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Ethnic differences in 25-hydroxyvitamin D levels and response to treatment in CKD

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Abstract
Aim Nutritional vitamin D [25(OH)D] deficiency is common in patients with chronic kidney disease (CKD). No studies have specifically examined the differences between ethnic groups in response to ergocalciferol ("D2") therapy.
Methods A retrospective analysis was performed to evaluate the effectiveness of D2 therapy as recommended by the KDOQI guidelines in 184 Hispanic and Caucasian nondialysis CKD patients.
Results Low 25(OH)D levels (<75 nmol/L) were found in 89.4 % of Hispanics versus 61.4 % of Caucasians, despite similar degrees of CKD. Treatment per KDOQI guidelines resulted in 85.5 % of treated Hispanics and 66.7 % of treated Caucasians remaining vitamin D-deficient. Although both Hispanics and Caucasians had significant ($P < 0.0001$) changes in 25(OH)D levels, absolute changes were modest (12.5 ± 2.0 nmol/mL in Hispanics, 20.0 ± 3.5 nmol/L in Caucasians). The increase seen in Caucasians was significantly greater than in Hispanics ($P < 0.0001$). In multiple logistic regression modeling, Hispanic ethnicity remained independently associated with poorer response to therapy ($P = 0.0055$), even after adjustment for other factors.
Conclusions While both Hispanics and Caucasians demonstrated suboptimal response to the KDOQI-guided vitamin D repletion strategy, Hispanic ethnicity was significantly associated with poorer response. Our findings may have implications for other darker-skinned populations, even in solar-rich environments.

Keywords 25-hydroxyvitamin D · Vitamin D · Mineral metabolism · Race · Ethnicity · Chronic kidney disease

Iris Sanchez and Roberto Mangoo-Karim contributed equally to this work.

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Introduction

Deficiency in nutritional vitamin D [25(OH)D] is common in patients with chronic kidney disease (CKD) [1–8]. Several factors are hypothesized as contributing factors [3], including limited sunlight

exposure, dietary deficiencies, catabolism to inactive metabolites [9], ongoing losses of protein-bound vitamin D in the urine [4, 10], uremia-induced decreased binding of the vitamin D receptor [11], and, possibly, metabolic abnormalities of the liver [12]. Insufficiency in the 25(OH)D substrate and impaired renal hydroxylation contribute to $1,25(OH)_2D$ deficiency in patients with CKD and promote the synthesis of parathyroid hormone (PTH), which ultimately results in parathyroid gland hypertrophy and hyperplasia [13–15]. In addition to its classical effects on mineral metabolism, 25(OH)D deficiency is a potential contributor to several other adverse outcomes associated with patients with CKD, including the metabolic syndrome [16, 17], congestive heart failure [18], cardiovascular disease [19], and a host of other pathophysiologic processes [20–23]. As a result, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend the repletion of 25(OH)D to achieve and maintain levels above 75 nmol/L (30 ng/mL) [24].

However, anecdotal experiences in our group suggest that the KDOQI-recommended repletion strategy is suboptimal. The effectiveness of this therapeutic regimen seems to be particularly disappointing in individuals of Hispanic ethnicity, who, like non-Hispanic black individuals [7], may have lower mean pretreatment 25(OH)D levels relative to Caucasians, even in a solar-rich environment.

To our knowledge, there is no published data that compares the effectiveness of 25(OH)D repletion using ergocalciferol ("D2") therapy by employing the KDOQI protocol among patients of different ethnicities with CKD, not on dialysis, who reside in the same geographic area. We undertook a study in the solar-rich environment of southern Texas, USA, in order to investigate whether there is evidence of a differential frequency of 25(OH)D deficiency in Hispanic versus non-Hispanic Caucasian populations with CKD, whether the effectiveness of 25(OH)D repletion with ergocalciferol varies by ethnicity, and whether the presence of either proteinuria or diabetes appears to affect the response to therapy. We specifically sought to study Hispanics since this population may serve as a model for other populations characterized by generally darker skin (relative to Caucasians) and, potentially, by lower levels of 25(OH)D.

Subjects, materials, and methods

Study design and participants

A retrospective analysis of 283 Hispanic ($n = 227$) and non-Hispanic Caucasian ($n = 56$) patients with nondialysis-requiring CKD was performed between 2006 and 2008. Participants were drawn from a community nephrology practice located in southern Texas at latitude 26.22 North, longitude 98.24 West. There were 226 and 205 clear sunny days in 2006 and 2007, respectively, in this area, which is therefore designated a "sunny area" by the U.S. National Weather Center. The clinical practice group is located in an underserved area in which the vast majority (>90 %) of the Hispanics seen in clinic would characterize themselves as being "Indian" or aboriginal ("first nations") in origin.

We first sought to characterize the frequency of 25(OH)D deficiency. Nearly all prevalent CKD patients seen in this practice (>95 %) were screened for 25(OH)D levels ($n = 286$). Three did not have weights recorded (due to nonambulatory status), and therefore, 283 participants constituted the "frequency estimate sample" for 25(OH)D deficiency.

We next sought to evaluate the effectiveness of 25(OH)D repletion. Repletion was given as part of routine clinical care. Treated individuals who were analyzed comprised a subset ($n = 184$) of the initially screened patients and consisted of all individuals who followed up after the completion of ergocalciferol therapy within 7 months and who returned with their pill bottles as counseled. (This subset is hereafter referred to as the "treatment sample".) Because it was our intent to utilize as many patients as possible for determining the frequency of 25(OH)D deficiency, the frequency estimate sample was larger than the treatment sample, since not all individuals who contributed information to the frequency estimate sample either required or completed D2 therapy.

Exclusion criteria of the study were current receipt of nutritional or activated vitamin D [$1,25(OH)_2D$] supplementation, contraindications to 25(OH)D therapy such as recurrent calcium nephrolithiasis or hypercalcemia, or a history of kidney transplantation or renal cancer. Secondary hyperparathyroidism was neither a requirement of, nor barrier to, participation in the study.

Treatment regimen

All participants received oral D2 supplementation following the KDOQI guidelines [24]. The medication was by prescription only. 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 and 37.5 nmol/L (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 up to 75 nmol/L (30 ng/mL) were prescribed ergocalciferol 50,000 IU monthly for 6 months.

Approval for the study was obtained the University of Kansas Institutional Review Board and was conducted in accordance with the principles of the Declarations of Helsinki.

Laboratory analysis

Circulating levels of 25(OH)D, calcium (Ca), phosphate (P), parathyroid hormone (PTH), and creatinine were measured in all participants within 2 weeks before and within 1 month after the attempted repletion course. Fasting venous morning blood samples were used for all measurements. Greater than 90 % of the patients had 25(OH)D levels measured by LabCorp (Houston, Texas), which uses the Diasorin LIASON instrument for an immunochemilluminometric assay, while the remaining <10 % used a mixture of laboratories employing the same immunochemilluminometric assay or liquid chromatography with tandem mass spectrometry. The estimated glomerular filtration rate creatinine clearance was calculated using the Modification of Diet in Renal Disease (MDRD) study equation [25].

Statistical analysis

We conducted a descriptive analysis of baseline demographic and laboratory characteristics of both the entire cohort ("frequency estimate sample") and those who completed treatment ("treatment sample"). Differences in ethnicity, gender, diabetes status, cause of CKD, and CKD stage distributions between treatment groups were evaluated with χ^2 tests. Participants' age, weight, estimated glomerular filtration rate (eGFR), proteinuria, baseline 25(OH)D, and PTH levels were examined using both nonparametric and *t* tests, assuming equal and unequal variances when appropriate. (As we did not consistently record patient height, we were unable to calculate body mass index; weight was therefore used as a surrogate.)

We analyzed between- and within-group absolute changes in 25(OH)D levels after 6 months of ergocalciferol therapy, controlling for ethnicity and diabetic status. Since the absolute and standardized (per 100,000 units of ergocalciferol) changes in 25(OH)D levels had a distribution which departed significantly from normalilty, the nonparametric Wilcoxon signed rank test (for within-group comparisons) and Kruskal–Wallis test (for between-group comparisons) were utilized. We also tested for significant changes in 25(OH)D levels per 100,000 units of ergocalciferol in Hispanics, stratified by level of proteinuria. In addition, we inspected for significant changes over the observation period for calcium (Ca) and phosphorous (P) levels.

Multiple regression modeling, undertaken to isolate the factors associated with statistically significant effects on the change in 25(OH)D levels per 100,000 units of ergocalciferol, was performed as follows. The initial fitting model included the following as exploratory factors: age, sex, ethnicity, weight, eGFR, diabetes, proteinuria, baseline 25(OH)D level, and parathyroid hormone (PTH) level, as well as all second-order interactions between ethnicity, eGFR, diabetes, and proteinuria. In search of the optimum set of explanatory variables, we used backward elimination of variables with preset cutoff ("drop") significance level 0.25. The variables of ethnicity, diabetes, and proteinuria were kept in all model modifications. Lastly, to test the robustness of our findings, we then performed logistic regression modeling to determine the odds ratios (ORs) and associated 95 % confidence intervals (CI's) for the association between ethnicity and 25(OH)D repletion by using several different 25(OH)D cutpoints; key covariates identified by the initial multiple regression modeling were incorporated in this analysis.

The software employed was JMP 8.0.2 (2009), SAS Institute, Inc. (Cary, NC). A type I error probability of 5 % was used to determine statistical significance.

Results

Characteristics of the frequency estimate sample, defined as individuals who had a 25(OH)D level

Table 1 Baseline characteristics of the participants with initial 25(OH)D level <75 nmol/L and who underwent treatment

Characteristic	All ($n = 184$)	Hispanics ($n = 157$)	Caucasians ($n = 27$)	P value
Age (years)	67.2 ± 11.8	66.6 ± 12.1	71.0 ± 9.36	0.07
Female sex, *n* (%)	90 (48.9)	80 (51.0)	10 (37.0)	0.18
Weight (kg)	85.4 ± 20.0	84.2 ± 19.3	92.3 ± 22.5	0.06
Diabetes, *n* (%)	92 (50.0)	79 (50.3)	13 (48.1)	0.84
Cause of CKD				0.03
Diabetes, *n* (%)	92 (50.0)	79 (50.3)	13 (48.2)	
Hypertension, *n* (%)	41 (22.3)	37 (23.6)	4 (14.8)	
Glomerulonephritis, *n* (%)	14 (7.6)	14 (8.9)	0 (0)	
Other, *n* (%)	37 (20.1)	27 (17.2)	10 (37.0)	
CKD stage, MDRD				0.27
1–2	13 (7.1)	11 (7.0)	2 (7.4)	
3–5	171 (92.9)	146 (93.0)	25 (92.6)	
Estimated GFR (mL/min)	36.0 ± 15.7	35.4 ± 15.9	39.5 ± 14.4	0.11
Proteinuria (mg/day)	1058 ± 1693.0	1126.5 ± 1790.6	661.8 ± 864.2	0.20
25(OH)D level (nmol/L)	40.0 ± 15.8	38.5 ± 15.5	48.8 ± 15.3	0.002
PTH level (ng/mL)	77.6 ± 72.5	79.7 ± 76.0	64.9 ± 46.7	0.46

Data shown as mean ± standard deviation for continuous variables

P values represent the comparison between Hispanics and Caucasians

CKD chronic kidney disease, *MDRD* modification of diet in renal disease equation, *GFR* glomerular filtration rate, *25(OH)D* 25-hydroxyvitamin D, *PTH* parathyroid hormone

measured, are shown in Supplementary Table 1. Reflective of the demography of the study site, the participants were 80.2 % Hispanic. The age range was 21–89 years. Nearly 9 in 10 patients had advanced chronic kidney disease (CKD stage 3 or worse). Mean 25(OH)D was only slightly below 70 nmol/L in the Caucasians, but was just 45.0 ± 22.3 ng/mL in the Hispanics, a difference that was highly statistically significant. Fully 89.4 % of the Hispanics, as well as 61.4 % of the Caucasians, had levels <75 nmol/L.

Table 1 shows demographic and laboratory values for the 184 individuals who had initial 25(OH)D levels <75 ng/mL and who therefore underwent attempted repletion and follow-up testing. Overall, the characteristics of treatment sample were very similar to those of the frequency estimate sample.

Figure 1 provides more detail on the baseline level of nutritional vitamin D in the patients subsequently treated, demonstrating the distribution of 25(OH)D levels before therapy commenced. The values for the Hispanics were clearly distributed over a lower range than for the Caucasians, with the former having a median value of 38.5 nmol/L and the latter 50.3 nmol/L.

Among the 203 Hispanics who had levels <75 nmol/L, 157 (77.3 %) completed therapy, returned, and had follow-up levels drawn following the attempted repletion. A total of 134 individuals (85.4 % of these 157 returnees) still had levels <75 nmol/L after attempted repletion. Among the 35 Caucasians who had initial levels <75 nmol/L, 27 (77.1 %) completed therapy, returned, and had follow-up levels drawn following attempted repletion; 18 individuals (66.7 % of the 27 returnees) still had levels <75 nmol/L after attempted repletion.

Table 2 demonstrates the results of attempted repletion with ergocalciferol by ethnicity. Results are shown for both within-group and between changes in 25(OH)D levels, both in absolute changes as well as standardized (i.e., per 100,000 units of ergocalciferol) changes. For the Hispanics, both the absolute and standardized increases were statistically significant. However, the absolute increase in 25(OH)D levels was only about 12.5 nmol/L, highlighting the difference between clinically significant and statistically significant results. For the Caucasians, a similar pattern was observed, with absolute increases being minor. Examination of the between-group changes demonstrated that Caucasians as a whole had a better response to D2 replacement compared with Hispanics ($P = 0.005$ for the standardized overall between-group change, $P = 0.03$ for the absolute overall between-group change).

Because proteinuria may result in the loss of vitamin D binding protein and, subsequently, in lower circulating levels of 25(OH)D, we examined whether the change in 25(OH)D levels varied by strata of

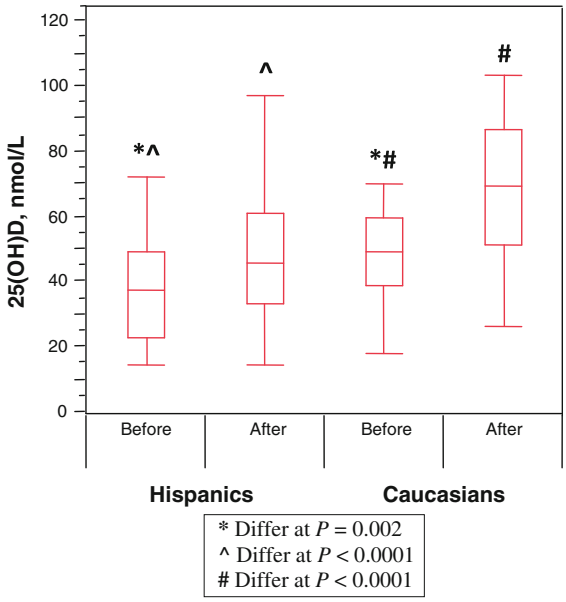

Fig. 1 Baseline distributions of 25(OH)D levels in the participants who were subsequently treated, by ethnicity

proteinuria. Two thresholds, or "cutpoints", of proteinuria were selected, 300 and 1,000 mg/day; because of the relatively small numbers of Caucasians, only Hispanics were examined for this analysis. Table 3 demonstrates change in 25(OH)D level per 100,000 units of ergocalciferol in the Hispanics. At a proteinuria level of 300 mg/day, individuals with less than 300 mg/d of proteinuria responded significantly better than those with a higher level of proteinuria ($P = 0.0039$); a similar pattern was observed at a proteinuria cutoff of 1,000 mg/d, in which individuals with less than this level had a significantly better ($P = 0.044$) response to ergocalciferol than individuals with greater proteinuria.

Table 4 demonstrates the result of multiple regression modeling for factors associated with change in 25(OH)D levels, standardized per 100,000 units of ergocalciferol. Age, eGFR, and PTH level were all below the prespecified drop threshold upon bivariate analysis, so they were not included in subsequent multivariable modeling. In the final multivariable model, sex and weight were not associated with change in 25(OH)D levels. However, ethnicity was independently associated with change in 25(OH)D level ($P = 0.0055$), with Hispanic individuals demonstrating poorer response than Caucasians. Proteinuria was significantly associated with a poorer response ($P = 0.023$).

We then examined our findings in another way. Using logistic regression and incorporating the above-mentioned factors that were shown to be significant in the above-mentioned modeling, we determined the independent association between ethnicity and 25(OH)D repletion. Because manual inspection of the data showed that very few individuals were successfully repleted, a threshold of 65 nmol/L was used for analysis, accompanied by sensitivity analyses using more liberal (60 nmol/L) and conservative (70 nmol/L) cutpoints. As shown in Table 5, Hispanics had an OR for repletion at 65 nmol/L of 0.25 (95 % CI's, 0.10–0.63, $P = 0.0032$) compared with Caucasians, after adjustment for baseline 25(OH)D level and degree of proteinuria. At a threshold of 60 nmol/L, the OR for Hispanics was 0.33 (0.13–0.82, $P = 0.017$), while at 70 nmol/L, the OR was 0.27 (0.11–0.68, $P = 0.033$), indicating overall robustness to our results under varying conditions.

There were no significant changes in mean Ca and P levels following therapy: Ca decreased 0.02 ± 0.01 (SEM) mmol/L and 0.02 ± 0.05 mmol/L in the Hispanics and Caucasians, respectively, while P increased 0.01 ± 0.02 (SEM) mmol/L and 0.04 ± 0.03 mg/dL in the Hispanics and Caucasians, respectively. None of the participants developed overt hypercalcemia or hyperphosphatemia, nor did any develop nephrolithiasis during therapy.

Table 2 Between- and within-group changes in 25(OH)D levels after 6 months of ergocalciferol therapy, by ethnicity

Increase in 25(OH)D	Hispanics	*P* value of Δ from baseline	Caucasians	*P* value of Δ from baseline	Between-group *P* value
Absolute	12.5 ± 2.0	<0.0001	19.8 ± 3.5	<0.0001	0.03
Per 100,000 units	3.0 ± 0.5	<0.0001	6.0 ± 1.0	<0.0001	0.005

Data shown as mean ± standard error of the mean. Units of 25(OH)D are in nmol/L

Δ change, *DM* diabetes mellitus

Table 3 Change in 25(OH)D level per 100, 000 units of ergocalciferol replacement in Hispanics, stratified by level of proteinuria

	300 mg/day proteinuria			1,000 mg/day proteinuria		
	Below ($n = 71$)	Above ($n = 86$)	*P* value	Below ($n = 103$)	Above ($n = 54$)	*P* value
25 (OH)D	4.5 ± 0.8	1.8 ± 0.8	0.0039	3.5 ± 0.8	2.0 ± 1.0	0.044

Data shown as mean ± standard error of the mean. Units of 25(OH)D are in nmol/L

DM diabetes mellitus

Table 4 Multiple regression model for change in 25(OH)D level, standardized by 100,000 units of ergocalciferol

Covariate	Estimate	Standard error	*P* value
Intercept	5.539	1.131	<0.0001
Female sex	−0.292	0.209	0.17
Hispanic ethnicity	−0.817	0.289	0.0055
Weight	−0.006	0.005	0.16
Baseline 25(OH)D	−0.132	0.034	<0.0001
DM	−0.466	0.286	0.10
Proteinuria	−0.001	0.001	0.023
Hispanic ethnicity × DM	0.342	0.280	0.22

DM diabetes mellitus

"Hispanic ethnicity × DM" represents the interaction of these covariates

Table 5 Logistic regression model for factors associated with attainment of 25(OH)D level of 65 nmol/L

Covariate	OR	95 % CI's	*P* value
Hispanic race	0.25	0.10–0.62	0.0032
Baseline 25(OH)D	1.04	1.01–1.06	0.0029
Proteinuria	0.99	0.99–0.99	0.038

OR odds ratio, *CI* confidence interval

Discussion

Previous studies have demonstrated that non-Hispanic black and Hispanic populations with CKD have a greater prevalence of 25(OH)D deficiency compared with Caucasian populations [7]. We have confirmed a higher rate of 25(OH)D insufficiency in prevalent Hispanic, compared with Caucasian, CKD patients, and have quantified the clinically trivial increases in 25(OH)D levels when D2 supplementation is used per the KDOQI protocol. We also demonstrate an independent effect of ethnicity on response to D2 therapy, characterized by a particularly blunted response to D2 therapy in Hispanics. Finally, we demonstrate that proteinuria is associated with particularly suboptimal response to "real-world" attempts at therapy.

Our observation of an overall poor response to the KDOQI regimen is consistent with the findings of other studies. Al-Aly et al. [26] administered an "accelerated" ergocalciferol regimen to 66 stage 3 and 4 CKD patients (12 weekly 50,000 IU doses followed by 3 monthly doses) and found that, while 25(OH)D levels increased significantly, they went up to a mean of only 68 nmol/L (27.2 ng/mL), up from 41.5 nmol/L (16.6 ng/mL) at baseline. Zisman et al. [27] treated 52 stage 3 and stage 4 CKD patients, also using an aggressive regimen in which patients with 25(OH)D levels of 37.7–62.5 nmol/L (15-25 ng/mL) received weekly (rather than monthly) ergocalciferol doses for 4 weeks. Levels of 25(OH)D went from 48.8 nmol/L (19.5 ng/mL) to only 83.5 nmol/L (33.4 ng/mL), with many patients remaining insufficient. While another group of investigators had more success in raising 25(OH)D levels with ergocalciferol dosing, provoking an increase from 42.5 to 104.8 nmol/L (17.0 to 41.9 ng/mL) in 85 stage 3–5 CKD patients, this required a particularly intense regimen of 16 doses in 2 months [28].

Our findings suggest that the KDOQI protocol provides inadequate 25(OH)D repletion in many patients with CKD and that alternative approaches may be required. As recently reviewed by Kandula et al. [29], "accelerated" or intensive regimens of ergocalciferol repletion may be required to achieve clinically meaningful results. Alternatively, other forms of nutritional vitamin D, such as cholecalciferol, may prove to be more effective for repletion than ergocalciferol [30]. More impressive results in raising 25(OH)D levels were achieved by investigators in a smaller study (20 patients in total) by utilizing cholecalciferol ["D3"] supplementation of

50,000 IU once weekly [31], indicating that perhaps the animal-derived sterol is more effective than the plant-based product. This conclusion is consistent with evidence from investigations in humans with normal renal function [30, 32] and suggests that not only might the total dose of nutritional vitamin D be important, but that particular compound might be as well, with ergocalciferol being suboptimal for use in a monthly replacement regimen. A separate question, which we did not seek to answer, was the effectiveness of 25(OH)D repletion in treating secondary hyperparathyroidism.

We found that Hispanics had lower levels of 25(OH)D relative to Caucasians, a finding consistent with observations in both the general and CKD populations. For example, Mexican-Americans had lower 25(OH)D levels than Caucasians in the National Health and Nutrition Examination Survey (NHANES) 3 [33]. Additionally, a recent meta-analysis supported these findings by demonstrating that an effect of latitude on 25(OH)D levels was operative only in Caucasians [34]. This suggests that Hispanic individuals may follow patterns of 25D levels of other darker-skinned populations described by multiple studies [4, 7, 35], although it should be acknowledged that in a single study, levels of 25(OH)D in Hispanics were similar to Caucasians (with both groups having higher 25(OH)D levels than African-Americans) [36]. Full investigation of this issue is probably incomplete in the absence of characterization of both nutritional vitamin D intake as well as sun exposure in the studied groups.

On an absolute scale, we had initially expected the latitude of our study site would have resulted in higher 25(OH)D levels in both races than were actually observed. However, in one study that compared the relationship of 25(OH)D levels in CKD patients across many different U.S. geographic areas, only individuals in Florida (the sunniest region examined) had significantly higher levels than in the country as a whole; even in south Texas, 25(OH)D levels were relatively low and were no different than in the other areas examined [8]. These findings may support the hypothesis that patients with CKD have an inherent defect in the generation of pre-vitamin D3 in the skin following UV radiation [37]. Taken together, our observations and those of others imply that nephrologists should not expect ambient sunlight to yield clinically important benefits on 25(OH)D levels in non-Caucasians, or potentially in any patient with advanced CKD.

Similar to other investigators, we observed an inverse relationship between 25(OH)D levels and the degree of proteinuria [4, 38–40]. We attribute this relationship largely to losses of vitamin D binding protein in the urine. An early study in humans with nephrotic syndrome demonstrated lower levels of serum vitamin D binding protein (VDBP) [41], which was complemented and expanded by a later study in children with nephrotic syndrome that showed that reductions in serum 25(OH)D levels correlated with reduced serum VDBP levels [42]. In the latter study, proteinuria correlated with both serum VDBP and loss of VDBP in the urine, suggesting that the link between low 25(OH)D and proteinuria was loss of VDBP in urine and subsequent reductions in circulating levels of the carrier protein. Our observation of an inferior response to ergocalciferol therapy in patients with ongoing proteinuria would suggest a need for the creation of a unique 25(OH)D repletion protocol for patients with ongoing proteinuria. We did consider the possibility that poorer nutritional status of patients with higher levels of proteinuria (a potential marker for worse CKD, other comorbidities, and lower functional status) could be factor, but this seems less likely in an ambulatory setting of almost exclusively community-dwelling individuals.

We acknowledge several important limitations to our study. The study was not a prospective clinical trial, but rather was retrospective in nature; this introduces the classical biases of an observational design. The number of Caucasian individuals was small, which limited the power of our study when comparing the effects of ergocalciferol between ethnic groups; this is a reality of our practice demography. The 25(OH)D levels were drawn randomly at various times of the year, so it is theoretically possible that seasonal variation could play a role in our results. However, because south Texas is a subtropical region with >300 sunny or partly sunny days per year and a very mild winter characterized by few days below freezing, seasonal variation is unlikely to have been a major contributor to our findings. There was also variability in the assay used to measure 25(OH)D levels, but since >90 % of our patients utilized an immunochemiluminometric assay, modest degrees of assay variability seem unlikely to be responsible for our findings. Additionally, while there is no guarantee that patients were adherent to their therapy, standard practice in our group is to heavily counsel patients to return with their pill bottles (even if empty) to every clinic visit and to

have patients undergo a brief, nurse-driven medication-reconciliation process at each visit. As a defense against potential nonadherence, we analyzed only individuals who returned with their ergocalciferol pill bottles and who therefore gave every indication of being adherent to therapy. Finally, we cannot provide a definitive mechanism by which repletion rate was unexpectedly poor; the answer may lie in investigating the contributions of other mediators of mineral metabolism such as fibroblast growth factor-23 (FGF23), a vitamin D counter-regulatory hormone that is elevated in CKD and both antagonizes the production and enhances the degradation of 1,25(OH)D.

In summary, we found that the KDOQI protocol for the repletion of circulating 25(OH)D levels with ergocalciferol performed suboptimally in our patient population, which consisted primarily of Hispanics in a solar-rich environment; such patients may be model for other populations characterized by relatively darker skin. Hispanics have lower 25(OH)D levels than non-Hispanic Caucasians and respond less well to D2 therapy. Individuals with proteinuria seem particularly prone to low serum 25(OH)D levels and are more likely to be resistant to D2 therapy. Our findings are a sobering warning to physicians not to have unrealistic expectations about the effectiveness of repletion. Given both the implications of 25(OH)D insufficiency on cardiovascular, immune, and bone health, more efforts should focus on defining a successful repletion strategy and further risk factors for repletion failure. Whether repletion of 25(OH)D levels can ultimately reduce morbidity and mortality in patients with CKD requires further investigation through prospective trials.

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

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