Efficacy and safety of a short course of very-high-dose cholecalciferol in hemodialysis[1–3]

Haimanot Wasse, Rong Huang, Qi Long, Salman Singapuri, Paolo Raggi, and Vin Tangpricha

ABSTRACT

Background: Vitamin D deficiency is highly prevalent among hemodialysis patients, but little data exist in support of an optimal repletion regimen.

Objective: The objective was to ascertain the efficacy of weekly very-high-dose cholecalciferol (vitamin D_3) in correcting vitamin D insufficiency and deficiency in patients with stage 5D chronic kidney disease.

Design: We conducted a prospective, double-blind, randomized controlled pilot study that compared placebo with very high doses of oral cholecalciferol for 3 wk (200,000 IU/wk) in hemodialysis patients. We examined the rate of correction of vitamin D insufficiency or deficiency and the effect of treatment on markers of mineral metabolism and routine laboratory variables.

Results: Twenty-seven subjects received placebo, and 25 received cholecalciferol. The majority (94%) of subjects had serum 25-hydroxyvitamin D [25(OH)D] concentrations <30 ng/mL. Study groups were similar with respect to baseline clinical characteristics, with the exception of hemoglobin concentrations, which were lower in the cholecalciferol-treated group ($P < 0.04$). At follow-up, 90.5% of subjects treated with cholecalciferol achieved serum 25(OH)D concentrations ≥30 ng/mL in contrast to 13.6% of the placebo group. There were no significant changes in serum calcium, phosphate, or intact parathyroid hormone during the study.

Conclusion: Short-term, high-dose oral cholecalciferol treatment of vitamin D deficiency in hemodialysis patients appears to be effective and with no evidence of toxic effects. This trial was registered at clinicaltrials.gov as NCT00912782. *Am J Clin Nutr* 2012;95:522–8.

INTRODUCTION

Although the prevalence of vitamin D insufficiency and deficiency in CKD[4] patients receiving chronic renal replacement therapy (CKD stage 5D) is estimated between 78% and 91% (1–4), the KDOQI guidelines provide recommendations for vitamin D repletion only to patients with stages 3 and 4 CKD who have 25(OH)D concentrations <30 ng/mL (5).

Nevertheless, because of mounting observational data linking vitamin D insufficiency and deficiency to increased risk of cardiovascular mortality (4, 6), and decreased survival (7) in patients with stage 5D CKD, it is increasingly common for practitioners to obtain serum 25(OH)D concentrations in CKD stage 5D patients and to initiate vitamin D supplementation where indicated. In many cases, a modified version (2, 8, 9) of the KDOQI-recommended regimen (5) for vitamin D–deficient patients with stages 3 and 4 CKD is used for dialysis patients, which is generally a variation on 50,000 IU vitamin D/wk for a period of 6–12 wk. Nephrologists are hesitant to administer higher doses of vitamin D to dialysis patients for fear of vitamin D toxicity, characterized by hypercalcemia, hyperphosphatemia, and oversuppression of PTH (10, 11).

Limited prospective randomized clinical trials (12–15) examined the safety and efficacy of alternative vitamin D supplementation regimens, and none examined patients with stage 5D CKD. We conducted a double-blind, placebo-controlled 6-wk pilot study to ascertain the efficacy of weekly very-high-dose cholecalciferol (vitamin D_3) in correcting vitamin D insufficiency and deficiency in patients with stage 5D CKD. The primary study endpoint was change in serum 25(OH)D concentrations within and between the cholecalciferol-treated and placebo patient groups. Secondary endpoints examined were change in iPTH, serum calcium, and phosphorus in response to therapy.

SUBJECTS AND METHODS

Subjects

Adult patients with stage 5D CKD receiving in-center maintenance hemodialysis at an Emory University–affiliated dialysis center between March 2009 and November 2010, and who planned to undergo AVF creation within 4 wk, were eligible to enroll in the study. Subjects were enrolled as part of a study to examine the effect of vitamin D on AVF maturation, which is currently reaching conclusion. At the time of enrollment, 50

[1] From the Divisions of Nephrology (HW, RH, and SS) and Cardiology (PR), Emory University, Atlanta, GA; the Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA (QL); and the Division of Endocrinology, Diabetes, and Lipids, Emory University and Atlanta VA Medical Center, Atlanta, GA (VT).

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[3] Address correspondence to H Wasse, Emory University School of Medicine, Renal Division, Woodruff Memorial Research Building, Room 338, 1639 Pierce Drive, Atlanta, GA 30322. E-mail: hwasse@emory.edu.

[4] Abbreviations used: AVF, arteriovenous fistula; CKD, chronic kidney disease; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone; KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; Kt/V, product of dialyzer urea clearance (K) and treatment time (t) divided by the urea distribution volume (V); PTH, parathyroid hormone; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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patients were using a central venous catheter, one used a peritoneal catheter, and one used a femoral catheter for dialysis, which remained in place from the time of study enrollment to the time follow-up laboratory tests were obtained (**Figure 1**). Patients were excluded if they had a corrected serum calcium >10.5 mg/dL within 4 wk of study screening or were taking >2000 IU vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) per day. Subjects unable to provide informed consent or who planned to relocate outside of Atlanta during the study duration were excluded. The institutional review board of Emory University approved the study protocol, and informed consent was obtained from each patient before study enrollment. Human subjects procedures followed were in accordance with the ethical standards of the institutional review board and with the Helsinki Declaration of 1975. Our study was registered at clinicaltrials.gov (NCT00912782).

Study medication and random assignment to treatment arm

Enrolled subjects were randomly assigned by using block randomization to receive either a total of 600,000 IU vitamin D_3 (cholecalciferol) or placebo manufactured by Bio-Tech Pharmacal Inc over the 3-wk study period. Study personnel and subjects were blinded to the treatment arm, and random assignment was conducted by an independent clinical trial pharmacist at Emory University Hospital. Vitamin D_3 and placebo pills were taken orally and were identical in shape and color. Subjects in the cholecalciferol treatment group were administered 200,000 IU cholecalciferol (4 pills of 50,000 IU vitamin D_3) once weekly for 3 wk (total of 600,000 IU) under direct observation of the study coordinator to confirm subject compliance. Treatment allocation was not revealed until study completion.

Data collection and laboratory analyses

At the time of subject enrollment, demographic characteristics, medical and social history, medication use, and clinical and dialysis treatment data were collected via direct patient interview and review of patient records. Blood was collected at study enrollment to establish baseline concentrations of serum 25(OH)D and $1,25(OH)_2D$, and 3 wk after study drug completion to establish posttreatment serum 25(OH)D and $1,25(OH)_2D$ concentrations.

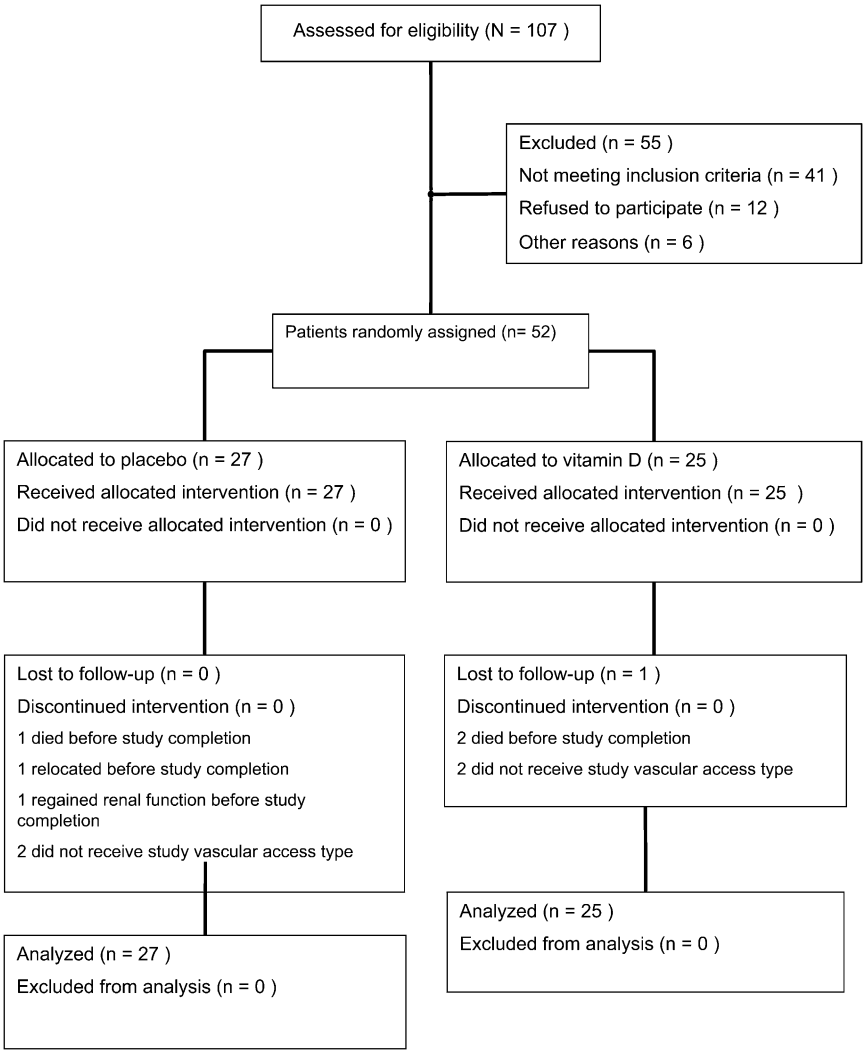

FIGURE 1. Flow diagram of patient enrollment.

Monthly routine dialysis unit laboratory test results that had been drawn ≤4 wk before subject enrollment date and ≤4 wk after study drug completion date were abstracted from the dialysis unit medical record.

Definition of variables

We analyzed several covariates including age, sex, self-reported race, dialysis duration (d), BMI, systolic and diastolic blood pressure, smoking status (never, former, current), season of blood collection, and vitamin D analog therapy. Comorbidities included diabetes (defined by use of diabetes medications), hypertension, lactose intolerance, and systolic and diastolic blood pressure. Results of serum calcium, phosphorus, iPTH, serum albumin, alkaline phosphatase, hemoglobin, Kt/V (used to quantify hemodialysis adequacy), total cholesterol, LDL and HDL cholesterol, and triglycerides were abstracted from the outpatient dialysis records and included in the analysis.

25(OH)D and 1,25$(OH)_2$D measurements

Serum 25(OH)D concentrations were measured by using chemiluminescence immunoassay (Diasorin Inc; CV over multiple runs: 6.3–12.9%), and 1,25$(OH)_2$D was measured by using solid-phase extraction and radioimmunoassay by ARUP Laboratories.

Baseline and follow-up samples from each patient were analyzed in the same batch along with known standards to ensure quality of test. Vitamin D deficiency was defined as <20 ng/mL, and insufficiency was defined as 20 to <30 ng/mL. Terminology from the Endocrine Society guidelines (16) was used because the Institute of Medicine guidelines are intended for a normal healthy population, not those with chronic disease.

Statistical analysis

Baseline characteristics including demographic characteristics and blood chemistry measures were compared between study groups by using Wilcoxon's rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Wilcoxon's signed-rank tests were performed to test whether changes in blood chemistry measures from baseline to final treatment were different from 0, and Wilcoxon's rank sum tests were performed to compare changes in blood chemistry measures between study groups to test treatment effects. Multiple linear regression analysis was performed to estimate the adjusted treatment effect (cholecalciferol-treated compared with placebo) on change in each blood chemistry measure from pre- to posttreatment, with its pretreatment value controlled for. For 25(OH)D and 1,25$(OH)_2$D, the regression analysis also adjusted for the season at the time of enrollment and pretreatment hemoglobin concentration. The analyses were performed on an intention-to-treat basis and by using the free programming language and software environment for statistical computing, R (http://www.r-project.org). A P value ≤0.05 was considered significant.

RESULTS

Baseline subject characteristics

Fifty-two in-center hemodialysis subjects were enrolled and randomly assigned to the placebo group (n = 27) or to the cholecalciferol treatment group (n = 25). During study follow-up, 3 subjects died, one regained renal function, one relocated before study completion, 3 received a vascular access other than an AVF, and one never received a permanent access. Of these 9 subjects, 5 were in the placebo group and 4 in the vitamin D group, and they were excluded only from analyses for which they had missing data. The only significant difference between these and the remaining study patients was that there were more women in the dropout group (77.8% compared with 30.2%, P = 0.02). The mean (±SD) study duration was 53 ± 36 d, from time of subject enrollment to the end of follow-up. The baseline patient characteristics of all enrolled subjects by assigned study group are shown in **Table 1**. At baseline, the study groups did not differ with respect to age, race, sex, dialysis duration, BMI,

TABLE 1
Baseline subject characteristics by treatment group

Characteristics	Placebo (n = 27)	Cholecalciferol (n = 25)	P^1
Age (y)	52 ± 14[2]	49 ± 13	0.44
Race (n)			1.00
African American	23	24	
White	4	1	
Sex (n)			1.00
Female	10	10	
Male	17	15	
Duration of dialysis (d)	839.48 ± 1284.09	258.84 ± 278.61	0.14
BMI (kg/m^2)	27.6 ± 7.7	30.1 ± 8.4	0.17
Diabetes [n (%)]	14 (51.9)	12 (48)	1.00
Hypertension [n (%)]	24 (88.9)	22 (88)	1.00
Lactose intolerance [n (%)]	3 (11.1)	7 (29.2)	0.16
Clinical blood pressure (mm Hg)			
Systolic	152.5 ± 22.9	154.4 ± 26.0	0.90
Diastolic	87.1 ± 16.7	88.0 ± 17.8	0.76
Current use of intravenous vitamin D analogs [n (%)]	18 (66.7)	17 (68)	1.00

[1] P value for testing whether the baseline value was different between the 2 treatment groups by using Wilcoxon's rank sum tests for continuous variables and Fisher's exact tests for categorical variables.
[2] Mean ± SD (all such values).

diabetes, hypertension, lactose intolerance, or use of active intravenous vitamin D during hemodialysis.

Baseline blood chemistry measurements

Overall, the mean (±SD) baseline concentration of serum 25(OH)D was 16.2 ± 7.2 ng/mL. Vitamin D insufficiency [25(OH)D of 20 to <30 ng/mL] was present in 29.4% of subjects, and vitamin D deficiency [25(OH)D <20 ng/mL] was present in 64.7% of subjects. The mean serum $1,25(OH)_2D$ concentration was 17.3 ± 9.5 pg/mL. There was no significant difference in baseline values of serum 25(OH)D concentrations (17.1 ± 7.6 compared with 15.3 ± 6.8 ng/mL; $P = 0.35$) or iPTH concentrations (617.6 ± 890.2 compared with 701.1 ± 689.9 pg/mL; $P = 0.39$) between the study groups. The only significant difference at baseline was a higher mean hemoglobin concentration in the placebo group (11.2 ± 1.4 compared with 10.3 ± 1.8 g/dL; $P = 0.04$). Serum calcium, phosphorus, PTH, albumin, alkaline phosphatase, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Kt/V were similar between study groups. Each subject was directly observed taking his or her assigned medication, and there was 100% compliance in each treatment group.

Changes in 25(OH) D, $1,25(OH)_2D$, PTH, calcium, phosphorus, and alkaline phosphatase

Changes in markers of mineral metabolism over time between the 2 study groups are shown in **Table 2**. Three weeks after completing high-dose vitamin D or placebo treatment, the mean serum 25(OH)D concentration in the cholecalciferol-treated group was 52.4 ± 17.9 ng/mL compared with 18.4 ±7.4 ng/mL in the placebo group ($P < 0.001$). After therapy with 600,000 IU cholecalciferol for 3 wk, 100% of subjects with a baseline serum 25(OH)D concentration <20 ng/mL achieved a vitamin D concentration ≥20 ng/mL; 90.5% achieved vitamin D sufficiency after treatment, in contrast to the placebo group, in which only 13.6% of subjects achieved vitamin D sufficiency after treatment. In addition, mean serum $1,25(OH)_2D$ increased by 14.6 ± 16.2 pg/mL in the cholecalciferol-treated group ($P < 0.001$), whereas it decreased by a mean of 3.2 ± 12.6 pg/mL in the placebo group ($P = 0.35$).

Whereas iPTH concentration decreased by a mean of 23.2 ± 177.8 pg/mL in the placebo group ($P = 0.72$), it decreased by a mean of 47.9 ± 394 pg/mL in the cholecalciferol-treated group ($P = 0.23$) but failed to reach significance when the changes in PTH between the 2 study groups were compared ($P = 0.30$). Serum calcium remained well within the normal range, and the increase in corrected calcium was not significant in either the cholecalciferol-treated group (increase from 8.8 ± 0.8 to 9.0 ± 0.8 mg/dL; $P = 0.25$) or the placebo-treated group (increase from 9.0 ± 0.6 to 9.2 ± 0.8 mg/dL; $P = 0.35$). Overall, the average treatment effect on calcium ($P = 0.96$) and phosphorus ($P = 0.14$) was similar between the placebo- and cholecalciferol-treated groups. Compared with the placebo group, there was a trend toward a decline in alkaline phosphatase among the cholecalciferol-treated group (103 ± 80.4 to 91.4 ± 57.8 U/L; $P = 0.09$).

Changes in additional laboratory endpoints

The mean changes in additional laboratory endpoints were examined to evaluate their response to high-dose cholecalciferol compared with placebo and are shown in **Table 3**. No significant differences between the 2 study groups were observed in serum albumin, hemoglobin, alkaline phosphatase, total cholesterol, triglycerides, HDL cholesterol, LDL, cholesterol, or Kt/V at the end of the study period.

After adjustment for baseline 25(OH)D concentration, season, and hemoglobin concentration, the treatment effect on change in laboratory endpoints between study groups was similar to the unadjusted results; the mean change in 25(OH)D from baseline to posttreatment was 40 ng/mL higher ($P < 0.001$) and the mean change in $1,25(OH)_2D$ was 18.8 pg/mL higher ($P < 0.001$) in the cholecalciferol-treated group than in the placebo group. There was no significant difference in changes in hemoglobin, calcium, phosphorus, PTH, albumin, alkaline phosphatase, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Kt/V between the 2 study groups.

TABLE 2
Baseline and final values of markers of mineral metabolism by treatment group[1]

	Placebo ($n = 27$)			Cholecalciferol ($n = 25$)			
Characteristics	Baseline	6 wk	Pre–post P[2]	Baseline	6 wk	Pre–post P[2]	Between-treatment group P[3]
25(OH)D (ng/mL)	19.0 ± 6.5[4]	18.4 ± 7.4	0.52 [22]	14.3 ± 5.7	52.4 ± 18	<0.001 [21]	<0.001
25(OH)D [n (%)]							
<20 ng/mL	11 (50)	14 (63.6)		16 (76.2)	0 (0)		
20 to <30 ng/mL	9 (40.9)	5 (22.8)		5 (23.8)	2 (9.5)		
≥30 ng/mL	2 (9.1)	3 (13.6)		0 (0)	19 (90.5)		
$1,25(OH)_2D$ (pg/mL)	20.9 ± 9.9	17.7 ± 8.5	0.35 [22]	14.7 ± 6.3	29.3 ± 17.1	<0.001 [20]	<0.001
iPTH (pg/mL)	623.9 ± 925.5	600.7 ± 927.1		722.2 ± 696.4	674.4 ± 913.3		0.30
Corrected calcium (mg/dL)	9.0 ± 0.6	9.2 ± 0.8		8.8 ± 0.8	9.0 ± 0.8		0.96
Phosphorus (mg/dL)	4.8 ± 1.2	5.9 ± 1.8		5.0 ± 1.4	5.5 ± 1.6		0.14
Alkaline phosphatase (U/L)	132.8 ± 137.3	128.7 ± 121.3		103.0 ± 80.4	91.4 ± 57.8		0.32

[1] Results are presented as means ± SDs for continuous variables. Only subjects with both baseline and final laboratory values were included; n values that differ from those in column headings are shown in brackets. iPTH, intact parathyroid hormone; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

[2] P value for testing whether the change from baseline to posttreatment was different from 0 by using Wilcoxon's signed-rank tests.

[3] P value for testing whether the change from baseline to posttreatment was different between 2 treatment groups (ie, whether the treatment effect was significant) by using Wilcoxon's rank sum tests.

[4] Mean ± SD (all such values).

TABLE 3
Mean change in blood chemistry measures by treatment group[1]

	Placebo (n = 27)		Cholecalciferol (n = 25)			
Analyte	Baseline	Change	Baseline	Change	Cholecalciferol–placebo[2]	P[3]
Hemoglobin (g/dL)[4]	11.2 ± 1.4	0.6 ± 1.6	10.3 ± 1.8	0.6 ± 1.8	0.03	0.88
Albumin (g/dL)	3.6 ± 0.5	−0.01 ± 0.4	3.5 ± 0.6	0.2 ± 0.5	0.2	0.41
Total cholesterol (mg/dL)	177.2 ± 51.5	−14.8 ± 39.7	163.9 ± 44.1	−14.9 ± 30.9	−0.2	0.99
Triglycerides (mg/dL)	152.4 ± 110.8	−11.4 ± 47.3	140.0 ± 75.5	−22.2 ± 59.9	−10.9	0.80
HDL cholesterol (mg/dL)	44.2 ± 12.3	0.7 ± 7.2	43.4 ± 15	−2.6 ± 9.4	−3.2	0.43
LDL cholesterol (mg/dL)	107 ± 39.6	−12.7 ± 32.0	91.2 ± 36.4	−1.3 ± 25.2	11.4	0.28
Kt/V[5]	1.3 ± 0.2	−0.03 ± 0.3	1.3 ± 0.3	0.1 ± 0.6	0.1	0.43

[1] All values are means ± SDs. Only subjects with both baseline and final values were included.
[2] Difference in the average change between the cholecalciferol and placebo groups.
[3] P value for testing whether the change from baseline to posttreatment was different between 2 treatment groups (ie, whether the treatment effect was significant) by using Wilcoxon's rank sum tests.
[4] Significant difference in hemoglobin between groups at baseline.
[5] Kt/V, product of dialyzer urea clearance (K) and treatment time (t) divided by the urea distribution volume (V).

DISCUSSION

In this pilot study, we observed that the correction of vitamin D deficiency and insufficiency in patients with stage 5D CKD can be safely and effectively performed with one weekly dose of 200,000 IU oral cholecalciferol for 3 wk without apparent toxicity. We selected cholecalciferol given its greater potency compared with ergocalciferol (17, 18). Furthermore, several important metabolic markers improved in the study group compared with the placebo group; however, due to the short follow-up period and the small sample size, these values did not differ significantly.

There has been recent interest in higher and more rapid correction of vitamin D status in patients with CKD and ESRD. Several studies have shown that guidelines for vitamin D therapy suggested by the KDOQI are ineffective, prompting the development of alternative vitamin D regimens. Tokmak et al (19) reported that 20,000 IU cholecalciferol/wk for 36 wk resulted in correction of vitamin D [25(OH)D >30 ng/mL] concentrations in only 57% of subjects with ESRD. A study by Jakopin et al (20) showed that monthly administration of 40,000 IU cholecalciferol over 3 mo, with continued treatment on the basis of reevaluation every 4 mo over the 24-mo study period, was ineffective in restoring vitamin D sufficiency in nearly 77% of hemodialysis patients. A larger and longer-term study conducted by Jean et al (21) found that directly observed monthly administration of 100,000 IU cholecalciferol over 15 mo effectively corrected vitamin D status in 90% of subjects with ESRD with no reported toxicity. In a critically ill, nondialysis population, Amrein et al (22) recently showed that a single dose of 540,000 IU cholecalciferol compared with placebo rapidly corrected vitamin D deficiency without evidence of toxicity. Similarly, our study shows excellent safety and efficacy with a very high dose of cholecalciferol given over a 3-wk period. Whether more rapid correction of vitamin D status is more advantageous in this population is worthy of further investigation.

As renal function declines, the conversion of 25(OH)D to $1,25(OH)_2D$ is impaired (23, 24). In fact, the KDOQI guidelines do not recommend vitamin D therapy with cholecalciferol or ergocalciferol in patients with ESRD due to presumed inactivity of renal 1-α-hydroxylase. Earlier trials did not show significant increases in $1,25(OH)_2D$ in response to vitamin D therapy in subjects with stage 2–4 CKD, likely due to insufficient dosing of vitamin D (12, 13). In contrast, recent studies suggest that 1-α-hydroxylase is active. In 43 subjects receiving hemodialysis, Jean et al (25) observed significant increases in $1,25(OH)_2D$ after 6 mo of $25(OH)D_3$ therapy. Pooled observational studies reported a significant increase in serum $1,25(OH)_2D$ concentration after vitamin D supplementation (26), which was similar to increases we observed in our study. These studies suggest that 1-α-hydroxlyase still remains intact, possibly originating from residual renal 1-α-hydroxylase or from several extrarenal tissues that express the 1-α-hydroxylase to convert 25(OH)D to $1,25(OH)_2D$ locally to function as a paracrine or autocrine hormone.

The increasing recognition that vitamin D may have other potentially important pleiotropic effects, such as regulation of cellular proliferation in prostate, breast, and colon tissue (27, 28); cytokine production (29, 30); and immunomodulatory effects (31) has contributed to the growing interest in vitamin D supplementation of patients receiving chronic dialysis. Subjects with stage 5D CKD often suffer from secondary hyperparathyroidism, which is exacerbated by vitamin D deficiency. Several studies have shown that vitamin D therapy may lower parathyroid hormone concentrations, although less effectively than vitamin D analog compounds. Intervention with vitamin D and/or prevention of vitamin D deficiency earlier in the course of CKD would likely be more effective in preventing secondary hyperparathyroidism.

The more recent KDIGO (Kidney Disease: Improving Global Outcome) recommendations suggest that serum 25(OH)D concentrations be measured in patients with stage 3–5 CKD, that insufficiency be determined by more than one measurement, and that repletion occur as recommended for the general population (32). Whether these measures will result in a better overall outcome for patients with stage 5D CKD remains to be shown in randomized clinical trials.

The strength of our study was the directly observed administration of cholecalciferol to ensure 100% compliance. Another major strength was the double-blind, randomized controlled design, allowing for causal inference of our observations. Our study was limited by a smaller sample size, although it was sufficiently powered to detect differences in our primary endpoint of serum 25(OH)D.

Because several laboratory results were abstracted from theoutpatient dialysis records, blood sample batching was not possible, and this may have influenced study results. Another potential limitation of our study was that we did not perform liquid chromatography–tandem mass spectrometry for our serum 25(OH)D determinations, because high doses of vitamin D_3 may translate into a significant concentration of circulating vitamin D_3 and/or 24,25 dihydroxyvitamin D, which may both be potentially measured in our serum 25(OH)D assay. Our final serum 25(OH)D measurements were performed 3 wk after the last vitamin D_3 dose, which would make this possibility less likely. It is known that serum vitamin D_3 concentrations are expected to increase and decrease within 72 h after ingestion of vitamin D_3 as the vitamin D_3 is redistributed to tissues, including fat and muscle (33), and converted to serum 25(OH)D (34). Due to limitations in our radioimmunoassay for serum 25(OH)D, we cannot completely rule out that other circulating metabolites of vitamin D were measured in place of 25(OH)D, although this potential limitation has not been previously studied in detail. Our interpretations were also limited by a short follow-up period, thus potentially limiting our ability to detect significant changes in other metabolic markers.

In summary, we report a novel method of rapidly correcting vitamin D status in patients with ESRD receiving renal replacement therapy. Subjects who received vitamin D had both significant increases in serum 25(OH)D and in $1,25(OH)_2D$ without any toxicities. The importance of correction and maintenance of optimal vitamin D status in patients with stage 5D CKD remains to be established and should be evaluated in longer-term studies using liquid chromatography–tandem mass spectrometry for the analysis of vitamin D metabolites.

The authors' responsibilities were as follows—HW, RH, VT: designed the study; RH and SS: recruited participants and performed data collection; QL: analyzed the data; and HW, PR, and VT: drafted the manuscript. All of the authors revised the manuscript. None of the authors reported a conflict of interest.

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