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Variation in Oral Calcitriol Response in Patients With Stage 3-4 CKD

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Abstract

BACKGROUND—Oral calcitriol lowers parathyroid hormone (PTH) concentrations among patients who have chronic kidney disease (CKD); however, treatment response is highly variable. We evaluated whether patient characteristics affect the PTH response to oral calcitriol among non-dialysis CKD patients in a clinic-based setting.

STUDY DESIGN—Cohort study.

SETTING & PARTICIPANTS—This study included 379 new oral calcitriol users in the Veterans' Affairs Northwest Health Network. All had stages 3-4 CKD, hyperparathyroidism, and a serum PTH measurement before and 1-6 months after initiating oral calcitriol.

PREDICTORS—Patient-level characteristics hypothesized to affect calcitriol response: race, body size, concurrent medications, and kidney function.

OUTCOMES—Relative reduction in serum PTH concentration after starting oral calcitriol.

MEASUREMENTS—Data were abstracted from the Veterans' Affairs Northwest Health Network (VISN 20) Data Warehouse, which includes electronic pharmacy and laboratory records.

RESULTS—Mean estimated GFR was 30 ml/min/1.73m² and mean initial PTH concentration was 199 pg/mL. Regular dose (0.25 ug/day) and low-dose (<0.25 ug/day) oral calcitriol were associated with, on average, 23% and 13% relative reductions in serum PTH concentrations, respectively. After adjustment for calcitriol dosage, initial PTH concentration, and time to follow-up measurement, African American race was associated with a blunted calcitriol response (geometric mean final PTH value, 26% higher; 95% CI, 8%-47%). A serum albumin concentration <3.5 g/dL was also associated with a diminished calcitriol response (geometric mean final PTH,

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Supplementary Material

Table S1: Baseline characteristics of study population and eligible excluded population.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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19% higher; 95% CI, 6%-35%). Although numbers were small, concurrent use of benzodiazepenes and non-activated vitamin D supplements were associated with a significantly greater PTH response.

LIMITATIONS—Clinic-based study is limited by availability of PTH measurements after starting calcitriol. Study among a predominantly older, male population.

CONCLUSION—Among patients with stages 3-4 CKD, African American race and low serum albumin are associated with a diminished PTH response to oral calcitriol.

Index Words

Activated vitamin D; calcitriol; parathyroid hormone; hyperparathyroidism; drug metabolism

Oral calcitriol is commonly used to treat secondary hyperparathyroidism among patients who have chronic kidney disease (CKD). In clinical trials, oral calcitriol and activated vitamin D analogs lower parathyroid hormone (PTH) concentrations in the setting of CKD; however, the magnitude of PTH response to activated vitamin D treatment is highly variable.¹⁻³ In a recent meta-analysis of trials designed to assess the effect of calcitriol on PTH lowering, the 95% confidence interval for the effect of oral calcitriol on serum PTH concentrations ranged from -36.3 to +2.0 pmol/L, with a mean response of -17.2 pmol/L.⁴ Reasons for the substantial inter-individual variability in response to activated vitamin D therapy remain unknown.

Vitamin D metabolism differs by race. African Americans have substantially lower serum 25-hydroxyvitamin D concentrations,⁵ different allele frequencies for major polymorphisms within the vitamin D receptor,⁶ and higher circulating PTH concentrations.^{7, 8} Moreover, African American dialysis patients require higher dosages of activated vitamin D analogs to suppress PTH compared to Caucasians.⁹ These differences suggest the potential for race-related variation in response to oral calcitriol therapy.

The response to activated vitamin D treatment may also be influenced by other medications. Calcitriol is metabolized by cytochromes CYP24A1 and CYP3A4, which degrade calcitriol through a side chain 24-hydroxylation.^{10, 11} CYP24A1 is primarily involved in the metabolism of anti-convulsant agents, whereas a wide variety of medications interact with CYP3A4.

The purpose of this study is to evaluate whether patient characteristics affect the magnitude of PTH reduction achieved in response to oral calcitriol treatment in a real-world clinical setting. To address this objective we evaluated 379 new oral calcitriol users who had stages 3-4 CKD and hyperparathyroidism. We hypothesized that race, body size, concurrent medications, and kidney function would influence the PTH response to oral calcitriol treatment.

METHODS

Data source

We abstracted data from the Veterans' Affairs (VA) Northwest Health Network (VISN 20) Data Warehouse, which acquires data directly from the VA Information Systems and Technology Architecture (VISTA), the computerized medical record used throughout the VA system. The VISN 20 Data Warehouse includes demographics, pharmacy records, diagnosis and procedure codes, laboratory values, and vital signs for all inpatient and outpatient visits to VA Northwest Health Network, a collection of eight facilities located in Washington State, Idaho, Oregon, and Alaska.

Study population

We identified all veterans who initiated oral calcitriol within the VA Northwest Health Network between 2002-2010. Oral activated vitamin D analogs (paricalcitol, hectoral) were rarely prescribed within the network and therefore were not evaluated in this study. We restricted the incident calcitriol cohort to individuals who had (1) two outpatient serum creatinine measurements at least three months apart that indicated an estimated glomerular filtration rate (GFR) between 15-60 ml/min/1.73m² with the latest GFR measurement within 6 months before first calcitriol use, (2) hyperparathyroidism, defined by a serum PTH concentration >70 pg/mL within 6 months before first calcitriol use, and (3) an outpatient Nephrology visit to either the Seattle or Portland VA within the previous year. We restricted the study population to Seattle and Portland sites, which composed the majority of visits, to ensure consistency of the PTH assay. We excluded veterans who were receiving chronic dialysis or had a kidney transplant, those who initiated calcitriol at a dose of 0.5 ug/day or greater, those who had an uncorrected serum calcium level >10.2 mg/dl within the year prior to first calcitriol use, and those who were missing data for race (Figure 1). To focus on the biologic effect of oral calcitriol on PTH we further excluded patients who used calcitriol for less than 50% of the period between calcitriol initiation and follow-up PTH measurement and those who initiated dialysis or received a kidney transplant during this follow-up period.

Ascertainment of calcitriol dosage

We examined computerized pharmacy records to identify the fill date, dosage, and the number of pills prescribed for each oral calcitriol prescription. We excluded doses of greater than 0.50 ug per day as they were rarely prescribed (<1%, figure 1). We then calculated average daily calcitriol dosage from the index (first) prescription by dividing the number of pills dispensed by the physician-indicated days supply. We defined two doses of calcitriol: “regular dose” for regimens of 0.25 ug per day and “low dose” for regimens of less than 0.25 ug per day. The regimen for those on “low dose” was most often 0.25 ug 3 or 4 times per week.

Ascertainment of outcomes

Primary study outcomes were (1) the final serum PTH concentration 1-6 months after starting calcitriol, and (2) a greater than 30% decrease in serum PTH concentration from baseline. We defined the baseline PTH concentration as the most recent outpatient PTH measurement prior to calcitriol initiation and within 6 months before first use. We defined the follow up PTH concentration as the first outpatient PTH measurement that was more than 30 days, but less than 6 months after starting calcitriol. For the inclusive study dates 2002-2010, both Seattle and Portland laboratories measured intact serum PTH using the same Roche Elecsys automated immunoassay. The intra-assay and inter-assay coefficients of variation for this assay are 5.4% and 5.9%, respectively.¹² We also evaluated the change in serum calcium and phosphorus concentrations by ascertaining outpatient measurements that were closest to the follow-up PTH concentration, up to 7 days after the PTH follow-up date.

Ascertainment of other study data

We defined prevalent medical conditions by examining all available International Classification of Diseases Clinical Modification 9th Edition (ICD9-CM) diagnosis and procedure codes prior to the calcitriol start date. We defined diabetes by either two outpatient or one inpatient ICD9-CM code for diabetes or a filled prescription for an oral hypoglycemic medication, insulin, glucose test strips, or a glucometer. We defined prevalent cardiovascular disease by a prior diagnosis code for myocardial infarction, stroke, or peripheral vascular disease, or a prior procedure code for coronary artery bypass grafting,

coronary angioplasty, carotid endarterectomy, or amputation. We defined baseline laboratory measurements as the value closest to the date of first calcitriol use and within the previous year. We used the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation to define baseline estimated glomerular filtration rate (eGFR) using the most recent outpatient serum creatinine concentration. We defined the use of non-calcitriol medications by at least 50% of follow-up time spent on the drug, determined by fill dates and pill supply.

We used the University of Washington Metabolism & Transport Drug Interaction Database (<http://www.druginteractioninfo.org/>) to identify potent and moderate inducers and inhibitors of cytochromes CYP24 and CYP3A4, which metabolize calcitriol. Excepting vitamin D supplements, which induce CYP24, we found fewer than 5 patients to be using any potent-moderate CYP24 inducer or inhibitor, or any potent-moderate CYP3A4 inducer; therefore we could only evaluate the CYP3A4 inhibitor class. We also evaluated medications that are commonly prescribed in CKD and weakly inhibit CYP3A4 (calcium channel blockers, statins, benzodiazepenes) or weakly induce CYP3A4 (steroids).

Statistical analysis

We tabulated means and proportions of baseline characteristics with respect to calcitriol dosage. We defined the beginning of study time as the first fill date for oral calcitriol in the VA pharmacy and defined the end of study time as the date of final PTH measurement. We calculated the percent change in PTH as $(final - initial) / initial \times 100\%$. Our basic model estimated associations of calcitriol use with change in PTH during follow-up by including log final PTH concentration as the outcome variable and calcitriol dose, log initial PTH concentration, and follow-up time as independent variables. Exponentiated coefficients from these models represent the relative change in the geometric mean final PTH between groups of interest (e.g., non-activated vitamin D users vs. non-user) after basic adjustment for initial concentration, follow-up time, and dose. We estimated fully adjusted associations by adding age, race (coded as African American *versus* Caucasian or other), estimated GFR, body mass index category, and diabetes to the multivariable models.

For the common secondary outcome of a greater than 30% reduction in PTH concentration, we modeled the absolute proportion of patients achieving this drop as a linear variable. Coefficients from this model represent the absolute risk difference of the outcome. For example, an estimated risk difference of 0.18 for regular dose calcitriol indicates that regular dose calcitriol was associated with a 0.18 higher probability of achieving a 30% or greater reduction in PTH concentration compared to the low dose. We used the Huber-White sandwich estimator to calculate robust standard errors.¹³ This binary outcome is not expected to have normally distributed errors, but the use of the robust standard errors allows for valid inference with a common outcome.¹⁴ Using linear regression for binary data assumes that the linear association is of interest (as in all linear models) and that the probability of the outcome is away from the extremes (probabilities away from 0 and 1) in the range of interest. The use of the robust standard errors assumes that the sample size is adequate for asymptotic results. All assumptions are reasonable in this setting with these data. Data were analyzed using STATA 10.2 and R 2.9.1.

RESULTS

Description of the study population

Baseline characteristics of incident calcitriol users describe a generally older, male CKD population, with greater than 50% prevalent diabetes (Table 1). The mean estimated GFR was 30.2 ml/min/1.73m². Patients who started on a daily 0.25 ug calcitriol regimen ("regular dose", n=141) had a modestly lower baseline eGFR compared to those who started on lower dose calcitriol regimens (n=238). Patients who received regular dose calcitriol also had a

modestly greater body mass index and a lower prevalence of cardiovascular diseases compared to those who received low dose calcitriol. Other co-morbidities and medication use patterns were similar between the two dosage groups. Adherence to calcitriol among the study population was very high (mean adherence 96%) and was similar by dose and by race. The study population was similar to those eligible for the study but excluded due to lack of follow up PTH, incident dialysis, low adherence, or missing race (n=244; Table S1, available as online supplementary material). Baseline characteristics were also similar comparing whites to African Americans, except that African Americans tended to have higher body mass indexes, and some differences in concurrent medication use (less Statin use, more ACE/ARB use).

Unadjusted PTH response

The mean time between starting oral calcitriol and the follow up PTH (follow up time) was 94 days in the regular dose group and 105 days in the low dose group (Table 2). Among patients who received regular dose calcitriol, the mean baseline PTH concentration was 234.0 pg/mL and the mean final PTH concentration was 178.9 pg/mL (mean relative change -22.9%; Table 2, Figure 2). Among patients who received low dose calcitriol, the mean baseline PTH concentration was 177.5 pg/mL and the mean final PTH concentration was 151.6 pg/mL for a mean relative change of -13.4%. A 30% or greater reduction in serum PTH was achieved by 48% of patients who received regular dose calcitriol, while only 30% of those who received low dose achieved a reduction in serum PTH of 30% or more. Non-response, defined by no reduction in PTH during follow-up, occurred in 16.3% and 30.7% of patients in the regular and lower dose calcitriol groups, respectively.

Adjusted PTH response

After adjustment for initial PTH concentration and follow-up time, regular dose calcitriol use was associated with an estimated 12.2% lower final geometric mean PTH concentration compared to low dose regimens (95% CI, 20.9%-2.6%; $p=0.01$; Table 3). Additional adjustment for age, race, estimated GFR, diabetes, and body mass index category did not materially alter the magnitude of this association (final geometric mean PTH concentration 14.4% lower; 95% CI, 22.8%-5.0%; $p=0.003$).

Associations with diminished PTH response

African American race was associated with a significantly diminished PTH response to oral calcitriol in both the low dose and regular dose calcitriol groups (Table 3; Figure 3). In the fully adjusted model, African American race was associated with a 23.5% higher final geometric mean PTH concentration (95% CI, 5.9%-44.0%; Table 3). The PTH reduction among African Americans who received regular dose calcitriol was less than that of Caucasians who received low dose regimens (Figure 3). A serum albumin concentration <3.5 g/dL was also associated with a blunted PTH response to oral calcitriol. In the fully adjusted model, a low serum albumin concentration was associated with a 16.4% higher final geometric mean PTH concentration (95% CI, 2.8%-31.9%).

Associations with greater PTH response

Concurrent use of non-activated vitamin D (cholecalciferol or ergocalciferol) and benzodiazepines were each associated with an augmented PTH response to oral calcitriol (Table 3). In the fully adjusted model, non-activated vitamin D use was associated with an estimated 19.2% lower final geometric mean PTH concentration (95% CI, 33.5%-1.8%). Benzodiazepine use was associated with a 26.9% lower final geometric mean PTH concentration (95% CI, 40.1%-10.8%).

Lack of Association of BMI with PTH response

An increased BMI was not associated with a diminished calcitriol response, particularly in the adjusted model (table 3). This lack of association between BMI and PTH response did not differ by race; a 10 kg/m² increase in BMI was associated with an estimated 2.6% increase in final geometric mean for whites and 0.6% increase in final geometric mean for blacks (p for interaction of 0.7).

Achieving a 30% or greater reduction in PTH concentration

Similar results were observed for the binary outcome of achieving a 30% or greater reduction in serum PTH concentration during follow-up (Table 4). African American race and a low serum albumin concentration were each associated with a decreased likelihood of achieving a 30% reduction in PTH during follow-up. Higher calcitriol dosage and concurrent use of non-activated vitamin D and benzodiazepines were each associated with a greater probability of achieving a 30% PTH reduction.

Changes in calcium and phosphorus levels

Among the 362 participants with serum calcium measured within 7 days of the final PTH, mean serum calcium concentrations increased by 0.2 mg/dL in the regular dose calcitriol group and were unchanged in the low dose group. Hypercalcemia (Ca>10.2 mg/dL) was observed in 5 participants (1.5%), all of whom were white. Hypocalcemia (Ca<9.0 mg/dL) was observed in 40% of these participants; 38% of whites (126 of 329) and 52% of African Americans (17/33).

Among the 357 participants with serum phosphorus measured within 7 days of the final PTH, mean phosphorus concentrations increased by 0.3 mg/dL in the regular dose group and 0.1 mg/dL in the low dose group. Hyperphosphatemia (>4.5 mg/dL) was observed in 17.6% of these participants; 16.0% of whites (52/324) and 33.3% of African Americans (11/33). Adjustment for baseline calcium and phosphorus values does not change the results.

DISCUSSION

In this clinic-based cohort of veterans with stages 3-4 CKD, we found African American race to be the strongest predictor of PTH response to oral calcitriol. After adjustment for calcitriol dosage, initial PTH concentration, time to follow-up measurement, age, kidney function, diabetes, and body mass, African American race was associated with an estimated 23.5% lesser PTH response to oral calcitriol. A serum albumin concentration <3.5 g/dL was also associated with a blunted PTH response. In contrast, use of non-activated vitamin D and benzodiazepines were each associated with a greater PTH response to oral calcitriol. There was no difference in calcitriol treatment response across age, body mass index, and kidney function. These findings suggest potentially different calcitriol dosing strategies by race.

Diminished PTH responsiveness to oral calcitriol among African Americans may reflect differences in pharmacokinetics, pharmacodynamics or both. Calcitriol is carried in the bloodstream by the vitamin D binding protein (VDBP) and to a lesser extent albumin.¹⁵ The secondary carrier function of albumin could explain the observed association of low serum albumin concentration with diminished calcitriol response. Polymorphisms in the VDBP gene differ by race and are linked with modest variation in serum calcitriol concentrations in the general population.^{16, 17} However, circulating VDBP concentrations exceed those of calcitriol by more than 10⁶ fold, and VDBP levels are generally similar among Caucasians and African Americans.^{16, 18} Calcitriol induces its own metabolism by binding to the vitamin D receptor (VDR), thereby stimulating expression of the CYP24 cytochrome, which inactivates calcitriol via a 24-hydroxylation step.¹⁰ Cytochrome CYP3A4, which

participates in the metabolism of a wide variety of commonly used drugs, also degrades calcitriol via 24-hydroxylation.¹¹ It is possible that genetic polymorphisms in VDR and CYP24, which can differ between African Americans and Caucasians, could explain some of the observed variation in treatment effect.

An alternate explanation for the observed race-related difference in calcitriol response is increased resistance of parathyroid tissue among African Americans. This could be due to greater parathyroid hyperplasia caused by rapid parathyroid growth or a longer duration of impaired kidney function. Among CKD patients and individuals in the general population African American race is associated with higher circulating PTH concentrations compared to Caucasians.^{7, 8} African American dialysis patients require higher dosages of activated vitamin D analogs to maintain serum PTH concentrations within treatment guidelines, possibly indicating more recalcitrant hyperparathyroidism.⁹ Measurement of serum calcitriol levels among treated patients in future studies might help distinguish the relative contributions of pharmacokinetics *versus* pharmacodynamics to race-related variation in treatment response.

An intriguing possibility to explain the observed variation in oral calcitriol response is differences in dietary calcium intake. It is possible that lower dietary calcium consumption could further provoke hypocalcemia and provide a continuous stimulus for PTH secretion even in the presence of calcitriol treatment. This hypothesis may be difficult to prove as most late stage CKD patients are generally in positive calcium balance regardless of dietary calcium intake. The current study was conducted using electronic medical records from a CKD clinic, therefore information regarding micronutrient intake were not available.

Although patient numbers were limited, we found a relatively larger decline in serum PTH concentrations among patients who were receiving concurrent non-activated vitamin D supplements. On one hand, parathyroid tissue is able to directly convert substrate 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D through an autocrine pathway that suppresses PTH secretion. On the other hand, 25-hydroxyvitamin D stimulates 24-hydroxylase, which metabolizes calcitriol, raising concern that vitamin D supplementation could interfere with the calcitriol treatment response. Our findings suggest that autocrine suppression of PTH by vitamin D supplements is likely to outweigh the induction of calcitriol metabolic pathways, and can be used as a combination therapy without antagonistic effects. We also observed a modestly greater calcitriol treatment response among subjects who were using benzodiazepenes, which weakly inhibit cytochrome CYP3A4; however, small patient numbers mandate replication of this finding in other populations.

We speculated that greater body mass index might diminish the PTH response to a fixed oral calcitriol dose. However, we did not observe differences in the magnitude of PTH response across body size in this study. The similar response may reflect the relatively limited tissue distribution of calcitriol. Similar to body mass index, we also did not find differences in calcitriol treatment response by age, estimated kidney function, or baseline serum concentrations of calcium or phosphorus.

An important strength of this study is the evaluation of oral calcitriol treatment in a real-world clinical setting, thereby enhancing generalizability of these findings and suggesting that they could be replicated in other clinic-based studies. A second strength of this study is the use of automated pharmacy records, which provide complete capture of prescription dates and dosages for all medications that were used throughout the study. The real-world setting of this study also leads to important limitations. First, to focus on biological differences in treatment response we limited our analysis to patients who received a follow up PTH measurement within 6 months of calcitriol initiation. However, many incident

calcitriol users did not receive a follow up PTH measurement within this time frame. If such excluded patients were to respond differently to calcitriol, our results would be less applicable to the entire population. A second important limitation is the relatively small number of African American patients in this study, as well as a relatively small number of individuals who concurrently used other medications. Replication of our findings in other study populations is necessary to confirm their validity. A third limitation is the evaluation of a male, predominantly older CKD study population, which limits external validity.

Much attention is currently focused on the promise of personalized medicine – the notion that drug and other therapies can be targeted to specific subpopulations that respond differently to different treatments. Studying variation in treatment response in a clinical setting is an appealing approach, because it could better inform clinicians as to how different patients might respond to therapies and provide opportunities to tailor treatment based on patient characteristics. Here we show a tendency for a diminished calcitriol response among African American patients, suggesting that greater calcitriol dosages may be required to suppress PTH among CKD patients. Additional work is needed to confirm these findings and to uncover potential mechanisms for the observed variation in response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Flow chart of inclusion and exclusion criteria
Sequential exclusions are shown on the right hand side of the figure.

Figure 2. Percent change in PTH by calcitriol dosage

Shaded area of the figure represents a >30% decrease in serum PTH concentration within 6 months.

Figure 3. Percent change in PTH by dose and race

Box-plots of relative PTH change within 6 months, stratified by dosage and race.

Table 1

Description of the study population by calcitriol dosage.

	% missing	Low Dose	Regular Dose
		(n=238)	(n=141)
<i>Demographics</i>			
Age	0	70.3 ± 10.5	67.8 ± 10.9
Male	0	235 (99)	136 (96)
Race	0		
White		216 (91)	114 (81)
Black		15 (6)	21 (15)
Other		7 (3)	6 (4)
<i>Co-morbidity</i>			
Diabetes	0	151 (63)	107 (76)
Cardiovascular disease	0	117 (49)	59 (42)
eGFR(ml/min/1.73m ²)	0	31.3 ± 9.4	28.4 (9.6)
eGFR category			
15-30 ml/min/1.73m ²		115 (48)	85 (60)
30-45 ml/min/1.73m ²		101 (42)	48 (34)
45-60 ml/min/1.73m ²		22 (9)	8 (6)
Body mass index	0		
<25 kg/m ²		32 (14)	23 (16)
25-30 kg/m ²		80 (34)	36 (26)
30-35 kg/m ²		71 (30)	42 (30)
>35 kg/m ²		54 (23)	40 (28)
<i>Medication use</i>			
CYP3A4 inhibitors	0	16 (7)	4 (3)
Non-activated vitamin D	0	10 (4)	7 (5)
Calcium channel blocker	0	123 (52)	75 (53)
Statin	0	147 (62)	87 (62)
Benzodiazapine	0	10 (4)	6 (4)
Steroid	0	11 (5)	8 (6)
ACE inhibitor or ARB	0	142 (60)	74 (52)
Erythropoietin	0	30 (13)	17 (12)
<i>Laboratory values</i>			
Creatinine (mg/dL)	0	2.4 ± 0.7	2.7 ± 0.8
Hemoglobin (g/dL)	0.3	12.6 ± 1.5	12.4 ± 1.7
Calcium (mg/dL)	0	9.0 ± 0.5	8.8 ± 0.7
Phosphorus (mg/dL)	0.3	3.6 ± 0.7	3.9 ± 0.8
Low albumin (<3.5 g/dL)	2.9	34 (15)	30 (22)

Note: Continuous variables expressed as mean $\pm$ standard deviation, binary variables as number (%). Conversion factors for units: creatinin in mg/dL to mol/L, $\times 88.4$; hemoglobin and albumin in g/dL to g/L $\times 10$; calcium in mg/dL to mmol/L $\times 0.2495$; phosphorous in mg/dL to mmol/L $\times 0.3229$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$.

eGFR = estimated glomerular filtration rate; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

Table 2

Unadjusted PTH response by calcitriol dosage group.

	% missing	Low Dose	Regular Dose
		(n=238)	(n=141)
Initial serum PTH (pg/mL)	0	177.5 ± 76.8	234.0 ± 119.9
Final serum PTH (pg/mL)	0	151.6 ± 87.4	178.9 ± 128.2
Follow-up time (days)	0	105.3 ± 37.2	94.3 ± 38.4
Absolute change serum PTH (pg/mL)	0	-25.9 ± 61.4	-55.1 ± 89.0
Relative change serum PTH (%)	0	-13.4% ± 32.7%	-22.9% ± 36.4%
Relative PTH drop ≥ 15%	0	131 (55%)	96 (68%)
Relative PTH drop ≥ 30%	0	72 (30%)	68 (48%)
Initial serum calcium (mg/dL)	0	9.0 ± 0.5	8.8 ± 0.7
Final serum calcium (mg/dL)	4.5	9.0 ± 0.7	9.0 ± 1.0
Mean change serum calcium (mg/dL)	4.5	-0.0 ± 0.7	+0.2 ± 0.9
Initial serum phosphorus (mg/dL)	0.3	3.6 ± 0.7	3.9 ± 0.8
Final serum phosphorus (mg/dL)	5.5	3.7 ± 0.9	4.1 ± 1.1
Mean change serum phosphorus (mg/dL)	6.1	+0.1 ± 0.9	+0.3 ± 0.9

Note: PTH = parathyroid hormone. Continuous variables expressed as mean ± standard deviation, binary variables as number (%). Conversion factors for units: calcium in mg/dL to mmol/L $\times 0.2495$; phosphorous in mg/dL to mmol/L $\times 0.3229$. no conversion necessary for PTH in pg/mL and ng/L.

Table 3

Associations with geometric mean final PTH concentration.

	Basic model (95% CI) ¹	Adjusted model (95% CI) ²
Regular (versus low) dose	-12.2% (-20.9%, -2.6%)*	-14.4% (-22.8%, -5.0%)**
Age (per 10 years older)	-4.4% (-8.7%, -0.0%)*	-3.5% (-8.0%, 1.2%)
African American (versus Caucasian/other)	25.8% (8.1%, 46.5%)**	23.5% (5.9%, 44.0%)**
eGFR (per 5 ml/min/1.73m ² lower)	-0.6% (-3.1%, 1.9%)	-0.3% (-2.7%, 2.3%)
Diabetes	5.7% (-3.8%, 16.3%)	4.3% (-5.2%, 14.8%)
Body mass index category ^a		
25-30 kg/m ²	-0.5% (-13.2%, 14.0%)	-1.0% (-13.8%, 13.8%)
30-35 kg/m ²	4.0% (-10.1%, 20.4%)	0.3% (-13.4%, 16.2%)
>35 kg/m ²	5.4% (-8.7%, 21.8%)	0.0% (-14.4%, 16.9%)
Serum albumin <3.5 g/dL	19.4% (5.7%, 34.9%)**	16.4% (2.8%, 31.9%)*
Serum calcium (per 1 mg/dL)	-1.7% (-10.0%, 7.3%)	-1.7% (-10.0%, 7.4%)
Serum phosphorus (per 1 mg/dL)	0.2% (-6.5%, 7.3%)	-0.3% (-7.8%, 7.8%)
CYP3A4 inhibitor use	5.0% (-10.4%, 23.1%)	6.8% (-9.7%, 26.3%)
Non-activated vitamin D use	-20.0% (-34.2%, -2.8%)*	-19.2% (-33.5%, -1.8%)*
Calcium channel blocker use	4.2% (-5.2%, 14.5%)	2.8% (-6.6%, 13.1%)
Statin use	-3.8% (-12.6%, 5.8%)	-2.4% (-10.8%, 6.8%)
Benzodiazepine use	-28.4% (-41.3%, -12.8%)**	-26.9% (-40.1%, -10.8%)**
Steroid use	-4.8% (-25.8%, 22.1%)	-8.5% (-28.6%, 17.4%)

^a <25 kg/m² is the reference group

CI = confidence interval; eGFR = estimated glomerular filtration rate; PTH, parathyroid hormone

*
p < 0.05**
p < 0.01***
p < 0.001¹ Basic model adjusted for log baseline PTH, follow up time and calcitriol dose² Adjusted model adds age, race, eGFR, diabetes, and body mass index category

Table 4

Associations with probability of achieving a 30% or greater drop in PTH.

	Basic model (95% CI)	Adjusted model (95% CI)
Regular (versus low) dose	0.18 (0.07, 0.28)	0.20 (0.10, 0.31)
Age (per 10 years older)	0.05 (0.01, 0.09)	0.03 (-0.01, 0.08)
African American	-0.19 (-0.34, -0.04)	-0.17 (-0.32, -0.02)
eGFR (per 5 ml/min lower)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)
Diabetes	-0.06 (-0.17, 0.04)	-0.04 (-0.14, 0.07)
Body mass index *		
25-30 kg/m ²	-0.04 (-0.19, 0.12)	-0.02 (-0.19, 0.14)
30-35 kg/m ²	-0.12 (-0.27, 0.04)	-0.08 (-0.24, 0.08)
>35 kg/m ²	-0.11 (-0.27, 0.05)	-0.07 (-0.24, 0.10)
Serum albumin <3.5 g/dL	-0.13 (-0.26, -0.01)	-0.12 (-0.25, 0.01)
Serum calcium (per 1 mg/dL)	0.09 (0.00, 0.19)	0.09 (-0.00, 0.19)
Serum phosphorus (per 1 mg/dL)	-0.01 (-0.08, 0.06)	0.01 (-0.07, 0.08)
CYP3A4 inhibitor use	-0.09 (-0.29, 0.10)	-0.12 (-0.31, 0.08)
Non-activated vitamin D use	0.25 (0.01, 0.48)	0.23 (-0.01, 0.47)
Calcium channel blocker use	-0.08 (-0.18, 0.01)	-0.07 (-0.16, 0.03)
Statin use	-0.04 (-0.14, 0.06)	-0.05 (-0.15, 0.05)
Benzodiazepine use	0.33 (0.10, 0.57)	0.32 (0.08, 0.57)
Steroid use	0.06 (-0.18, 0.29)	0.09 (-0.15, 0.33)

Cell contents are estimated absolute differences in the probability of achieving a 30% or greater drop in PTH.

CI = confidence interval; eGFR = estimated glomerular filtration rate; PTH, parathyroid hormone

¹ Basic model adjusted for log baseline PTH, follow up time and calcitriol dose² Adjusted model adds age, race, eGFR, diabetes, and body mass index category.* <25 kg/m² is the reference group