blood and urine samples were collected between 7:00 and 9:00 AM at weeks 0, 4, 8, and 12. Fractional excretion of phosphate [\( PF_{\text{PO}_4} \) (urine \( \text{PO}_4 \times \text{serum creatinine} \)/ (serum \( \text{PO}_4 \times \text{urine creatinine} \)] and creatinine clearance were calculated (21–23). Compliance was assessed by review of diaries and returned medication counts. Subjects were monitored for hypo- or hypercalcemia at each visit and withdrawn if necessary.

**Laboratory Methods**

Testing was performed on previously unthawed samples that were stored at \(-80^\circ\text{C}\). 25OHD was measured by CLIA (Diasorin, Stillwater, MN) with sensitivity of 2 ng/ml and intra- and interassay coefficients of variation (CVs) of 6%–8% and 12%–16%, respectively, and as prespecified in our study design by the gold-standard liquid chromatography/tandem mass spectroscopy (LC/MS/MS) with sensitivity of 6 ng/ml and interassay CV of 6%–9%. Serum 1,25(OH)\(_2\)D was measured using a radioimmunoassay (Diasorin, Stillwater, MN) with intra- and interassay CVs of 7%–11% and 11%–15%, respectively. Serum FGF23 was measured using an immunometric assay (Kainos, Tokyo, Japan) with sensitivity of 3 pg/ml and intra- and interassay CVs of \( \leq 3\% \) and \( \leq 4\% \), respectively. Serum and urine phosphate were measured using a colorimetric method (Roche Diagnostics, Indianapolis, IN) with intra- and interassay CVs of <2% and <4%, respectively. Parathyroid hormone (PTH) was measured using a two-site immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA) with sensitivity of 1 pg/ml and intra- and interassay CVs of 2%–3% and 6%, respectively.

**25OHD: CLIA Versus LC/MS/MS**

At weeks 4, 8, and 12, 25OHD was measured with both methodologies. The regression line for the assays differed based on group assignment (Supplemental Figure 1). Thus, it was not possible to create a linear regression equation defining the relationship between the two assays. Supplemental Figure 2 shows the 25OHD measurements from both assays. Unless otherwise specified, the reported 25OHD levels were measured using LC/MS/MS. Supplemental Figure 3 shows on-study 25OHD\(_2\) and 25OHD\(_3\) levels.

**Statistical Analyses**

The primary endpoint was a comparison of the change in circulating FGF23, which is expressed as the area under the curve between the VIT-D and PBO groups. Secondary endpoints included the change in 25OHD, 1,25(OH)\(_2\)D, serum phosphate, calcium, PTH, and \( F_\text{ePO}_4 \) between the groups.

The endpoints were assessed using a mixed model ANOVA. Within-group changes in the endpoints (compared with baseline) were assessed by repeated measures ANOVA using Dunnett’s test to adjust for multiple comparisons. Baseline characteristics were compared using t, Wilcoxon rank sum, chi-squared, or Fisher exact tests as appropriate. Multivariate linear regression models were used to identify which variables were independent predictors of the 12-week change in FGF23 from baseline to week 12 in the VIT-D group. The predictor variables in the models included the change from baseline to week 12 in 1,25(OH)\(_2\)D, 25OHD, serum phosphate, and PTH, as well as sex and race. As a posthoc analysis, we also assessed the relationship between the 12-week absolute change in 25OHD and the 12-week absolute change in 1,25(OH)\(_2\)D in the treatment group. Data are expressed as mean ± SD unless specified otherwise. Comparisons were performed by two-sided tests, and resulting P values <0.05 are considered statistically significant. SAS V9.2 was used for these analyses.

**Results**

**Subject Characteristics**

Baseline characteristics are described in Table 1. Dietary vitamin D intake was somewhat higher in the treatment than placebo group. However, the median daily intake of vitamin D was lower than the recommended daily allowance (24); less than 10% of the cohort consumed a daily multivitamin. Otherwise, there were no between-group differences. The cohort was racially diverse, and subjects were recruited equally across the four seasons.

At enrollment, all subjects had 25OHD levels measured by CLIA that were \( \leq 20 \text{ ng/ml} \). At visit 1 (week 0), however, 25OHD levels measured by LC/MS/MS were \( \leq 20 \text{ ng/ml} \) in 60 subjects, \( >20 \text{ to} \leq 30 \text{ ng/ml} \) in 27 subjects, and \( >30 \text{ ng/ml} \) in 3 subjects. At visit 1 (week 0), we observed a negative association between 25OHD and PTH levels \( (R=-0.28, P=0.006) \); 11 subjects had PTH levels >60 pg/ml.

**Subject Withdrawal and Compliance**

One subject was withdrawn after the baseline visit because of medication noncompliance, and one subject was withdrawn because of pregnancy (their data were not included). No subject developed hypercalcemia; one subject receiving placebo had asymptomatic hypocalcemia at week 12. Five subjects (two subjects receiving VIT-D and
three subjects receiving PBO) took 85% of the study medication; the remaining subjects were 100% compliant. Dietary vitamin D did not increase during the study or differ between groups (data not shown).

FGF23, 25OHD, and 1,25(OH)2D

Figure 1 shows FGF23, 25OHD, and 1,25(OH)2D at week 0 and weeks 4, 8, and 12 after ergocalciferol administration. FGF23 ($P=0.003$), 25OHD ($P<0.0001$), and 1,25(OH)2D ($P=0.01$) increased more in the subjects treated with ergocalciferol than in the subjects in the PBO group. In the VIT-D group, 25OHD increased from 18$\pm$7 ng/ml at baseline to 40$\pm$12 ng/ml at week 4 ($P<0.0001$), 45$\pm$15 ng/ml at week 8 ($P<0.0001$), and 43$\pm$12 ng/ml at week 12 ($P<0.0001$) (Figure 1A); 1,25(OH)2D increased from 42$\pm$17 pg/ml at baseline to 52$\pm$18 pg/ml at week 4 ($P<0.001$), 49$\pm$15 pg/ml at week 8 ($P=0.03$), and 49$\pm$17 pg/ml at week 12 ($P=0.01$) (Figure 1B), and FGF23 increased from 43$\pm$17 pg/ml at baseline to 60$\pm$33 pg/ml at week 8 ($P=0.001$) and 74$\pm$42 pg/ml at week 12 ($P<0.0001$) (Figure

<table>
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<th>Table 1. Baseline characteristics</th>
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<tr>
<td><strong>Clinical or Biochemical Endpoints</strong></td>
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<td>Age (years)$^a$</td>
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<td>Total VIT-D intake (international units)$^a$</td>
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<td>25OHD (ng/ml) by CLIA$^b$</td>
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<td>25OHD (ng/ml) by LC/MS/MS$^c$</td>
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<td>25OHD $\leq$20 ng/ml$^f$ (n)</td>
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<td>FGF23 (pg/ml)</td>
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<td>Creatinine clearance (ml/min per 1.73m2)</td>
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<td>FePO4 (%)</td>
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Values are presented as mean $\pm$ SD unless otherwise indicated. VIT-D, vitamin D; PBO, placebo; BMI, body mass index; MVI, multivitamin; 25OHD, 25-hydroxyvitamin D; CLIA, chemiluminescent immunoassay; LC/MS/MS, liquid chromatography/tandem mass spectroscopy; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; 1,25(OH)2D, 1,25-dihydroxyvitamin D; FePO4, fractional excretion of phosphate. Systeme International conversion factors: 25OHD (nM), 2.496; PTH (ng/L), 1; 1,25(OH)2D (pmol/L), 2.6; calcium (mM), 0.2495; phosphate (mM), 0.3229; and creatinine (mM), 88.4.

$^a$Age and vitamin D intake are presented as median (25th percentile, 75th percentile).

$^b$The 25OHD by CLIA was performed at screening.

$^c$The 25OHD by LC/MS/MS, similar to the other biochemical data, was performed at week 0 or baseline.
In the PBO group, there was no significant change in 25OHD, 1,25(OH)2D, or FGF23. As a posthoc analysis, we assessed the relationship between the 12-week absolute change in 25OHD and the 12-week absolute change in 1,25(OH)2D in the treatment group. There was a trend for a positive relationship with $R=0.308$ ($P=0.05$). The equation describing this relationship was 12-week change in 1,25(OH)2D=0.4022×(12-week change in 25OHD)−2.6776.

**Multivariate Analyses**

To differentiate the effects of 25OHD from 1,25(OH)2D on FGF23, we created four multivariate regression models with 12-week change in FGF23 as the response variable in the VIT-D–treated group. The predictor variables were 12-week change in 1,25(OH)2D, 25OHD, serum phosphate, and PTH, as well as sex and race (in the largest model) and 12-week change in 1,25(OH)2D and 25OHD (in the most parsimonious model). The 12-week change in FGF23 was not independently predicted by any variable in any of the models.

**Discussion**

In this study, we have shown that administration of weekly high-dose ergocalciferol for 12 weeks increases circulating FGF23 levels in a cohort of otherwise healthy subjects with low 25OHD levels. The observed increase in
FGF23 levels occurred in the context of significant increases in circulating 25OHD and 1,25(OH)2D levels. Although FePO4 increased within the VIT-D group, there were no between-group differences in FePO4, serum phosphate, PTH, or calcium levels. Prior studies have shown that 1,25(OH)2D increases FGF23 synthesis and its circulating levels (13,14,25). This study is the first to show that ergocalciferol administration is associated with increased FGF23 production; however, in this model, we were unable to determine if the increase was because of ergocalciferol, 25OHD, or 1,25(OH)2D.

We have previously shown that dietary phosphate loading stimulates FGF23 production in normal volunteers (16). Additionally, we and others have shown that dietary phosphate deprivation suppresses FGF23 production (12,16,17). In this study, within the treatment group, FGF23 levels and FePO4 increased, but serum phosphate and PTH levels were unchanged. The observed increase in FePO4 is likely a direct result of the observed increase in circulating FGF23. This increase in FePO4 is likely an adaptive response to counteract VIT-D-mediated dietary phosphate absorption and thus, maintain serum phosphate levels at baseline. Because of the duration of the study, subjects consumed an ad libitum diet, which may explain our inability to show between-group changes in urinary or serum phosphate indices; additionally, our sampling schedule may have missed early and transient increases in serum phosphate in the VIT-D group. If we had obtained daily measurements during the first 4 weeks of the study or if we had obtained postprandial measurements, we may have observed changes in serum phosphate levels in the treatment group. At baseline, we observed the anticipated negative association between 25OHD and PTH levels; however, PTH levels were stable with vitamin D administration. This finding may be because of our cohort being healthier and having milder vitamin D deficiency (only 11 subjects had PTH >60 pg/ml). Alternately, our results may be because of study duration or choice of vitamin D compound (26,27). Given that our primary endpoint was the change in FGF23 with vitamin D administration and data that PTH may stimulate FGF23 (28,29) (conversely declining PTH levels may suppress FGF23 levels), the stable PTH levels in this experimental model simplify interpretation of our data. The observed changes in FGF23 are not confounded by concurrent and sustained changes in circulating PTH levels.

FGF23 and vitamin D display classic endocrine feedback signaling, where 1,25(OH)2D stimulates FGF23 and FGF23 suppresses the production of 1,25(OH)2D (13,14,18,30–32). Consistent with that physiology, we first noted increases in circulating 25OHD and 1,25(OH)2D levels and then, increases in FGF23. In contrast to the relationship between 1,25(OH)2D and FGF23, the relationship between vitamin D and FGF23 has not been well-characterized. Our study shows that the administration of pharmacologically dosed ergocalciferol is associated with increased FGF23 production. Our findings are in contrast to a recently reported study where FGF23 decreased with vitamin D repletion (33). There are, however, differences in the two studies that make comparisons challenging. Namely, we recruited 90 healthy, community-based subjects who were randomized to a placebo-controlled study, whereas the 18 subjects in the other study (33) were hospitalized and their post-vitamin D repletion FGF23 levels were compared with baseline. Additionally, the studies differed in baseline 25OHD levels (18 versus 8 ng/ml), end of study 25OHD

Figure 2. Changes in fractional excretion of phosphate (FePO4), phosphate, parathyroid hormone (PTH), and calcium with ergocalciferol administration. Mean (±SEM) of (A) FePO4, (B) serum phosphate, (C) PTH, and (D) serum calcium at weeks 0, 4, 8, and 12 in the vitamin D (solid line) and placebo (dashed line) groups. The horizontal lines represent the normal range for the variables. None of the changes over time by repeated measures ANOVA compared with placebo were statistically significant. Systeme International conversion factors are serum phosphate (mM), 0.2495; PTH (ng/L), 1; and serum calcium (mM), 0.3229.
levels (43 versus 15 ng/ml), study duration (12 versus 6 weeks), vitamin D preparation (ergocalciferol versus cholecalciferol), cumulative vitamin D dose (600,000 versus 186,960 international units), and FGF23 assay (intact versus C-terminal assay). Although the differing effects of vitamin D on FGF23 in these studies may reflect differences in circulating intact FGF23 versus C-terminal fragments, alternate explanations may be differences in assay performance (16) or differences in FGF23 when measured during an acute illness versus the healthy state (10).

In a posthoc analysis, the observed increase in 1,25(OH)2D was positively associated with the increase in 25OHD in the VIT-D group. In prior studies of vitamin D repletion, there is lack of consensus regarding the effect of vitamin D administration on circulating 1,25(OH)2D levels, with some studies showing an increase in 1,25(OH)2D with vitamin D administration (34–36) and others not showing this outcome (37–44). Comparisons between those studies and our findings are made difficult by differences in study design that include the ages of the subjects, type and dose of vitamin D administered, duration of vitamin D administration, baseline 25OHD levels, and assays used. Given prior studies (13,14,18,25,32), the observed increase in FGF23 is likely caused by the observed increase in 1,25(OH)2D, although a direct effect of ergocalciferol, 25OHD, or increased dietary phosphate absorption because of increased 1,25(OH)2D cannot be excluded. Vitamin D deficiency is widespread and typically treated with oral ergocalciferol or cholecalciferol (but not calcitriol). Our data show that routine management of vitamin D deficiency may affect FGF23 levels. This observation suggests that, when FGF23 assays are approved for clinical use (similar to PTH), the measured FGF23 level will need to be interpreted in light of that patient’s concurrent 25OHD level. Whereas vitamin D deficiency may elevate PTH (20), these data suggest that vitamin D deficiency may lower circulating FGF23.

Limitations of this study deserve mention. Some reports suggest that ergocalciferol does not replete 25OHD levels as effectively as cholecalciferol (45–47), but other reports contradict that perspective (48,49). Because of assay availability at our institution at the time of subject enrollment, subjects were enrolled based on a 25OHD level as measured by CLIA; however, as part of our prespecified study design, we assessed the change in 25OHD with ergocalciferol administration using 25OHD measured by LC/MS/MS. Notably, there were differences in the data obtained from LC/MS/MS 25OHD measurement compared with CLIA, wherein the 25OHD levels were higher with the LC/MS/MS measure. These differences are likely caused by differences in assay performance, which have been previously reported (50). Notably, the majority of subjects (60/90) still had 25OHD levels ≤20 ng/ml as measured by LC/MS/MS; 27 of 90 subjects had 25OHD levels >20 and ≤30 ng/ml by LC/MS/MS. We did not assess other important factors in vitamin D metabolism such as 25OHD-24-hydroxylase activity or vitamin D binding protein levels; however, randomization should have balanced potential differences. Subjects consumed an ad libitum diet. Although we assessed calcium and vitamin D intake over the course of the study, which were both stable, we did not assess or control for dietary phosphate intake. Finally, given our sample size (n=40 for the multivariate model) and study design, we are unable to differentiate the effects of ergocalciferol, 25OHD, or 1,25(OH)2D on the associated increase in FGF23.

In summary, we have shown that, in subjects with low vitamin D levels, treatment with weekly high-dose ergocalciferol increases circulating 25OHD and 1,25(OH)2D levels and is associated with increased FGF23 production. Increasing numbers of patients, with both normal renal function and CKD, are being screened for vitamin D deficiency and repleted with oral vitamin D. Additional studies are needed to determine the short- and long-term clinical effects of increased FGF23 stimulation in health and CKD.

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Disclosures

None.

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