Paricalcitol does not improve glucose metabolism in patients with stage 3-4 chronic kidney disease

Ian H. de Boer, MD, MS,
Division of Nephrology and Kidney Research Institute, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA

Michael Sachs, PhD,
Division of Nephrology and Kidney Research Institute, Department of Medicine, University of Washington, Seattle, WA

Andrew N. Hoofnagle, MD, PhD,
Department of Laboratory Medicine, University of Washington, Seattle, WA

Kristina M. Utzschneider, MD,
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and the University of Washington, Seattle, WA

Steven E. Kahn, MB, CHB,
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and the University of Washington, Seattle, WA

Bryan Kestenbaum, MD, MS, and
Division of Nephrology and Kidney Research Institute, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA

Jonathan Himmelfarb, MD
Division of Nephrology and Kidney Research Institute, Department of Medicine, University of Washington, Seattle, WA

Abstract

Patients with chronic kidney disease are often insulin resistant and glucose intolerant; abnormalities that promote cardiovascular disease. Administration of 1,25-dihydroxyvitamin D (calcitriol) has improved glucose metabolism in patients with end stage renal disease. We conducted a randomized, placebo-controlled clinical trial to test whether paricalcitol, a 1,25-dihydroxyvitamin D analogue, changes glucose tolerance in earlier stages of chronic kidney disease. In a cross-over design, 22 non-diabetic patients with estimated glomerular filtration rates of stage 3-4 chronic kidney disease and fasting plasma glucose 100-125 mg/dL were given daily oral paricalcitol for 8 weeks and matching placebo for 8 weeks, separated by an 8-week washout period. The order of interventions was random and blinded to both participants and investigators.

Correspondence: Ian de Boer, MD, MS, Box 359606, 325 9th Ave, Seattle, WA 98104, Telephone: (206) 616-5403, Fax: (206) 685-9399, deboer@u.washington.edi.

Paricalcitol significantly reduced serum concentrations of parathyroid hormone, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D while significantly increasing serum concentrations of fibroblast growth factor-23 and 24,25-dihydroxyvitamin D. Paricalcitol, however, had no significant effect on glucose tolerance (the primary outcome measure), insulin sensitivity, beta-cell insulin response, plasma free fatty acid suppression, or urinary F2-isoprostane excretion. Thus, despite substantial effects on vitamin D metabolism, paricalcitol did not improve glucose metabolism in non-diabetic patients with stage 3-4 chronic kidney disease.

Introduction

Animal experimental models demonstrate diverse metabolic effects of vitamin D receptor agonists (1,25-dihydroxyvitamin D [$1,25(OH)_2D$] and its analogues). These include suppression of the renin-angiotensin system (RAS), regulation of cell proliferation and differentiation, modulation of immune cell function, and enhancement of insulin sensitivity and secretion.[1-4] However, intervention studies testing whether these actions are clinically relevant are scarce, particularly in persons with chronic kidney disease (CKD). As a result, appropriate use of vitamin D receptor agonists in clinical practice remains undefined.

Glucose metabolism is a clinically relevant intermediate outcome with which to test effects of vitamin D receptor agonists in CKD. Patients with CKD are often insulin resistant and glucose intolerant, and these abnormalities appear to promote cardiovascular disease.[5-10] In animal-experimental models, $1,25(OH)_2D$ (calcitriol) augments both insulin sensitivity and insulin secretion, which together determine glucose tolerance.[11,12] Moreover, small studies of hemodialysis patients have consistently demonstrated that $1,25(OH)_2D$ administration improves glucose metabolism,[4,13-20] but effects have not been reported in earlier stages of CKD. Insulin resistance is tightly linked with oxidative stress, which is also abnormal in CKD and which may be reduced by vitamin D receptor agonists.[21-24]

We performed a randomized, placebo-controlled clinical trial to test whether paricalcitol (19-nor-1,25-$(OH)_2$-vitamin D_2, a vitamin D receptor agonist) improves glucose metabolism in non-diabetic persons with stage 3-4 CKD. Specifically, we hypothesized that paricalcitol, compared with placebo, would improve glucose tolerance and reduce oxidative stress, thereby providing rigorous data supporting diverse beneficial effects in stage 3-4 CKD. We also tested effects of paricalcitol on established and novel biomarkers of vitamin D metabolism.

Results

Participant characteristics

Twenty-two participants were enrolled in the study (Table 1). At baseline, mean age was 65.8 years, and mean values were 39.5 mL/min/1.73m^2 for estimated GFR, 106.4 mg/dL for fasting glucose, 30.7 ng/mL for 25-hydroxyvitamin D [25(OH)D], and 61.2 pg/mL for parathyroid hormone (PTH, geometric mean). Ten participants (45%) reported taking cholecalciferol supplements, and an additional four participants (18%) reported taking

multivitamins that may have contained cholecalciferol. No participant reported taking ergocalciferol, and only one participant reported taking a phosphorus binder.

Retention and adherence

All 22 participants received paricalcitol, and all 22 participants were included in intention-to-treat analyses (Figure 1). Of 11 participants assigned to placebo first, one participant was noted to have hypercalcemia 11 days into the paricalcitol treatment period; as specified in the study protocol, the study medication was discontinued and the final study visit was conducted the following day. Of 11 participants assigned to paricalcitol first, one participant was lost to follow-up after completing the paricalcitol treatment period. Adherence by pill count was 54% of expected for one subject during the placebo treatment period but 87-114% for the other 42 completed treatment periods.

Effects of paricalcitol on vitamin D metabolism

Paricalcitol had large effects on vitamin D metabolism, including suppression of circulating parathyroid hormone (PTH), $1,25(OH)_2D$, and $25(OH)D$ concentrations and increased circulating fibroblast growth factor-23 (FGF-23) and 24,25-dihydroxyvitamin D $(24,25(OH)_2D)$ concentrations (Table 2). Among the 10 participants assigned to paricalcitol first who went on to the placebo treatment phase, all paricalcitol effects on vitamin D metabolism were resolved by the end of the 8-week wash-out period.

Effects of paricalcitol on glucose metabolism

Geometric mean glucose area under the curve (AUC) was 20,817 mg/dL/min (range 16,387-30,842 mg/dL/min) after 8 weeks of treatment with paricalcitol and 21,139 mg/dL/min (range 16,322-29,135 mg/dL/min) after 8 weeks of treatment with placebo (Figure 2, Figure 3). The difference in glucose AUC comparing the end of the paricalcitol and placebo treatment periods, the primary study outcome, was -1.5% (95% confidence interval -5.9%, 3.2%, p=0.54). Adjusting for glucose AUC at the beginning of each treatment period, the difference in glucose AUC at the end of treatment was -1.2% (95% confidence interval -5.3%, 3.0%, p=0.78). Results were similar excluding from analysis the participant who developed hypercalcemia and the participant who was lost to follow-up prior to receiving placebo. The primary outcome did not vary within subgroups defined by key aspects of glucose or vitamin D metabolism, measured at baseline (Figure 4). Paricalcitol did not affect the insulin sensitivity index, the insulinogenic index, fasting plasma glucose or insulin concentrations, free fatty acid suppression, or urinary excretion of F2-isoprostanes (Figure 2, Table 2).

Adverse events

One participant developed hypercalcemia during paricalcitol treatment (serum calcium 11.2 mg/dL confirmed on two consecutive days, 10.0 mg/dL 4 weeks after discontinuing treatment). No other adverse event clearly related to study interventions was observed (Table 3).

Discussion

The effect of paricalcitol on glucose tolerance was robustly null in this study of non-diabetic stage 3-4 CKD. The cross-over study design and precise outcome ascertainment contributed to tight confidence intervals that exclude clinically relevant effects. No subset of participants was identified for which paricalcitol appeared to improve glucose tolerance. Moreover, paricalcitol did not change insulin sensitivity or the early insulin response to oral glucose (the biologic determinants of glucose tolerance), free fatty acid suppression (a measure of insulin action at the level of adipose tissue), or urinary F2-isoprostane excretion (a measure of oxidative stress). In contrast, paricalcitol had substantial effects on endogenous vitamin D metabolism, including the expected suppression of PTH along with less well-described increases in plasma FGF-23 concentration and decreases in plasma $1,25(OH)_2D$ and $25(OH)D$ concentrations, probably due in part to accelerated vitamin D catabolism.

Our results contrast with those of nine studies reporting that $1,25(OH)_2D$ administration improved glucose metabolism among hemodialysis patients.[4,13-20] Differences likely relate to the study population, the intervention, or both. First, renal $1,25(OH)_2D$ production may fall to a level that impairs glucose homeostasis in ESRD but not in stage 3-4 CKD. While effects of paricalcitol on glucose tolerance did not vary by baseline $1,25(OH)_2D$ concentration in our study, these $1,25(OH)_2D$ concentrations likely do not overlap with those observed in ESRD. Second, our study population was largely $25(OH)D$ replete, due in part to the 45% prevalence of vitamin D supplementation, whereas vitamin D supplementation is unlikely to have been as common in the older studies. Treatment with a vitamin D receptor agonist may not be beneficial among people with adequate $25(OH)D$. Third, our study administered paricalcitol rather than $1,25(OH)_2D$. Paricalcitol was created to reduce PTH concentration while minimizing hypercalcemia.[25] $1,25(OH)_2D$ has been hypothesized to improve glucose metabolism through mechanisms involving intracellular calcium signaling,[26] and it is possible that paricalcitol and $1,25(OH)_2D$ have differential effects on glucose metabolism. If so, the reduction in serum $1,25(OH)_2D$ observed with paricalcitol treatment may have counterbalanced any direct beneficial effect of paricalcitol on glucose metabolism. One recent study of hemodialysis patients reported no effect of intravenous paricalcitol on insulin sensitivity measured by euglycemic clamp, compared with cinacalcet.[27] Notably, that study included $25(OH)D$ repletion with ergocalciferol in its design and also administered paricalcitol, rather than $1,25(OH)_2D$.

Vitamin D receptor agonists reduce oxidative stress in animal-experimental models,[23] perhaps due to suppression of the RAS or improved insulin sensitivity. In our study, paricalcitol did not significantly reduce urinary excretion of F2-isoprostanes, a reliable biomarker of oxidative stress.[28] However, we cannot rule out effects of paricalcitol on other oxidative stress biomarkers.

Our study demonstrates clear effects of paricalcitol on endogenous vitamin D metabolism. In addition to suppressing serum PTH concentration, as observed in prior studies,[25,29,30] paricalcitol markedly increased serum FGF-23 concentration. This result is consistent with those of animal-experimental studies and two human studies of dialysis patients without placebo controls, in which FGF-23 concentrations rose substantially after treatment with

vitamin D receptor agonists.[31-35] $1,25(OH)_2D$ is known to directly stimulate osteoblast FGF-23 transcription as part of an endocrine feedback loop.[31-33,36] Interestingly, the large increase in FGF-23 occurred despite PTH suppression, which would be expected to lower FGF-23.[37,38] Together, these data suggest that vitamin D receptor agonist therapy, and by extension endogenous $1,25(OH)_2D$, is an important regulator of FGF-23 in CKD.

A surprising finding was that paricalcitol substantially reduced serum 25(OH)D concentration, probably by inducing 25(OH)D catabolism. Paricalcitol increased serum concentration of $24,25(OH)_2D$, the predominant product of 25(OH)D catabolism by the cytochrome P450 enzyme CYP24A1, which is also responsible for catabolism of $1,25(OH)_2D$.[39] The increase in $24,25(OH)_2D$ concentration occurred despite decreased 25(OH)D concentration, strongly suggesting increased CYP24A1 activity. Vitamin D receptor agonists are known to directly induce CYP24A1, which serves to prevent $1,25(OH)_2D$ intoxication. In addition, effects of paricalcitol on PTH (lowering) and FGF-23 (increasing) would be expected to augment renal CYP24A1 activity.[40] Serum concentration of $1,25(OH)_2D$, presumably generated through endogenous renal metabolism, fell even more markedly than that of 25(OH)D. This is probably due to both decreased $1,25(OH)_2D$ production and increased CYP24A1-mediated catabolism.

Our results highlight the current uncertainty in appropriate clinical use of vitamin D receptor agonists in CKD. Much promise for vitamin D receptor agonists has been generated by animal-experimental studies demonstrating remarkable effects on diverse metabolic outcomes coupled with observational human studies demonstrating associations of low circulating vitamin D metabolite concentrations with increased risks for kidney and cardiovascular disease and associations of vitamin D receptor agonist use with decreased mortality. [1-4,41-46] However, clinical trials, which provide the strongest evidence for clinical application, have not consistently validated these findings. In the VITAL study, paricalcitol modestly reduced albuminuria in advanced diabetic kidney disease,[29] but paricalcitol had no effect on left ventricular mass in the PRIMO study[30] or on glucose tolerance in our study. Moreover, each of these trials has focused on a specific intermediate outcome over relatively short-term follow-up, which is unlikely to capture beneficial or harmful effects on other targets. Given their diverse biologic effects, only a large, long-term clinical trial can adequately determine the risks and benefits of vitamin D receptor agonists in CKD.

Limitations of this study include the relatively homogenous study population and the lack of an active $1,25(OH)_2D$ comparator. Effects of paricalcitol on glucose metabolism among persons with established diabetes, who were excluded by design, may differ. Strengths include the randomized, placebo-controlled design, adequate power, and the assessment of intermediate outcomes that are relevant to patients with CKD and supported by prior studies of vitamin D receptor agonists.

In conclusion, paricalcitol did not improve glucose metabolism in non-diabetic stage 3-4 CKD. This study highlights the uncertain net clinical effect of vitamin D receptor agonist treatment in CKD, which can only be resolved with long-term trials targeting clinically relevant health outcomes.

Methods

Study population

Study subjects were recruited from Nephrology clinics at three medical centers associated with the University of Washington. Inclusion criteria included age 18 years; estimated GFR 15-59 mL/min/1.73m^2; and fasting serum glucose 100-125 mg/dL. Exclusion criteria included a clinical diagnosis of diabetes or use of glucose-lowering medications; history of maintenance dialysis or kidney transplantation; use within past 8 weeks of prednisone, immunosuppressive medications, or other medications known to strongly affect blood glucose; change in dose of any medication within 8 weeks; and serum calcium >10.1 mg/dL. The study was approved by the University of Washington Institutional Review Board, and all participants provided written informed consent. The study was registered with clinicaltirals.gov (NCT01003275).

Study intervention

The study was a cross-over trial with a total duration of 24 weeks. Each participant was allocated paricalcitol for 8 weeks and matching placebo for 8 weeks, separated by an 8-week washout period. The order of paricalcitol and placebo treatment periods was randomly assigned by the University of Washington Investigational Drug Services and was blinded to both participants and investigators. The active intervention was paricalcitol (19-nor-1,25-(OH)$_2$-vitamin D$_2$) 2 mcg daily by mouth. This dose was chosen because it reliably suppresses PTH with minimal risk of hypercalcemia.[25] The 8-week treatment duration was chosen because prior studies of hemodialysis patients consistently reported improvements in glucose metabolism within this time frame.[4] Participants were encouraged not to change their use of non-study medications during the course of the study.

Study outcomes

Study outcomes were measured at the beginning and end of each 8-week treatment period (4 measurements per participant). The primary study outcome was change in glucose tolerance, assessed as glucose AUC during a two-hour oral glucose tolerance test. Plasma samples were drawn -10, -5, -1, 10, 20, 30, 60, 90, and 120 minutes after oral administration of 75g glucose. Plasma samples were placed immediately in an ice-water slurry and centrifuged, aliquoted, and frozen at -80°C within 60 minutes. Additional plasma samples were drawn at -10, -5, 30, 60, and 120 minutes into vials containing orlistat (tetrahydrolipstatin) for measurement of free fatty acids.

Plasma glucose, insulin, and free fatty acid concentrations were measured at study end at the Northwest Lipid Research Laboratories, Seattle, WA. Glucose was measured using the glucose hexokinase method on a Roche Module P Chemistry autoanalyzer (Roche Diagnostics, Inc., Indianapolis, IN, inter-assay coefficient of variation [CV] 1.2-1.7%). Insulin was measured using a two site immune-enzymometric assay on the Tosoh 2000 auto-analyzer (CV 2.0-2.8%), calibrated to WHO IRP 66/304. Non-esterified free fatty acids were measured using reagents from Wako Diagnostics (Richmond, VA) on a Roche Hitachi Modular P analyzer (Roche Diagnostics, Inc., Indianapolis, IN, CV 3.7%).

Time 0 (fasting) concentrations were calculated as the mean of values from -10, -5, and -1 minutes to increase precision. Total glucose AUC was calculated using the trapezoidal method. Results were similar evaluating incremental glucose AUC. Insulin sensitivity index was calculated using the Matsuda formula: (10,000/square root of [time 0 glucose × time 0 insulin] × [mean glucose × mean insulin]), where mean glucose and insulin values are obtained from time 0 and 30, 60, 90, and 120 minutes.[47] Insulinogenic index, a measure of insulin response to glucose challenge, was calculated as change in plasma insulin concentration divided by change in plasma glucose concentration from 0 to 30 minutes.[48] Free fatty acid suppression was evaluated as percent difference from time 0.

24-hour urine samples were collected on ice. Albumin was measured immediately after collection using a turbidimetric assay. F2-isoprostanes were measured in urine aliquots stored at -80°C using gas chromatography-tandem mass spectrometry at Vanderbilt University.[28] Albumin and F2-isoprostane concentrations were indexed to urine creatinine concentration for assessment of treatment effect.

PTH was measured from fresh serum using a second generation immunoassay on a Beckman-Coulter DxI platform. Concentrations of 25(OH)D, 1,25(OH)$_2$D, and 24,25(OH)$_2$D were measured from serum stored at -80°C by immunoaffinity extraction and HPLC-mass spectrometry (Xevo TQ, Waters Corp., Milford, MA).[39,49] This method has no cross-reactivity with paricalcitol. Intact FGF-23 was measured from serum stored at -80°C by ELISA (Kainos Laboratories Inc., Tokyo, Japan).

Statistical analysis

All analyses were performed according to intention to treat, i.e. all available data were included regardless of adherence. Differences in the primary and secondary outcomes at the end of paricalcitol treatment compared with the end of placebo treatment were tested using the paired t-test. Highly skewed outcome variables were log-transformed prior to analysis, yielding differences on the relative scale. Values for the participant who did not complete the placebo treatment period were not included in summary statistics, but data from the beginning and end of the paricalcitol treatment period were used to multiply impute treatment effect. Results from the multiple imputed datasets were pooled using Rubin's rules.[50]

We evaluated for temporal trends in study outcomes, including the possibility of incomplete waning of treatment effect during the washout period, by testing changes in outcomes from the beginning of the first to second chronologic treatment period by assigned treatment order. Of all primary and secondary outcomes, only one displayed evidence of temporal trend: among participants assigned to placebo first, glucose AUC increased by 6.3% from the beginning of placebo treatment to the beginning of paricalcitol treatment (p=0.03 within the group assigned to placebo first, p=0.55 versus the group assigned to paricalcitol first). We therefore created a linear mixed effects model to test the difference in glucose AUC at the end of paricalcitol treatment versus the end of placebo treatment, adjusted for glucose AUC at the beginning of each treatment period. Random intercepts were included by participant to account for the crossover design.

Study power

We calculated that completion of the study by 20 participants would give 97% power to detect a 10% or greater difference in glucose AUC comparing the end of paricalcitol treatment to the end of placebo treatment. In comparison, intervention studies of cinnamon and sitagliptin have demonstrated reductions in glucose AUC of 10-26%.[51,52] Our calculations allowed for a type 1 error rate of 0.05 (two-sided) and assumed the intra-individual variation in glucose AUC observed in a previous study (reference supplemented with a personal communication from Dr. Utzschneider).[48] We enrolled 22 participants to allow for 10% non-completion.

Acknowledgments

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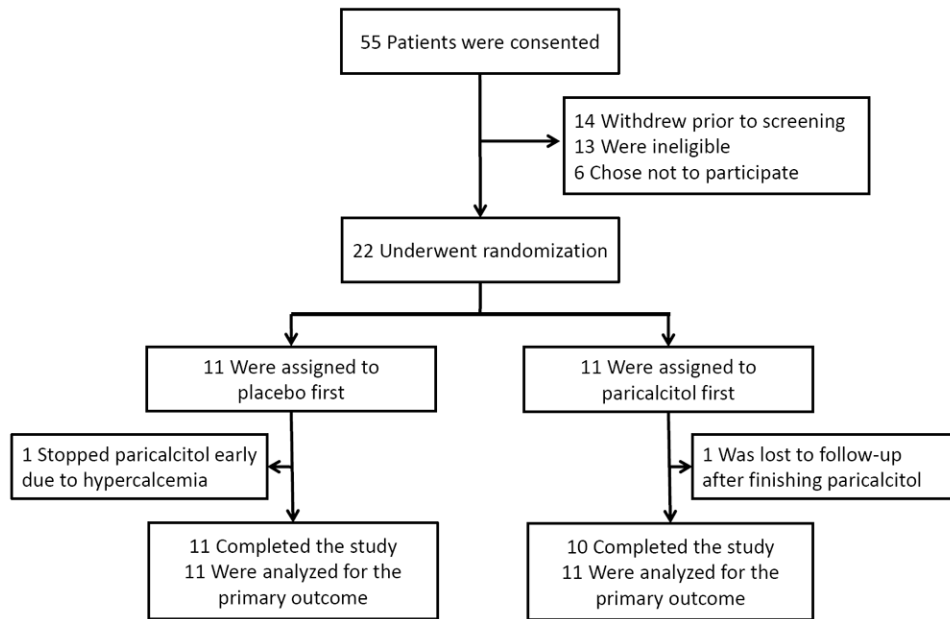
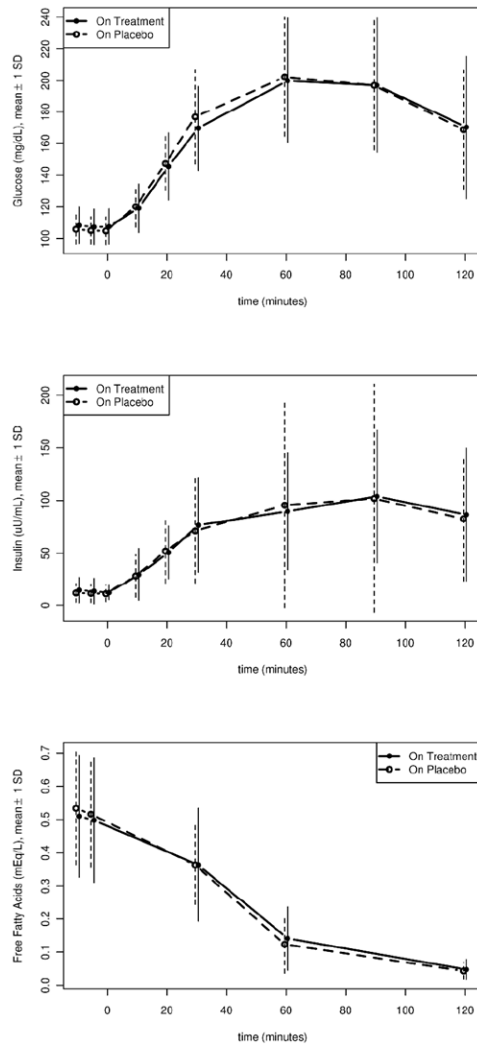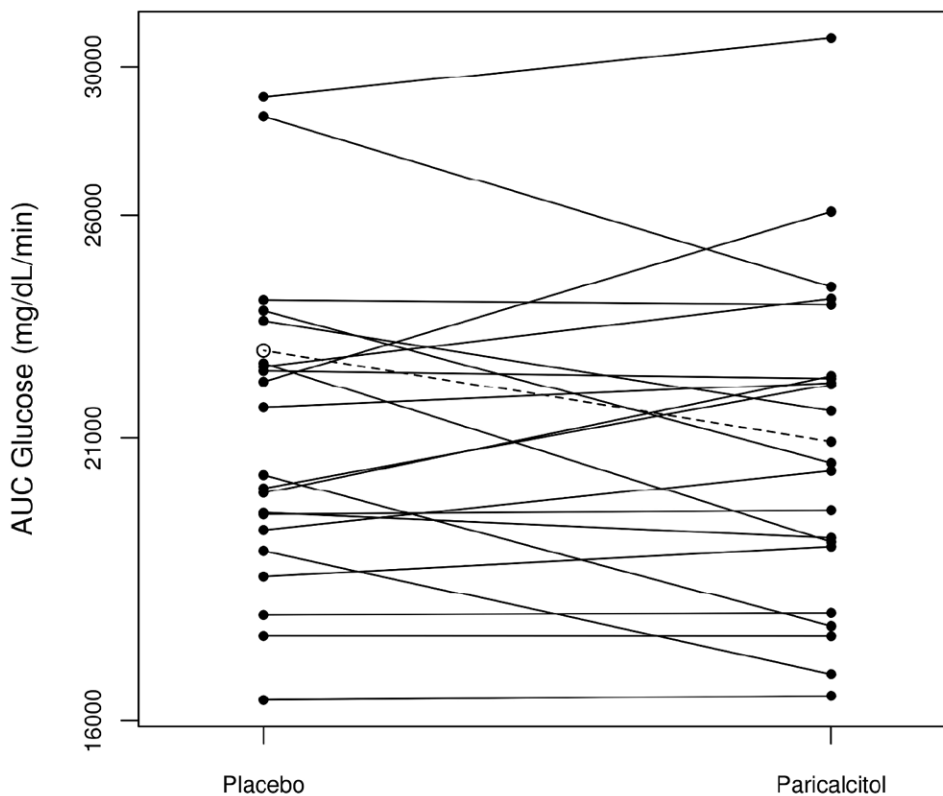**Figure 1. Enrollment, randomization, and follow-up of study participants**

Figure 2. Mean plasma concentrations of glucose (A), insulin (B), and free fatty acids (C) by treatment period

Mean ± SD are presented for each time point.

Figure 3. Effects of paricalcitol on glucose tolerance for each individual study participant
Glucose tolerance is measured as glucose area under the curve (AUC) from oral glucose tolerance tests. Individual glucose AUC values measured at the end of each participant's paricalcitol treatment period and the end of each participant's placebo treatment period. The open circle (with dotted line) represents glucose AUC at the beginning of the paricalcitol treatment period for the one participant who did not complete placebo treatment.
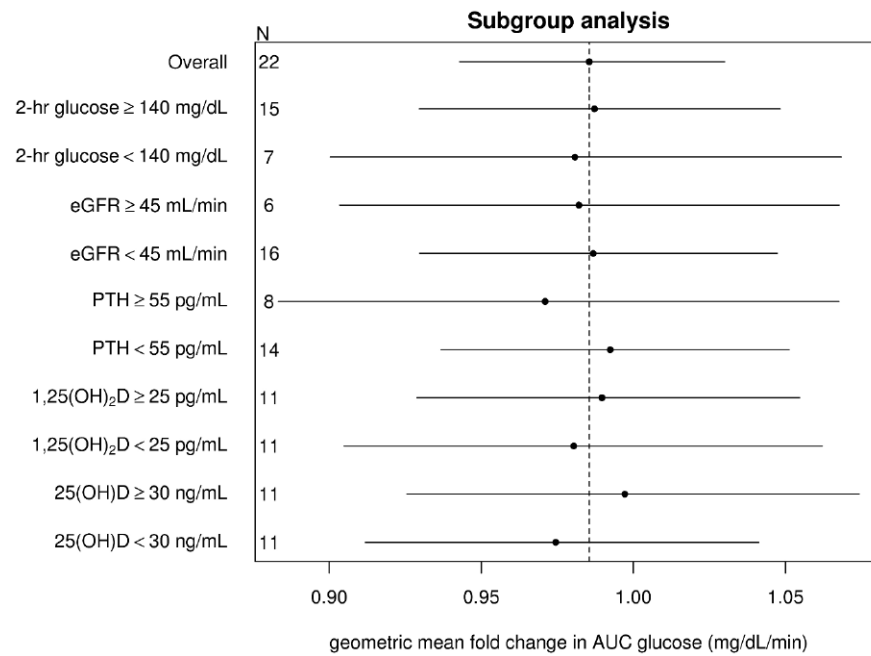
Figure 4. Effects of paricalcitol on glucose tolerance among subsets of participants defined by baseline characteristic

Geometric mean fold change in glucose area under the curve (AUC) during oral glucose tolerance tests, comparing values from the end of the paricalcitol treatment period to the end of the placebo period, are presented on the X axis with 95% confidence interval. Numbers of participants in each subgroup are listed on the left. eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; 1,25(OH)$_2$D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D.

Table 1

Baseline participant characteristics

	All participants	Paricalcitol first	Placebo first
N	22	11	11
Demographics			
Age (years)	65.8 (11.6)	66.0 (10.4)	65.5 (13.1)
Male sex	20 (90.1%)	10 (90.1%)	10 (90.1%)
Race			
Caucasian	17 (77.2%)	8 (72.7%)	9 (81.8%)
African American	3 (13.6%)	2 (18.1%)	1 (9.1%)
Asian	2 (9.1%)	1 (9.1%)	1 (9.1%)
Medical history			
Hypertension	21 (95%)	10 (91%)	11 (100%)
Cardiovascular disease	9 (41%)	4 (36%)	5 (45%)
Current smoking	3 (14%)	2 (18%)	1 (10%)
Medical treatment			
Antihypertensive medications	21 (95%)	10 (91%)	11 (100%)
RAAS inhibitors	18 (82%)	8 (73%)	10 (91%)
Vitamin D supplements	10 (45%)	5 (45%)	5 (45%)
Physical examination			
Body mass index (kg/m^2)	30.5 (7.9)	31.8 (10.5)	29.2 (4.1)
Systolic BP (mmHg)	131.7 (15.9)	132.3 (15.2)	131.1 (17.4)
Diastolic BP (mmHg)	76.6 (10.6)	77.1 (12.8)	76.2 (8.4)
Laboratory data			
Estimated GFR (mL/min/1.73m^2)	39.5 (11.7)	38.5 (11.6)	40.4 (12.3)
45-59	8 (36.4%)	4 (36.4%)	4 (36.6%)
30-44	9 (40.1%)	4 (36.4%)	5 (45.5%)
15-29	5 (22.7%)	3 (27.3%)	2 (18.2%)
Albumin excretion rate (mg/24 hr)	94.3 (6.6)	89.8 (8.1)	99.1 (5.8)
<30	7 (31.2%)	4 (36.4%)	3 (27.3%)
30-299	10 (45.5%)	4 (36.4%)	6 (54.5%)
300	5 (22.7%)	3 (27.3%)	2 (18.2%)
Fasting serum glucose (mg/dL)	106.4 (5.7)	105.7 (5.1)	107.1 (6.3)
Fasting plasma insulin (μU/mL)	14.4 (11.9)	16.9 (15.7)	12.0 (6.2)
2-hr OGTT glucose (mg/dL)	155.2 (33.2)	158.1 (30.7)	152.3 (36.9)
Parathyroid hormone (pg/mL)	61.2 (1.5)	73.8 (1.5)	50.6 (1.4)
25-hydroxyvitamin D (ng/mL)	30.7 (9.4)	28.6 (8.3)	33.0 (10.3)
Calcium (mg/dL)	9.4 (0.4)	9.6 (0.4)	9.3 (0.4)
Phosphorus (mg/dL)	3.72 (0.73)	3.93 (0.66)	3.51 (0.76)

	All participants	Paricalcitol first	Placebo first
Fibroblast growth factor-23 (pg/mL)	58.9 (1.6)	54.2 (1.7)	64.1 (1.6)

Data are N (%) for categorical variables; geometric mean (geometric SD) for albumin excretion rate, parathyroid hormone, and fibroblast growth factor-23; or mean (SD) for other continuous variables. OGTT = oral glucose tolerance test.

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Table 2

Effects of paricalcitol on glucose metabolism, oxidative stress, and vitamin D metabolism.

	Mean values		Difference		
	Paricalcitol	Placebo	Absolute difference (95% CI)	Percent difference (95% CI)	p-value
Glucose metabolism					
Glucose AUC (mg/dL/min)	20,817 (1.2)	21,139 (1.2)		-1.5 (-5.9, 3.2)	0.542
Insulin sensitivity index	3.16 (1.84)	3.31 (2.27)		-5.3 (-20.7, 13.2)	0.564
Insulinogenic index (mg/dL/μU/mL)	1023 (2.22)	970 (2.17)		5.4 (-20.2, 39.3)	0.705
Fasting plasma glucose (mg/dL)	108.0 (11.0)	105.7 (9.0)	2.3 (-1.3, 5.8)		0.219
Fasting plasma insulin (μU/mL)	13.4 (10.3)	13.2 (11.7)	0.2 (-2.5, 2.9)		0.895
Free fatty acid suppression (%)	70.7 (18.8)	73.8 (18.1)	-3.0 (-9.0, 3.0)		0.327
Urinary biomarkers					
F2-isoprostanes (mg/g) **	0.89 (0.46)	1.00 (0.48)	-0.12 (-0.28, 0.05)		0.170
Albumin (mg/g) **	51.5 (8.2)	60.5 (6.8)		-14.9 (-39.9 to 20.6)	0.314
Vitamin D metabolism					
Parathyroid hormone (pg/mL)	29.4 (2.3)	71.2 (1.9)		-58.6 (-69.5, -43.8)	<0.001
Fibroblast growth factor-23 (pg/mL)	118.4 (1.8)	68.1 (1.7)		73.7 (39.6, 116.1)	<0.001
1,25-dihydroxyvitamin D (pg/mL)	10.8 (6.2)	26.3 (12.6)	-15.6 (-20.5, -10.7)		<0.001
25-hydroxyvitamin D (ng/mL)	23.7 (7.3)	30.4 (11.2)	-6.7 (-10.2, -3.1)		0.001
24,25-dihydroxyvitamin D (ng/mL)	3.8 (2.2)	2.6 (1.8)	1.2 (0.7, 1.7)		<0.001
Calcium (mg/dL)	9.5 (0.6)	9.0 (0.3)	0.5 (0.3, 0.7)		<0.001
Phosphorus (mg/dL)	4.0 (0.7)	3.8 (0.7)	0.2 (-0.01, 0.5)		0.069

Mean values and differences in mean values are evaluated at the end of each treatment period. Mean (SD) values and absolute differences (in units specific to each outcome) are presented for fasting plasma glucose and insulin, free fatty acid suppression, urinary F2-isoprostanes, 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D, calcium, and phosphorus. Geometric mean (geometric SD) values and relative differences (percent differences) are presented for glucose area under the curve (AUC), insulin sensitivity index, insulinogeinc index, urinary albumin, parathyroid hormone, and fibroblast growth factor-23.

CI = confidence interval.

*
Primary study outcome

**
Urinary biomarkers expressed in mg per g creatinine

Table 3

Adverse events

	During/after paricalcitol treatment	During/after placebo treatment
Endocrine		
Hypercalcemia*	1	
Renal		
Elevated serum creatinine	1	
Fistula placement	1	
Renal artery stent	1	
Cardiovascular		
Dyspnea with palpitations and lightheadedness	1	
Dyspnea		1
Elevated blood pressure†	1	1
Bradycardia†	1	1
Musculoskeletal		
Low back pain	1	
Muscle cramps	1	
Paresthesias		1
Gout flare	1	
Other		
Fever	1	
Common cold**	1	3
Allergies**		2
Vertigo	1	
Rash*	1	
Cataract surgery		1
Skin cancer removal		1
Any adverse event	14	11

*
Hypercalcemia was the only adverse event deemed to be probably related to study interventions. Rash was deemed to be possibly related to study interventions.

**
Each episode of common cold and allergies was experienced by a separate participant.

†
One participant developed unique episodes of elevated blood pressure and bradycardia during each treatment period (4 separate events).