Nutritional Vitamin D Supplementation in Dialysis: A Randomized Trial

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Abstract

Background and objectives Vitamin D (25-hydroxyvitamin D; 25[OH]D) deficiency is common in patients initiating long-term hemodialysis, but the safety and efficacy of nutritional vitamin D supplementation in this population remain uncertain.

Design, setting, participants, & measurements This randomized, placebo-controlled, parallel-group multicenter trial compared two doses of ergocalciferol with placebo between October 2009 and March 2013. Hemodialysis patients (n=105) with 25(OH)D levels ≤32 ng/ml from 32 centers in the Northeast United States were randomly assigned to oral ergocalciferol, 50,000 IU weekly (n=36) or monthly (n=33), or placebo (n=36) for a 12-week treatment period. The primary endpoint was the achievement of vitamin D sufficiency (25[OH]D >32 ng/ml) at the end of the 12-week treatment period. Survival was assessed through 1 year.

Results Baseline characteristics were similar across all arms, with overall mean±SD 25(OH)D levels of 21.9±6.9 ng/ml. At 12 weeks, vitamin D sufficiency (25[OH]D >32 ng/ml) was achieved in 91% (weekly), 66% (monthly), and 35% (placebo) (P<0.001). Mean 25(OH)D was significantly higher in both the weekly (49.8±2.3 ng/ml; P<0.001) and monthly (38.3±2.4 ng/ml; P=0.001) arms compared with placebo (27.4±2.3 ng/ml). Calcium, phosphate, parathyroid hormone levels, and active vitamin D treatment did not differ between groups. All-cause and cause-specific hospitalizations and adverse events were similar between groups during the intervention period. Lower all-cause mortality among ergocalciferol-treated participants was not statistically significant (hazard ratio, 0.28; 95% confidence interval, 0.07 to 1.19).

Conclusions Oral ergocalciferol can increase 25(OH)D levels in incident hemodialysis patients without significant alterations in blood calcium, phosphate, or parathyroid hormone during a 12-week period.

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Introduction

Renal 25-hydroxyvitamin D 1-α hydroxylase (CYP27B1) converts 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), the active form of the hormone (1). CYP27B1 activity declines with progressive kidney disease, and thus management of secondary hyperparathyroidism in patients with ESRD who are undergoing hemodialysis (HD) has focused largely on replacement of 1,25$(OH)_2$D with the native hormone (calcitriol) or one of its congeners (2). Measurement of 25(OH)D levels and correction of 25(OH)D deficiency with nutritional vitamin D (*e.g.*, ergocalciferol or cholecalciferol) have traditionally been considered unimportant in patients with ESRD.

Vitamin D may have additional actions beyond its expected effects on mineral metabolism (3–6). Most tissues express vitamin D receptors (1). Local conversion of 25(OH)D to 1,25$(OH)_2$D by macrophages and other immune cells leads to autocrine regulation of immune function, including production of the antimicrobial peptide cathelicidin, enhancement of autophagy, alteration of the Th1/Th2 balance, and induction of regulatory T cells (7–10). As autocrine and paracrine processes do not depend on renal CYP27B1, some postulate that replacement of 25(OH)D would be beneficial even in patients with ESRD.

Insufficiency of 25(OH)D (*i.e.*, 25[OH]D≤30–32 ng/ml) is common in patients receiving HD and is associated with poor outcomes, including increased mortality (11–13). A clear cause-and-effect relationship, however, has not been established. Data are inconsistent regarding the effect of 25(OH)D on markers of mineral metabolism, and studies of nutritional vitamin D supplementation for secondary hyperparathyroidism in advanced CKD have yielded mixed results (14–21). Practice patterns vary, and prospective studies examining the safety and efficacy of nutritional vitamin D replacement in ESRD have been limited. We performed a three-arm, randomized, placebo-controlled clinical trial in incident dialysis patients (Dialysis Infection and Vitamin D in New England [DIVINE]) to evaluate the safety and efficacy of short-term treatment

with nutritional vitamin D and to inform the feasibility of a larger outcome study.

Materials and Methods

Design

This three-arm, double-blinded, randomized controlled trial compared two dosing regimens of ergocalciferol with placebo. It was approved by the Human Subject Committees of the Massachusetts General Hospital (MGH), Fresenius Medical Care North America, DaVita HealthCare Partners, and Dialysis Clinic, Inc, and adhered to the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients were considered for inclusion if they were adults (age ≥18 years) within 2 months of long-term HD initiation at MGH, Brigham and Women's Hospital, or Beth Israel Deaconess Medical Center, with a planned transfer to a Massachusetts long-term HD facility. Screening laboratory data (Table 1) were used to define eligibility. Patients were required to have a serum 25(OH)D level ≤32 ng/ml, corrected calcium <10.2 mg/dl, phosphate <5.5 mg/dl, and albumin >3 g/dl. Patients were excluded if they were pregnant, breastfeeding, or of childbearing potential and not practicing birth control; if they had a history of allergic reaction to ergocalciferol; or if the investigator considered the patient unsuitable. Informed consent was required for all participants.

Recruitment and Study Procedures

Recruitment for the DIVINE study took place between October 2009 and March 2013 at the three study hospitals. Eligible participants were randomly assigned by a pharmacy-maintained computer-generated random-number list to weekly ergocalciferol, monthly ergocalciferol, or matching placebo. At baseline and weeks 4 and 8, all randomly assigned participants received a four-pill blister pack and were instructed to take one tablet each week. Packs contained four pills of 50,000 IU ergocalciferol (weekly arm), one ergocalciferol and three placebo pills (monthly arm), or all placebo pills (placebo arm). Placebo pills were prepared by the MGH Research Pharmacy and were indistinguishable from active compound. The ergocalciferol content of a random sample of three ergocalciferol capsules and three placebo capsules was verified in the laboratory of Drs. Michael Holick and Tai Chen of Boston University. Patients, research staff, laboratory technicians, and clinical providers were blinded to study arm enrollment until the last patient had completed 16 weeks of follow-up.

Follow-up visits were performed at 4, 8, 12, and 16 weeks at one of 32 separate facilities in the New England area. Participants received study drug from initiation through week 12. A 16-week follow-up visit was included to assess durability of responses. Blood samples were collected at all five time points. Additional ergocalciferol and cholecalciferol were not permitted throughout the 16-week study period. Use of active vitamin D analogues (*e.g.*, calcitriol, paricalcitol, or doxercalciferol) was not restricted. For subgroup analyses, active vitamin D use was defined as the use of active vitamin D for three or more visits.

Hospitalization data were collected at 4, 8, 12, and 16 weeks. Mortality data were collected through 1 year. Hospital records were obtained and adjudicated by two practicing nephrologists who were part of the study staff (I.B., S.K.) but blinded to study treatment. Hospitalizations and mortality were categorized as cardiac, infectious, or neither. If the two adjudicators did not agree, the data were reviewed by a third nephrologist adjudicator (S.N.) to break the tie.

Primary and Secondary Endpoints

The primary endpoint was the achievement of vitamin D sufficiency (25[OH]D>32 ng/ml) at the end of the 12-week treatment period. Secondary endpoints included measures of mineral metabolism (calcium, phosphate, and parathyroid hormone [PTH] levels). Fibroblast growth factor-23 (FGF-23) was included as an exploratory measure. All-cause and cause-specific hospitalization rates as well as overall mortality were also included in the analysis.

Plasma levels of 25(OH)D, serum calcium, albumin, and PTH for all participants were measured in the MGH clinical laboratories. Levels of $1,25(OH)_2$ D were assessed in a random subset of 85 participants. $25(OH)D_2$ and $25(OH)D_3$ levels were measured by liquid chromatography–tandem mass spectrometry, with interassay coefficients of variation of 9.1% for $25(OH)D_2$ and 8.6% for $25(OH)D_3$. Intact PTH was measured on the Cobas E160 automated analyzer (Roche Diagnostics, Indianapolis, IN; interassay coefficient of variation, 4.2%). C-terminal FGF-23 was measured by commercial ELISA (Immutopics, San Clemente, CA) as previously done (22,23).

Sample Size Determination

On the basis of prior research (16,19,20,24), we assumed that following treatment, 90% of participants treated with high-dose ergocalciferol, 50% of low-dose participants, and 10% of placebo participants would become 25(OH)D replete (blood levels of 25(OH)D >32 ng/ml) in 12 weeks. With use of an α of 0.05, 35 participants per arm (total, n=105) would provide 97% power for comparisons of repletion rates between groups.

Statistical Analyses

Efficacy analyses were prespecified and conducted in the intention-to-treat population (all randomized participants); all took at least one dose of study drug.

The primary efficacy outcome was defined as the proportion of participants who achieved serum 25(OH)D sufficiency (> 32 versus ≤ 32 ng/ml) at 12 weeks. These proportions were compared using a chi-squared test. In addition, we examined change in serum 25(OH)D level from baseline to week 12 comparing groups using a mixed-effect model of repeated measures (MMRM) of all longitudinal observations collected for intention-to-treat participants. Individuals with a baseline value and at least one follow-up value were included in MMRM. Unstructured covariance was determined using Akaike's information criteria. Satterthwaite's approximation was used to estimate denominator degrees of freedom. Type III sums-of-squares and least-squares means were used for statistical comparisons. MMRM models were also used to examine changes in other laboratory measures, including serum calcium, serum phosphate, and natural log–transformed PTH between randomization groups. Because FGF-23 was highly right skewed, values were summarized

Table 1. Baseline characteristics by treatment group

Characteristic	Monthly Ergocalciferol	Weekly Ergocalciferol	Placebo
Patients (*n*)	33	36	36
Age (yr)	58±16	53±17	59±17
Men (%)	28 (84.9)	25 (69.4)	29 (80.6)
Race (%)			
White	21 (63.6)	23 (63.9)	22 (61.1)
Black	9 (27.3)	13 (36.1)	9 (25.0)
Asian	2 (6.1)	0 (0.0)	4 (11.1)
Multiple-race	1 (3.0)	0 (0.0)	1 (2.8)
Ethnicity (%)			
Hispanic	5 (15.2)	4 (11.1)	6 (16.7)
Non-Hispanic	28 (84.9)	32 (88.9)	30 (83.3)
Vascular access (%)			
Arterial venous fistula	10 (30.3)	11 (30.6)	11 (30.6)
Arterial venous graft	1 (3.0)	3 (8.3)	3 (8.3)
Catheter	22 (66.7)	22 (61.1)	22 (61.1)
Vital signs			
Body mass index (kg/m^2)	32.0±9.5	30.5±9.8	30.1±6.5
Systolic BP (mmHg)	146±22	146±28	145±27
Diastolic BP (mmHg)	77±16	81±19	75±17
Heart rate (beats/min)	75±10	77±13	78±14
Laboratory values			
Calcium (mg/dl)	8.7±0.6	8.8±0.7	8.8±0.7
Creatinine (mg/dl)	5.0 (3.0, 6.7)	6.0 (4.2, 7.4)	5.4 (3.7, 6.7)
Alkaline phosphatase (IU/L)	75.5 (54.0, 103.0)	77.5 (52.0, 107.0)	87.0 (68.0, 115.0)
Albumin (g/dl)	3.4±0.6	3.5±0.5	3.6±0.5
PTH (pg/ml)	253.0 (160.0, 338.0)	265.0 (169.5, 492.5)	248.5 (155.0, 382.5)
Phosphate (mg/dl)	4.2±1.1	4.2±1.5	4.1±1.0
White blood count (×10^9/L)	7.2±2.2	7.4±2.4	7.8±2.6
Hemoglobin (g/dl)	9.5±1.3	8.7±1.7	9.3±1.0
TIBC (μg/dl)	244.4±43.7	241.0±65.3	226.2±41.4
Iron (μg/dl)	57.0 (40.0, 67.0)	60.0 (45.0, 85.0)	45.0 (26.0, 61.0)
Ferritin (ng/ml)	157.0 (107.0, 235.0)	187.0 (93.0, 349.0)	203.0 (113.5, 332.5)
Urea reduction ratio (%)	71.5±10.0	66.6±8.6	71.2±9.9
25(OH)D (ng/ml)	22.3±6.5	21.8±7.0	21.7±7.3
25(OH)D$_2$ (ng/ml)	6.4±7.5	7.6±8.0	6.0±8.1
25(OH)D$_3$ (ng/ml)	16.2±7.9	14.2±8.2	15.6±7.4
Medication			
β-blocker (%)	23 (69.7)	30 (83.3)	28 (77.8)
ACE inhibitor (%)	7 (21.2)	4 (11.1)	5 (13.9)

Values are expressed as mean±SD, median (Q1, Q3), or *n* (%). PTH, parathyroid hormone; TIBC, total iron binding capacity; ACE, angiotensin-converting enzyme; 25(OH)D, 25-hydroxyvitamin D.

using medians (quartile 1, quartile 3) and compared between randomization groups using Kruskal–Wallis tests. The number of participants receiving active vitamin D, iron supplementation, or erythropoietin as well as experiencing adverse events and hospitalizations was compared between randomization groups using chi-squared tests. A Cox proportional hazards model was used to compare 1-year mortality by randomization group. Statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Enrollment

Of 180 participants assessed for study eligibility, 75 were excluded before randomization. Reasons for screening failures are detailed in Figure 1.

Baseline Characteristics

Groups were similar with respect to age, sex, race, baseline laboratory values, and clinical characteristics (Table 1). Baseline measures of mineral metabolism, including 25(OH)D, calcium, phosphate, and PTH, were also similar. Although this was not an exclusion criterion, none of the participants were taking cholecalciferol or ergocalciferol at the time of enrollment.

Mineral Metabolism

After 12 weeks of therapy with ergocalciferol, 91% of patients in the weekly dosing arm and 65% in the monthly dosing arm achieved sufficiency compared with 35% in the placebo group. Overall differences between groups were statistically significant ($P<0.001$) and all between-group comparisons (each treatment arm versus placebo and weekly

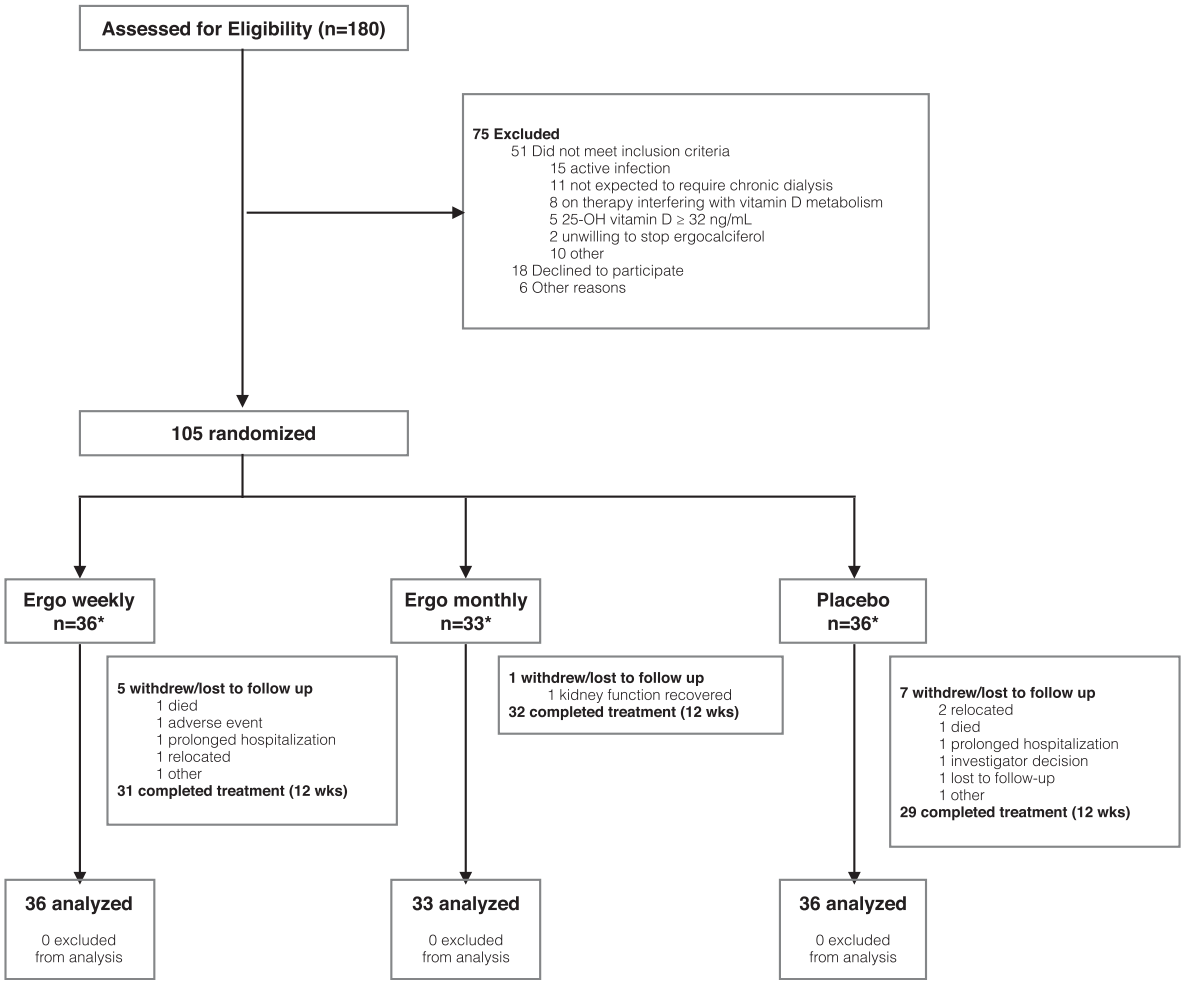

Figure 1. | **Patient enrollment in the Dialysis Infection and Vitamin D in New England (DIVINE) study**. *In addition to explicit exclusion criteria, patient's primary provider or the investigator could exclude a patient from enrollment if participation was felt to be too complex for the patient or logistically impractical (*e.g.,* because of travel). 25(OH)D, 25-hydroxyvitamin D; Ergo, ergocalciferol.

versus monthly ergocalciferol) were significant at 12 weeks ($P<0.02$ in all cases). Both ergocalciferol arms had significantly higher 25(OH)D levels at each visit following treatment initiation. Adjustment for season did not materially affect the results. Calcium, phosphate, PTH, and 25(OH)D levels during the treatment period and immediate post-treatment period (*i.e.,* through week 16) are shown in Figure 2.

Primary analyses revealed no differences in calcium or phosphate between groups throughout the study period. When single time points were examined, a significant difference in calcium levels was noted only at week 8, when the weekly treatment arm had a higher mean calcium level than the placebo group (mean [95% confidence interval (95% CI)], 9.3 [9.1 to 9.6] versus 8.9 [8.7 to 9.1] mg/dl; $P=0.02$). This difference did not persist on subsequent visits. No differences in PTH were detected between groups at any of the study visits.

Active vitamin D use during the treatment period was present in approximately half of the participants (weekly, $n=19$ of 36 [53%]; monthly, $n=18$ of 33 [55%]; placebo, 20 of 36 [56%]; $P=0.97$). While participants being treated with active vitamin D generally had higher PTH levels, analyzing the active vitamin D treated and nontreated groups separately showed no effect of ergocalciferol treatment (Figure 3) on PTH. A relationship between ergocalciferol use and calcium levels was seen only among participants not receiving active vitamin D: Calcium levels were significantly higher in the weekly ergocalciferol group at weeks 8 and 12 compared with placebo (mean [95% CI]: week 8, 9.4 [9.0 to 9.9] mg/dl versus 8.7 [8.2 to 9.1] mg/dl, $P=0.03$; week 12, 9.2 [8.9 to 9.6] mg/dl versus 8.6 [8.3 to 9.0] mg/dl, $P=0.05$). No consistent pattern was observed in phosphate levels among active vitamin D subgroups. $1,25(OH)_2D$ did not differ between groups at week 12 (median [Q1, Q3]: weekly, 95 [66, 135] pg/ml; monthly, 100 [68, 140] pg/ml; placebo, 120 [62, 149] pg/ml; $P=0.92$), nor did these levels change significantly within groups between baseline and week 12 measurements ($P>0.05$ for all comparisons).

Other Factors

At week 12 (end of the treatment period), there were no differences in predialysis systolic BP (monthly, 146±4 mmHg; weekly, 140±4 mmHg; placebo, 145±4 mmHg; $P=0.85$) or predialysis diastolic BP (monthly, 80±3 mmHg; weekly,

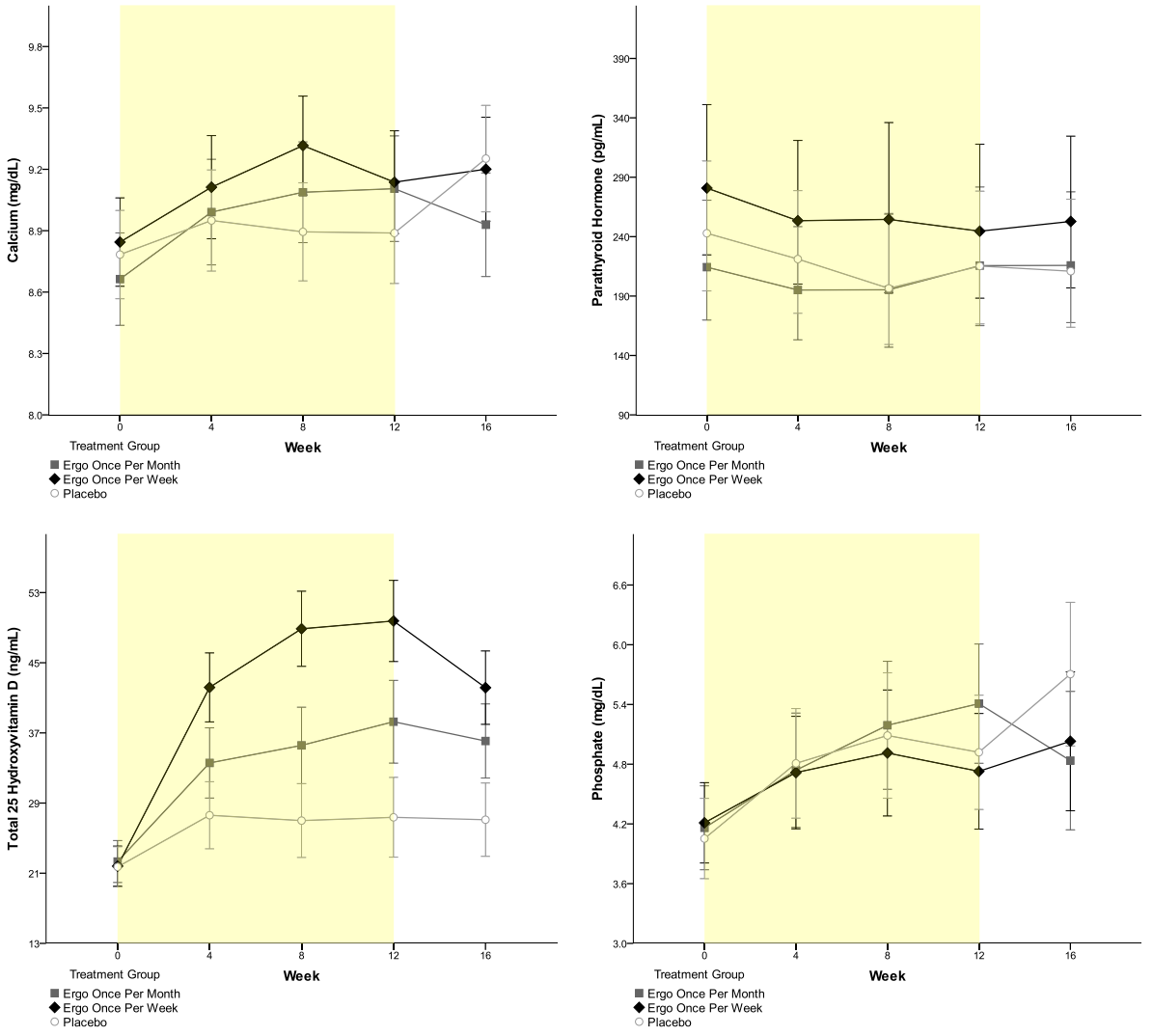

Figure 2. | **Ergocalciferol (Ergo) treatment: effects on 25-hydroxyvitamin D (25[OH]D levels, calcium, phosphate, and parathyroid hormone (PTH).** Participants receiving 50,000 IU of ergocalciferol weekly exhibited the greatest increase in 25(OH)D level, although levels remained higher in both ergocalciferol arms compared with the placebo group. Figures show adjusted mean values and 95% confidence intervals of the estimate. PTH and its 95% confidence interval were exponentiated from natural log–transformed estimates.

77±3 mmHg; placebo, 76±3 mmHg; P=0.86). The frequency of intravenous iron supplementation (monthly, 39%; weekly, 39%; placebo, 51%; P=0.49) and erythropoietin use (monthly, 71%; weekly, 69%; placebo, 60%; P=0.61) were also similar. While total iron binding capacity was significantly higher throughout the study in the weekly versus the placebo group (P<0.05 for all comparisons), no consistent changes in iron, ferritin, or hemoglobin were observed. FGF-23 levels were similar at baseline (median [Q1, Q3]: monthly, 874 [538, 2240] pg/ml; weekly, 1165 [654, 2560] pg/ml; placebo, 990 [564, 2290] pg/ml; P=0.73) and week 12 (monthly, 1337 [748, 2500] pg/ml; weekly, 1915 [956, 3700] pg/ml; placebo, 1666 [927, 2940] pg/ml; P=0.66). However, FGF-23 increased significantly between baseline and week 12 (P<0.05 for all groups).

Adverse Events

Adverse events (Table 2) were present in the majority of participants in all three arms during treatment (monthly ergocalciferol, 26 of 33 [79%]; weekly ergocalciferol, 33 of 36 [92%]; placebo, 28 of 36 [78%]; P=0.34). Elevations in phosphate, calcium, and PTH (corrected calcium >10.2 mg/dl, phosphate >5.5 mg/dl, PTH>450 pg/ml) were similar between groups.

Hospitalizations and Death

Approximately one third of all participants were hospitalized during the treatment period, but overall and cause-specific (cardiac or infection-related) hospitalization frequency did not differ between groups (Table 2). All-cause 1-year mortality did not differ significantly during the 1-year study period, with rates of 0% (zero of 33) in the monthly ergocalciferol group, 8.3% (three of 33) in the weekly ergocalciferol group, and 13.9% (five of 36) in the placebo group (P=0.08). In an exploratory analysis, a nonsignificant trend favoring the combined ergocalciferol arms was noted at 1 year (hazard ratio, 0.28; 95% CI, 0.07 to 1.19; P=0.07).

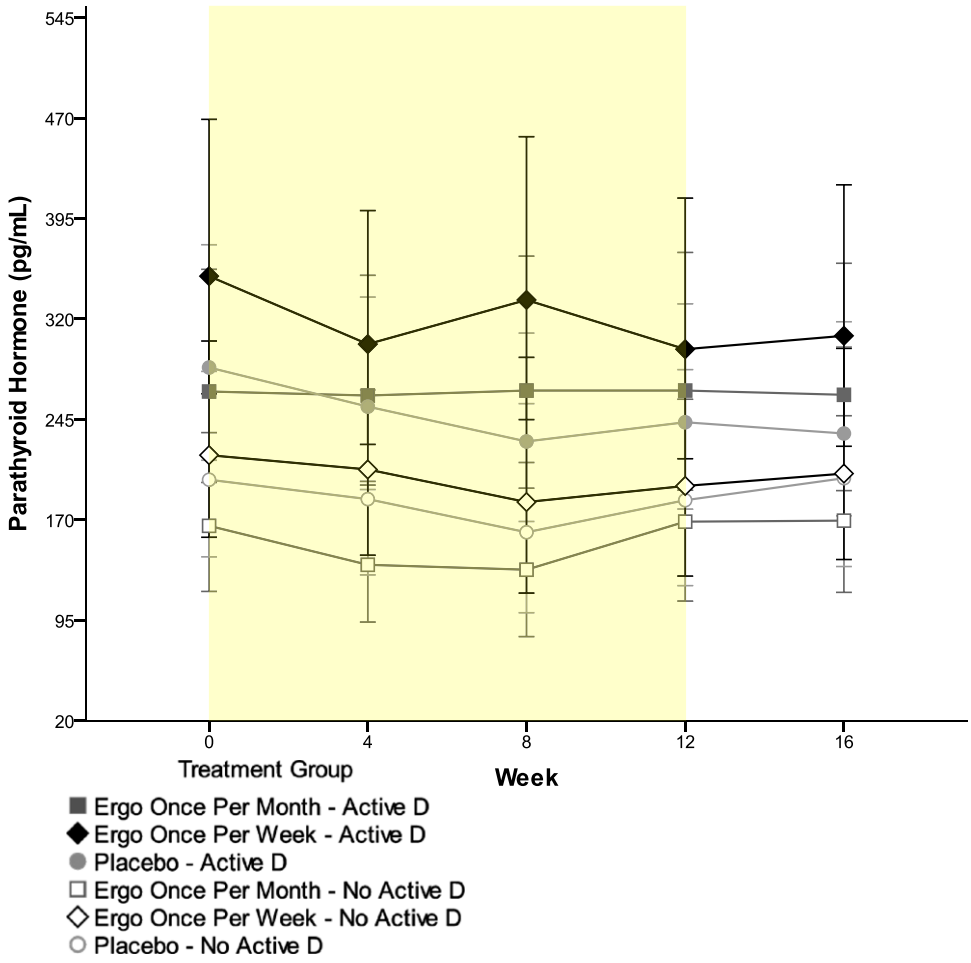

Figure 3. | **Effects of ergocalciferol (Ergo) treatment on PTH values by active vitamin D use.** Treatment arm assignment did not affect PTH levels, regardless of use of active vitamin D. Active vitamin D use was defined as treatment with calcitriol, paricalcitol, or doxercalciferol at three or more study visits. Figures show adjusted mean values and 95% confidence intervals of the estimate. PTH and its 95% confidence interval were exponentiated from natural log–transformed estimates.

Discussion

Increasing biologic evidence surrounding the pleotropic effects of vitamin D has emerged in recent years. Some of these effects may rely on extrarenal conversion of 25(OH)D to $1,25(OH)_2$ D and thus do not require activity of renal CYP27B1. Consequently, there has been emerging optimism that supplementation of 25(OH)D with nutritional vitamin D (cholecalciferol, ergocalciferol) may have benefit beyond existing therapies in ESRD (21). However, randomized trials are lacking, and data regarding appropriate dosing, safety, and efficacy are limited. Despite the high prevalence of 25(OH)D deficiency in dialysis patients (13), nephrologists remain uncertain about the effects of nutritional vitamin D supplementation in this population. To inform clinical treatment and future studies, we conducted DIVINE, a prospective, double-blinded, randomized controlled trial studying two doses of ergocalciferol, the most widely used formulation of nutritional vitamin D available in high-dose oral form in the United States.

Weekly dosing of 50,000 IU of ergocalciferol provided a robust repletion of vitamin D (attaining 91% sufficiency) with 12 weeks of treatment. There were no notable persistent changes in any measures of mineral metabolism, including calcium, phosphate, and PTH levels. There was similarly no increase in adverse events, including hospitalization. Monthly administration of this dose was less effective at establishing vitamin D sufficiency in the studied time frame. Thus, we conclude that the weekly ergocalciferol regimen is a well tolerated and effective strategy to replenish vitamin D levels into the "sufficient" range for most incident HD patients.

The bulk of evidence surrounding vitamin D repletion in CKD, and particularly in ESRD, has been limited to observational studies. Prospective, randomized trials of nutritional vitamin D replacement have generally been small in size, limited in follow-up duration, and largely characterized by negative findings. Chandra *et al.* found no significant benefit with respect to control of PTH in a 3-month study of stages 3–4 CKD (25). Similarly, Kovesdy *et al.* found no benefit for control of PTH with ergocalciferol in patients with stages 3–4 CKD (26). In contrast, Dogan *et al.* found that large 300,000 IU bolus of cholecalciferol significantly reduced PTH in stages 3–4 CKD (versus no intervention), but follow-up was limited to 1 month (27). A larger study by Oksa *et al.* compared 5000 IU versus 20,000 IU of cholecalciferol and

Table 2. Frequency of adverse events during treatment period (weeks 0–12)

Adverse Event	Monthly (*n*=33)	Weekly (*n*=36)	Placebo (*n*=36)	*P* Value[a]
Any adverse event	26 (78.8)	33 (91.7)	28 (77.8)	0.22
Elevated phosphorous	13 (39.4)	13 (36.1)	15 (41.7)	0.89
Elevated calcium	1 (3.0)	2 (5.6)	1 (2.8)	0.80
Elevated PTH	2 (6.1)	6 (16.7)	4 (11.1)	0.38
Elevated potassium	0 (0.0)	0 (0.0)	3 (8.3)	0.05
Elevated white blood count	0 (0.0)	0 (0.0)	1 (2.8)	0.38
Low albumin	0 (0.0)	0 (0.0)	1 (2.8)	0.38
Hospitalization	11 (33.3)	14 (38.9)	13 (36.1)	0.89
Infection	11 (33.3)	11 (30.6)	8 (22.2)	0.56
Cardiovascular	2 (6.1)	6 (16.7)	3 (8.3)	0.31
Respiratory	2 (6.1)	3 (8.3)	3 (8.3)	0.92
Constipation	0 (0.0)	2 (5.6)	1 (2.8)	0.38
Fluid overload	0 (0.0)	1 (2.8)	2 (5.6)	0.38
Nausea/vomiting/diarrhea	4 (12.1)	2 (5.6)	3 (8.3)	0.62
Hypotension	3 (9.1)	0 (0.0)	2 (5.6)	0.20
Hypertension	0 (0.0)	1 (2.8)	0 (0.0)	0.38
Fall	3 (9.1)	3 (8.3)	1 (2.8)	0.51
Other	2 (6.1)	4 (11.1)	2 (5.6)	0.62

Unless otherwise noted, values are expressed as *n* (%).
[a]Significant at $P<0.05$.

found the larger dose was more effective in suppressing PTH, but this study included CKD stages as early as 2–4 (28). The results from DIVINE suggest that any potential effects of nutritional vitamin D on PTH suppression are no longer present by the time patients progress to ESRD.

Only a handful of prospective trials of ergocalciferol or cholecalciferol have included patients receiving HD. Marckmann *et al.* studied a mixture of 52 pre-ESRD CKD and HD patients and found significant PTH-lowering effects of cholecalciferol only in the pre-ESRD patients (29). Another small (*n*=42) 15-week trial of cholecalciferol in HD patients similarly found no effects on calcium, phosphate, and PTH (30). A trial of 38 HD patients found no effect on PTH, monocytes, T-cell differentiation, or cytokine production (31). A recent study by Hewitt *et al.* (*n*=60) similarly found no effects of cholecalciferol supplementation on muscle strength, functional capacity, pulse wave velocity, or health-related quality of life (32).

Despite its modest size, DIVINE is the largest prospective, randomized, placebo-controlled, double-blinded trial of nutritional vitamin D supplementation in long-term HD to date. Given the potential broad-ranging actions of nutritional vitamin D, we also examined a wide range of parameters in addition to markers of mineral metabolism to fully assess any potential adverse effects of treatment. We found no differences in a host of adverse events, including abnormalities in mineral metabolism, hospitalizations, infectious events, and cardiovascular events. In contrast to prior observational studies, we did not find an effect on anemia or related measures (33–35). We found that FGF-23 levels rose in all groups between baseline and week 12, but unlike previous studies in individuals without kidney disease, we did not find that supplementation with ergocalciferol augmented this effect (36). Calcium and phosphate rose in all groups, which may reflect normalization of calcium through the dialysis procedure itself, active vitamin D use (stimulating calcium and phosphate absorption), and increase dietary intake following correction of uremia. We found no differences between or within groups with respect to 1,25(OH)D levels, suggesting that there is no significant conversion of 25(OH)D to $1,25(OH)_2$ D and that any actions of nutritional vitamin D that affect outcomes likely do so by localized effects (*e.g.,* autocrine, paracrine) rather than systemic conversion.

When the two ergocalciferol arms were combined, we noted a trend toward reduction in all-cause mortality among ergocalciferol-treated participants compared with placebo-treated participants. Because mortality was not our primary endpoint, these findings must be interpreted with caution. DIVINE was not powered to detect differences in mortality or other specific adverse events. Despite these caveats, our findings are consistent with observational data associating lower vitamin D levels with mortality in patients with ESRD (11). Given the absence of novel therapies that affect dialysis survival, dedicated mortality studies of vitamin D repletion are warranted.

Our study has several limitations. DIVINE included only incident HD patients initiating treatment at an academic medical center. While this removed potential effects of previous dialysis treatment, our population may not be representative of the general HD population. Similarly, DIVINE's geographic restriction to the Northeast United States may limit generalizability to other regions. Lastly, this analysis did not incorporate measures of vitamin D binding protein or "bioavailable" vitamin D, which has been gaining increasing attention as a potentially more accurate measure of vitamin D status; debate is ongoing regarding optimal methods to determine bioavailable vitamin D status (37–41).

Both ergocalciferol (D_2) and cholecalciferol (D_3) can be metabolized *via* the hepatic 25-hydroxylase (CYP2R1) and

the renal 1α-hydroxylase (CYP27B1); some have argued that cholecalciferol is more biologically relevant to humans (42,43). We selected ergocalciferol because the high-dose nutritional vitamin D is largely available only as ergocalciferol in the United States. However, our results may not be generalizable to cholecalciferol.

In conclusion, we found that a weekly ergocalciferol dosing of 50,000 IU over 12 weeks corrected vitamin D insufficiency in a population of incident HD patients. Despite the marked effects on 25(OH)D levels, we found no adverse effects of such treatment on several markers of mineral metabolism, including calcium, phosphate, and PTH.

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Disclosures

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