

Ergocalciferol versus Cholecalciferol for Nutritional Vitamin D Replacement in CKD

Roberto Mangoo-Karim^{a, b} Juliana Da Silva Abreu^a George P. Yanev^c
Ninfa N. Perez^a Jason R. Stubbs^d James B. Wetmore^e

^aGamma Medical Research, Inc., Edinburg, Tex., ^bSouth Texas Kidney Specialists, PA, McAllen, Tex., ^cDepartment of Mathematics, University of Texas-Pan American, Edinburg, Tex., ^dDivision of Nephrology and Hypertension, University of Kansas Medical Center, Kansas City, Kans., ^eDivision of Nephrology, Hennepin County Medical Center, Minneapolis, Minn., USA

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Key Words

25-hydroxyvitamin D · Vitamin D · Cholecalciferol · Ergocalciferol · Mineral metabolism · Chronic kidney disease

Abstract

Background/Aims: Is cholecalciferol (D₃) superior to ergocalciferol (D₂) in treating nutritional vitamin D deficiency in chronic kidney disease (CKD)? The answer to this question has not been fully explored. **Methods:** A retrospective analysis of 57 patients with non-dialysis-requiring CKD was conducted to assess the relative effectiveness of D₂ versus D₃ replacement on circulating 25(OH)D levels. Levels of 25(OH) D were assessed at baseline, after attempted repletion with D₂, and then after attempted repletion with D₃. The relative paired differences of the drug treatment effects were tested using t-tests. Multiple regression modeling was used to determine the factors significantly associated with differential responsiveness to the drugs. **Results:** The mean (SEM) age was 66.4 ± 1.4 and mean eGFR was 40.5 ± 2.2 ml/min/1.73 m². The baseline 25(OH)D level was 15.3 ± 0.8 ng/ml. After standardizing to 100,000 units of drug, increases after cholecalciferol (2.7 ± 0.3 ng/ml) were more than twice as great as those from ergocalciferol (1.1 ± 0.3 ng/ml) (p < 0.0001). A sensitivity analysis, which pooled the results of an

additional 109 individuals treated with ergocalciferol alone, revealed similar findings (standardized change 2.7 ± 0.3 vs. 1.6 ± 0.3 ng/ml, p = 0.0025). Factors associated with a superior response to cholecalciferol were lower baseline 25(OH) D level at the start of therapy (p = 0.015) and the interaction of sex and age (p = 0.0048), with younger females tending to benefit relatively more from cholecalciferol than older males did. **Conclusion:** Cholecalciferol may be superior to ergocalciferol in treating nutritional vitamin D deficiency in non-dialysis CKD.

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Introduction

Nutritional vitamin D (25(OH)D) deficiency is common in patients with chronic kidney disease (CKD) [1–8]. Contributing factors likely include limited sunlight exposure, dietary deficiencies, ongoing losses of protein-bound vitamin D in the urine [4, 9], catabolism to inactive metabolites [10], and possibly even metabolic abnormalities of the liver [11].

Insufficiency in the 25(OH)D substrate as well as impaired renal hydroxylation contribute to 1,25(OH)₂D deficiency in patients with CKD, promoting the synthesis of parathyroid hormone (PTH) and contributing to para-

thyroid gland hypertrophy and hyperplasia [12–14]. Further, deficiency in 25(OH)D may have more widespread consequences than traditionally appreciated, including associations with the metabolic syndrome [15, 16], congestive heart failure [17], cardiovascular disease [18], and a host of other pathophysiologic processes [19–22]. As result, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend repletion of 25(OH)D in patients with CKD to achieve and maintain levels above 75 nmol/l (30 ng/ml) [23].

Unfortunately, anecdotal experiences in our group suggested that the KDOQI-recommended repletion strategy was suboptimal. We have previously reported that in a predominantly Hispanic population with CKD, unexpectedly large doses of ergocalciferol (25(OH)D₂), the agent recommended by the KDOQI guidelines, increased circulating 25(OH)D levels only modestly, even in a solar-rich environment [24]. The effectiveness of this therapeutic regimen seemed to be particularly disappointing in individuals of Hispanic ethnicity, who, like non-Hispanic black individuals [7], may have had lower mean pretreatment 25(OH)D levels relative to Caucasians.

As an alternative to the plant-based sterol ergocalciferol, cholecalciferol (25(OH)D₃) is an animal-based compound. Thus, there is a theoretical basis for hypothesizing that the latter may be more effective than the former in treating nutritional vitamin D deficiency. To test this hypothesis, we initiated a protocol using which Hispanic patients who previously failed to achieve 25(OH)D concentrations >30 ng/ml with an ergocalciferol regimen based on current KDOQI guidelines would then be treated with a cholecalciferol regimen of general comparable dose and duration. Changes in response to cholecalciferol were then compared to the change resulting from ergocalciferol, and demographic and laboratory factors associated with a differential response were modeled. We specifically sought to study Hispanics, since this population may be representative of other populations characterized by generally darker skin (relative to Caucasians) and, potentially, by lower levels of 25(OH)D.

Materials and Methods

Study Design and Participants

A retrospective analysis of Hispanic patients with non-dialysis-requiring CKD was performed between 2006 and 2009. Participants were from a community nephrology practice located in Southern Texas at latitude 26.22 North, longitude 98.24 West. Because there are more than 200 clear sunny days annually, this area is designated a ‘sunny area’ by the US National Weather Center.

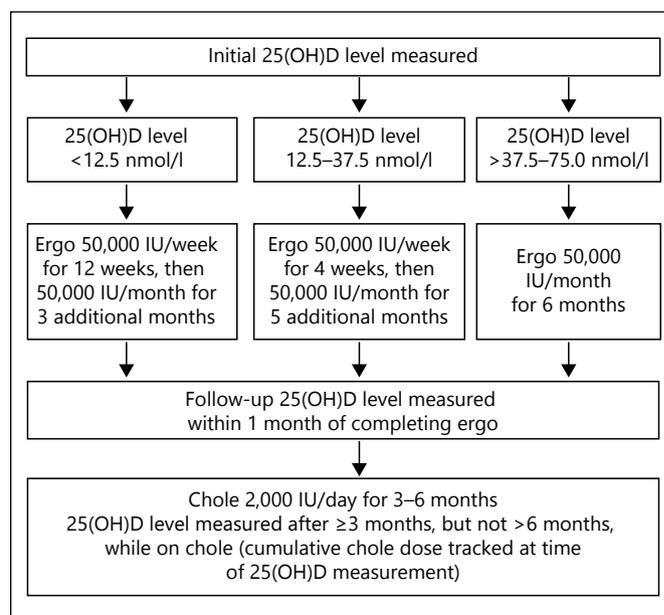


Fig. 1. Treatment protocol for repletion of 25(OH)D deficiency.

All participants studied had insufficiency or frank deficiency in 25(OH)D. Exclusion criteria were current receipt of nutritional or activated (1,25(OH)₂D) vitamin D, contraindications to 25(OH)D therapy such as recurrent calcium nephrolithiasis or hypercalcemia, or a history of kidney or liver transplantation, or renal cancer. Secondary hyperparathyroidism was neither a requirement nor a barrier to participation.

The primary analysis was a comparison in 57 patients who received ergocalciferol followed by cholecalciferol. To provide additional insights into how cholecalciferol performed relative to ergocalciferol, a second analysis also included 109 additional patients who only ever received ergocalciferol and did not continue on to receive cholecalciferol for a variety of reasons (e.g. were successfully replete with ergocalciferol alone, had progressed to dialysis, were transplanted, were lost to follow-up, or were not enrolled in or did not consent to continue into the second phase of the study). This second analysis therefore utilized all available ergocalciferol-related data, drawing from participants who did not subsequently receive cholecalciferol as well as those who did.

Treatment Regimen

Treatment was initiated as part of a rigorous protocol, and was prescribed as part of routine clinical care. The treatment regimen is shown in figure 1. Participants initially received oral D₂ supplementation, by prescription only, following the KDOQI guidelines [23]. Specifically, participants with 25(OH)D levels <12.5 nmol/l (<5 ng/ml) received ergocalciferol 50,000 international units (IU) weekly for 12 weeks followed by 50,000 IU monthly for 6 months. Participants with levels between 12.5 nmol/l and 37.5 nmol/l (5–15 ng/ml) were given 50,000 IU weekly for 4 weeks, then 50,000 IU monthly for 6 months. Participants with levels >37.5 nmol/l up to 75 nmol/l (>15–30 ng/ml) were prescribed ergocalciferol 50,000 IU monthly for 6 months. Circulating levels of 25(OH)D were then measured within 1 month of completing therapy. Cholecalciferol

was then begun at a regimen of 2,000 units per day, and measured after 3–6 months of continuous therapy (i.e. while still actively taking cholecalciferol).

Participants were heavily counseled on the importance of taking their prescribed regimen of nutritional vitamin D, and asked to bring their pill bottles with them when coming to clinic.

Laboratory Analysis

Fasting venous blood samples were used for all measurements. Greater than 90% of the participants had 25(OH)D levels measured by LabCorp (Houston, Tex., USA), which used the Diasorin LIASON instrument for an immunochemiluminometric assay, while the remaining <10% used a mixture of laboratories employing the same immunochemiluminometric assay or liquid chromatography with tandem mass spectrometry. The estimated glomerular filtration rate creatinine clearance was calculated using the CKD-EPI study equation [25].

Statistical Analysis

We first described the baseline demographic and laboratory characteristics of the participants. We analyzed, separately, the data for the 57 patients who received ergocalciferol followed by cholecalciferol and the data from the 109 patients who received ergocalciferol only. Hypothesis-testing procedures were performed to assess the similarities between the characteristics of the two populations; in cases of significant deviation from normality, the nonparametric Kruskal-Wallis test was used instead of the t-test. Continuous values were shown as means \pm the standard error of the mean (SEM).

We then analyzed changes in 25(OH)D levels after ergocalciferol therapy, and, separately, cholecalciferol therapy in the 57 who received both therapies. The difference in 25(OH)D levels after ergocalciferol (ΔD_2) was then compared to the change after cholecalciferol (ΔD_3), both in absolute terms and standardized to 100,000 units of drug. (Standardization was undertaken specifically to account for potential differences in duration between the two therapeutic courses.) In a sensitivity analysis, we pooled the results of all ergocalciferol treatments (i.e. by combining the 57 from the primary analysis with the 109 who only ever received ergocalciferol) and compared the change after ergocalciferol in all 166 total individuals to the change after cholecalciferol in the 57 participants who received both therapies.

Multiple linear regression modeling was then undertaken to isolate the factors associated with statistically significant differences between responses to the two therapies (i.e. between ΔD_2 and ΔD_3). Variables included in the modeling approach were age, sex, weight, presence of diabetes, level of proteinuria, estimated glomerular filtration rate (as calculated by the CKD-EPI formula), levels of 25(OH)D and PTH before treatment with both ergocalciferol and cholecalciferol, as well as all 2-way interaction terms. Race and ethnicity were not modeled since, as stated, all participants were Hispanic. Backward elimination was then performed to construct the final model. Factors were retained if their coefficients had p values ≤ 0.10 , with the exception of age, sex, weight, diabetes, and proteinuria, which were forced into the model. The software employed was JMP 11 (2013). Statistical significance level of 5% was used. Approval for the study was obtained by the University of Kansas Institutional Review Board and was conducted in accordance with the principles of the Declarations of Helsinki.

Table 1. Baseline characteristics of the participants

Characteristic	Mean \pm SEM (n = 57)
Age, years	66.4 \pm 1.4
Female sex, n (%)	36 (63.2)
Weight, kg	86.3 \pm 2.8
Diabetes, n (%)	27 (47.4)
eGFR, ml/min/1.73 m ²	40.5 \pm 2.2
Proteinuria, mg/day	959 \pm 274
PTH level, pg/ml	56.4 \pm 4.6
25(OH)D level, ng/ml	15.3 \pm 0.8

SEM = Standard error of the mean; eGFR = estimated glomerular filtration rate (as calculated by the CKD-EPI equation); PTH = parathyroid hormone; 25(OH)D = 25-hydroxyvitamin D.

Results

Characteristics of the participants are shown in table 1. The mean age was 66.4 \pm 1.4, 63.2% were female, and 47.4% were diabetic. The mean eGFR was 40.5 \pm 2.2 ml/min/1.73 m², mean urine protein was 959 \pm 274 mg/day, and mean PTH was 56.4 \pm 4.6 pg/ml. The baseline 25(OH)D level was 15.3 \pm 0.8 ng/ml. At the start of treatment with cholecalciferol, the level of 25(OH)D had risen to 19.6 \pm 0.6 ng/ml.

The characteristics of the 109 participants who only ever received ergocalciferol were examined and compared to the 57 participants who subsequently received cholecalciferol. These results are shown in online supplementary table 1 (www.karger.com/doi/10.1159/000430813). Compared to the 57 participants who received cholecalciferol, the 109 ergocalciferol-only patients had slightly lower eGFR (36.0 vs. 40.5 ml/min/1.73 m², p = 0.034) and slightly more proteinuria (1,326 vs. 959 mg/day, p = 0.020).

Changes in 25(OH)D levels after ergocalciferol and cholecalciferol are shown in table 2. After a course of therapy with ergocalciferol, 25(OH)D increased only by 3.3 \pm 1.0 ng/ml, as compared to 9.8 \pm 1.0 with cholecalciferol (p < 0.0001). When standardized to 100,000 units of drug, increases after cholecalciferol (2.7 \pm 0.3 pg/ml) were more than twice as much as those from ergocalciferol (1.1 \pm 0.3 ng/ml), a difference that remained highly significant (p < 0.0001). Relative paired differences (i.e. the increase of 25(OH)D attributable to cholecalciferol minus the increase attributable to ergocalciferol) were 6.5 \pm 1.1 ng/ml in absolute terms and 1.6 \pm 0.3 ng/ml per 100,000 units in standardized terms.

In a sensitivity analysis in which the results of ergocalciferol treatment in all 166 individuals were included, cholecalciferol remained superior to ergocalciferol in absolute (9.8 ± 1.0 vs. 4.7 ± 1.6 ng/ml, $p < 0.0001$) and standardized (2.7 ± 0.3 vs. 1.6 ± 0.3 , $p = 0.0025$) terms. (Of note, true 'paired' differences could not technically be calculated, as all individuals were not represented in both samples.) These results are shown in table 3.

Next, we modeled factors associated with differential response to the two therapies, testing the factors associated with change after cholecalciferol (ΔD_3) compared to change after ergocalciferol (ΔD_2). The model was modestly, but significantly, predictive of the outcome ($R^2 = 0.39$, $p = 0.0056$). As can be seen in table 4, after controlling for the other variables in the model, 25(OH)D level prior to ergocalciferol treatment was significantly associated with greater response to D_3 relative to D_2 ($p = 0.015$), suggesting that at higher initial levels of 25(OH)D, cholecalciferol was superior to ergocalciferol. The 25(OH)D level prior to cholecalciferol treatment was also significantly associated with response to D_3 ($p = 0.030$), but in the opposite direction, suggesting that at higher levels of 25(OH)D after ergocalciferol treatment, cholecalciferol was relatively less superior to ergocalciferol. The interaction of age and sex was also significant ($p = 0.0048$), suggesting that younger females benefitted relatively more from cholecalciferol than from ergocalciferol compared to older males. Other terms were not significantly associated with the outcome, while eGFR and level of proteinuria did not meet the model's univariate inclusion threshold, and so were not included in the final model.

Discussion

In this study, we compared changes in circulating 25(OH)D levels in response to ergocalciferol and cholecalciferol utilizing a sequential-treatment study design in which participants served as their own controls. We observed cholecalciferol to yield standardized increases in 25(OH)D concentrations, which were two-fold greater than ergocalciferol in patients who received both therapies. In a sensitivity analysis leveraging the results of all ergocalciferol treatments (i.e. also including patients who only ever received ergocalciferol), cholecalciferol yielded standardized increase over 1.5-fold greater than ergocalciferol. The relative superiority of cholecalciferol was greater in participants exhibiting higher baseline (pre-ergocalciferol) 25(OH)D levels, while younger females ap-

Table 2. Changes in 25(OH)D levels after therapy in participants treated with both ergocalciferol and cholecalciferol

Increase in 25(OH)D	Ergocalciferol (n = 57)	Cholecalciferol (n = 57)	Paired difference	p value
Absolute	3.3 ± 1.0	9.8 ± 1.0	6.5 ± 1.1	< 0.0001
Per 100,000 units	1.1 ± 0.3	2.7 ± 0.3	1.6 ± 0.3	< 0.0001

Data shown as mean \pm standard error of the mean. Units of 25(OH)D are in ng/ml. Absolute paired difference = cholecalciferol absolute difference - ergocalciferol absolute difference. Relative paired difference = cholecalciferol difference per 100,000 units - ergocalciferol difference per 100,000 units.

Table 3. Changes in 25(OH)D levels after therapy in participants ever treated with ergocalciferol

Increase in 25(OH)D	Ergocalciferol (n = 166)	Cholecalciferol (n = 57)	p value
Absolute	4.7 ± 0.8	9.8 ± 1.0	< 0.0001
Per 100,000 units	1.6 ± 0.3	2.7 ± 0.3	0.0025

Data shown as mean \pm standard error of the mean. Units of 25(OH)D are in ng/ml.

Table 4. Multiple regression model for difference in change in 25(OH)D level after ergocalciferol versus after cholecalciferol

Covariate	Estimate	SE	p value
Intercept	2.27	2.70	0.40
Age	0.05	0.04	0.24
Female sex	-0.29	0.34	0.40
Weight	-0.01	0.01	0.15
Diabetes	-0.26	0.32	0.42
Proteinuria	-0.001	0.001	0.31
25(OH)D level before ergo	0.14	0.05	0.015
25(OH)D level before chole	-0.20	0.09	0.030
Age \times sex ¹	-0.12	0.04	0.0048
Weight \times sex ¹	0.01	0.01	0.089
25(OH)D level before chole \times sex ¹	0.16	0.09	0.069

¹ Represents interactions of these covariates.

SE = Standard error; 25(OH)D = 25-hydroxyvitamin D; ergo = ergocalciferol; chole = cholecalciferol.

peared likely to benefit more from cholecalciferol, relative to ergocalciferol, than older males.

Clinicians frequently encounter CKD patients with low 25(OH)D levels, particularly when their practices contain substantial numbers of patients with darker

skin, who generally exhibit lower serum 25(OH)D concentrations than lighter-skinned individuals [7]. While current KDOQI clinical practice guidelines recommend an ergocalciferol-based repletion strategy for CKD patients with nutritional vitamin D insufficiency, anecdotal and experiential evidence suggests that ergocalciferol performs poorly in repleting 25(OH)D levels to the recommended targets in CKD and non-CKD patients [24, 26–30]. We therefore designed the present ‘real-world’ study, which mimics the provider’s approach through which a guideline-based strategy is initially employed, followed by an alternative therapeutic approach when the ‘orthodox’ strategy is unsuccessful. The current study suggests that practitioners who experience suboptimal results using the recommended ergocalciferol-based approach may find more success in switching to cholecalciferol after failure to achieve circulating targets with ergocalciferol.

There has also been relative paucity of prospective investigations comparing ergocalciferol and cholecalciferol in CKD patients specifically, a population prone to vitamin D insufficiency in conjunction with a unique profile of mineral metabolism derangements. Perhaps the most complete study investigating the comparative effects of these therapies in a healthy population was conducted by Lehmann et al. [31], who showed that cholecalciferol was superior to ergocalciferol in increasing 25(OH)D levels. However, this study was conducted in community-dwelling adults without CKD, and so this investigation may not be generalizable to a CKD population that possesses inherent defects in pathways that regulate vitamin D metabolism. More definitive answers in the predialysis CKD and dialysis populations therefore await an appropriately powered randomized trial.

As previously noted, we found several factors that appeared to influence the relative superiority of cholecalciferol compared to ergocalciferol. When participants had lower initial (pre-ergocalciferol) 25(OH)D levels, the two compounds exhibited comparable effectiveness; higher initial levels favored cholecalciferol. However, higher post-ergocalciferol (i.e. pre-cholecalciferol) levels decreased the relative effectiveness of cholecalciferol relative to ergocalciferol. This finding, which may at first appear paradoxical, might be explained by positing that for those individuals who actually demonstrated a robust response to ergocalciferol during the initial treatment phase, cholecalciferol might indeed be expected to perform relatively less well subsequently. That is, individuals who responded well to ergocalciferol might likely respond to either agent, diminishing the relative superior-

ity of cholecalciferol to ergocalciferol. This hypothesis is purely speculative, however, and requires further investigation. Moreover, the possible implications of the interaction between age and sex require further study, since neither characteristic was individually associated with superiority of cholecalciferol over ergocalciferol.

Our study has several limitations. It was not a true clinical trial, and so cannot be used to infer causality. Additionally, the primary analysis was conducted in patients who were exposed to cholecalciferol only if the ergocalciferol treatment failed. However, a sensitivity analysis utilized the results of an additional group of patients who only ever received ergocalciferol, permitting us to compare the pooled results of all ergocalciferol treatments in order to compare them with all available cholecalciferol treatments; the results of this latter analysis also demonstrated a marked superiority of cholecalciferol. Additionally, since ergocalciferol has a shorter half-life than cholecalciferol, post-treatment measurements that were performed more distal to the completion of the study would be more likely to favor cholecalciferol. That said, it is sustained, rather than transient, increases in 25(OH)D levels that are the goal of repletion, so failure to sustain acceptable levels would further strengthen the rationale for cholecalciferol.

In conclusion, we demonstrated greater standardized increases in circulating 25(OH)D levels with cholecalciferol than with ergocalciferol in a Hispanic CKD population residing in a solar-rich environment. While the nature of our study design does not permit causal inferences, it does reflect a frequently encountered real-world scenario faced by everyday practitioners, who naturally and appropriately attempt to use clinical practice guidelines to direct therapy but who also see the need to try alternative approaches when results are suboptimal. Future studies, such as clinical trials, should be conducted to determine the relative effects of these agents in CKD patients.

Disclosures

The authors do not have any conflicts of interest to disclose.

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