

The Effect of Combined Calcium and Vitamin D₃ Supplementation on Serum Intact Parathyroid Hormone in Moderate CKD

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Background: Studies addressing the effects of vitamin D₃ supplementation on secondary hyperparathyroidism in patients with moderate chronic kidney disease are scarce.

Study Design: Post hoc analysis of the randomized clinical trial Vitamin D, Calcium, Lyon Study II (DECALYOS II) to assess effects according to baseline estimated glomerular filtration rate (eGFR).

Setting & Participants: Multicenter, randomized, double-blinded, placebo-controlled study of 639 elderly women randomly assigned to calcium–vitamin D₃ fixed combination; calcium plus vitamin D₃ separate combination, or placebo.

Interventions: Placebo or calcium (1,200 mg) and vitamin D₃ (800 IU) in fixed or separate combination.

Outcomes & Measurements: Proportion of participants with a mean decrease in intact parathyroid hormone (iPTH) level of 30% or greater. eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation and categorized as 60 or greater, 45 to 59, and less than 45 mL/min/1.73 m².

Results: 610 participants had an eGFR at baseline: 288 (47.2%), 222 (36.4%), and 100 (16.4%) were in each decreasing eGFR category. Across decreasing eGFR groups, 88%, 86%, and 89% had 25-hydroxyvitamin D (25[OH]D) levels less than 15 ng/mL at baseline. On treatment, similar improvements in the proportion of participants achieving 25(OH)D levels greater than 30 ng/mL at 6 months were seen in all kidney function groups (43%, 49%, and 41%, respectively). Active regimens versus placebo increased mean 25(OH)D levels from baseline in all eGFR groups at all times ($P < 0.001$ for all). The proportion with a 30% or greater decrease in iPTH level at 6 months was 50% in all eGFR groups on treatment versus 6% to 9% for placebo ($P < 0.001$ for all). The effects of the intervention on iPTH levels did not differ according to baseline eGFR (interaction $P > 0.1$ for all times).

Limitations: This study included only elderly white women.

Conclusion: Vitamin D₃ was effective in increasing 25(OH)D and decreasing iPTH levels in patients with moderate chronic kidney disease.

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INDEX WORDS: Vitamin D₃; chronic kidney disease; secondary hyperparathyroidism.

Vitamin D deficiency increasingly is being recognized and is highly prevalent in chronic kidney disease (CKD) populations.¹⁻⁷ Similarly, secondary hyperparathyroidism (SHPT) is a well-recognized occurrence in patients with CKD, and increases in intact parathyroid hormone (iPTH; >65

pg/mL) levels begin to occur at estimated glomerular filtration rates (eGFRs) of approximately 45 mL/min/1.73 m².^{6,8-10} Most discussions about the cause of SHPT in patients with CKD have focused primarily on functional vitamin D deficiency, more specifically calcitriol (1,25[OH]₂D₃) deficiency secondary to decreased activity of 1 α -hydroxylase. Recently, low levels of the substrate 25-hydroxyvitamin D (25[OH]D) as a key pathogenic mechanism for SHPT in patients with kidney disease has been raised.¹⁰⁻¹²

As such, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Mineral Metabolism and Disease in CKD have recommended measurement of vitamin D stores and supplementation if 25(OH)D levels are less than 30 ng/mL in patients with CKD stage 3 or 4.¹² The rationale behind this recommendation is that low 25(OH)D levels are likely to have a role in the development of SHPT through limiting

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1,25(OH)₂D₃ synthesis. However, evidence of the effectiveness of this approach in decreasing iPTH levels is inconclusive.

A previous report from the Vitamin D, Calcium, Lyon Study II (DECALYOS II), performed in French elderly women,¹³ showed that combined calcium and vitamin D₃ supplementation can improve iPTH levels in elderly women; however, there is a lack of proven efficacy of this intervention on achieving iPTH targets recommended by the KDOQI in patients with concomitant moderate CKD and SHPT.¹⁰ Thus, the purpose of the present analysis is to determine the effect of combined calcium and vitamin D₃ (cholecalciferol) supplementation on SHPT in participants with mainly stage 3 CKD and severe 25(OH)D deficiency.

METHODS

DECALYOS II Database

We obtained a copy of the database of the DECALYOS II by submitting a written request to Merck KGaA (Darmstadt, Germany). None of the authors are members of the DECALYOS Investigators and thus none was involved in the conduct or initial analysis of the trial.

Study Population, Recruitment, Study Regimens, and Follow-up

Recruitment methods, randomization, and follow-up results of the DECALYOS II have been previously published.¹³ In this 2-year, double-blinded, placebo-controlled, comparative trial, 639 participants living in apartment houses for the elderly were enrolled. Participants were excluded if they were nonambulatory; had intestinal malabsorption, hypercalcemia (serum calcium > 10.5 mg/dL), or advanced kidney disease (serum creatinine > 1.7 mg/dL); received drugs known to alter bone metabolism within the past year (ie, corticosteroids, anticonvulsants, or high-dose thyroxine); or had life expectancy less than 24 months.¹³

In this study, 610 of 639 enrolled participants were assigned randomly to 1 of the 2 active groups (calcium-vitamin D₃ fixed-combination [Ca-D₃] group or separate calcium and vitamin D₃ [Ca + D₃] supplement group) or the placebo group. The sachet of the Ca-D₃ fixed combination (Ostram-vitamin D₃; Merck KGaA) contained a fixed combination of 1,200 mg of elemental calcium in the form of tricalcium phosphate and 800 IU of vitamin D₃ in a single tablet. In the group that received separate tablets of Ca + D₃, calcium (Ostram) content was 1,200 mg of elemental calcium in the form of tricalcium phosphate, and the vitamin D₃ (Devaron; ie, cholecalciferol; Durphar Solvay, Leiderdorp, the Netherlands) was given in 2 tablets of 400 IU each.¹³

Measurement of Kidney Function

Because a number of factors, such as age, ethnicity, and sex, can influence serum creatinine concentrations, level of

kidney function was defined by means of eGFR using the formula developed and validated in the Modification of Diet in Kidney Disease (MDRD) Study.¹⁴ The 4-variable MDRD Study equation is as follows: $GFR = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times 0.742$ (if female). Serum creatinine was assessed by means of the Jaffé rate-biased and compensated method using a kinetic colorimetric assay on the Roche/Hitachi Modular P analyzer (F. Hoffman-LaRoche Inc Ltd, Basel, Switzerland).

All participants were classified into 1 of 3 eGFR categories: 60 or greater, 45 to 59, and less than 45 mL/min/1.73 m². These categories were chosen because eGFR less than 45 mL/min/1.73 m² is considered a more advanced state of kidney disease within CKD stage 3 and less than 2% of participants were in the category of CKD stage 4. Each eGFR category was then divided further based on the intervention arm to 1 of the 2 active groups or the placebo group.

Biochemical Measurements

Laboratory tests were performed after an overnight fast at each investigation site and sent to a centralized laboratory for measurement. All samples were kept frozen at -70°C until analysis. Serum iPTH was measured by means of immunochemoluminometric assay (Ciba-Corning Diagnostic, Medfield, MA), and bone alkaline phosphatase was measured by using a 2-site radioimmunoassay (Tanden-R-Ostase kit; Beckman-Coulter, Fullerton, CA). Serum 25(OH)D was measured using an Incstar 25(OH)D 2-step assay procedure with a coefficient of variation less than 10%. The first step in the procedure involves rapid extraction of 25(OH)D from serum by using acetonitrile. After extraction, the treated sample is assayed by using an equilibrium radioimmunoassay procedure. This method is based on an antibody with specificity to 25(OH)D. The sample, antibody, and tracer are incubated at 20°C to 25°C for 90 minutes. A second antibody-precipitating complex is used to achieve phase separation. This method does not recognize 25(OH)D₂ and 25(OH)D₃ separately. The normal range for adults given by the manufacturer of the kit (Incstar, Saluggia, Italy) is 15 to 50 ng/mL. Standard laboratory methods were used for the measurements of calcium and phosphate.¹³

Statistical Analysis

All statistical analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC). Baseline clinical characteristics and biochemical parameters were summarized for the 3 eGFR levels. Differences among the 3 eGFR levels were tested by using nonparametric Kruskal-Wallis tests for continuous variables and χ^2 statistics for categorical variables.

For analysis examining changes in mean iPTH levels over time, the placebo and both active groups were examined separately following the design of the DECALYOS II to better evaluate changes in 25(OH)D and serum calcium levels across kidney function groups during follow-up. Because changes in iPTH levels were identical between the 2 active groups, these were combined in a single active treatment to further examine the effects of combined therapy on prespecified iPTH targets.

A mixed model was performed on the repeated iPTH levels. Because of the skewed distribution of iPTH, its log

was analyzed. The covariance structure of the repeated measures over time was modeled as autoregressive. In each of the 2 models, time was entered as a linear term with 1 *df*. Two-way interactions between treatment, time, and eGFR level (time by treatment, time by eGFR, and treatment by eGFR) were entered into the model, as was the single 3-way interaction. The 3-way interaction was not significant. Only the 2-way interaction between treatment and time was significant and retained in the model.

The mixed model was performed at each time (6, 12, 18, and 24 months) to examine the effect of eGFR and active treatment (pooled active arms versus placebo) on log iPTH, with covariate adjustment for baseline iPTH level. Proportions of participants achieving a mean 30% or greater decrease in iPTH levels from baseline were compared at 6 and 24 months across the active/placebo dichotomy of treatment by CKD status by using Cochran-Mantel-Haenszel tests. Parallel Cochran-Mantel-Haenszel analyses were performed on the binary outcomes of iPTH level greater than 70 pg/mL and greater than 110 pg/mL at 2 key times, 6 and 24 months. These efficacy treatment targets were chosen on the basis of previous studies of the treatment of SHPT in persons with CKD.¹⁵⁻¹⁷

The association between increases in 25(OH)D levels from baseline, dichotomized at an increase to greater than 30 ng/mL at months 6 and 24, was tested against change in iPTH levels from baseline at 6 and 24 months by using a rank-based test (Kruskal-Wallis). We used the 25(OH)D cutoff level of greater than 30 ng/mL, in keeping with the definition of 25(OH)D repletion.¹²

RESULTS

Demographics and Baseline Characteristics

The 610 participants who were randomly assigned to 1 of 3 treatment arms were assessed at

visit 1 (6-month visit). In these patients, eGFR was 60 mL/min/1.73 m² or greater in 288 women (47.2%), 90 of whom were given Ca + D₃, 101 were given Ca-D₃, and 97 were given placebo; 45 to 59 mL/min/1.73 m² in 222 women (36.4%), 73 of whom were given Ca + D₃, 79 were given Ca-D₃, and 70 were given placebo; and less than 45 mL/min/1.73 m² in 100 women (16.4%), 36 of whom were given Ca + D₃, 26 were given Ca-D₃, and 38 were given placebo. Baseline demographics by level of kidney function were similar in all groups except for age, which increased with decreasing eGFR (Table 1). Likewise, all biochemical parameters at baseline by kidney function level were similar with the exception of serum iPTH levels (Table 1). Furthermore, within each eGFR level, no differences in participant characteristics were observed at baseline between the active treatment groups and the placebo group (not shown).

25(OH)D Levels and Other Biochemical Parameters According to Kidney Function Group

Baseline mean serum 25(OH)D levels were low in all 3 kidney function categories (Table 1) and all 3 treatment arms (Table 2). Across decreasing eGFR groups, 87.9%, 85.9%, and 89.1% had 25(OH)D levels less than 15 ng/mL at baseline. At the 24-month follow-up visit, 25(OH)D deficiency had improved in participants receiv-

Table 1. Demographic and Baseline Characteristics by eGFR

Characteristics	eGFR ≥ 60 mL/min/ 1.73 m ²	eGFR 45-59 mL/min/ 1.73 m ²	eGFR < 45 mL/min/ 1.73 m ²	<i>P</i> for Trend
eGFR (mL/min/1.73 m ²)	71.7 ± 9.8	53.1 ± 4.2	38.3 ± 4.5	
No. of patients (%)	288 (47.2)	222 (36.4)	100 (16.4)	
Age (y)	84 ± 7	86 ± 7	87 ± 7	<0.001
Weight (kg)	58 ± 12	60 ± 12	60 ± 13	0.09
Height (cm)	155 ± 7	154 ± 7	155 ± 7	0.5
Body mass index (kg/m ²)	25 ± 5	25 ± 5	25 ± 5	0.2
Calcium intake (mg/d)	557 ± 244	555 ± 221	594 ± 262	0.3
Vitamin D intake (IU/d)	40 ± 26	41 ± 29	43 ± 30	0.3
Biochemical measurements				
Serum calcium (mg/dL)	9.1 ± 0.4	9.3 ± 0.4	9.2 ± 0.4	0.8
Serum phosphorus (mg/dL)	3.2 ± 0.5	3.2 ± 0.4	3.3 ± 0.5	0.4
Bone alkaline phosphatase (ng/mL)	16 ± 16.8	15.3 ± 9.1	15.8 ± 12.5	0.2
25(OH)D (ng/mL)	8.8 ± 6.4	9.1 ± 5.8	8.7 ± 6.6	0.5
iPTH (pg/mL)	62.3 ± 44.3	72.7 ± 67.4	86.3 ± 60	<0.001

Note: Values expressed as mean ± SD. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; 25(OH)D in ng/mL to nmol/L, ×2.496; eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667. iPTH levels expressed in pg/mL and ng/L are equivalent.

Abbreviations: eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Table 2. Effect of the Study Medication on 25(OH)D Levels per eGFR Group

eGFR Group	Baseline	6 Months	12 Months	18 Months	24 Months
eGFR ≥ 60 mL/min/1.73 m²					
Placebo	9.2 ± 7.8	7.5 ± 5.5	7.9 ± 6.0	5.6 ± 4.9	6.7 ± 6.0
Ca + D ₃	8.7 ± 6.7	33.6 ± 9.4*	32.5 ± 10.1*	30.0 ± 8.4*	28.3 ± 9.6*
Ca-D ₃	8.4 ± 4.9	32.5 ± 10.0*	34.0 ± 10.2*	29.7 ± 8.8*	29.0 ± 9.7*
No. of patients (placebo, Ca + D ₃ , Ca-D ₃)	97, 90, 101	89, 86, 92	84, 79, 87	77, 72, 80	76, 78, 80
eGFR 45-59 mL/min/1.73 m²					
Placebo	10.2 ± 6.5	8.2 ± 5.2	8.9 ± 6.7	6.2 ± 4.8	6.3 ± 5.5
Ca + D ₃	8.3 ± 5.2	37.0 ± 12.1*	38.6 ± 13.3*	35.2 ± 12.2*	34.2 ± 12.8*
Ca-D ₃	8.8 ± 5.7	33.2 ± 9.1*	35.3 ± 9.7*	30.0 ± 10.2*	28.7 ± 10.3*
No. of patients (placebo, Ca + D ₃ , Ca-D ₃)	70, 73, 79	54, 69, 70	49, 66, 67	43, 59, 64	48, 57, 67
eGFR < 45 mL/min/1.73 m²					
Placebo	7.2 ± 3.5	6.5 ± 2.5	8.0 ± 3.6	7.3 ± 5.6	4.5 ± 3.1
Ca + D ₃	11.3 ± 9.2	35.3 ± 8.2*	37.5 ± 9.5*	35.0 ± 10.4*	33.5 ± 12.1*
Ca-D ₃	7.1 ± 4.8	32.8 ± 9.5*	32.6 ± 10.2*	30.1 ± 12.6*	27.1 ± 8.8*
No. of patients (placebo, Ca + D ₃ , Ca-D ₃)	38, 36, 26	32, 30, 23	30, 27, 21	26, 24, 20	28, 20, 18

Note: Values expressed as mean ± SD. 25(OH)D levels in nanograms per milliliter. Conversion factors for units: 25(OH)D in ng/mL to nmol/L, ×2.496; eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: Ca + D₃, group using calcium plus vitamin D₃ in separate tablets; Ca-D₃, group using calcium–vitamin D₃ in single tablet; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D.

**P* < 0.001 for comparison of changes in 25(OH)D levels from baseline for groups receiving Ca + D₃ or Ca-D₃ versus changes in placebo from baseline for each eGFR group.

ing active treatment, such that only 35.5%, 34.2%, and 33.0% of participants across decreasing eGFR categories had levels less than 15 ng/mL. Changes in 25(OH)D levels from baseline in both active treatment groups significantly improved regardless of kidney function level compared with placebo at all follow-up evaluations (*P* < 0.001 for all; Table 2).

Serum calcium, phosphorus, and bone alkaline phosphatase levels for randomized participants receiving active treatment and placebo per eGFR group at baseline and 6- and 24-month follow-up are listed in Table 3. At the end of the study, change from baseline in serum calcium levels was slightly different in the Ca + D₃ group, but not in the group randomized to Ca-D₃ compared with placebo across kidney function groups. In addition, bone alkaline phosphatase levels changed significantly in only the Ca + D₃ group in participants with eGFR less than 45 mL/min/1.73 m². No significant change was observed in serum phosphorus levels.

Changes in iPTH Levels

The mixed model showed an overall treatment effect on iPTH levels (*P* = 0.02), with the active arms showing lower levels. Changes in mean iPTH values over all times were statistically significant over all eGFR categories (*P* = 0.02) and were

observed as early as 6 months postrandomization (Fig 1). Changes over time were significantly different by treatment arm (*P* < 0.001), but not by baseline eGFR level (*P* = 0.2). The effect on treatment over time did not vary by baseline kidney function group (ie, interaction between treatment group, baseline eGFR, and time was not significant; *P* = 0.4). Finally, the effect of vitamin D₃ and calcium supplementation had an identical effect in elders with and without reduced eGFR at 6, 12, 18, and 24 months of follow-up (*P* > 0.1 for interaction in all cases). In addition, at all follow-up evaluations in the placebo group, mean iPTH levels increased from baseline and were outside the KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease recommendations for the appropriate corresponding stage of CKD. This is in contrast to participants who received active treatment in whom mean iPTH level decreased and were maintained within KDOQI targets (Fig 1).

Because no significant differences were observed between the Ca-D₃ and Ca + D₃ treatment groups, for subsequent analysis, both active groups were combined into a single active treatment group. At 6 months, 50% of participants in each of 3 different kidney function groups and on active treatment had a 30% or greater decrease in iPTH levels from baseline compared with 6% to 9% in the placebo group (*P* < 0.001 for all

Table 3. Serum Calcium, Phosphorus, and Bone Alkaline Phosphatase Levels in Groups Receiving Active Treatment and Placebo per eGFR Group

eGFR Group	Baseline	6 Months	24 Months
eGFR \geq 60 mL/min/1.73 m ²			
Placebo			
Calcium (mg/dL)	9.2 \pm 0.5	9.0 \pm 0.5	9.0 \pm 0.4
Phosphorus (mg/dL)	3.2 \pm 0.5	3.3 \pm 0.4	3.3 \pm 0.5
Bone alkaline phosphatase (ng/mL)	18.2 \pm 26.4	18.5 \pm 24.5	16.7 \pm 12.3
Ca + D ₃			
Calcium (mg/dL)	9.2 \pm 0.5	9.3 \pm 0.5*	9.3 \pm 0.6*
Phosphorus (mg/dL)	3.2 \pm 0.4	3.4 \pm 0.4	3.4 \pm 0.4
Bone alkaline phosphatase (ng/mL)	13.7 \pm 8.3	12.9 \pm 8.5	15.0 \pm 9.9
Ca-D ₃			
Calcium (mg/dL)	9.2 \pm 0.5	9.2 \pm 0.5*	9.1 \pm 0.5
Phosphorus (mg/dL)	3.2 \pm 0.4	3.4 \pm 0.4	3.4 \pm 0.4
Bone alkaline phosphatase (ng/mL)	14.7 \pm 7.2	12.0 \pm 5.4*	14.4 \pm 6.7
eGFR 45-59 mL/min/1.73 m ²			
Placebo			
Calcium (mg/dL)	9.2 \pm 0.4	9.0 \pm 0.4	9.0 \pm 0.5
Phosphorus (mg/dL)	3.2 \pm 0.4	3.3 \pm 3.6	3.3 \pm 0.5
Bone alkaline phosphatase (ng/mL)	14.4 \pm 7.3	15.0 \pm 6.8	18.0 \pm 12.2
Ca + D ₃			
Calcium (mg/dL)	9.2 \pm 0.5	9.3 \pm 0.5*	9.3 \pm 0.6*
Phosphorus (mg/dL)	3.3 \pm 0.5	3.5 \pm 0.5	3.3 \pm 0.5
Bone alkaline phosphatase (ng/mL)	14.5 \pm 7.9	12.4 \pm 7.4*	12.9 \pm 5.4
Ca-D ₃			
Calcium (mg/dL)	9.3 \pm 0.4	9.3 \pm 0.4*	9.4 \pm 0.6
Phosphorus (mg/dL)	3.3 \pm 0.6	3.4 \pm 0.4	3.4 \pm 0.5
Bone alkaline phosphatase (ng/mL)	14.6 \pm 8.3	11.5 \pm 6.2*	13.4 \pm 7.5
eGFR < 45 mL/min/1.73 m ²			
Placebo			
Calcium (mg/dL)	9.3 \pm 0.5	9.1 \pm 0.4	9.3 \pm 0.6
Phosphorus (mg/dL)	3.3 \pm 0.6	3.5 \pm 5.2	3.4 \pm 0.6
Bone alkaline phosphatase (ng/mL)	18.7 \pm 18.9	17.3 \pm 6.5	20.4 \pm 16.2
Ca + D ₃			
Calcium (mg/dL)	9.1 \pm 0.5	9.3 \pm 0.5	9.3 \pm 0.7*
Phosphorus (mg/dL)	3.2 \pm 0.5	3.5 \pm 0.4	3.4 \pm 0.4
Bone alkaline phosphatase (ng/mL)	16.4 \pm 11.4	10.8 \pm 3.9*	14.4 \pm 11.7*
Ca-D ₃			
Calcium (mg/dL)	9.2 \pm 0.5	9.5 \pm 0.8	9.2 \pm 0.4
Phosphorus (mg/dL)	3.2 \pm 0.5	3.4 \pm 0.6	3.2 \pm 0.4
Bone alkaline phosphatase (ng/mL)	15.9 \pm 8.9	13.4 \pm 6.1*	13.5 \pm 7.3

Note: Values expressed as mean \pm SD. Conversion factors for units: calcium in mg/dL to mmol/L, $\times 0.2495$; phosphorus in mg/dL to mmol/L, $\times 0.3229$; 25(OH)D in ng/mL to nmol/L, $\times 2.496$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$.

Abbreviations: Ca + D₃, group using calcium plus vitamin D₃ in separate tablets; Ca-D₃, group using calcium-vitamin D₃ in single tablet; eGFR, estimated glomerular filtration rate.

* $P < 0.05$ for the comparison of changes from baseline between the Ca + D₃ or Ca-D₃ group versus changes in placebo from baseline for each eGFR group.

groups). Similarly, the percentage of participants with a 30% or greater decrease from baseline iPTH levels in the groups receiving active treatment was significantly greater compared with placebo at the 24-month visit across eGFR groups ($P < 0.001$ for all groups). Furthermore, kidney function was categorized as eGFR of 60 mL/min/1.73 m² or greater versus less than 60 mL/min/

1.73 m². In participants with CKD (ie, eGFR < 60 mL/min/1.73 m²), 50% and 42% of participants had a 30% or greater decrease from baseline iPTH levels at 6 and 24 months, respectively ($P < 0.001$; Fig 2). In addition, a greater proportion of participants receiving placebo had an iPTH level greater than the KDOQI target range for stage 3 CKD (35 to 70 pg/mL) at 6 and 24

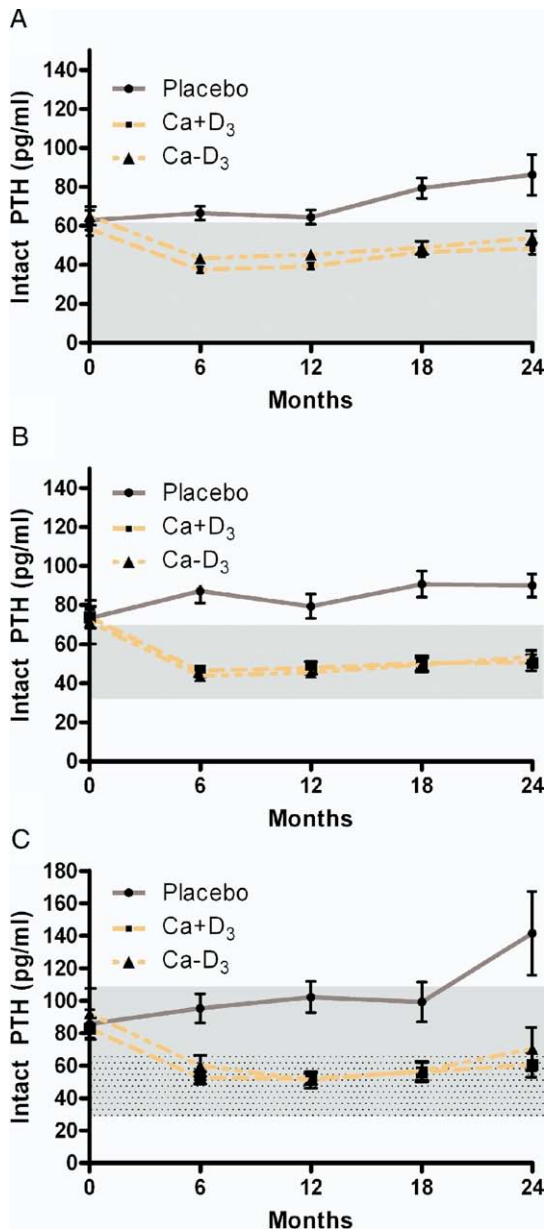


Figure 1. (A-C) Effect of study medication on intact parathyroid hormone (iPTH) levels per estimated glomerular filtration rate (eGFR; $P = 0.02$ for treatment effect). (A) eGFR of 60 mL/min/1.73 m² or greater and iPTH target less than 60 pg/mL, (B) eGFR of 59 to 45 mL/min/1.73 m² and iPTH target of 35 to 70 pg/mL, and (C) eGFR less than 45 mL/min/1.73 m² and iPTH target for stage 3 CKD of 35 to 70 pg/mL and for stage 4 CKD of 70 to 110 pg/mL. iPTH levels expressed in pg/mL to ng/L are equivalent. Abbreviations: Ca + D₃, group using calcium plus vitamin D₃ in separate tablets; Ca-D₃, group using calcium-vitamin D₃ in a single tablet.

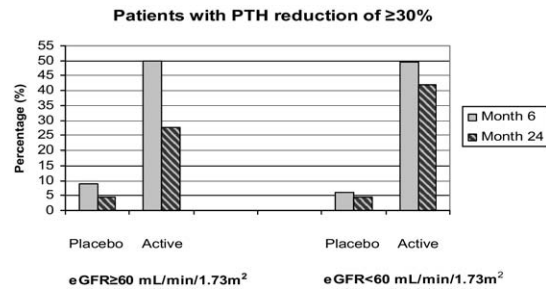


Figure 2. Proportion of patients with a 30% or greater decrease from baseline in intact parathyroid hormone (iPTH) level in the groups receiving active treatment versus placebo per chronic kidney disease (CKD) status ($P < 0.001$ for comparison between the active treatment group versus placebo at 6 and 24 months for participants with and without CKD). Abbreviation: eGFR, estimated glomerular filtration rate.

months compared with participants receiving active treatment across eGFR groups ($P < 0.001$ for all; Fig 3). Similar results were obtained when an iPTH cutoff level of 110 pg/mL was used ($P < 0.01$ for all; data not shown).

Additional analysis was performed to examine changes in iPTH levels from baseline in the group of participants receiving active treatment. Participants were dichotomized to an increase in 25(OH)D level to greater than 30 ng/mL at 6 and 24 months. Participants who achieved a 25(OH)D level greater than 30 ng/mL had a significant decrease in median iPTH level from baseline compared with those not achieving a level greater than 30 ng/mL at each time examined: -23 pg/mL; (25th and 75th percentiles, -8 and -46) versus -13 pg/mL (25th and 75th percentiles, -1 to -30) at 6 months ($P < 0.001$) and -17 pg/mL (25th and 75th percentiles, -36 to 2.0) versus -5 pg/mL (25th and 75th percentiles, -25 and 6.0) at 24 months ($P = 0.02$).

DISCUSSION

The findings from this study provide evidence that supplementation with 800 IU/d of vitamin D₃ as either a fixed or separate combination with 1,200 mg/d of calcium significantly improved serum 25(OH)D levels and decreased serum iPTH concentrations in an elderly group of women with predominantly CKD stage 3 with severe vitamin D deficiency. The effectiveness of cholecalciferol in our cohort did not vary according to level of kidney function and persisted up to 24 months after the initiation of 25(OH)D replacement therapy.

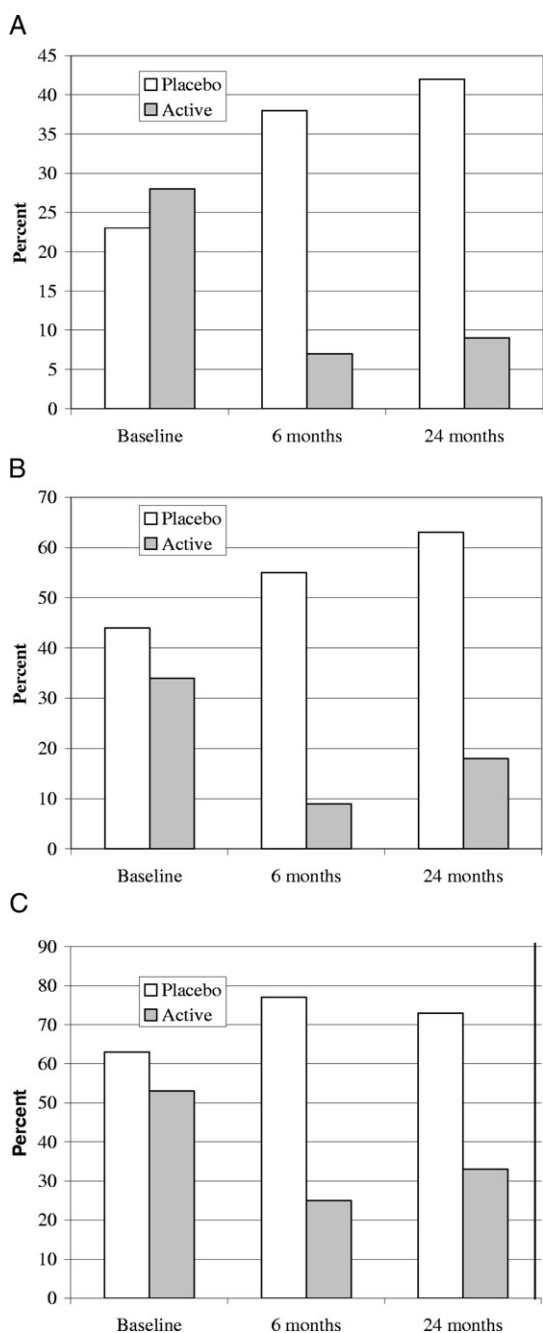


Figure 3. (A-C) Proportion of participants with an intact parathyroid hormone (iPTH) level greater than 70 pg/mL per estimated glomerular filtration rate (eGFR) category in the groups receiving active treatment versus placebo ($P < 0.001$ for comparison between active treatment group versus placebo at 6 and 24 months for all kidney function groups). (A) eGFR of 60 mL/min/1.73 m² or greater, (B) eGFR of 59 to 45 mL/min/1.73 m², and (C) eGFR less than 45 mL/min/1.73 m².

This cohort of elderly women with moderate CKD was found to have an exceptionally low mean baseline 25(OH)D level. In all categories of eGFR, the percentage of participants with baseline serum 25(OH)D levels greater than 30 ng/mL was only 1% or less. Despite profound deficiency, our analyses confirm that replacement with cholecalciferol increases average 25(OH)D levels close to those considered sufficient by the KDOQI (ie, >30 ng/mL)¹² across different eGFR levels compared with placebo. In addition, up to 50% of patients with CKD (ie, eGFR < 60 mL/min/1.73 m²) had a 30% or greater decrease in iPTH levels from baseline after 6 months of randomization to active treatment. That up to half the participants with CKD experienced this degree of iPTH level decrease with cholecalciferol supplementation is substantial compared with 56% and 91% of patients with a 30% or greater decrease in iPTH levels seen in cinacalcet- and oral paracalcitol-treated patients with CKD, respectively.^{15,16} Hence, the 30% decrease in iPTH levels from baseline provides a measure of efficacy of vitamin D₃, as well as a means of comparison with other active agents that have been developed to decrease iPTH levels.¹⁵⁻¹⁷

The rationale for combining 25(OH)D and calcium in the DECALYOS II was that oral calcium supplementation in vitamin D-depleted participants had been reported to prevent significant loss of bone mineral density at the femoral neck, which was one of the aims of DECALYOS II.^{13,18} In this post hoc analysis, we cannot separate the independent effects of calcium and cholecalciferol on iPTH levels. Of note, changes in serum calcium levels at the end of the study were statistically, although not clinically, greater in the Ca + D₃ group versus placebo, but not in participants randomized to Ca-D₃ despite similar changes in iPTH levels. Nonetheless, normalization of calcium homeostasis has been shown to prevent the development of hyperparathyroidism in vitamin D receptor-ablated mice.¹⁹ Liu et al²⁰ evaluated the influence of non-calcium- and calcium-containing binders on iPTH levels in patients with hyperphosphatemia receiving hemodialysis. In this study, mean change in serum calcium level during the 8 weeks of treatment was 0.12 mg/dL for the non-calcium-containing group and 0.82 mg/dL for the calcium-containing group ($P < 0.001$). Median changes in iPTH

levels were -69.0 and -178 pg/mL ($P = 0.002$) for the non-calcium- and calcium-containing groups, likely because of the greater serum calcium levels achieved with calcium-containing binders, respectively. Although the population studied in our analysis is limited mainly to patients with CKD stage 3, changes in serum calcium levels were similar to those reported by Liu et al²⁰ in hemodialysis patients receiving non-calcium- binders, suggesting that the small changes seen in the Ca + D₃ group likely did not have an important contribution to decreasing iPTH concentrations. In addition, Zhu et al²¹ evaluated the effects of calcium and ergocalciferol supplementation on iPTH levels in elderly women. In participants with baseline iPTH levels greater than the median, the calcium and ergocalciferol group had significantly lower iPTH concentrations compared with the calcium-only group ($P = 0.003$), thus supporting that vitamin D supplementation is an important component of the intervention in decreasing iPTH levels.

To our knowledge, only 1 other randomized controlled trial has examined the impact of vitamin D supplementation in patients with CKD on serum iPTH levels.²² However, this study differs from the present study in that participants were randomized to receive once-weekly cholecalciferol doses of 50,000 IU or placebo for only 12 weeks. With this regimen, the investigators found a significant improvement in serum 25(OH)D concentration in the cholecalciferol-treated group, which increased from an average of 17.3 ng/mL at baseline to 49.4 ng/mL at week 12, with a trend toward decreasing iPTH levels ($P = 0.07$). Other retrospective studies²³⁻²⁵ have evaluated vitamin D supplementation in patients with CKD; however, these studies had much shorter follow-up (90 days to 7.4 months) compared with the present study (24 months); evaluated the impact of ergocalciferol supplementation, not daily cholecalciferol supplementation; and were not compared with a placebo arm.

The major form of vitamin D used by clinicians to determine body stores of vitamin D is 25(OH)D. This form of vitamin D then must be converted in the kidneys by 25-hydroxyvitamin D-1 α -hydroxylase to the biologically active form 1,25(OH)₂D₃, known as calcitriol.²⁶⁻²⁸ Calcitriol decreases the synthesis and secretion of iPTH by the parathyroid glands and decreases its own synthesis through

negative feedback. Recently, Ritter et al²⁹ also reported that 25(OH)D can suppress iPTH synthesis in bovine parathyroid cells, and activation to 1,25(OH)₂D₃ apparently is not required, suggesting a direct interaction of 25(OH)D with the vitamin D receptor.²⁹ Thus, a decrease in serum 25(OH)D levels may aggravate SHPT in those with CKD and decreased kidney function.

This study has several limitations. First, it was a study of predominantly elderly white women with CKD stage 3 and hence may not be applicable to other populations and patients with more advanced stages of CKD. Second, a gold-standard measure of eGFR, such as inulin or radioisotope clearance, was not performed. Also, serum creatinine was not calibrated to the MDRD Study laboratory and was measured on a single blood specimen. Thus, it is possible that within-person variation in serum creatinine levels resulted in misclassification of kidney function. However, the MDRD Study equation is easy to calculate and currently represents the prediction equation of choice in the elderly.³⁰ Third, 1,25(OH)₂D₃ levels were not measured in this study; thus, information regarding change in its level in response to vitamin D₃ supplementation, correlation with 25(OH)D levels at baseline and follow-up, and relationship to iPTH levels cannot be ascertained. Finally, this study examined the effect of only a single dose of 800 IU of vitamin D₃. Therefore, the impact of higher doses or supplementation with vitamin D₂ (ergocalciferol) in this population and the impact of this regimen in CKD populations different from the present study are not known.

In conclusion, our results are in accord with the current KDOQI guidelines for replacing vitamin D in the setting of SHPT in patients with CKD stage 3. In this study, cholecalciferol was found to effectively decrease iPTH levels and has the benefits of being relatively inexpensive and widely available. Furthermore, the findings of our study support the concept that participants with CKD have a more 25(OH)D-substrate-dependent increase in iPTH levels that can be corrected at least partially with vitamin D₃ supplementation. However, additional research is needed to define the optimal dose, frequency, and target level of 25(OH)D in patients with all stages of CKD, as well as the role of combined vitamin D₂ or D₃ supplementation with active vitamin D compounds or calcimetic agent

initiation in participants with stages 3 and 4 CKD and persistent SHPT.

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