Effects of Cholecalciferol on Functional, Biochemical, Vascular, and Quality of Life Outcomes in Hemodialysis Patients

Nathan A. Hewitt, Alicia A. O'Connor,* Denise V. O'Shaughnessy,† and Grahame J. Elder‡§*

Summary

Background and objectives Observational studies suggest that calciferol supplementation may improve laboratory and patient-level outcomes of hemodialysis patients with reduced 25-hydroxyvitamin D [25(OH)D] levels. This randomized controlled trial examined effects of cholecalciferol supplementation in patients on hemodialysis.

Design, setting, participants, & measurements Sixty patients with 25(OH)D levels ≤24 ng/ml (≤60 nmol/L) were randomized to receive 50,000 IU oral cholecalciferol or placebo, once weekly for 8 weeks and then monthly for 4 months. At baseline (autumn 2011) and 6 months, testing evaluated muscle strength, functional capacity, laboratory parameters, pulse wave velocity (PWV), and health-related quality of life (HRQOL) using the Kidney Disease Quality of Life-36 survey.

Results Patients were well matched by treatment allocation. Median age was 62 years (range, 20–86), 52% were women, 55% had a history of diabetes, and mean serum 25(OH)D was 17±5 ng/ml (43±13 nmol/L). Patients were assessed over 6 months by repeated-measures ANOVA. Patients allocated to cholecalciferol had significantly higher values of 25(OH)D ($P<0.001$), 1,25-dihydroxyvitamin D ($P=0.04$), and tartrate-resistant acid phosphatase-5b) ($P=0.04$) and a greater reduction in phosphorus values ($P=0.03$) than placebo-treated patients Values of serum calcium, intact parathyroid hormone, and episodes of hypercalcemia and hyperphosphatemia did not differ significantly between the groups. No significant differences were detected in muscle strength, functional capacity, PWV, or HRQOL.

Conclusions In this randomized controlled trial, patients supplemented with cholecalciferol had higher 25(OH)D, 1,25-dihydroxyvitamin D, and tartrate-resistant acid phosphatase-5b levels, without increased calcium or phosphorus values. However, no effects were detected in muscle strength, functional capacity, PWV, or HRQOL.

Clin J Am Soc Nephrol 8: 1143–1149, 2013. doi: 10.2215/CJN.02840312

*Postgraduate Medical School, University of Notre Dame, Sydney, Australia; †Renal Resource Centre, Sydney Dialysis Centre, Royal North Shore Hospital, Sydney, Australia; ‡Department of Renal Medicine, Westmead Hospital, Sydney, Australia; and §Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, Sydney, Australia

Correspondence: Dr. Grahame J. Elder, Department of Renal Medicine, Westmead Hospital, Westmead NSW 2145, Australia. Email: g.elder@garvan.org.au

Introduction

In the general population, levels of 25-hydroxyvitamin D [25(OH)D] >20–30 ng/ml (50–75 nmol/L) are commonly regarded as optimal, although these ranges are not based upon rigorous studies (1). Patients with CKD on dialysis (CKD-5D) frequently have low 25(OH)D levels, varying from <10 ng/ml (25 nmol/L) in 65% of patients in one study (2), to levels <15 ng/ml (37.5 nmol/L) in 14%–23% of patients in other studies (3,4). Patients on dialysis lack normal renal conversion of 25(OH)D to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], and evidence to support the benefits of increasing 25(OH)D levels with calciferol (cholecalciferol or ergocalciferol) is weak. On the other hand, lower 25(OH)D levels have been associated with increased mortality on dialysis (5,6), and treatment with calcitriol or its analogs has been associated with reduced cardiovascular risk in some, but not all, observational studies (7–10). Limitations of therapy with calcitriol and analogs include increased levels of calcium and phosphate that may counteract potential benefits.

The importance of vitamin D to mineral metabolism is established, but its role also encompasses modulation of immune and inflammatory responses (11), regulation of the renin-angiotensin system (12), and cellular proliferation, differentiation, and apoptosis (13). Some of these actions may be mediated by local conversion of 25(OH)D to 1,25$(OH)_2$D at target sites, including muscles, blood vessels and parathyroid glands (14,15). This could explain associations described in CKD-5D, between 25(OH)D levels and pulse wave velocity (PWV), a surrogate for vascular calcification (16), bone mineral density (17), early mortality on dialysis (6), muscle strength, falls risk, and quality of life (18,19).

This study was designed to assess the effects of cholecalciferol treatment on patient-level outcomes of muscle strength, functional muscle capacity, and

health-related quality of life (HRQOL), in addition to PWV and laboratory parameters.

Materials and Methods

Design

The study was conducted over 6 months as a double-blind, randomized, placebo controlled trial (RCT) of cholecalciferol versus placebo. The study was approved by the Human Research Ethics Committees of the Sydney West Area Health Service and the University of Notre Dame and was conducted in accordance with the Declaration of Helsinki. Written consent was obtained from each participant. The study was registered on February 21, 2011, with the Australian New Zealand Clinical Trials Registry (no. 12611000199910).

Participants

Potential participants were identified from January to March 2011 at latitude 34°S. Those invited to enter the study were aged >18 years, were on thrice-weekly hemodialysis for ≥3 months, and had screening levels of 25 (OH)D ≤24 ng/ml (60 nmol/L). Exclusion criteria were parathyroid surgery or treatment with cinacalcet in the preceding 3 months, hypercalcemia defined as an albumin-corrected serum calcium >10.4 mg/dl (2.60 mmol/L), bisphosphonate treatment at any time, and planned surgery except for dialysis access. Seventy eligible patients received study information and 60 agreed to participate. They were allocated to treatment in autumn (March 2011).

Randomization and Treatment Protocol

Treatment allocation was by computer-generated random numbers and an odd–even system. Participants were allocated 10 ml of an oral solution of medium chain triglyceride containing 50,000 IU of cholecalciferol (OsteVit D; Key Pharmaceuticals, Sydney, Australia), or an indistinguishable medium chain triglyceride placebo, to be taken weekly for the first 8 weeks, followed by monthly doses for the remaining 4 months of the study. The oral solution was provided to patients by dialysis staff at the completion of routine dialysis sessions on scheduled dates to ensure compliance. Participants treated with calcium-based phosphate binders or calcitriol before study commencement remained on treatment with doses unchanged in the 4 weeks before study entry. Those medications could be altered during the study to achieve acceptable levels of serum calcium and phosphate at the discretion of the patient's renal physician, but physicians were asked to avoid altering doses if possible. When prescribed, calcitriol was administered after blood collection and no other analogs were administered. Dialysate ionized calcium levels were either 2.6 or 3 mEq/L (1.3 or 1.5 mmol/L), and levels were not altered during the study.

Demographics, Functional Testing, and Analytical Methods

Patients were interviewed for baseline demographic data, and information on comorbidities was obtained from the Australia and New Zealand Dialysis and Transplant Registry. For muscle strength testing, grip strength was assessed using a Jamar gauge (Sammons Preston, Chicago, IL) in the second handle position, and shoulder abduction, elbow flexion and extension, hip flexion, and knee flexion and extension were assessed using a hand-held Chatillon dynamometer (Ametek, Largo, FL). The best of three attempts was recorded for the participant's dominant side. Functional tests included repeated chair stands, in which participants stood five times from a standard chair without using their arms and returned to a seated position as quickly as they could. Postural stability measurements were performed in side-by-side, semi-tandem, and tandem positions and maintained for 10 seconds where possible. The 6-minute walk test was conducted over 15 m, with participants walking as fast as possible and the distance covered measured.

Blood samples were collected at the same time before routine dialysis after the 3-day break at baseline, second-monthly for routine analyses, and at 6 months. Serum 25 (OH)D was measured using the Liaison assay (DiaSorin Inc, Stillwater, MN) with an 8.2% intra-assay coefficient of variation. The testing laboratory is enrolled in the Royal College of Pathologists Australasia Quality Assurance and the Vitamin D External Quality Assessment Scheme. Intact parathyroid hormone (iPTH) was measured using the Immulite 2000 system (Siemens Healthcare Diagnostics, Deerfield, IL) and $1,25(OH)_2D$ by RIA (DiaSorin Inc) using an in-house reference range. Bone-specific alkaline phosphatase (b-ALP) was measured using the Access Ostase assay (Beckman Coulter Inc, Brea, CA). Serum tartrate-resistant acid phosphatase isoenzyme-5b (TRAcP-5b) was measured by ELISA (SBA Sciences, Turku, Finland) on batched serum stored at −80°C. PWV was assessed at baseline and 6 months using the SphygmoCor-PVx system (Atcor Medical, Sydney, Australia). Baseline and 6-month BP readings were the mean of automated measurements taken immediately before the three most proximate dialysis sessions. HRQOL was assessed at baseline and 6 months using the Kidney Disease Quality of Life-36 (KDQOL-36) survey. This is a 36-item, reliable, easy-to-use, and validated instrument, with domains that measure symptoms and problems, effects of kidney disease on daily life, and the burden of kidney disease, with a subscale measuring physical and mental functioning, general health, activity limits, ability to accomplish desired tasks, depression and anxiety, energy levels, and social activities. It was scored online using KDQOL Complete (http://www.kdqol-complete.org). Each participant kept a falls and adverse events diary that was checked weekly by dialysis nursing staff.

Statistical Analyses

The prespecified primary endpoint was the effect of cholecalciferol versus placebo on tests of muscle strength. Secondary endpoints were changes in levels of 25(OH)D, $1,25(OH)_2D$, iPTH, calcium, phosphate and bone turnover markers, functional capacity, HRQOL, and PWV. Due to a lack of interventional studies, calculations of effect size and sample size were imprecise. The minimum sample size of 60 was based on the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Workgroup requirement that studies must have 50 participants for inclusion in meta-analyses (20), the number of eligible

patients with 25(OH)D levels ≤24 ng/ml (60 nmol/L), and an estimated 20% dropout over 6 months. Data were analyzed using SPSS software (version 20; SPSS Inc., an IBM Company, Chicago, IL). Variable interdependence was assessed using the Pearson correlation coefficient or Spearman's ρ when data were not normally distributed, and backward stepwise regression was used for exploratory analyses when ≥2 continuous, independent variables were significantly associated with a dependent variable. Repeated-measures ANOVA was used to assess between-group differences in dependent variables over time, and independent *t* tests or Mann–Whitney *U* tests were used to determine differences in the means of treatment groups. Analyses were conducted by intention to treat and significance was determined by *P* values <0.05. Staff members were blinded to treatment allocations until analyses were completed.

Results

The median age of patients was 62 years (range, 20–86) and 52% were women. Their mean body mass index (BMI) was 29±8.5 kg/m^2, 55% had a history of diabetes, and 10% had suffered a fall in the previous month. At entry, all patients had 25(OH)D levels ≤24 ng/ml (60 nmol/L). However, at randomization, 5 patients (included in all evaluations) had levels from 24 to 28 ng/ml (60–70 nmol/L) and the mean 25(OH)D level was 17±5 ng/ml (43±13 nmol/L). Patients were well matched by treatment allocation, with BMI being the only characteristic that differed (Tables 1 and 2). There were no statistically significant differences in muscle strength, functional tests, PWV, or HRQOL (data not shown).

Table 1. Baseline patient characteristics and drug doses by treatment allocation

Characteristic	Placebo	Cholecalciferol
Age (yr)	67 (54, 72)	60 (53, 71)
Male sex	43	53
Time on dialysis (mo)	42 (18, 89)	38 (25, 66)
Body mass index (kg/m^2)[a]	31.3±9.5	26.6±6.4
Individuals with a previous fracture	12	8
Individuals falling within the previous month	1	5
Caucasoid (%)	36.7	50.0
Diabetes[b]	18	15
Cardiovascular disease[b]	19	17
Peripheral vascular disease[b]	10	10
Cerebrovascular disease[b]	6	3
Current or ex-smoker	15	13
Never smoked	15	17
Calcitriol (μg/d)	0.11 (0, 0.25)	0.11 (0, 0.25)
Calcium carbonate (g/d)	4.6 (2.2, 9.6)	5.2 (1.1, 9)
Sevelamer (g/d)	0 (0, 3)	0 (0, 4.2)
Darbepoetin alfa (μg/wk)	40 (15, 85)	40 (20, 80)

n=30 for each group. Data are given as median (interquartile range), number, or mean ± SD, unless otherwise specified.
[a]*P*=0.03.
[b]Present or suspected.

Baseline Evaluation

At baseline, 25(OH)D levels were lower in patients with diabetes (16±5 versus 19±4 ng/ml; *P*=0.002) but did not differ by age, sex, or BMI. Levels of 25(OH)D and 1,25 $(OH)_2D$ correlated positively (*r*=0.27; *P*=0.04), and 25 (OH)D levels correlated to the distance covered in a 6-minute walk (*r*=0.32; *P*=0.02) but not to muscle strength, functional tests, or HRQOL. Baseline HRQOL scores using the KDQOL-36 were <50 for physical and mental component summaries and for the burden of kidney disease. The mean PWV was 10.3±4.0 m/s and values were positively associated with age and inversely associated with 25(OH) D values (adjusted r^2=0.15; *P*=0.02; part correlations, 0.31 and −0.27, respectively).

Interim and 6-Month Evaluation

Between baseline and 6 months, interim 25(OH)D samples were collected on 18 patients. Their results indicated that peak 25(OH)D levels were achieved by 8–12 weeks from the commencement of cholecalciferol treatment, with mean values of 39±10 ng/ml (98±26 nmol/L), and did not differ from 6-month levels of 36±8 ng/ml (91±19 nmol/L) (*P*=0.33). At 6 months, 21 patients in the cholecalciferol group and 24 in the placebo group (75%) were available for follow-up. Table 3 details adverse events and causes of study withdrawal. At 6 months, patients allocated to cholecalciferol had higher levels of 25(OH)D (35±9 versus 16±7 ng/ml; *P*<0.001), 1,25$(OH)_2D$ (18±8 versus 12±5 pg/ml; *P*=0.001), and TRAcP-5b (5.92±1.9 versus 4.50±1.79 U/L; *P*=0.04). Assessed over time, these treatment group differences remained significant; 25(OH)D (*P*<0.001), 1,25(OH)2D (*P*=0.04), TRAcP-5b (*P*=0.04), and a reduction in phosphorus values were greater in the cholecalciferol than the placebo group (*P*=0.03). There were no statistically significant differences over time between treatment groups in tests of functional capacity or muscle strength (Table 4). Values of calcium, iPTH, alkaline phosphatase (ALP), b-ALP, and C-reactive protein were not influenced by treatment allocation. At 6 months, PWV was 10.5±2.8 m/s in patients allocated to placebo and 9.3±3.3 m/s in patients allocated to cholecalciferol, with no significant between-group differences over time (*P*=0.76). Similarly, there were no significant differences in HRQOL domains, diastolic or systolic BP, episodes of vascular catheter sepsis, or positive blood cultures. Levels of 25(OH)D at 6 months correlated positively to 1,25$(OH)_2D$ (*r*=0.55; *P*<0.001) and TRAcP-5b levels (*r*=0.37; *P*=0.04).

Patients allocated to cholecalciferol were prescribed less calcium carbonate at 6 months than patients allocated to placebo (median 3.7 g/d [interquartile range, 0, 9] versus median 7.5 g/d [interquartile range, 3.1, 9]; *P*=0.05]. There were no between-group differences in dosages of calcitriol or noncalcium-based phosphate binders. Levels of hemoglobin and erythropoiesis stimulating agents did not differ between the groups.

Table 2. Baseline laboratory results by treatment allocation

Laboratory Parameter (Normal Range)	Placebo	Cholecalciferol
25(OH)D (adequacy ≥20–30 ng/ml)	16±5	18±5
$1,25(OH)_2D$ (15–50 pg/ml)	18±10	18±5
iPTH (9–55 pg/ml)	222±224	335±327
ALP (30–115 U/L)	116±57	147±172
b-ALP (3.7–20.9 μg/L)	16.7±9.0	22.1±19.9
TRAcP-5b (upper limits: 4.15, 4.82 U/L)	4.50±2.06	5.00±2.35
Calcium (8.5–10.5 mg/dl)	9.4±0.6	9.4±0.5
Phosphorus (2.5–5.8 mg/dl)	4.8±1.6	5.4±1.6
Albumin (3.5–5.0 g/dl)	3.9±0.4	3.8±0.4
C-reactive protein (≤10 mg/L)	10 (5, 20)	9 (5, 17)
Hemoglobin (11.5–18.0 g/dl)	11.2±1.7	11.0±1.7
Ferritin (30–300 μg/L)	348±200	407±249
Transferrin saturation (11%–45%)	24±9	30±15

n=30 for each group. Data are presented as mean ± SD or median (interquartile range). Multiply by 2.5 to convert 25(OH)D values to nmol/L; multiply by 2.4 to convert $1,25(OH)_2D$ values to pmol/L; multiply by 0.11 to convert iPTH values to pmol/L; multiply by 0.25 to convert calcium values to mmol/L; and multiply by 0.32 to convert phosphorus values to mmol/L. 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; TRAcP-5b, tartrate-resistant acid phosphatase isoenzyme-5b (upper limits indicated for women and men, respectively).

Table 3. Adverse events and causes of study withdrawal

Adverse Events and Causes of Study Withdrawal	Placebo (*n*)	Cholecalciferol (*n*)
Falls during the study period	2	5
Fractures during the study period	0	1
Serum Ca >10.4 mg/dl on ≥1 occasions	2	3
Serum PO_4 >5.0 mg/dl on ≥1 occasions	20	17
Gastrointestinal events (study withdrawal); withdrawal due to other causes[a]	3 (2); 0	3 (2); 2
Positive blood cultures/ central venous catheter sepsis	1	1
Withdrawal due to death[b]	1	1
Withdrawal due to transplant (*n*=2) or major surgery (*n*=1)	0	3
Loss to follow-up	3	1

There were no significant differences between the groups. Multiply by 0.25 to convert calcium values to mmol/L, and multiply by 0.32 to convert phosphorus values to mmol/L.
[a]Dizziness or breathlessness after medication.
[b]One cerebrovascular and one cardiovascular death.

Discussion

Numerous association studies have suggested biochemical and patient-level benefits of calciferol supplementation in patients on dialysis. Paradoxically, few studies have assessed effects of supplementation on laboratory, functional, vascular, or quality of life outcomes. Despite a lack of evidence, KDIGO CKD-MBD guidelines do suggest calciferol supplementation to patients with CKD-5D and low 25(OH)D levels (20). This study was developed to investigate both patient-level and laboratory outcomes of this therapy over 6 months.

Cholecalciferol Supplementation and 25(OH)D and $1,25(OH)_2D$ Levels

Allocation to cholecalciferol increased mean 25(OH)D levels >30 ng/ml (75 nmol/L) at 6 months. Such levels are often regarded as optimal in the general population (21) and were not associated with an increased risk of hypercalcemia or hyperphosphatemia in this study. In the subgroup of cholecalciferol-treated patients for whom interim 25(OH)D levels were available, maximal levels were achieved by 8–12 weeks from commencement of therapy. This is consistent with another CKD-5D study, in which mean 25(OH)D levels of 30 ng/ml (75 nmol/L) were attained between 40 and 60 days from initiation of therapy (22). However, compared with this study, those patients had lower baseline 25(OH)D levels and were treated with lower cholecalciferol doses.

In this study, between-group $1,25(OH)_2D$ values differed significantly over time; at 6 months, mean $1,25(OH)_2D$ levels were 54% higher in patients allocated to cholecalciferol than placebo, whose reduced $1,25(OH)_2D$ levels possibly reflected seasonal change. A similar relationship of 25(OH)D to $1,25(OH)_2D$ levels has been reported in anephric patients (23) and in a recent RCT of patients on dialysis (22). Whereas the former article supports the concept of extrarenal conversion of 25(OH)D to $1,25(OH)_2D$, the latter study and current trial cannot exclude the possibility of preserved or less inhibited 1-α-hydroxylase activity in vitamin D–supplemented patients.

Mineral Metabolism and Bone Turnover

Calciferol therapy has been reported to improve parameters of mineral metabolism in observational studies, with associations to decreased parathyroid hormone (PTH) and b-ALP levels (2,24,25). However, treatment allocation did not influence values of iPTH, ALP, or b-ALP in this study. PTH appears to transition from being responsive to being unresponsive to calciferol supplementation between CKD stages 3 and 4, and others studies have also failed to show

Table 4. Baseline and 6-month muscle group strength

Muscle Group	Time	Placebo	Cholecalciferol	*P* Value
Grip strength	Baseline	21 (17, 25)	23 (19, 28)	
	6 mo	21 (17, 24)	24 (21, 28)	0.28
Shoulder abduction	Baseline	5 (4, 6)	5 (4, 6)	
	6 mo	6 (4, 7)	7 (5, 9)	0.53
Elbow flexion	Baseline	12 (9, 14)	12 (9, 14)	
	6 mo	14 (11, 16)	15 (12, 18)	0.63
Elbow extension	Baseline	10 (8, 11)	10 (9, 12)	
	6 mo	11 (19, 13)	13 (11, 14)	0.41
Hip flexion	Baseline	12 (10, 15)	13 (11, 15)	
	6 mo	16 (14, 17)	16 (15, 18)	0.83
Knee flexion	Baseline	11 (9, 12)	12 (10, 13)	
	6 mo	14 (12, 16)	13 (11, 15)	0.93
Knee extension	Baseline	15 (12, 17)	14 (12, 17)	
	6 mo	19 (16, 21)	19 (16, 22)	0.97

Data are shown in kilograms of force (95% confidence interval). *P* values represent differences in strength between treatment groups over time (repeated-measures ANOVA). There were 30 patients in each group at baseline and 24 patients in the placebo group and 21 patients in the cholecalciferol group at 6 months.

an association of 25(OH)D to PTH in CKD-5D (22,26). At this late stage of renal impairment, if responses to calciferol do occur, it is likely that they are overshadowed by altered levels of ionized calcium, phosphate, $1,25(OH)_2D$, fibroblast growth factor-23, and the development of parathyroid nodular hyperplasia. Calcium values and the risk of developing hypercalcemia did not differ significantly between treatment groups and, compared with patients allocated to placebo, patients treated with cholecalciferol had a reduction in values of serum phosphorus and were prescribed lower doses of calcium carbonate at 6 months.

In this study, levels of b-ALP and TRAcP-5b were measured because these markers do not accumulate in patients on dialysis and, together with PTH and ALP, correlate to features of renal osteodystrophy (27). A direct effect of calciferol on bone turnover is quite likely, because recent human and animal studies report the metabolism by osteoblasts and osteoclasts of 25(OH)D to $1,25(OH)_2D$ (28). Patients receiving cholecalciferol had higher TRAcP-5b levels, suggesting increased osteoclast numbers or activity; however, bone biopsies would be required to accurately interpret these changes.

PWV

PWV increases with age and is a surrogate for vascular calcification (29). In patients with CKD-5D, PWV may be increased by dosing with calcium, calcitriol, or its analogs and by phosphate exposure (30–32), although physiologic levels of 25(OH)D and $1,25(OH)_2D$ may maintain stability of the vascular smooth muscle phenotype (33). In this study, baseline PWV values were directly associated with age and inversely to 25(OH)D levels. Nevertheless, no significant between-group differences in PWV were detected over the 6 months of cholecalciferol therapy, suggesting that steady state 25(OH)D levels might influence vascular stiffness, but that short-term supplementation does not.

Muscle Strength, Functional Capacity, and HRQOL

Calciferol supplementation in the elderly general population has been associated with a reduction in falls and fractures as well as improvement in myopathy, including grip and lower limb strength (34–36). However, contrasting results have been reported with high-dose therapy (37). In CKD-5D, lower 25(OH)D levels have been associated with quadriceps weakness and falls risk (18). In this study, baseline 25(OH)D levels correlated to the distance covered in a 6-minute walk test, but not to muscle strength, and no changes were detected over the study duration. This suggests that if benefits do accrue from calciferol treatment, periods >6 months will be necessary for muscle adaptation to improved 25(OH)D levels.

HRQOL is significantly reduced in CKD-5D and predicts hospitalization and mortality (38). Low 25(OH)D levels have been associated with reduced HRQOL in CKD-5D (19), but an earlier study that assessed only the Short Form-36 physical component score reported no effect after 6 months of ergocalciferol supplementation (39). In this study, HRQOL scores using the KDQOL-36 did not change significantly with treatment allocation.

Limitations

This study has a number of limitations relating to relatively small patient numbers and the 25% withdrawal rate. In addition, the 6-month treatment exposure, with maximal levels likely to have been achieved by 8–12 weeks, may not have been sufficient to identify changes in PWV, functional capacity, or muscle strength. Values of 25(OH)D required to provide benefit for most of the population also remain controversial, with 20 ng/ml (50 nmol/L) suggested as a reasonable estimate in the 2011 Institute of Medicine report (1). In this study, some baseline 25(OH)D values exceeded 20 ng/ml, possibly reducing the potential for supplementation to influence any outcome. The normal lower limit of our $1,25(OH)_2D$ reference range is lower than the limit cited by some other studies (40).

Therefore, between-group differences at 6 months, in which the mean $1,25(OH)_2D$ value of patients treated with cholecalciferol was within our normal range, should be interpreted cautiously. It is more important to assess these differences in terms of biologic and clinical outcomes than specific values. Finally, the oral medication was administered directly by dialysis staff, which ensured compliance but might not be practical in other facilities.

Clinical Implications

This small RCT shows that cholecalciferol supplementation increases levels of 25(OH)D to a range regarded as optimal in the general population, and does not exacerbate hypercalcemia or hyperphosphatemia. Cholecalciferol treatment maintains higher $1,25(OH)_2D$ levels than in placebo-treated patients and influences some parameters of bone turnover. In addition, our baseline data suggest that 25(OH)D levels may positively influence vascular compliance and some tests of functional capacity. These findings support the establishment of larger, longer RCTs to test these potential benefits.

Acknowledgments

The authors thank Penelope Murie, Susanne Rhodes, and Nishi Punnoose for their assistance with study documentation, blood collection, and processing.

Roche Products Pty Ltd (Australia) funded this study through an unrestricted research grant and Key Pharmaceuticals Pty Ltd (Sydney) provided cholecalciferol (OsteVit-D). The investigators were solely responsible for the design, conduct, analysis, and publication of the study.

Disclosures

G.J.E. has acted on advisory boards of Amgen, Shire, and Sanofi Australia, and has received speakers fees from Amgen Australia.

References

1. Institute of Medicine: *Dietary Reference Intakes for Calcium and Vitamin D*, Washington, DC, The National Academies Press, 2011
2. Jean G, Terrat J-C, Vanel T, Hurot J-M, Lorriaux C, Mayor B, Chazot C: Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: Effects on mineral metabolism and bone markers. *Nephrol Dial Transplant* 23: 3670–3676, 2008
3. Coen G, Mantella D, Manni M, Balducci A, Nofroni I, Sardella D, Ballanti P, Bonucci E: 25-hydroxyvitamin D levels and bone histomorphometry in hemodialysis renal osteodystrophy. *Kidney Int* 68: 1840–1848, 2005
4. Del Valle E, Negri AL, Aguirre C, Fradinger E, Zanchetta JR: Prevalence of 25(OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. *Hemodial Int* 11: 315–321, 2007
5. Drechsler C, Verduijn M, Pilz S, Dekker FW, Krediet RT, Ritz E, Wanner C, Boeschoten EW, Brandenburg V; NECOSAD Study Group: Vitamin D status and clinical outcomes in incident dialysis patients: Results from the NECOSAD study. *Nephrol Dial Transplant* 26: 1024–1032, 2011
6. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R: Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 72: 1004–1013, 2007
7. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349: 446–456, 2003
8. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernán MA, Camargo CA Jr, Thadhani R: Activated injectable vitamin D and hemodialysis survival: A historical cohort study. *J Am Soc Nephrol* 16: 1115–1125, 2005
9. Tentori F, Albert JM, Young EW, Blayney MJ, Robinson BM, Pisoni RL, Akiba T, Greenwood RN, Kimata N, Levin NW, Piera LM, Saran R, Wolfe RA, Port FK: The survival advantage for haemodialysis patients taking vitamin D is questioned: Findings from the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 24: 963–972, 2009
10. Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koyama H, Inaba M, Fukumoto S, Ishimura E, Miki T, Tabata T, Nishizawa Y: Lower risk for cardiovascular mortality in oral 1α-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant* 19: 179–184, 2004
11. Tokuda N, Kano M, Meiri H, Nomoto K, Naito S: Calcitriol therapy modulates the cellular immune responses in hemodialysis patients. *Am J Nephrol* 20: 129–137, 2000
12. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao L-P: 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 110: 229–238, 2002
13. Elstner E, Linker-Israeli M, Said J, Umiel T, de Vos S, Shintaku IP, Heber D, Binderup L, Uskokovic M, Koeffler HP: 20-epi-vitamin D3 analogues: A novel class of potent inhibitors of proliferation and inducers of differentiation of human breast cancer cell lines. *Cancer Res* 55: 2822–2830, 1995
14. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M: Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab* 86: 888–894, 2001
15. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N: 25-hydroxyvitamin D3-1α-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 111: 1666–1671, 2005
16. London GM, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, Mëtivier F: Mineral metabolism and arterial functions in end-stage renal disease: Potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol* 18: 613–620, 2007
17. Elder GJ: Vitamin D levels, bone turnover and bone mineral density show seasonal variation in patients with chronic kidney disease stage 5. *Nephrology (Carlton)* 12: 90–94, 2007
18. Boudville N, Inderjeeth C, Elder GJ, Glendenning P: Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure. *Clin Endocrinol (Oxf)* 73: 299–304, 2010
19. Anand S, Kaysen GA, Chertow GM, Johansen KL, Grimes B, Dalrymple LS, Kurella Tamura M: Vitamin D deficiency, self-reported physical activity and health-related quality of life: The Comprehensive Dialysis Study. *Nephrol Dial Transplant* 26: 3683–3688, 2011
20. Kidney Disease Improving Global Outcomes: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int* 76: S1–S130, 2009
21. Working Group of the Australian and New Zealand Bone and Mineral Society; Endocrine Society of Australia; Osteoporosis Australia: Vitamin D and adult bone health in Australia and New Zealand: A position statement. *Med J Aust* 182: 281–285, 2005
22. Armas LAG, Andukuri R, Barger-Lux J, Heaney RP, Lund R: 25-Hydroxyvitamin D response to cholecalciferol supplementation in hemodialysis. *Clin J Am Soc Nephrol* 7: 1428–1434, 2012
23. Lambert PW, Stern PH, Avioli RC, Brackett NC, Turner RT, Greene A, Fu IY, Bell NH: Evidence for extrarenal production of 1 alpha, 25-dihydroxyvitamin D in man. *J Clin Invest* 69: 722–725, 1982
24. Jean G, Souberbielle J-C, Chazot C: Monthly cholecalciferol administration in haemodialysis patients: A simple and efficient strategy for vitamin D supplementation. *Nephrol Dial Transplant* 24: 3799–3805, 2009
25. Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, Gil C, Cortez J, Ferreira A: Cholecalciferol supplementation in hemodialysis patients: Effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol* 5: 905–911, 2010

26. González EA, Sachdeva A, Oliver DA, Martin KJ: Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol* 24: 503–510, 2004
27. Chu P, Chao T-Y, Lin Y-F, Janckila AJ, Yam LT: Correlation between histomorphometric parameters of bone resorption and serum type 5b tartrate-resistant acid phosphatase in uremic patients on maintenance hemodialysis. *Am J Kidney Dis* 41: 1052–1059, 2003
28. Kogawa M, Anderson PH, Findlay DM, Morris HA, Atkins GJ: The metabolism of 25-(OH)vitamin D3 by osteoclasts and their precursors regulates the differentiation of osteoclasts. *J Steroid Biochem Mol Biol* 121: 277–280, 2010
29. Reference Values for Arterial Stiffness' Collaboration: Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'Establishing normal and reference values'. *Eur Heart J* 31: 2338–2350, 2010
30. Henley C, Colloton M, Cattley RC, Shatzen E, Towler DA, Lacey D, Martin D: 1,25-Dihydroxyvitamin D3 but not cinacalcet HCl (Sensipar/Mimpara) treatment mediates aortic calcification in a rat model of secondary hyperparathyroidism. *Nephrol Dial Transplant* 20: 1370–1377, 2005
31. Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GFM: Meta-analysis: Vitamin D compounds in chronic kidney disease. *Ann Intern Med* 147: 840–853, 2007
32. London GM, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul M-C: Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 19: 1827–1835, 2008
33. Shroff R, Egerton M, Bridel M, Shah V, Donald AE, Cole TJ, Hiorns MP, Deanfield JE, Rees L: A bimodal association of vitamin D levels and vascular disease in children on dialysis. *J Am Soc Nephrol* 19: 1239–1246, 2008
34. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, Thomas J, Lowndes C, Hopper JL, Wark JD: Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc* 53: 1881–1888, 2005
35. Bischoff HA, Stähelin HB, Dick W, Akos R, Knecht M, Salis C, Nebiker M, Theiler R, Pfeifer M, Begerow B, Lew RA, Conzelmann M: Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. *J Bone Miner Res* 18: 343–351, 2003
36. Zhu K, Austin N, Devine A, Bruce D, Prince RL: A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *J Am Geriatr Soc* 58: 2063–2068, 2010
37. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC: Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. *JAMA* 303: 1815–1822, 2010
38. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK: Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 64: 339–349, 2003
39. Blair D, Byham-Gray L, Lewis E, McCaffrey S: Prevalence of vitamin D [25(OH)D] deficiency and effects of supplementation with ergocalciferol (vitamin D2) in stage 5 chronic kidney disease patients. *J Ren Nutr* 18: 375–382, 2008
40. Clive DR, Sudhaker D, Giacherio D, Gupta M, Schreiber MJ, Sackrison JL, MacFarlane GD: Analytical and clinical validation of a radioimmunoassay for the measurement of 1,25 dihydroxy vitamin D. *Clin Biochem* 35: 517–521, 2002

Received: March 20, 2012 **Accepted:** January 27, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Cholecalciferol in Chronic Dialysis Patients: Not Strong Enough?," on pages 1064–1065.