



Treatment of vitamin D deficiency in CKD patients with ergocalciferol: are current K/DOQI treatment guidelines adequate?

W.Y. Qunibi¹, A. Abdellatif¹, S. Sankar¹, Z. Hamdan¹, F.-Y. Lin¹, J. Ingle¹, A. Cadena¹, J. Gelfond² and B. Kasinath¹

Nephrology Division, ¹Department of Medicine and ²Epidemiology and Biostatistics, University of Texas Health Science Center, San Antonio, TX, USA

Key words

chronic kidney disease – calcitriol – 25-hydroxyvitamin D – parathyroid hormone – vitamin D – secondary hyperparathyroidism

Abstract. **Background:** Vitamin D deficiency/insufficiency (VDDI) is common in CKD patients and may be associated with abnormal mineral metabolism. It is not clear whether the K/DOQI recommended doses of ergocalciferol are adequate for correction of VDDI and hyperparathyroidism. **Methods:** Retrospective study of 88 patients with CKD Stages 1 – 5 and baseline 25-hydroxyvitamin D level < 30 ng/ml (< 75 nmol/l). Patients treated with ergocalciferol as recommended by K/DOQI guidelines. Only 53 patients had elevated baseline PTH level for the CKD stage. Patients were excluded if they received vitamin D preparations other than ergocalciferol or phosphate binders. 25-hydroxyvitamin D level, intact PTH level (iPTH), and other parameters of mineral metabolism were measured at baseline and after completion of ergocalciferol course. **Results:** 88 patients with CKD were treated with ergocalciferol. Mean age 56.8 ± 9.5 years and 41% were males. The mean ($\pm$ SD) GFR was 28.3 ± 16.6 ml/min. At the end of the 6-month period of ergocalciferol treatment, the mean 25-hydroxyvitamin D level increased from 15.1 ± 5.8 to 23.3 ± 11.8 ng/ml (37.75 ± 14.5 to 58.25 ± 29.5 nmol/l) ($p < 0.001$). Treatment lead to ≥ 5 ng/ml (12.5 nmol/l) increases in 25-hydroxyvitamin D level in 54% of treated patients, and only 25% achieved levels ≥ 30 ng/ml (75 nmol/l). Mean iPTH level decreased from 157.9 ± 125.9 to 150.7 ± 127.5 pg/ml ($p = 0.5$). Only 26% of patients had $\geq 30\%$ decrease in their iPTH level after treatment with ergocalciferol. **Conclusions:** Current K/DOQI guidelines are inadequate for correcting VDDI or secondary hyperparathyroidism in CKD patients. Future studies should examine the effects of higher or more frequent dosing of ergocalciferol on these clinical endpoints.

Introduction

Vitamin D deficiency or insufficiency (VDDI) is very prevalent in the general population and in those with all stages of CKD [3, 7, 17, 18, 19, 25, 27, 35, 42]. Previous studies have reported an association between VDDI and increased intact parathyroid hormone (iPTH) levels [24, 32], reduced bone mineral density, increased rates of hip fractures [9] as well as increased risk of death [5, 23, 33]. Moreover, 25-hydroxyvitamin D may play a role in decreasing the risk of many chronic illnesses, including infectious diseases, autoimmune diseases, cardiovascular disease, and cancer [19, 28, 30, 45, 46]. 25-hydroxyvitamin D is derived mainly from cholecalciferol (vitamin D₃) which is produced by the solar UV-B irradiation of the skin exposed to sunlight and, to a limited extent, from cholecalciferol or ergocalciferol (vitamin D₂) ingested from dietary sources or supplements [7, 19].

Reduction of serum 25-hydroxyvitamin D leads to reduced calcitriol production by the kidney and secondary hyperparathyroidism (SHPT) in individuals with CKD [35]. Previous studies have reported that 25-hydroxyvitamin D level correlate positively with calcitriol level and negatively with iPTH level in patients with CKD Stages 3 and 4 [17]. Parathyroid hormone usually plateaus to a minimum steady-state level as serum 25-hydroxyvitamin level approaches and rises above 30 ng/ml [45]. Plasma levels of iPTH begin to rise when the glomerular filtration rate (GFR) falls below 45 ml/min/1.73 m² and increase further in the course of progressive loss of renal function [27]. Thus, approxi-

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Correspondence to
Prof. W.Y. Qunibi, MD,
Medical Director of
Dialysis Services,
University of Texas
Health Science Center
at San Antonio,
7703 Floyd Curl Drive,
San Antonio, TX
78229-3900, USA
qunibi@uthscsa.edu

mately 40% of patients with Stage 3 CKD and 80% of patients with Stage 4 have SHPT due to low levels of calcitriol [27]. Calcitriol, which plays an important role in suppression of PTH synthesis via its actions on vitamin D receptors (VDR) in the parathyroid cells, is derived from the enzymatic conversion of 25-hydroxyvitamin D by the 1- α -hydroxylase enzyme in the kidneys. However, calcitriol level does not reflect the body's vitamin D status as its level is usually normal or even elevated despite the presence of vitamin D deficiency [19]. In contrast, the serum level of 25-hydroxyvitamin D level more likely reflects the total body stores of vitamin D and therefore is used as the standard clinical measure of vitamin D status. In practice, vitamin D deficiency is determined by documenting low serum levels of 25-hydroxyvitamin D.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism in Chronic Kidney Disease recommend that serum levels of 25-hydroxyvitamin D be measured in patients with CKD Stages 3 and 4 who have increased iPTH levels. Moreover, the guidelines recommend that, in patients with low 25-hydroxyvitamin D, supplementation with ergocalciferol should be initiated; the dosage must be guided by the initial vitamin D level [35]. The objectives of these recommendations were to correct the VDDI and to simultaneously decrease iPTH levels. Previous studies that attempted to evaluate the impact of the K/DOQI treatment guidelines on achieving these goals have used modified dosing protocols [1, 2, 13, 38, 39, 47]. The aim of the present study was to examine the impact of ergocalciferol, as recommended by the K/DOQI guidelines, on 25-hydroxyvitamin D and iPTH levels as well as on other parameters of mineral metabolism in nondialyzed CKD patients (ND-CKD).

Methods

Study population

Nondialyzed CKD patients who regularly attend the Renal Clinic at the University of Texas Health Science Center and Texas Diabetes Institute in San Antonio, Texas, USA routinely undergo measurement of 25-hy-

droxyvitamin D levels as part of the evaluation for VDDI and secondary SHPT. These levels are used to guide the initiation and titration of the doses of vitamin D in order to correct VDDI and reverse SHPT in our CKD patients. For the purpose of this study, vitamin D deficiency and insufficiency were defined as serum level of 25-hydroxyvitamin D < 15 ng/ml and 15 to < 30 ng/ml, respectively [27, 35]. 25-hydroxyvitamin D levels were considered adequate if they exceed 30 ng/ml [35].

Study design

This was a retrospective study, the primary objectives of which were to examine the efficacy of the current K/DOQI treatment guidelines for VDDI on 25-hydroxyvitamin D level and iPTH level in ND-CKD. Patients who had a serum level of 25-hydroxyvitamin D < 30 ng/ml were treated with ergocalciferol as recommended by K/DOQI guidelines. The guidelines recommend treatment of VDDI with ergocalciferol according to the 25-hydroxyvitamin D level. Thus for levels < 5 ng/ml, the guidelines recommend administration of ergocalciferol 50,000 IU/week orally for 12 weeks then monthly for a total of 6 months. For those with 25-hydroxyvitamin D levels between 5 and 15 ng/ml 50,000 IU/week orally for 4 weeks then monthly for a total of 6 months and for those with levels of 16–30 ng/ml with 50,000 IU monthly $\times$ 6 months. The guidelines also recommend to measure 25-OHD level after 6 months and to continue treatment if necessary [35]. Adult patients ($\geq$ 18 years) were regularly followed in the renal clinic and follow-up routine laboratory tests were obtained during each clinic visit. However, 25-hydroxyvitamin D and iPTH levels were only obtained at baseline and at the end of the 6-month treatment period. Patients receiving phosphate binders or vitamin D preparations other than ergocalciferol were excluded. The following data were abstracted from the patients' medical records: age, race, and gender, primary underlying renal diagnosis, serum electrolytes, blood urea nitrogen (BUN), serum creatinine, corrected total serum calcium, serum phosphorus, 24-hour urine protein excretion, iPTH level, and plasma albumin level. The stage of the kidney disease was assessed, as defined by the K/DOQI guidelines, by esti-

Table 1. Demographic and baseline laboratory parameters by CKD stage.

Characteristic	CKD 1/2	CKD 3	CKD 4	CKD 5	Total	p value
n	6 (100%)	24 (100%)	46 (100%)	12 (100%)	88 (100%)	
Male	2 (33.3%)	9 (37.5%)	20 (43.5%)	5 (41.7%)	36 (40.9%)	0.97 ²
Diabetes	3 (50%)	18 (75%)	43 (93.5%)	10 (83.3%)	74 (84.1%)	0.02 ²
Age ¹	58.8 ± 5	57.1 ± 8	56.1 ± 10	57.9 ± 12.2	56.8 ± 9.5	0.84 ³
Estimated GFR ¹	75.8 ± 13.8	38.1 ± 7.2	20.9 ± 3.8	13 ± 1.8	28.3 ± 16.6	< 0.001 ³
Serum creatinine (mg/dl) ¹	0.9 ± 0.1	1.7 ± 0.4	2.8 ± 0.7	4.1 ± 0.9	2.5 ± 1.1	< 0.001 ³
Serum albumin (g/dl) ¹	4.1 ± 0.3	4 ± 0.3	3.6 ± 0.7	3.8 ± 0.8	3.8 ± 0.6	0.02 ³
Proteinuria (g/24 h) ¹	0.8 ± 0.9	2.3 ± 2.7	3.2 ± 3.4	2.5 ± 1.9	2.7 ± 2.9	0.26 ³
Corrected serum calcium ¹	9.2 ± 0.5	9 ± 0.4	9.1 ± 0.7	9.8 ± 2.5	9.2 ± 1.1	0.69 ³
Serum phosphorus ¹	3.8 ± 0.9	3.7 ± 0.7	3.8 ± 0.7	4.8 ± 0.7	3.9 ± 0.8	< 0.001 ³
25-hydroxyvitamin D (ng/dl) ¹	13.7 ± 2.3	17 ± 5.5	14.1 ± 6.1	15.7 ± 5.6	15.1 ± 5.8	0.16 ³
25-hydroxyvitamin D < 30 (ng/dl)	2 (33.3%)	15 (62.5%)	19 (41.3%)	8 (66.7%)	44 (50%)	0.17 ²
25-hydroxyvitamin D < 15 (ng/d)	4 (66.7%)	9 (37.5%)	27 (58.7%)	4 (33.3%)	44 (50%)	0.17 ²
iPTH (pg/ml) ¹	23.7 ± 6	92.1 ± 39.7	188.2 ± 129.6	240.7 ± 151	157.9 ± 125.9	< 0.001 ³

1 = Mean ± standard deviation, 2 = Fisher's exact test, 3 = Kruskal-Wallis Test.

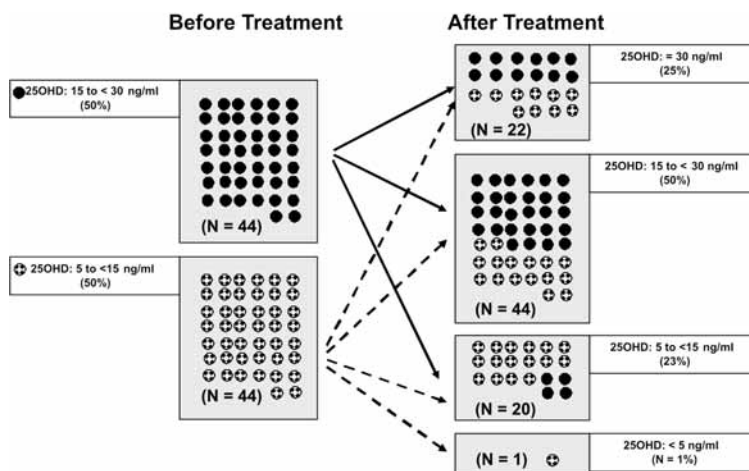


Figure 1. Change in individual patients' 25-hydroxyvitamin D levels after treatment of VDDI with ergocalciferol. One patient did not have 25-hydroxyvitamin D level measured after treatment.

matting the GFR from the MDRD (Modification of Diet in Renal Disease) equation using the following variables: race, age, BUN, serum creatinine, serum albumin and gender. Moreover, Stage 1 CKD was defined by the presence of proteinuria, cysts, or renal stones in patients with estimated GFR > 90 ml/min. Blood samples were analyzed at University Health System (UHS) Laboratory in San Antonio, Texas, USA. Serum calcium concen-

trations were corrected to a serum albumin level of 4.0 g/dl as follows: Corrected calcium (mg/dl) = serum calcium + (4.0-serum albumin (g/dl)) × 0.8. Intact PTH levels were analyzed by using the Siemens IMMULITE chemiluminescence direct immunoassay at the University Hospital laboratory. The 25-hydroxyvitamin D levels were measured by chemiluminescence assay (Arup Laboratories, Salt Lake City, Utah, USA) which measures and reports the sum of vitamin D₂ and vitamin D₃. Intact PTH levels were considered elevated if they were > 70 pg/ml in Stage 3; > 110 pg/ml in Stage 4; > 300 pg/ml in Stage 5 CKD.

Statistical methods

Summary statistics are presented as counts and proportions for categorical variables. Continuous variables were described using the mean and the standard deviation. Comparisons among levels for categorical variables were analyzed by χ^2 -test or Fisher's exact-test for small cell counts. Comparison among continuous variables was performed with a t-test or paired t-test as appropriate. The association between iPTH and 25-hydroxyvitamin D, serum calcium and phos-

Table 2. Change in parameters of mineral metabolism with treatment.

Characteristic	n	Pre mean $\pm$ SD	Post mean $\pm$ SD	95% CI ¹	p value ²
25-hydroxyvitamin D	87	15.1 $\pm$ 5.8	23.3 $\pm$ 11.8	(5.6, 10.7)	< 0.001
iPTH	88	157.9 $\pm$ 125.9	150.7 $\pm$ 127.5	(-28.2, 14)	0.5
Serum phosphorus	88	3.9 $\pm$ 0.8	4.2 $\pm$ 1	(0.1, 0.5)	0.003
Corrected serum calcium	86	9.2 $\pm$ 1.1	9.1 $\pm$ 0.6	(-0.3, 0.2)	0.44

¹CI is confidence interval for change; ²paired t-test.

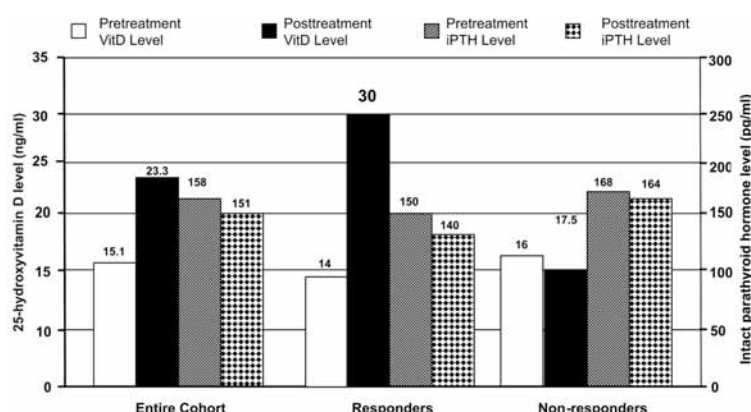


Figure 2. Mean 25-hydroxyvitamin D and iPTH levels. Responders are defined as those who had ≥ 5 ng/ml increases in 25-hydroxyvitamin D level.

phorus was examined by linear regression. All analyses were carried out using SAS Statistical Software package version 9.1 (SAS Institute Inc., Cary, NC, USA) and the R statistical package (R Project, Vienna, Austria).

Results

Between May 2005 and December 2007, we treated 101 ND-CKD patients with ergocalciferol. The doses of ergocalciferol were based on the severity of VDDI as recommended by the K/DOQI guidelines for bone and mineral metabolism. Two patients did not have 25-hydroxyvitamin D levels measured at baseline and 11 more had 25-hydroxyvitamin D levels ≥ 30 ng/ml. These 13 patients were excluded from the analyses. The remaining 88 patients had 25-hydroxyvitamin D levels < 30 ng/ml (< 75 nmol/l), and 1 patient was lost to follow-up. Table 1 shows the demographic and baseline laboratory data of treated patients. The mean age was $56.8 \pm$

9.5 years and 41% were males. The mean GFR as estimated by the MDRD equation was 28.3 ± 16.6 ml/min. The mean baseline 25-hydroxyvitamin D level was 15.1 ± 5.8 ng/ml and 50% of patients had levels < 15 ng/ml. There was no significant difference in the mean 25-hydroxyvitamin D levels between patients with various stages of CKD ($p = 0.16$). The mean baseline iPTH level for the group as a whole was 157.9 ± 125.9 pg/ml but was progressively higher in patients with worsening CKD stages; $p < 0.001$ (Table 1).

25-hydroxyvitamin D level

Each patient was treated with ergocalciferol for 6 months; the dose was based on baseline 25-hydroxyvitamin D level. Response was defined as ≥ 5 ng/ml increases in 25-hydroxyvitamin D level as this level was previously found to be associated with significant likelihood of $> 30\%$ decrease in iPTH level [1]. Changes in individual patients' 25-hydroxyvitamin D levels after treatment of VDDI with ergocalciferol are shown in Figure 1. Overall, 25-hydroxyvitamin level increased with treatment from 15.1 ± 5.8 to 23.3 ± 11.8 ng/ml ($p < 0.001$) (Table 2) (Figure 2). Only 25% of patients achieved the target 25-hydroxyvitamin D level of ≥ 30 ng/ml. There were 47 (53%) responders, defined as those who had ≥ 5 ng/ml increases in 25-hydroxyvitamin D level and 41 (47%) non-responders. Responders had significantly lower 25-hydroxyvitamin D levels at baseline (14 ± 5.0 vs. 16.4 ± 6.5 ng/ml; $p < 0.001$) and greater increase in 25-hydroxyvitamin D levels than non-responders at the end of the treatment period (15.9 ± 10.2 vs. -1.05 ± 5.4 ng/ml; $p < 0.001$) (Table 3).

Table 3. Baseline, final, and change in laboratory data of the study subjects stratified by > 5% increase in 25-hydroxyvitamin D level.

	Responders (n = 47)			Non-responders (n = 41)			
Characteristic	Initial	Final	Change	Initial	Final	Change	p value ²
n	47 (53.4%)	NA	NA	41 (46.6%)	NA	NA	NA
Estimated GFR ¹	30.7 ± 20.5	26.4 ± 16.9	-3.5 ± 9.3	25.4 ± 10.2	24.7 ± 12	-0.97 ± 6.6	0.15
Serum creatinine (mg/dl) ¹	2.4 ± 1.1	2.7 ± 1.4	0.3 ± 0.9	2.7 ± 1	3 ± 1.5	0.35 ± 1.1	0.98
Serum albumin (g/dl) ¹	3.8 ± 0.7	4 ± 0.4	0.3 ± 0.7	3.8 ± 0.6	4 ± 0.5	0.23 ± 0.5	0.76
Proteinuria (g/24 h) ¹	2.6 ± 3	2 ± 2.6	-0.2 ± 2.4	2.8 ± 3	1.8 ± 2.7	-0.53 ± 3	0.75
Corrected serum calcium (mg/dl) ¹	9.3 ± 1.3	9.2 ± 0.5	-0.1 ± 1.3	9 ± 0.7	8.9 ± 0.7	-0.09 ± 1	0.98
Serum phosphorus ¹	3.8 ± 0.8	4.3 ± 0.9	0.5 ± 0.9	4 ± 0.8	4.1 ± 1	0.07 ± 0.9	0.03
iPTH (pg/ml) ¹	149.6 ± 135.4	139.5 ± 120.7	-10.1 ± 116.3	167.4 ± 115.1	163.6 ± 135.2	-3.83 ± 78.4	0.76
25-hydroxyvitamin D (ng/dl) ¹	14 ± 5	30 ± 11.1	15.9 ± 10.2	16.4 ± 6.5	15.4 ± 6.4	-1.05 ± 5.4	< 0.001
25-hydroxyvitamin D 15 – 30 (ng/dl)	21 (44.7%)	46 (97.9%)	25 (53.2%)	23 (56.1%)	23 (56.1%)	0 (0%)	< 0.001
25-hydroxyvitamin D < 15 (ng/dl)	26 (55.3%)	1 (2.1%)	-25 (-53.2%)	18 (43.9%)	20 (50%)	2 (6.1%)	< 0.001
25-hydroxyvitamin D < 30 (ng/dl)	47 (100%)	26 (55.3%)	-21 (-44.7%)	41 (100%)	39 (97.5%)	-2 (-2.5%)	< 0.001

¹t-test between the differences on responders and non-responders, ²p value < 0.05 is significant.

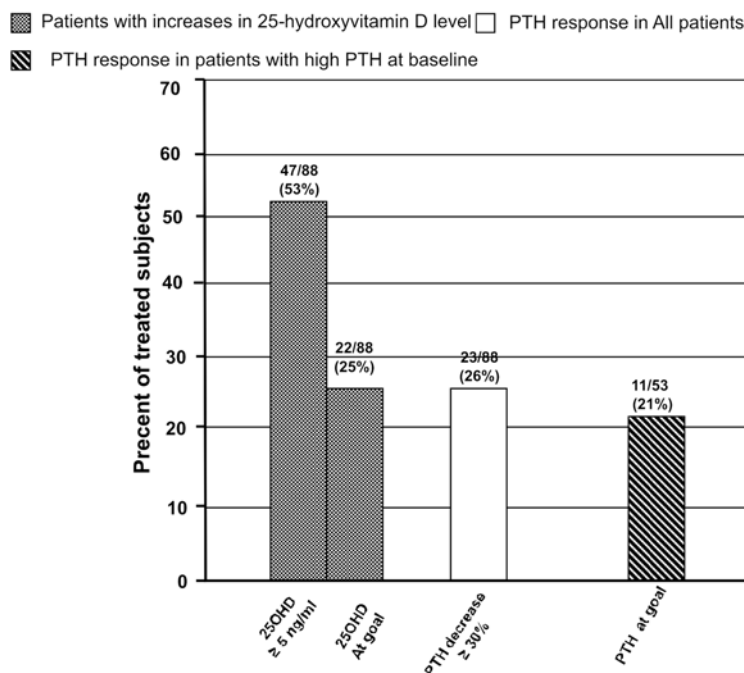


Figure 3. Proportion of patients with increases in 25-hydroxyvitamin D level and/or decrease in iPTH level.

Parathyroid hormone level

Response of PTH to treatment with ergocalciferol was evaluated in three different methods: any significant decrease in mean iPTH level; a decrease ≥ 30% in iPTH level;

and achieving target iPTH level for the CKD stage as previously reported [1]. For the 88 patients, treatment with ergocalciferol did not lead to a significant change in mean serum iPTH level (mean iPTH decreased from 157.9 ± 125.9 to 150.7 ± 127.5 pg/ml; p = 0.5) (Table 2) (Figure 2). Moreover, only 26% of these patients had ≥ 30% decrease in iPTH level with treatment (Figure 3).

Of the 53 patients who had elevated baseline iPTH level for their CKD stage, treatment with ergocalciferol resulted in achieving the target iPTH level for the stage in only 11 patients (21%) (Figure 3). The response was lower in patients with Stages 3 and 4 CKD compared with that for Stage 5 CKD (24% and 18% for CKD Stages 3 and 4, respectively, vs. 33% for CKD Stage 5). However, in responders who had an increase in 25-hydroxyvitamin D level of ≥ 5 ng/ml, 32% had ≥ 30% decrease in iPTH compared to 20% of the non-responders. Moreover, among patients who achieved 25-hydroxyvitamin D level > 30 ng/ml, 55% had ≥ 30% decrease in iPTH compared with only 17% of those who did not achieve the target vitamin D level (Figure 4). Yet, even when 25-hydroxyvitamin D level of 30 ng/ml was achieved, the iPTH level decreased to the target level for the stage of CKD in only 36% of patients (Figure 4). There was no correlation between pre-

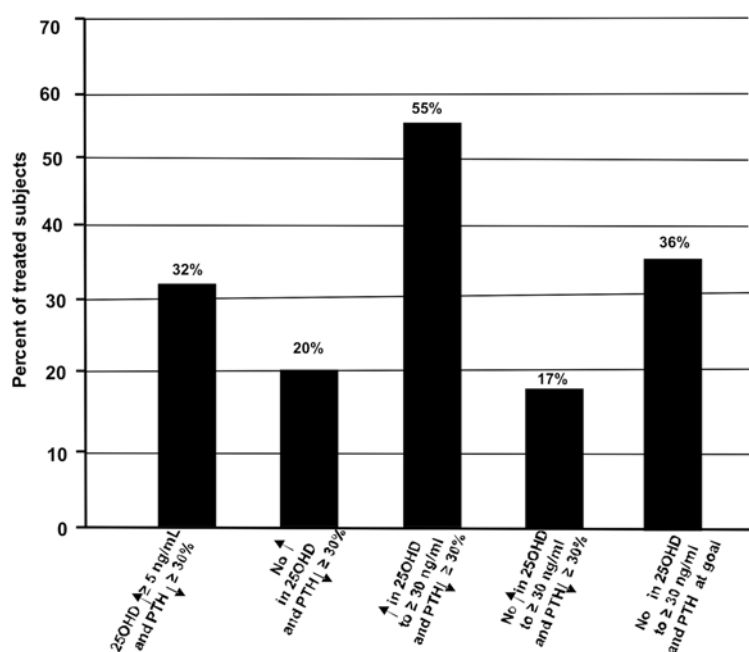


Figure 4. Proportion of patients with concomitant increase in 25-hydroxyvitamin D level and decrease in iPTH level.

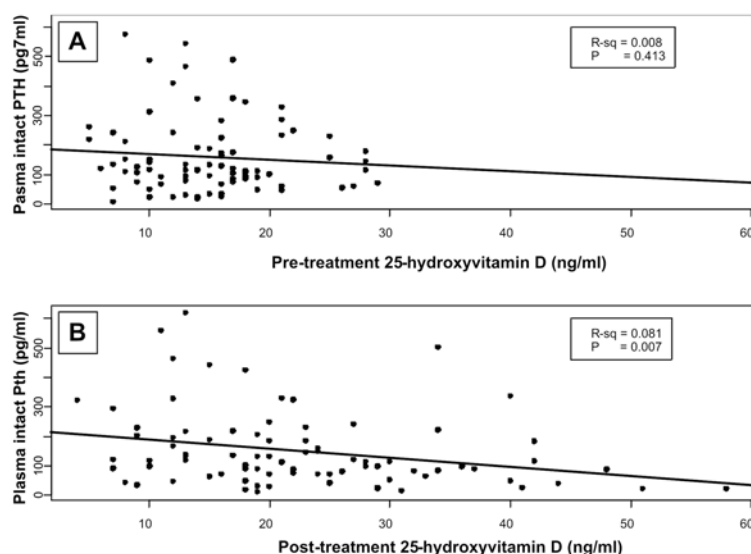


Figure 5. Correlation between (A) baseline 25-hydroxyvitamin level and iPTH and (B) between post-treatment 25-hydroxyvitamin level and iPTH.

treatment 25-hydroxyvitamin D and iPTH levels but a weak negative correlation between post-treatment 25-hydroxyvitamin D level and iPTH level (Figure 5A, B).

Treatment with ergocalciferol did not result in significant change in adjusted serum calcium levels (Table 3). However, responders had significant increase in the serum phosphorus concentration compared to non-re-

sponders (phosphorus increase of 0.5 ± 0.9 vs. 0.07 ± 0.9 mg/dl; $p = 0.03$) despite no significant difference in their final GFR.

Discussion

The K/DOQI guidelines for correction of VDDI and elevated PTH levels with ergocalciferol are important in improving bone and mineral disorders in CKD patients. However, the results of our study indicate that these dosing guidelines may not be adequate for attaining their intended goals of correction of VDDI and treatment of SHPT in ND-CKD patients. This conclusion was based on the following observations: First, the response to ergocalciferol supplementation was clearly suboptimal as the mean 25-hydroxyvitamin D level increased from $15.1 \pm 5.8 - 23.3 \pm 11.8$ ng/ml. Moreover, only 54% of treated patients had ≥ 5 ng/ml increases in their 25-hydroxyvitamin D level. More importantly, the ultimate goal of the treatment regimen of achieving the recommended 25-hydroxyvitamin D target level of ≥ 30 ng/ml was achieved in only 25% of patients. Similar results were reported by other investigators although they prescribed larger doses of ergocalciferol than currently recommended by the K/DOQI guidelines [1, 2, 13, 38, 39, 41, 47]. Al-Aly et al. [1] reported suboptimal response to treatment with ergocalciferol in a similar patient population. In their study, 24% of their patients had no increase in 25-hydroxyvitamin D level after treatment with ergocalciferol and almost half (45%) did not have an increase of at least 5 ng/ml in their 25-hydroxyvitamin D levels. In addition, only 18% of their patients had 25-hydroxyvitamin D greater than 40 ng/ml. Our findings are different from those of Zisman et al. [47] who were successful in raising 25-hydroxyvitamin D levels to the target of 30 ng/ml in 58% of their patients with Stages 3 and 4 CKD. However, their patients had higher mean baseline 25-hydroxyvitamin D levels than our patients and were prescribed a modified ergocalciferol treatment protocol than that recommended by the K/DOQI guidelines.

Second, there was no meaningful decrease in iPTH level in our study subjects. Only 21% of the 53 patients who had elevated baseline iPTH level achieved the target iPTH

levels for their CKD stage. In addition, among patients who achieved target 25-hydroxyvitamin D level of 30 ng/ml, only 36% had their iPTH level decreased to the target level for the stage of CKD. These results are similar to those reported from other studies [1, 47] and suggest that treatment of VDDI with ergocalciferol is only partially effective in decreasing iPTH level, at least in the doses recommended by the K/DOQI guidelines. However, the proportion of patients who had a decreased iPTH level or achieved target iPTH for their CKD stage increased when the 25-hydroxyvitamin level increased (Figure 4). Therefore, it may be reasonable to speculate that administering greater doses of ergocalciferol in order to achieve higher levels of 25-hydroxyvitamin D level may result in better response of PTH. This notion is strengthened by the fact that 25-hydroxyvitamin D itself has known direct action on the parathyroid glands although this action is less potent than that of calcitriol [11] and that 25-hydroxyvitamin D binds VDR 100 times less avidly than calcitriol [11, 34]. This is compensated for by the 1,000-fold higher concentration of 25-hydroxyvitamin D compared with that of calcitriol [14]. Thus, to overcome these limitations, larger doses or more frequent administration of 25-hydroxyvitamin D may be needed or administration of the active form of vitamin D may be necessary for control of elevated PTH level. 25-hydroxyvitamin D is converted to calcitriol by the 1- α -hydroxylase enzyme in the proximal convoluted tubules of the kidney. Calcitriol in turn binds to the high affinity VDR in the parathyroid glands leading to decreased production and secretion of PTH. We did not measure calcitriol levels in our patients and therefore we cannot ascertain whether the suboptimal effects of ergocalciferol on PTH was related to inadequate production of calcitriol. However, in the absence of adequate production of calcitriol by the diseased kidney, ergocalciferol supplementation alone may not be as effective in suppressing PTH production and secretion, at least in the doses currently recommended by the K/DOQI guidelines. This is substantiated by our finding that even when 25-hydroxyvitamin D level of 30 ng/ml was achieved, the iPTH level decreased to the target level for the stage of CKD in only one third of our patients. The same observation

was reported by Zisman et al. [47]. Again, we may not be targeting the optimal serum concentration of 25-hydroxyvitamin D. The currently recommended level of 30 ng/ml was based on finding that PTH levels plateau at 25-hydroxyvitamin D level of 30 ng/ml [45] but this level is probably too low and levels greater than 60 ng/ml may be needed [19].

Although the exact reasons for the suboptimal response of CKD patients to ergocalciferol are not clear, there are a number of possible explanations. Noncompliance may have played a role. However, this is unlikely since our findings are very similar to those reported by Al-Aly et al. [1] in that about half of the patients in our study as well as in theirs did not have a significant increase in their 25-hydroxyvitamin D levels. A more likely explanation is that the suboptimal effects of ergocalciferol may be related to the dose and/or frequency of its administration in ND-CKD patients. It is possible that we may be using doses that are insufficient for correcting the VDDI in our patients and thus, it may be necessary to administer much larger doses of ergocalciferol, than currently recommended by the K/DOQI guidelines, followed by maintenance doses. Large doses of vitamin D supplements have been shown to be relatively safe in one study where 10,000 IU of ergocalciferol were given daily to French patients with advanced CKD for periods longer than 1 year, with no evidence of vitamin D overload or renal toxicity [26]. Alternatively, more frequent administration or even small daily administration may be more effective in correcting VDDI than that currently achieved with intermittent administration of large doses [40]. This is because intermittent high doses of ergocalciferol may lead to up-regulation of the 25-hydroxyvitamin D-24-hydroxylase enzyme leading to increased catabolism of 25-hydroxyvitamin D [20, 31]. Whether the use of vitamin D₃ preparations is more effective than ergocalciferol is yet to be determined [4]. Clearly more studies are needed for establishing the optimal preparation and dose of vitamin D supplements as well as the frequency and duration of their administration.

We found no correlation between pretreatment 25-hydroxyvitamin D and iPTH levels and only a weak negative correlation between post-treatment 25-hydroxyvitamin

D level and iPTH level. A stronger negative correlation between 25-hydroxyvitamin D and plasma iPTH levels in renal transplant recipients was reported by Boudville and Hodsmann [10]. Al-Aly et al. [1] also reported a negative correlation between 25-hydroxyvitamin D and plasma iPTH levels in CKD patients. It is possible that a more consistent negative relationship between 25-hydroxyvitamin D level and plasma iPTH level may become manifest with higher doses of ergocalciferol. Nonetheless, the use of pharmacological doses of calcitriol may still be necessary for better control of SHPT in patients with 25-hydroxyvitamin D level greater than 30 ng/ml but persistently elevated iPTH level [6, 12, 19, 36]. In this regard, it is important to mention that the use of calcitriol and other vitamin D analogues offers a "bonus" effect in that their use may be associated with improved patients' survival; an effect repeatedly shown in observational studies in hemodialysis patients [21, 43, 44] and CKD patients not yet receiving dialysis [23].

This study has several limitations including its observational nature, the lack of a control group, and its relatively short duration. It is possible that the desired targets of 25-hydroxyvitamin D and iPTH would have been attained more frequently if treatment with ergocalciferol was continued in those patients who did not achieve 25-hydroxyvitamin D levels greater than 30 ng/ml with initial treatment. An important factor that may have impacted our results as well as those of others is the accuracy of the current 25-hydroxyvitamin D assays and also the ability of the levels obtained from these assays to reflect accurately the vitamin D status of our patients. Several studies have reported discrepancies between the results of assays used to measure 25-hydroxyvitamin D. The lack of agreement in assay results obtained by different methods might complicate the ability to define optimal levels of circulating 25-hydroxyvitamin D and hamper comparison between results from different populations [8, 15, 16, 29, 37]. Finally, our study was not designed to examine the potential beneficial effects of ergocalciferol supplementation on other aspects of health such as bone density, fracture risk, cancer, autoimmune diseases, cardiovascular disease or survival. These issues must be addressed in future studies in patients with CKD.

Are the new KDIGO guidelines for correcting VDDI in CKD patients sufficiently different from the K/DOQI guidelines to render our conclusions irrelevant? We do not believe so. This is because the KDIGO group did not recommend specific guidelines regarding the dose, frequency or duration of therapy [22]. These guidelines suggested the use of treatment strategies recommended for the general population. Unfortunately, these treatment strategies are also not well-established and may be inadequate. Indeed, Holick [19] recently suggested the use of larger doses of ergocalciferol in the general population with VDDI. We agree with the KDIGO group that, in order to clarify this issue, well-designed randomized controlled trials are needed.

In summary, the current K/DOQI guidelines for treatment of VDDI are probably inadequate for correcting VDDI or SHPT in most ND-CKD patients and thus should be revised. Future studies should examine the efficacy of alternative treatment regimens of vitamin D supplementation in these patients in order to find the optimal preparation, dose, cumulative dose, and the frequency of its administration.

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