AJKD

Original Investigation

Biochemical Parameters After Cholecalciferol Repletion in Hemodialysis: Results From the VitaDial Randomized Trial

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Background: The 2009 KDIGO (Kidney Disease: Improving Global Outcomes) chronic kidney disease–mineral and bone disorder clinical practice guideline suggests correcting 25-hydroxyvitamin D_3 (25[OH]D) levels < 30 ng/mL in patients treated with maintenance hemodialysis, but does not provide a specific treatment protocol.

Study Design: 2-center, double-blind, randomized, 13-week, controlled trial followed by a 26-week open-label study.

Setting & Participants: 55 adult maintenance hemodialysis patients with 25(OH)D levels < 30 ng/mL were recruited from June 2008 through October 2009.

Intervention: Cholecalciferol, 25,000 IU, per week orally versus placebo for 13 weeks, then 26 weeks of individualized cholecalciferol prescription based on NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines.

Outcomes: Primary end point was the percentage of patients with 25(OH)D levels ≥ 30 ng/mL at 13 weeks. Secondary outcomes included the percentage of patients with normal calcium, phosphorus, and intact parathyroid hormone (iPTH) blood levels. Safety measures included incidence of hypercalcemia and hypervitaminosis D.

Measurements: Blood calcium and phosphate were measured weekly; iPTH, 25(OH)D, 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D$), and bone turnover markers, trimonthly; fetuin A and fibroblast growth factor 23 (FGF-23) serum levels and aortic calcification scores were determined at weeks 0 and 39.

Results: The primary end point significantly increased in the treatment group compared with the placebo group (61.5% vs 7.4%; $P < 0.001$), as well as $1,25(OH)_2D$ levels (22.5 [IQR, 15-26] vs 11 [IQR, 10-15] pg/mL; $P < 0.001$) and the proportion of patients achieving the target calcium level (76.9% vs 48.2%; $P = 0.03$). Incidence of hypercalcemia and phosphate and iPTH levels were similar between groups. The second 26-week study phase did not significantly modify the prevalence of 25(OH)D level ≥ 30 ng/mL in patients issued from the placebo group.

Limitations: Small size of the study population.

Conclusions: Oral weekly administration of 25,000 IU of cholecalciferol for 13 weeks is an effective, safe, inexpensive, and manageable way to increase 25(OH)D and $1,25(OH)_2D$ levels in hemodialysis patients. Further evaluation of clinical end points is suggested.

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INDEX WORDS: Cholecalciferol; vitamin D; calcium; parathyroid hormone (PTH); hemodialysis; clinical practice guidelines; calcitriol; vascular calcification; aortic calcification score; fetuin A; fibroblast growth factor 23 (FGF-23); 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; nutritional vitamin D; vitamin D deficiency; vitamin D repletion; bone fracture; falls.

Levels of calcidiol (25-hydroxyvitamin D_3 (25[OH]D) < 30 ng/mL are observed frequently in patients treated with maintenance hemodialysis (HD) in Northern latitudes.[1-4] As with the general population, this is associated with poor outcomes in chronic kidney disease (CKD; for review, see Nigwekar et al[5]), including stage 5.[4,6-9]

To date, a limited number of randomized controlled trials designed to study the effect of nutritional vitamin D (either cholecalciferol or ergocalciferol) have been conducted in HD patients.[3,10-13] This lack of interest probably is multifactorial. As kidney function declines, production of calcitriol (1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$]) decreases in

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parallel.[14,15] Since the 1980s, 1α-hydroxylated forms of vitamin D (also called active vitamin D) became widely used in HD patients and low-priced nutritional forms of vitamin D were neglected.[5] The existence of extrarenal 1α-hydroxylases was suggested by the observation that anephric individuals were able to produce $1,25(OH)_2D$ in response to supraphysiologic nutritional vitamin D challenge.[16,17] However, these findings did not modify prescription habits. Further experimental studies demonstrated that extrarenal 1α-hydroxylases were present in a wide range of tissues acting locally in paracrine or autocrine circuits.[18] That led to the understanding of the pleiotropic properties of 25(OH)D[19-21] and revived interest in this molecule.[22-24] In addition, it was noted that 25(OH)D has an excellent safety profile.[16,22,25] For these reasons and despite the absence of any controlled trial or large prospective study, in 2009, KDIGO (Kidney Disease: Improving Global Outcomes) recommended restoration of 25(OH)D levels > 30 ng/mL in patients treated with maintenance HD.[26] However, targeted protocols are still lacking. The high cost of the 25(OH)D assay further complicates drug prescription and the setup of larger clinical trials.[22]

The present study, combining a 13-week randomized trial of oral cholecalciferol repletion versus placebo with an open-label study of customized cholecalciferol prescription derived from the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines[27] for 26 additional weeks aimed to provide valuable information about vitamin D repletion strategies and their possible impact on mineral and bone markers.

METHODS

Definitions

In this study, we defined levels of 25(OH)D ranging from 20 to <30 ng/mL as "insufficient" and levels < 20 ng/mL as "deficient."[5]

Study Design

Overview

This was an investigator-driven, prospective, multicenter, partly randomized, controlled trial (VitaDial) performed in 2 Belgian nephrology centers (Epicura [in Baudour] and Erasme university hospitals [in Brussels]). It was approved by the institutional review board at each site. This 39-week trial was divided into 2 periods as follows: a randomized period (13 weeks) during which enrolled patients were randomly assigned to receive either cholecalciferol or a placebo, and an open-label period (26 weeks) during which all patients, regardless of initial allocation, received a cholecalciferol dose adjusted to their most recent 25(OH)D assessment (at weeks 13 and 26; Fig 1). This design allowed investigators to collect data for a new cholecalciferol repletion protocol using substantial doses under safe conditions (first period limited to 13 weeks) and, in a second phase, gather data reflecting the use of NKF-KDOQI guidelines, usually prescribed for 6 months (second period of 26 weeks). Finally, by combining both periods, we investigated the biochemical outcomes of cholecalciferol repletion over a total period of 39 weeks. Another interest of the present design was to offer cholecalciferol access to all

2003 KDOQI GUIDELINES
Ergocalciferol administration in patients with CKD Stages 3 and 4
(to be revised after 6 months)

Serum 25(OH)D (ng/mL)	Ergocalciferol dose
< 5 ng/mL	50,000 IU/wk x 12 wks, then monthly
5 - 15 ng/mL	50,000 IU/wk x 4 wks, then 50,000 IU/mo
16 - 30 ng/mL	50,000 IU/mo
> 30 ng/mL	Vitamin-D-containing multi- vitamin preparation

VITADIAL STUDY
Cholecalciferol administration in patients with CKD Stage 5

PHASE I
RANDOMIZATION
(13 wks)

Serum 25(OH)D (ng/mL)	Cholecalciferol dose
< 30 ng/mL	25,000 IU/wk orally X 13 wks VS (1:1) Placebo

PHASE II
OPEN-PHASE
(26 wks with dose adjustment at midpoint)

Serum 25(OH)D (ng/mL)	Cholecalciferol dose
< 6 ng/mL	50,000 IU/wk x 13 wks
6 - 15 ng/mL	50,000 IU/wk x 4 wks, then 50,000 IU/mo x 2 mo
16 - 30 ng/mL	50,000 IU/mo x 3 mo
30 - 60 ng/mL	25,000 IU/mo x 3 mo
> 60 ng/mL	None

Figure 1. Diagram compares cholecalciferol prescription during both phases of the study to the reference 2003 NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines. Abbreviations: 25(OH)D, 25-hydroxyvitamin D_3; CKD, chronic kidney disease.

patients, avoiding possibly deleterious effects of long-term vitamin D deprivation.

Randomization Period

The enrollement period was from June 2008 through October 2009. Patients who fulfilled the study entry criteria were randomly assigned to receive either an oral cholecalciferol preparation or its vehicle every week for 13 weeks, according to a 1:1 randomization procedure. Randomization was stratified by center. We used block randomization with permuted blocks of 4 allocations.

Open-Label Period

After the 13-week randomization period, every participant entered a 26-week repletion phase and received a cholecalciferol dose adjusted to his or her previous 25(OH)D level as evaluated at weeks 13 and 26. Cholecalciferol prescriptions were based on the 2003 NKF-KDOQI guidelines for patients with CKD stages 3-4 and adapted for patients with CKD stage 5 due to the absence of targeted guidelines for these patients[27] (for details, see Fig 1).

Participants

Eligible patients were adults (aged $\geq$ 18 years) with CKD stage 5 who were receiving HD for at least 3 months with a minimum of 3 HD sessions per week and who had serum 25(OH)D levels $<$ 30 ng/mL and had signed the informed consent form approved by each center's ethics committee. Exclusion criteria were as follows: known hypersensitivity to any constituent of the study medications, pregnancy or lactation period, women without effective contraception, cholecalciferol and/or calcitriol and/or paricalcitol and/or alfacalcidol dosage adjustment 1 month prior to enrollment (the last 3 being the only active vitamin D formulations available in Belgium), plasma calcium level $>$ 10.2 mg/dL, concurrent enrollment in another clinical trial, prior parathyroidectomy, granulomatous disorder, active malignancy, and/or estimated life expectancy less than 1 year.

Investigational Product and Concomitant Medications

The study drug consisted of 1 mL of groundnut oil solution containing 25,000 IU of cholecalciferol (D-cure; S.M.B. [drug marketing authorization number 465S24F11]), whereas the placebo was made by our study pharmacist with the same groundnut oil as the active drug, coming directly from the D-cure factory. Placebo and active drug were indistinguishable from each other. Study preparations were administered orally at the end of the first or second HD session of the week, under the supervison of the nurse in charge of the patient. Any other cholecalciferol supplementation was withdrawn. Apart from cholecalciferol, any modification of the medical treatment, including mineral bone disorder–related drugs, was left to the discretion of the treating nephrologist following NKF-KDOQI guidelines.

Study Outcomes

The primary end point was the proportion of participants with 25(OH)D levels $\geq$ 30 ng/mL at week 13.

Secondary end points were the percentage of patients with appropriate blood levels of calcium, phosphorus, and intact parathyroid hormone (iPTH). Recommended concentrations were 8.5-10.2 mg/dL for calcium, $\leq$4.5 mg/dL for phosphate, and 146-657 pg/mL for iPTH (corresponding to 2-9 times the upper reference limit value in our laboratory) as suggested in the 2009 KDIGO recommendations.

Safety end points included the occurence of hypercalcemia (calcium $>$ 10.2 mg/dL), hypervitaminosis D (defined as 25(OH)D $>$ 100 ng/mL independent of calcium level), adverse events (fractures), serious adverse events, and malignancies. Hypercalcemia and/or hypervitaminosis D resulted in the immediate and definitive suspension of the study medication. The onset or worsening of hyperphosphatemia (phosphate $>$ 5.5 mg/dL) did not lead to the cessation of study drug, but was treated with calcium carbonate or calcium-free phosphate binders according to NKF-KDOQI guidelines.

Sample Size Calculation

Based on preliminary data, we hypothesized that the proportion of patients with a 25(OH)D level $<$ 30 ng/mL would decrease to 70% in the treatment arm compared to 100% in the placebo arm. We calculated that 22 patients were required in each group to reach statistical power of 80% with a type I error of 5%. Finally, we chose to recruit at least 20% extra patients (26 patients per group) in anticipation of dropouts.

Statistical Analysis

Results were expressed as mean $\pm$ standard deviation, median with interquartile range (IQR), or percentage. Continuous variables were compared using t test or Mann-Whitney test in cases of non-Gaussian distribution. Paired data were compared using paired t test, analysis of variance for repeated measures, or Friedman and Wilcoxon test in cases of non-Gaussian distribution. Categorical data were compared using χ^2 or Fisher exact test. Paired categorical data were compared using χ^2 McNemar test. Relevant results were expressed as number needed to treat (NNT; defined as the inverse of absolute risk reduction). All study end points were analyzed according to the intention-to-treat principle. Statistical analyses were performed using STATA software, version 12 (StataCorp LP). $P < 0.05$ was considered statistically significant.

Sampling

Blood samplings were performed regularly at the beginning of the first or second HD session of the week, through the arterial tubing. Plasma levels of calcium and phosphorus were checked every week. Serum levels of iPTH, osteocalcin, carboxy-terminal telopeptides, bone alkaline phosphatases, 25(OH)D, and $1,25(OH)_2D$ were assessed every 13 weeks. Extra serum was collected and frozen ($-20^{\circ}C$) at baseline and end of the study (week 39) in order to ultimately assess fetuin A and fibroblast growth factor 23 (FGF-23) levels. When available ($>$300 mL), a 24-hour urine sample was collected at baseline.

Biochemical Assessments

Plasma biochemistry samples were analyzed with a standard multichannel biochemical analyzer (Modular P; Roche), except for the following parameters: serum iPTH and 25(OH)D were measured according to a direct chemiluminescence method (module LIAISON M; DiaSorin Inc) in the Erasme Hospital laboratory, Brussels (accredited by DEQAS [Vitamin D External Quality Assessment Scheme]); serum $1,25(OH)_2D$ was measured in an experienced laboratory (Brugmann Hospital, Brussels, Belgium) after extraction, using a competitive radioimmunoassay (DiaSorin Inc); serum levels of osteocalcin and C-telopeptides were evaluated by electrochemiluminescence technology (module E170; Roche); serum bone alkaline phosphatases were assessed by a chemiluminescence-based immunoenzymatic assay with paramagnetic particles (Beckman Coulter Inc); serum fetuin A was measured by nephelometry (assay designed, developed, and performed by Prof W. Jahnen-Dechent, RWTH, Aachen University, Germany). Nephelometric readings were taken in a MiniNeph single cuvette nephelometer (The Binding Site). Purified human plasma fetuin A (Dade-Behring) served as support plotted to derive the calibration curve; FGF-23 carboxy-terminal fragments were measured by enzyme-linked immunosorbent assay (Immutopics Inc).

Radiologic Assessment of Anterior-Posterior Aortic Calcifications

All patients had lateral lumbar radiographs for semi-quantification of aortic calcifications at baseline and week 39. Aortic calcification scores, according to the method published by Kauppila et al,[28] were established by 2 independent observers in a blinded and randomized fashion. Scores ranged from 0 (no calcification) to 24.

RESULTS

Patient Characteristics and Demographics

Figure 2 shows patient flow throughout the trial. A total of 176 patients were screened: 26 patients subsequently entered the treatment arm and 29 entered the placebo arm. Both groups were well balanced with respect to patient demographics, comorbid conditions, and medications relative to mineral bone disorder, as well as season of enrollment (Table 1).

Efficacy End Points

At week 13, a total of 26 and 27 patients remained for analysis in the treament and placebo groups, respectively; 2 patients were lost to follow-up in the placebo group (n = 1, kidney transplantation; n = 1, death from arrhythmia). Regarding the primary end point, 16 of 26 (62%; 95% confidence interval [CI], 41%-80%) patients from the treatment group had their 25(OH)D levels normalized (≥30 ng/mL) at week 13 versus 2 of 27 (7%; 95% CI, 1%-24%) in the placebo group ($P < 0.001$; NNT = 1.8 [95% CI, 1.4-3.4]). Mean 25(OH)D levels were 35.2 ± 12.1 ng/mL in the treatment group versus 16.4 ± 7.8 ng/mL in the placebo group ($P < 0.001$). At the end of the first period, 1 of 26 (4%; 95% CI, 0.1%-20%) patients in the treatment group versus 17 of 27 (63%; 95% CI, 42%-81%) in the placebo group presented with 25(OH)D deficiency (<20 ng/mL; $P < 0.001$; NNT = 1.7 [95% CI, 1.3-2.85]; Fig 3).

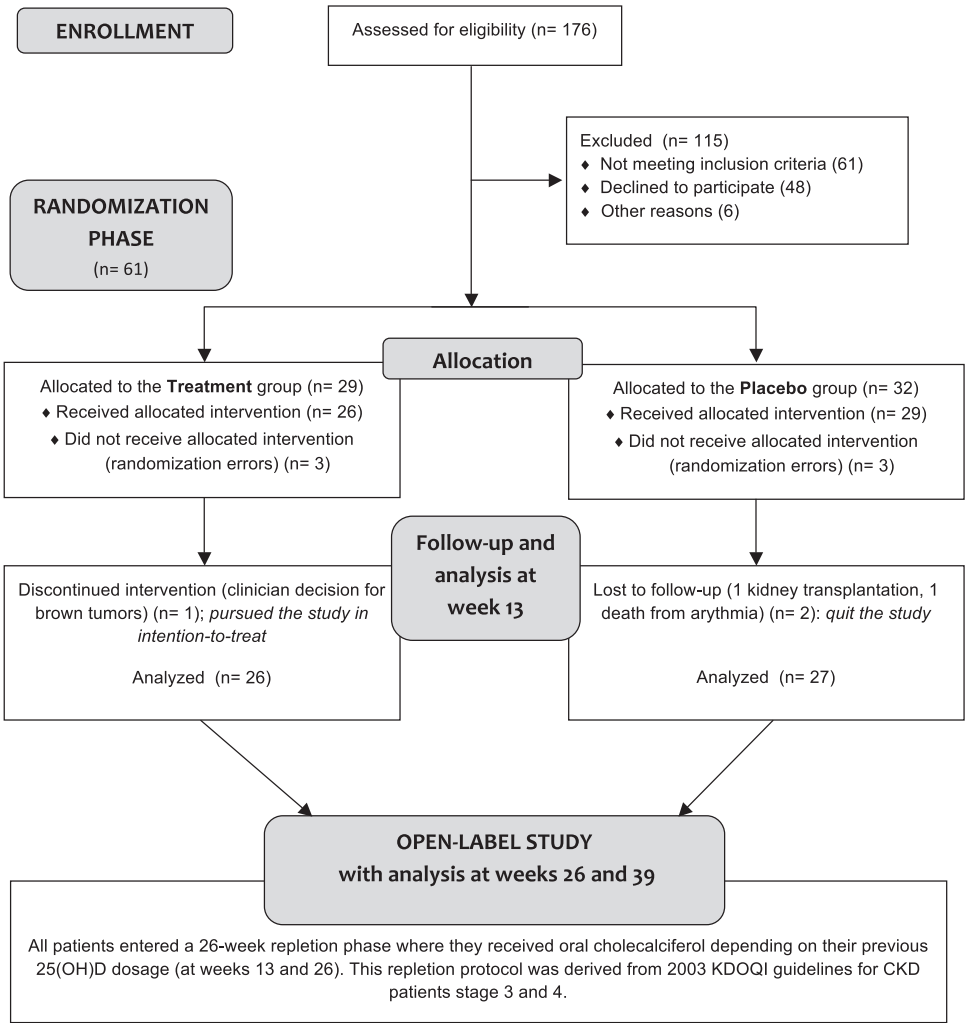

Figure 2. Study flow diagram. Randomized phase of the study was from baseline to week 13; open-label phase, from week 13 to week 39. Abbreviations: 25(OH)D, 25-hydroxyvitamin D_3; CKD, chronic kidney disease; KDOQI, Kidney Disease Outcomes Quality Initiative.

Table 1. Baseline Characteristics of the Patient Population

	Placebo (n = 29)	Cholecalciferol (n = 26)
Demographic variables		
Age (y)	66 ± 12.0	62 ± 12.3
Ethnicity		
Northern European	24 (83)	17 (65)
Maghrebian	4 (14)	7 (27)
Sub-Saharan	1 (3)	2 (8)
Male sex	16 (55)	18 (69)
Center ratio (Epicura/Erasme)	8/21	6/20
Hemodialysis vintage (mo)	41 [20-80]	46 [9-68]
Prior transplantation	7 (24)	5 (19)
Primary nephropathy		
Diabetic	10 (34)	5 (19)
Nephroangiosclerosis	4 (14)	7 (27)
Pyelonephritis	2 (7)	0 (0)
ADPKD	1 (3)	0 (0)
Renal vascular disease	0 (0)	2 (8)
Miscellaneous	7 (24)	5 (19)
Glomerulonephritis	3 (10)	4 (15)
Unknown	2 (7)	3 (12)
Comorbid conditions		
Arterial hypertension	26 (90)	23 (88)
Diabetes	16 (55)	13 (50)
Ischemic cardiomyopathy	11 (38)	10 (38)
Peripheral obliterative arterial disease	12 (41)	9 (35)
Prior neoplasia	7 (24)	3 (12)
Tobacco use	4 (14)	5 (19)
BMI (kg/m^2)	26.8 ± 5.97[a]	26.7 ± 7.32
Physical examination		
Systolic arterial BP (mm Hg)	138.7 ± 24.8	145.2 ± 35.6
Diastolic arterial BP (mm Hg)	71.5 ± 15.8	73.8 ± 18.5
Laboratory values		
Calcium (mg/dL)	8.7 ± 0.49	8.7 ± 0.63
Phosphorus (mg/dL)	4.7 ± 1.9	4.5 ± 1.3
iPTH (pg/mL)	426.9 ± 207.6	414.1 ± 281.9
25(OH)D (ng/mL)	18.4 ± 7.9	17.1 ± 6.4
20-<30 ng/mL	13 (45)	10 (38)
10-<20 ng/mL	10 (34)	11 (42)
<10 ng/mL	6 (21)	5 (19)
$1,25(OH)_2D$ (pg/mL)	14 [9-18]	13 [8-16]
<20 pg/mL	24 (83)	22 (85)
C-Telopeptide (pg/mL)	2,210 [1,550-3,390]	2,485 [1,530-3,260]
Osteocalcin (ng/mL)	250 [107-291]	179.5 [82-260]
Bone alkaline phosphatase (μg/L)	23.3 [13.6-29.3]	28.95 [16.3-41.1]
FGF-23 (pg/mL)	598 [259-1,202][a]	548.5 [302-1,783]
Fetuin A (mg/mL)	0.38 ± 0.06	0.38 ± 0.07
CRP (mg/dL)	0.9 [0.27-2.6]	0.9 [0.55-2.7]
Albumin (g/dL)	3.67 ± 0.43	3.66 ± 0.65
Prealbumin (g/dL)	27.1 ± 7.8	24.9 ± 9.3
PCR	1.14 ± 0.34	1.03 ± 0.27
Aortic calcification score	9.96 ± 7.3[a]	8.2 ± 7.4[a]
Residual diuresis > 300 mL/d	9 (33)	12 (48)
Current medications[a]		
Elemental calcium (g/d)	0.91 ± 0.57	0.85 ± 0.47
Sevelamer	8 (29)	4 (15)
Sevelamer dose (mg/d)	4,800 [4,000-4,800]	4,800 [3,200-6,000]
Lanthanum carbonate	2 (7)	3 (12)
Cholecalciferol	21 (75)	18 (69)
Alfacalcidol or calcitriol	10 (36)	8 (31)

(Continued)

Table 1 (Cont'd). Baseline Characteristics of the Patient Population

	Placebo (n = 29)	Cholecalciferol (n = 26)
Alfacalcidol or calcitriol dose (μg/wk)	3 [2.25-5]	2.6 [1.1-3]
Cinacalcet	6 (21)	2 (8)
Acenocoumarol	5 (18)	6 (23)
Dialysate calcium		
1.5 mEq/L	23 (79)	20 (77)
1.25 mEq/L	6 (21)	6 (23)
Weekly Kt/V_{urea}	3.97 ± 0.72	3.83 ± 0.60
Enrollment period		
June 2008	11 (38)	12 (46)
September 2008	6 (21)	7 (27)
December 2008	4 (14)	1 (4)
October 2009	8 (28)	6 (23)
Bone mineral parameters[b]		
Calcium = 8.5-10.2 mg/dL	20 (69)	15 (58)
Phosphorus ≤ 4.5 mg/dL	19 (66)	15 (58)
iPTH = 146-657 pg/mL	24 (83)	15 (58)

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495; 25(OH)D in ng/mL to nmol/L, ×2.496; 1,25$(OH)_2$D in pg/mL to pmol/L, ×2.6.

Abbreviations and definitions: 25(OH)D, 25-hydroxyvitamin D (also known as calcidiol); 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D (also known as calcitriol); ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BP, blood pressure; C-telopeptides; carboxy-terminal telopeptides; CRP, C-reactive protein; FGF-23, fibroblast growth factor 23; iPTH, intact parathyroid hormone; Kt/V_{urea}, coefficient of dialysis efficacy; PCR, protein catabolic ratio.

[a]In the placebo group, aortic calcification score was calculated from 25 patients, whereas BMI, FGF-23, and all medications (excepted cinacalcet, dialysate calcium, and Kt/V_{urea}) were calculated from 28 patients. In the treatment group, aortic calcification score was calculated from 18 patients.

[b]Adequacy according to 2009 KDIGO (Kidney Disaease: Improving Global Outcomes) and local laboratory reference ranges.

Patients in the control group had significantly increased serum 1,25$(OH)_2$D levels compared with those in the placebo group (median, 22.5 [IQR, 15-26] vs 11 [IQR, 10-15] ng/mL, respectively; $P < 0.001$), leading to a significantly higher percentage of patients with normalized 1,25$(OH)_2$D levels (54% [95% CI, 33%-73%] vs 12% [95% CI, 2%-30%]; $P = 0.001$; NNT = 2.3 [95% CI, 1.6-5.9]; Fig 3).

Regarding the secondary end points, at 13 weeks, a higher proportion of treated patients achieved the target for calcium of 8.5-10.2 mg/dL (77% [95% CI, 56%-91%] vs 44% [95% CI, 29%-68%]; $P = 0.02$; NNT = 3.1 [95% CI, 1.9-16.2]). Otherwise, the treatment did not significantly affect blood levels of calcium, phosphorus, or iPTH (Fig 4) or bone turnover parameters (data not shown; Table S1, available as online supplementary material).

Impact of Randomization Group on Drug Prescription

At week 13, bone mineral disorder–targeted treatments did not differ according to randomization group (Table S2).

Safety End Points

During the randomization period, one patient from the placebo group developed a plasma calcium level > 10.2 mg/dL (10.4 mg/dL). This event was concomitant to hypovitaminosis D (25[OH]D, 20 ng/mL; 1,25$[OH]_2$D, 14 pg/mL), hypoparathyroidism, and low-dose calcium supplements (iPTH, 40 pg/mL; elemental calcium intake, 0.4 g/d; Table S3). At week 27, hypercalcemia with a calcium level of 10.3 mg/dL occured in a second patient from the treatment group. Over 26 weeks, he received a total cumulative cholecalciferol dose of 400,000 IU. Hypercalcemia coexisted with an elevated 25(OH)D level (68 ng/mL), low 1,25$(OH)_2$D level (14 pg/mL), high iPTH level (700 pg/mL), and elemental calcium intake of 1.2 g/d (Table S3).

During the entire study, no patient developed a 25(OH)D level > 100 ng/mL. The highest levels recorded at weeks 13, 26, and 39 were 57, 81, and 43 ng/mL, respectively. Corresponding calcium levels were 9, 8.5, and 8.3 mg/dL, respectively.

Table 2 shows a summary of the incidence of serious adverse events. Patients who received cholecalciferol in the first 13 weeks of the study experienced no bone fractures and fewer hospitalizations for falls compared with patients who received placebo treatment in the first phase of the study. Nine patients from the placebo group experienced 10 distinct fracture episodes during the entire study period.

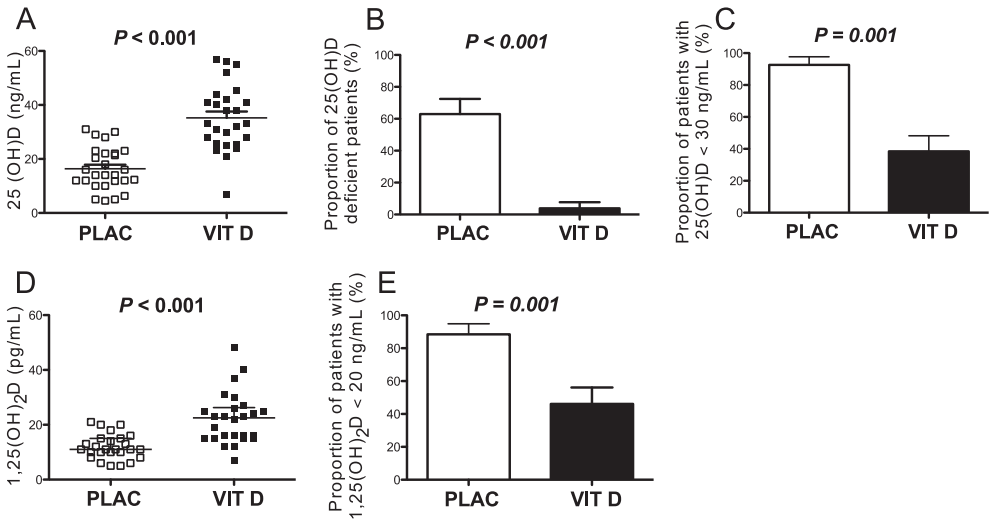

Figure 3. Primary end point and 1,25-dihydroxyvitamin D_3 (1,25[OH]$_2$D) levels after the randomization period (13 weeks). Treated patients (VIT D) are represented in black, and placebo patients (PLAC), in white outlined in black. (A) Serum 25-hydroxyvitamin D_3 (25 [OH]D) levels, (B) proportion of 25(OH)D-deficient patients, (C) proportion of patients with 25(OH)D levels < 30 ng/mL, (D) serum 1,25(OH)$_2$D levels, and (E) proportion of patients with 1,25(OH)$_2$D levels < 20 pg/mL.

Evolution of Mineral and Bone Parameters During the 39-Week Study Period

Despite receiving different treatment regimens during the first 13-week phase, patients in the treatment and placebo groups had similar 25(OH)D levels at 26 weeks (31.5 ± 15.5 vs 28.0 ± 9.3 ng/mL; $P = 0.3$) and 39 weeks (25.9 ± 9.2 vs 26.4 ± 9.1 ng/mL; $P = 0.9$). Because all patients underwent a 25(OH)D repletion program when the 39-week study period is considered as a whole, we were able to analyze them as a single cohort for the 39-week period. During the entire study, effective 25(OH)D

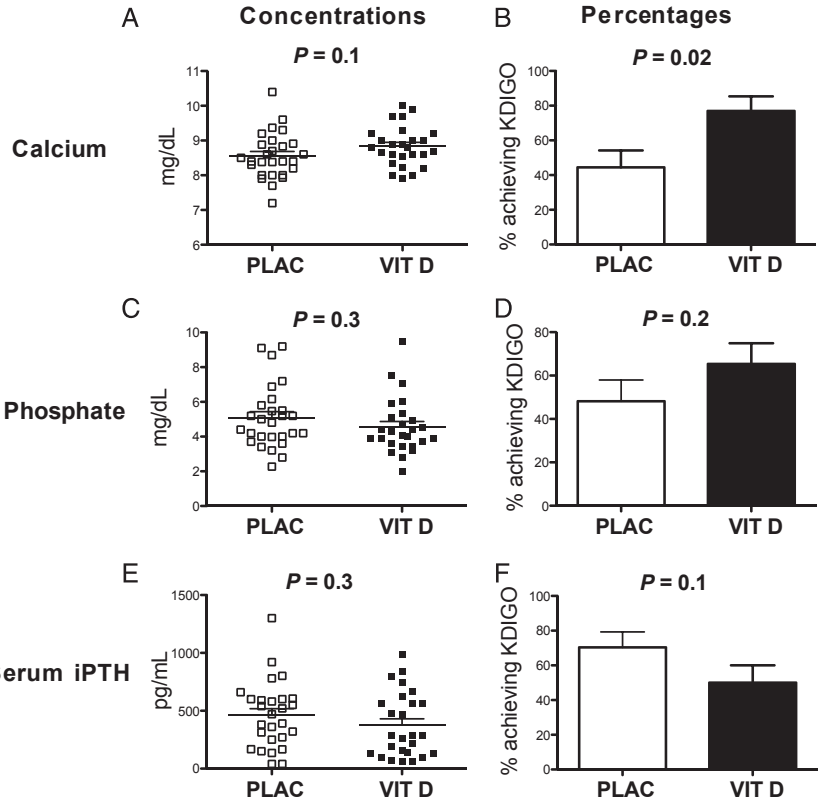

Figure 4. Blood levels of (A) total calcium, (C) phosphate, and (E) intact parathyroid hormone (iPTH) after 13 weeks of randomization in treated (VIT D) and placebo (PLAC) groups. (B, D, F) For each parameter, the corresponding proportion of patients achieving the 2009 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines targets is provided.

Table 2. Adverse Events Observed Throughout the Whole Study Period (39 weeks)

	Placebo (n = 29)	Cholecalciferol (n = 26)	*P*
Hypercalcemia (>10.2 g/dL)	1 (3)	1 (4)	0.9
Hypervitaminosis D > 100 ng/mL)	0 (0)	0 (0)	NA
Fractures phase I/phase II	5/5[a]	0/0	0.002
Hospitalization stays (d)	16 [0-40]	8 [2-18]	0.9[b]
No. of hospitalization stays	53	47	0.6
Infection[c]	17 (32)	24 (51)	0.2[b]
Cardiovascular disease[c]	9 (17)	4 (8)	0.2[d]
Fall[c]	5 (9)	0 (0)	NA
Vascular access issue[c]	8 (15)	8 (17)	0.9[b]
Other[c]	14 (26)	11 (23)	0.7[d]
Diagnosis of cancer, first year of trial	1 (3)	0 (0)	0.9
1-y survival	21 (72)	21 (81)	0.5
2-y survival	17 (59)	19 (73)	0.3

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables are given as median [interquartile range].

Abbreviation: NA, not applicable.

[a]In 9 participants.

[b]Univariate negative binomial regression model used to calculate related *P* values regarding multiple hospitalizations per patient.

[c]Reason for hospitalization is given; data are n (percentage of hospitalizations).

[d]Poisson regression used to calculate related *P* values regarding multiple hospitalizations per patient.

repletion was achieved (overall 25[OH]D level, 17.9 ± 7 ng/mL at baseline vs 26.2 ± 9 ng/mL at week 39; $P < 0.001$) without significant change in $1,25(OH)_2D$ levels (median of 13.5 [IQR, 9-17] pg/mL at week 0 vs 15 [IQR, 10-21] pg/mL at week 39; $P = 0.3$), calcium, phosphate, or iPTH (data not shown) blood levels. A statistically significant decrease in serum fetuin A levels was observed (median of 0.39 [IQR, 0.34-0.42] mg/mL at week 0 vs 0.33 [IQR, 0.29-0.36] mg/mL at week 39; $P < 0.001$). Levels of carboxy-terminal telopeptides, bone alkaline phosphatases, osteocalcin, and FGF-23 did not change significantly.

Vascular Calcification Scores

At week 39, patients had similar calcification scores (median, 4.5 [IQR, 1-12.5] vs 11 [IQR, 2-14]; $P = 0.4$) regardless of whether they had received treatment (n = 21) or placebo (n = 16) in the first 13 weeks of the study. Taking into account available paired scores (n = 30) for a longitudinal comparison between weeks 0 and 39, calcification scores remained stable (median, 7 [IQR, 2-14] vs 7.5 [IQR, 2-15]; $P = 0.3$). Of note, 15 of 53 patients without a history of cholecalciferol treatment had a higher calcification score at baseline (median, 13 [IQR, 6-18] vs 7 [IQR, 1-14]; $P = 0.05$).

Comparison of Our Repletion Protocol With NKF-KDOQI Guidelines

In patients who were in the placebo group for the first 13 weeks of the trial, cholecalciferol supplementation based on the 2003 NKF-KDOQI guidelines significantly reduced the proportion of patients with a 25(OH)D level < 30 ng/mL (from 92% to 54%) after 13 weeks (22/24 vs 13/24 at weeks 13 and 26, respectively; $P = 0.007$). This effect was not sustained at week 39, with this proportion increasing again to 65% (21/23 vs 15/23 at weeks 13 and 39, respectively; $P = 0.07$).

In the placebo arm, cholecalciferol supplementation based on the 2003 NKF-KDOQI guidelines significantly reduced the proportion of 25(OH)D-deficient patients (from 63% to 17%) after 13 weeks (15/24 vs 4/24 at weeks 13 and 26, respectively; $P < 0.001$) and also after 26 weeks (13/23 [57%] vs 5/23 [22%] at weeks 13 and 39, respectively; $P = 0.008$).

Finally, the respective proportions of patients with persistently low 25(OH)D levels (either <20 or <30 ng/mL) were compared between the treatment group at week 13 and the placebo group at weeks 26 and 39. There was a nominally lower proportion of patients with persistent 25(OH)D levels < 30 ng/mL in patients treated with our study repletion protocol at week 13 compared with patients from the placebo arm treated with the NKF-KDOQI recommendations after 26 weeks, but this result was not statistically significant (10 of 26 [38%] vs 14 of 21 [67%]; $P = 0.05$).

DISCUSSION

Therapeutic strategies to correct vitamin D deficiency have not been studied extensively in maintenance HD patients. Our randomized study showed that administration of a weekly dose of 25,000 IU of cholecalciferol over 13 weeks resulted in normalization of 25(OH)D levels (≥30 ng/mL) in 62% of patients, in $1,25(OH)_2D$ levels ≥ 20 pg/mL in 54%, and in calcium concentrations within the KDIGO normal range in 77% without serious adverse events. Patients in the treatment group experienced dramatically fewer bone fractures and hospitalizations for falls than patients in the placebo group. Despite the limited size of our patient cohort, our findings reinforce prior studies associating 25(OH)D deficiency with increased risk of fracture among patients on maintenance HD therapy or those supporting the positive impact of vitamin D on muscle strength and balance in the elderly and patients with CKD.[8,29-31]

Decades ago, it was shown that anephric humans and 5/6 nephrectomized dogs, unlike healthy individuals, increased their $1,25(OH)_2D$ levels in response

to a supraphysiologic cholecalciferol challenge.[16,17] Several clinical prospective studies confirmed the incremental effects of 25(OH)D supplementation on $1,25(OH)_2D$ levels in patients with CKD stage 5. However, inconsistent results were obtained for PTH and calcium levels.[2,3,11,32,33] Only a few randomized controlled studies described the increment of $1,25(OH)_2D$ levels after cholecalciferol challenge in HD patients.[10,11,13] None was able to confirm a significant impact on either PTH or calcium levels. However, the study of Hewitt et al[13] showed that patients receiving cholecalciferol were prescribed less calcium carbonate than controls. The present randomized study confirms that cholecalciferol, given at physiologic doses, triggers $1,25(OH)_2D$ synthesis in maintenance HD patients. This finding is in contrast to the absence of a $1,25(OH)_2D$ level increase in anephric patients receiving physiologic doses of cholecalciferol.[34,35] Together, these observations support residual renal 1α-hydroxylase activity rather than extrarenal production of $1,25(OH)_2D$. In our opinion, a challenge with 25(OH)D could precede the prescription of 1α-hydroxylated forms of vitamin D that are more expensive and associated with a higher risk of hypercalcemia and hyperphosphatemia.

Considering the open-label phase of the study, our results show that the repletion protocol based on the NKF-KDOQI guidelines resulted in a significant reduction in the prevalence of 25(OH)D deficiency. However, the treatment goal stated in the same guidelines (25[OH]D $>$ 30 ng/dL) was not reached. Our own repletion protocol yielded a higher proportion of patients within the 25(OH)D target. During the whole study, the only significant change in bone and mineral metabolism biological parameters observed was a significant decrease in fetuin A levels. Considering that current published reports are conflicting,[36,37] further investigations are needed.

In clinical practice, the choice of a vitamin D preparation is restricted by national market availability. However, calciferols should not be regarded as interchangeable.[38,39] In healthy individuals, administration of cholecalciferol gives rise to higher and more sustained 25(OH)D serum concentrations and is considered to be at least 2 times more potent than ergocalciferol. By giving cholecalciferol in doses quantitatively identical to ergocalciferol doses recommended by the NKF-KDOQI guidelines, we expected to have overestimated their effects. We suggest, as have others, that vitamin D dosing should be reconsidered with regard to the NKF-KDOQI goal.[40-42]

To conclude, our work emphasizes that physiologic doses of cholecalciferol affect various mineral and bone biochemical parameters among maintenance HD patients. These effects are likely to be based on residual renal 1α-hydroxylation of vitamin D compounds rather than activity in extrarenal sites. The present study did not directly test the impact of vitamin D repletion on hard clinical end points during long-term follow-up. However, it raised striking observations concerning fracture and fall rates that merit testing in larger randomized controlled studies.

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SUPPLEMENTARY MATERIAL

Table S1: Bone turnover markers at week 13 according to randomization group.

Table S2: Treatment data according to randomization group at 13 weeks.

Table S3: Characteristics of participants who developed hypercalcemia.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.04.020) is available at www.ajkd.org

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