Paricalcitol Reduces Albuminuria and Inflammation in Chronic Kidney Disease
A Randomized Double-Blind Pilot Trial

Pooneh Alborzi, Nina A. Patel, Carla Peterson, Jennifer E. Bills, Dagim M. Bekele, Zerihun Bunaye, Robert P. Light, Rajiv Agarwal

Abstract—Vitamin D receptor activation is associated with improved survival in patients with chronic kidney disease, but the mechanism of this benefit is unclear. To better understand the effects of vitamin D on endothelial function, blood pressure, albuminuria, and inflammation in patients with chronic kidney disease (2 patients stage 2, remaining stage 3), we conducted a pilot trial in 24 patients who were randomly allocated equally to 3 groups to receive 0, 1, or 2 µg of paricalcitol, a vitamin D analog, orally for 1 month. Placebo-corrected change in flow mediated dilatation with a 1-µg dose was 0.5% and 0.4% with a 2-µg dose (P>0.2). At 1 month, the treatment:baseline ratio of high sensitivity C-reactive protein was 1.5 (95% CI: 1.1 to 2.1; P=0.02) with placebo, 0.8 (95% CI: 0.3 to 1.9; P=0.62) with a 1-µg dose, and 0.5 (95% CI: 0.3 to 0.9; P=0.03) with a 2-µg dose of paricalcitol. At 1 month, the treatment:baseline ratio of 24-hour albumin excretion rate was 1.35 (95% CI: 1.08 to 1.69; P=0.01) with placebo, 0.52 (95% CI: 0.40 to 0.69; P<0.001) with a 1-µg dose, and 0.54 (95% CI: 0.35 to 0.83; P=0.01) with a 2-µg dose (P<0.001 for between group changes). No differences were observed in iothalamate clearance, 24-hour ambulatory blood pressure, or parathyroid hormone with treatment or on washout. Thus, paricalcitol-induced reduction in albuminuria and inflammation may be mediated independent of its effects on hemodynamics or parathyroid hormone suppression. Long-term randomized, controlled trials are required to confirm these benefits of vitamin D analogs. (Hypertension. 2008;52:249-255.)

Key Words: chronic kidney disease ■ vitamin D ■ albuminuria ■ ambulatory blood pressure ■ inflammation ■ endothelial function

It is now well established that people with chronic kidney disease (CKD), who compose 11% of the US population, have a higher risk of cardiovascular diseases compared with those without CKD. The rate of progression of CKD is quite variable, and patients who have a greater urine protein excretion rate have, in general, a faster decline in renal function. Although substantial progress has been made to slow the progression of kidney disease, which is centered around interrupting the renin-angiotensin-aldosterone system and improving blood pressure (BP) control, the growing numbers of patients with CKD attest that these therapies have been insufficient to halt the epidemic of CKD.

Vitamin D therapy may reduce the progression of CKD and improve cardiovascular outcomes in patients with CKD.1 Active vitamin D deficiency is common, occurs early in the course of CKD, and is associated with cardiovascular risk factors such as albuminuria, diabetes mellitus, and lower glomerular filtration rate (GFR).2 Among incident hemodialysis patients, vitamin D deficiency is common and is associated with increased early mortality.3 In prevalent hemodialysis patients, vitamin D use is associated with improved survival.1,4 The mortality benefits are greater with the newer vitamin D analogs, paricalcitol or doxercalciferol, when compared with calcitriol.5-7 It must be pointed out that there are no adequately powered randomized, controlled trials to allow a cause-and-effect relationship of these observations.

Although current activated vitamin D therapies are approved for treating secondary hyperparathyroidism, a large body of experimental data in animals confirms the effects of vitamin D that extend beyond mineral metabolism.8 For example, studies in mice have shown that vitamin D may delay the progression of CKD through prevention of interstitial fibrosis, mesangial proliferation, and podocyte loss.9 Vitamin D receptor knockout mice have an activated renin-angiotensin system, are more hypertensive, and have increased cardiac hypertrophy.10 Dahl salt-sensitive rats treated with a high-salt diet and paricalcitol experience less left ventricular hypertrophy. This cardiovascular protection is independent of arterial BP changes but associated with reduced plasma brain natriuretic peptide levels, as well as...
cardiac mRNA expression of brain natriuretic peptide, atrial natriuretic factor, and renin.11 Thus, the proposed mechanisms for beneficial effects of vitamin D therapy may include direct hemodynamic effects,10,12 as well as nonhemodynamic effects. The latter include regulation of cell proliferation, apoptosis, angiogenesis, and anti-inflammatory, antithrombogenic, fibrinolytic, and antiatherogenic effects.11,13–15

A large gap exists in our knowledge between epidemiological studies in humans that demonstrate improved outcomes with vitamin D use4,5 and observations in preclinical studies demonstrating the pleiotropic effects of vitamin D.11 To explore the provenance of epidemiological outcomes in patients with CKD, we conducted a pilot double-blind, placebo-controlled trial to determine whether the use of paricalcitol leads to improvement in markers that are linked to the progression of CKD. Because both hemodynamic and inflammatory mechanisms are involved in the progression of CKD, we studied both pathways in this exploratory trial. Specifically, we measured endothelial function, 24-hour ambulatory BP, and GFR to represent hemodynamic effects and serum C-reactive protein concentration, a marker of inflammation, to represent nonhemodynamic effects of this vitamin D analog.

Methods

Participants

Between November 2006 and June 2007, we recruited patients from the renal clinics at Wishard Memorial Hospital and Richard L. Roudebush Veterans’ Affairs Medical Center (Indianapolis, Ind). Patients were considered eligible for the study if they were >18 years, had CKD with an estimated GFR >30 mL/min, and were on a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for >1 month.16 Patients with poorly controlled hypertension (≥180/110 mm Hg), unstable BP control (change in BP medication within 1 month), poorly controlled diabetes mellitus (hemoglobin A1c of >11%), hyperphosphatemia (>6 mg/dL), or hypercalcemia (>10 mg/dL) or those taking vitamin D or its analogs were excluded.

The study protocol was approved by the institutional review boards and the Veterans’ Affairs Research and Development Committee, and all of the patients provided written informed consent.

Study Design

Randomization was carried out by means of a computer-generated sequence using blocks of 3. Concealed envelopes were kept by a hospital pharmacist, who assigned participants to their groups. Patients were randomly assigned in 3 equal proportions to receive a placebo or 1 μg or 2 μg of paricalcitol. Drug, including placebo, provided by Abbott, consisted of capsules that were identical in appearance to the active drug. Participants, those administering the intervention, and those assessing the outcomes were blinded to the group assignment.

Study Procedures

Baseline measurements were performed on 2 consecutive days in a research laboratory. After obtaining a medical history and performing a physical examination, we measured BP and ECG. Blood samples were collected for measurement of complete blood cell count and routine chemistries in the hospital laboratory. Serum or plasma was frozen at −86°C until it was analyzed for more specialized assays.

We then initiated a continuous subcutaneous infusion of iothalamate for the measurement of GFR, an ambulatory BP monitor for BP measurement, and dispensed a jug to collect 24-hour urine and asked the patient to return the following day. On the following day, brachial artery flow-mediated dilatation (FMD) was measured with an ultrasound by a sonographer.

Patients underwent random assignment on the second day, and the study medication was dispensed after baseline measurements were completed. Patients were instructed to take the medication by mouth 2 hours after their evening meals. A safety visit was scheduled 1 week after starting the study medication to monitor the calcium and phosphorus concentrations and to elicit any adverse events. The protocol specified withdrawal from the trial if serum calcium exceeded 11 mg/dL. After 1-month exposure to the drug, baseline procedures were repeated, as reported above on 2 consecutive days. Two weeks after the medication was stopped, all of the baseline tests, except FMD, were repeated, and the patient was discharged from the study.

GFR Measurement

An outpatient continuous infusion of iothalamate was used to measure GFR.17 On the first visit, a baseline plasma sample was drawn. Then a 1-mL bolus of iothalamate (Conray 60, Mallinckrodt Medical Inc) was injected intravenously. A subcutaneous catheter for infusion of iothalamate was inserted in the abdominal subcutaneous tissue. Iothalamate was infused at a constant rate of 125 μL/h through an insulin pump (model 506 or 507, MiniMed Inc). Approximately 24 hours after the start of the infusion, the subjects returned to the research laboratory. The insulin pump was repleted with iothalamate. An intravenous catheter was placed in the forearm, and 4 blood samples were obtained at 20-minute intervals for measurements of plasma iothalamate by high-performance liquid chromatography.18,19 Plasma clearance of iothalamate was calculated by dividing the infusion rate by the geometric mean of the plasma iothalamate concentration. Plasma iothalamate clearances have a coefficient of variation of 7.7% when measured 4 months apart.17

Ambulatory BP Monitoring

Ambulatory BPs were recorded every 20 minutes during the day (6 AM to 10 PM) and every 30 minutes during the night (10 PM to 6 AM) using a SpaceLab 90207 ABP monitor (SpaceLabs Medical Inc) in the nondominant arm. Accuracy of ambulatory BP recordings was confirmed against auscultated BP. Hourly averages were calculated, and the average of these averages represented the mean systolic and diastolic BPs.

Flow-Mediated Dilatation

FMD was performed as noted in the supplementary Methods (please see the data supplement online at http://hyper.ahajournals.org). In normal healthy volunteers, we found FMD to be 12.9% with a within-subject SD of 0.93% and between-subject SD of 1.77%. Thus, test-retest coefficient of variation was 7.2% in our laboratory.

Urine Albumin and Creatinine Determination

Total intact albumin was determined by a high-performance liquid chromatography–based assay (Accumax, AusAm Biotechnologies, Inc). This assay reduces the potential for false-negative results that may arise with antibody-based assays for albumin that fail to detect all of the intact albumin in the urine.20 Urinary creatinine concentration was determined using an end-point spectrophotometric method with an alkaline-picolate solution.

Biochemical Assays

Biochemical assays were performed using a commercial laboratory (Labcorp) Intact parathyroid hormone (PTH) and 25-hydroxy vitamin D were measured using immunochromeluminometric assays, high-sensitivity C-reactive protein (hsCRP) by latex immunoturbidimetry, and 1,25 dihydroxy vitamin D by radioimmunoassay.

Primary and Secondary End Points

The prespecified primary end points were endothelial function as measured by FMD and inflammation as measured by hsCRP after 1 month of therapy. The secondary end points were to assess the...
hemodynamic effects as assessed by ambulatory BP monitoring, GFR, and urinary albumin excretion.

Statistical Analysis
Because this was a pilot study, we selected a convenience sample of 24 participants, and we did not perform power calculations to determine minimal sample size. To compare baseline characteristics between groups, we used a 1-way ANOVA. Categorical data were analyzed using the χ² test. A generalized estimating equation model was fitted to analyze the effect of the drug compared with placebo during exposure and on withdrawal.21 This statistical model uses a repeated-measures design to account for correlated observations. Robust estimates were calculated using the Huber-White sandwich estimator.22 To approximate a normal distribution, the 24-hour urine albumin:creatinine ratio, intact PTH, and hsCRP were log transformed before analysis. All of the analyses were performed according to the intention-to-treat principle. Statistical analysis was performed using Stata 10.0 (Stata Corp). Significance was set at 2-sided P value of <0.05.

Results
A total of 169 patients were assessed for eligibility, of which 145 were excluded (Figure 1). Twenty-four patients were randomly assigned, of which 22 completed the study. Two patients, 1 from the placebo group and another from the 1-µg paricalcitol group, did not complete the study (details are provided at the end of the Results).

Baseline characteristics of the patients are listed in Table 1. Each patient was taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. No significant difference in baseline characteristics was present among the 3 groups.

The baseline level of FMD in the 3 groups was well matched. After exposure to paricalcitol or placebo, no differences in FMD emerged at 1 month. The mean change in FMD in the group receiving active drug was <0.5% and not clinically meaningful. Likewise, no changes in vascular smooth muscle function were observed (please see Table S1).

Table 2 and Figure 2 show the results of the inflammation marker. Sixty percent of our patients had an elevated baseline hsCRP (>3 mg/L). After 1 month, the placebo group had 1.5 times the baseline hsCRP, whereas the 1-µg group had 0.8 times the baseline hsCRP, and 2 µg had 0.5 times the baseline hsCRP (Figure 2). Two weeks after withdrawing the drug, the hsCRP level in the placebo group was 0.8 times the end-treatment level, the 1-µg group was 0.7 times the end-treatment level, and the 2-µg group was 1.7 times the end-treatment level. The rebound in hsCRP in the 2-µg group did not reach statistical significance (P=0.15). Although the width of the 95% CIs associated with these mean changes reflects the large variability in this biomarker and limits the power to detect a true effect on inflammation, the changes between groups after drug exposure were statistically significant (P=0.048 for between-group changes at 1 month).

Secondary outcomes consisted of changes in BP, GFR, and albuminuria. No significant differences emerged in the change of BP, either systolic or diastolic, after treatment or after washout. In fact, we observed a fall of 5.3 mm Hg in systolic BP with placebo (P=0.02 for within group change) but an increase of 2.5 mm Hg with 1-µg paricalcitol and 4.8 mm Hg with 2-µg paricalcitol, although the differences were not statistically significant between groups (P=0.25). A similar trend was seen with diastolic BP (Table S2).

The placebo group tended to have more albuminuria, although this did not reach statistical significance for between-group comparisons (P=0.08; Table S3). After 1 month, the placebo group had 1.35 times the baseline urinary albuminexcretion.
times the end-treatment level, the 1-µg group was 1.03 times the end-treatment level, and the 2-µg group was 1.38 times the end-treatment level. The rebound in urinary albumin excretion in the 2-µg group did not reach statistical significance ($P=0.10$). Although the 95% CIs associated with these mean changes were wide, reflecting the large variability in urinary albumin excretion and limited power to detect a true effect on albuminuria, the changes between groups after drug exposure were statistically significant ($P=0.0005$ for between-group changes at 1 month).

Although our recruitment criteria specified estimated GFR of ≥30 mL/min, 3 patients had measured GFR that was lower at 24.0, 26.6, and 27.3 mL/min, respectively. There was baseline imbalance in GFR; the placebo group had the highest GFR, and the 1-µg group had the lowest. However, at 1 month, there was a 5.6-mL/min fall in GFR in the placebo group, 6.9-mL/min increase in GFR in the 1-µg group, and 5.3-mL/min increase in GFR in the 2-µg group ($P=0.26$ for between-group differences in the 4-week change). Washout for 2 weeks only led to minimal changes in GFR (Table S4).

Hyperparathyroidism was not an entry criterion, and we were unable to detect statistically significant reductions in PTH levels at 1 month (Table S5). All of our study participants had baseline 25-OH vitamin D levels <30 ng/mL, and 43% had a level <10 ng/mL (Table S5)

One patient in the 1-µg paricalcitol group dropped out of the study 1 month after random assignment because of acute renal failure secondary to congestive heart failure and pericardial effusion. Another patient in the placebo group refused to complete the study because of mild abdominal pain 1 week after random assignment. Numbers of adverse events were similar between the different arms. No adverse events were noted to be definitely treatment related.

### Discussion

The key findings of this pilot double-blind, randomized, controlled trial are that short-term exposure to paricalcitol results in the following: (1) no significant improvement in endothelial function; (2) an anti-inflammatory effect; (3) 50%Albumin excretion, whereas the 1-µg group had 0.52 times the baseline level and 2 µg had 0.54 times the baseline albumin excretion rate (Figure 3). Two weeks after washout, urinary albumin excretion in the placebo group was 1.02

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Paricalcitol Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 µg/d</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>8</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.4±12.4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>35.4±7.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Past</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Never</td>
<td>2 (25)</td>
</tr>
<tr>
<td>CKD duration, y</td>
<td>5.1±5.0</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Etiology of CKD, n (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.5±1.8</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9±0.4</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.3±0.4</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>3.4±0.7</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>44.0±12.0</td>
</tr>
<tr>
<td>BP medications, n</td>
<td>2.9±1.1</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise specified.

### Table 2. Change in Inflammation Marker (hsCRP, mg/L)

<table>
<thead>
<tr>
<th>hsCRP (mg/L)</th>
<th>Paricalcitol Dose</th>
<th>0 µg/d</th>
<th>1 µg/d</th>
<th>2 µg/d</th>
<th>P Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>5.4</td>
<td>2.4</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>2.2 to 13.1</td>
<td>1.2 to 4.5</td>
<td>1.7 to 11.0</td>
<td>0.037</td>
</tr>
<tr>
<td>After treatment for 1 month</td>
<td></td>
<td>8</td>
<td>1.9</td>
<td>2.3</td>
<td>0.13</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>3.9 to 16.6</td>
<td>0.6 to 6.4</td>
<td>0.9 to 6.2</td>
<td>0.048</td>
</tr>
<tr>
<td>After washout</td>
<td></td>
<td>6.1</td>
<td>1.9</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>3.0 to 12.4</td>
<td>0.7 to 4.9</td>
<td>1.2 to 12.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean change treatment/baseball</td>
<td></td>
<td>1.5</td>
<td>0.8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.1 to 2.1</td>
<td>0.3 to 1.9</td>
<td>0.3 to 0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>P within group</td>
<td></td>
<td>0.02</td>
<td>0.62</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Mean change washout/treatment</td>
<td></td>
<td>0.8</td>
<td>0.7</td>
<td>1.7</td>
<td>0.81</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.4 to 1.3</td>
<td>0.3 to 1.6</td>
<td>0.8 to 3.4</td>
<td></td>
</tr>
<tr>
<td>P within group</td>
<td></td>
<td>0.32</td>
<td>0.37</td>
<td>0.15</td>
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</table>

Analyses were performed on log-transformed hsCRP concentrations.
reduction in albuminuria; and (4) that these changes are not attributable to changes in BP, GFR, or PTH concentrations. Thus, the anti-inflammatory and antialbuminuric effects appear to be mediated by nonhemodynamic, non-PTH mechanisms.

Vitamin D receptor stimulation can influence a number of genes associated with endothelial function and regeneration. For example, Wu-Wong et al. showed that paricalcitol altered the expression of 2 key receptors and 1 enzyme important for endothelial function. These include increased endothelin B receptor expression, which, in turn, increases NO synthesis; reduced oxytocin receptor expression, which causes vasoconstriction; and increased cyclooxygenase expression, which causes vasodilatation. In patients with end-stage renal disease, both vitamin D and active vitamin D serum concentrations are directly associated with FMD. Human endothelial cells have 1-α-hydroxylase, the enzyme responsible for vitamin D activation, and its level is increased

Figure 2. hsCRP in the 3 groups. hsCRP increased by 50% in the placebo group and decreased by 20% in the 1-µg paricalcitol group and 30% in the 2-µg paricalcitol group. One patient in the 1-µg paricalcitol group developed acute renal failure and a very high hsCRP level.

Figure 3. Twenty-four-hour albumin excretion rate in the 3 groups. Albuminuria increased by 35% in the placebo group and decreased by 48% in the 1-µg paricalcitol group and 46% in the 2-µg paricalcitol group.
in the presence of inflammatory cytokines. From this it follows that vitamin D receptor activation may result in improved endothelial function. However, we were unable to demonstrate a change in either endothelium-dependent or endothelium-independent vasodilatation with paricalcitol use. Longer-term and larger studies are needed because the CIs are wide and we cannot exclude a true effect.

Activated vitamin D has potent anti-inflammatory effects. For example, vitamin D reduces production of the T-helper type 1 cytokines interleukin-2, interferon-γ, and tumor necrosis factor-α and suppresses inflammatory macrophage reactions. In healthy British Bangladeshi adults, vitamin D deficiency was associated with elevated levels of C-reactive protein, and supplementation of this vitamin led to a 23% reduction in C-reactive protein concentration at 1 year. All of our study subjects were vitamin D deficient (<30 ng/mL). The majority (60%) of our patients had an elevated baseline hsCRP level, indicating subclinical inflammation. The magnitude and rapidity of improvement in hsCRP were impressive.

Arterial BP is closely linked to vitamin D concentration. The prevalence of hypertension and median level of systolic and diastolic BP increase with increasing latitude and are thought to be related to reduced sun exposure and vitamin D deficiency. An inverse relationship is seen between systolic BP and serum calcitriol concentration. Measured and diet-predicted 25-hydroxy vitamin D levels are related to incident hypertension; the hazard ratio for incident hypertension was 6.13 when measured 25-hydroxy vitamin D was <15 ng/mL compared with those with >30 ng/mL. A randomized, controlled trial found a significant reduction in systolic BP when 145 elderly women were supplemented with either vitamin D and calcium (mean reduction in systolic BP: 13.1 mm Hg) compared with calcium alone (mean reduction in systolic BP: 5.7 mm Hg). Finally, calcitriol is a negative endocrine regulator of the renin-angiotensin system in mice. Vitamin D receptor null mice were shown to have a 3.0-fold higher renin level, 2.5-fold higher angiotensin level, and 20-mm Hg higher systolic BP compared with vitamin D receptor-positive mice. Despite biological plausibility, we were unable to show any significant change in the systolic or diastolic BPs among the 3 groups. In fact, there was a statistically significant reduction in BP in the placebo group and a small but insignificant rise in BP with paricalcitol. There are several reasons possible for the lack of BP response. Blocking the renin-angiotensin system could be the mechanism by which vitamin D controls hypertension. But all of our participants were taking either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Another reason that we were not able to observe a reduction in BP may have been that BP of our patients was already well controlled; only 26% of our population had uncontrolled BP as defined by ambulatory BP ≥135/85 mm Hg. Another possible reason might be the short duration of follow-up. Despite the small size of the study, the BP findings are important because the change in albuminuria cannot be accounted for by BP. To further evaluate the hemodynamic effects of paricalcitol, we measured the GFR by iothalamate clearance at baseline, after treatment, and after washout. Again we were not able to demonstrate any meaningful changes in GFR on treatment or withdrawal of the drug. Thus, the fall in albuminuria cannot be ascribed to changes in GFR.

Vitamin D deficiency occurs early in the course of kidney disease, which is not surprising given that the renal tubule is the site of active vitamin D synthesis. However, the vitamin D receptor is downregulated in early stages of renal fibrosis; thus, deficiency of vitamin D signaling is magnified. Active vitamin D, other than serving as a ligand for the vitamin D receptor, also restores vitamin D receptor expression. It is not surprising, therefore, that paricalcitol decreases interstitial fibrosis and mesangial proliferation in the kidneys of experimental animals. Supplementation of active vitamin D in a subtotal nephrectomy model in mice leads to less podocyte injury, decreased podocytes loss, and abrogation of podocyte hypertrophy, findings that may also explain less pronounced albuminuria and glomerulosclerosis. Given this background, the reduction in albuminuria seen in our trial is plausible. Because the reduction in albuminuria occurred independent of changes in GFR or BP, it appears that the reduction was mediated not by hemodynamic mechanisms but through podocyte repair or repair of tubulointerstitial injury. Our data extend the observations of a posthoc analysis of a double-blind, controlled study that demonstrates a reduction in dipstick proteinuria in patients with stage 3 and 4 kidney disease treated with paricalcitol.

Our study did not show a decrease in PTH in subjects treated with either dose of paricalcitol. We did not require patients to have elevated PTH to participate in the study. Thus, it would be difficult to reduce a relatively normal PTH with paricalcitol over 1 month. The inability to observe the effect of active vitamin D on the parathyroid gland could be because of our small sample size and heterogeneity in PTH reduction. Because we saw no appreciable effect on plasma PTH concentration, it appears that the reductions in albuminuria and hsCRP were independent of the effect of paricalcitol on mineral metabolism.

The major strength of our study is that it is the first randomized, placebo-controlled trial examining the effects of paricalcitol on endothelial dysfunction, BP, GFR, and albuminuria. We used the most accurate and noninvasive methods to measure outcomes in our study. Instead of relying on clinic BP measurements, we obtained accurate 24-hour BP readings. Also, instead of using an estimated GFR, we measured GFR by iothalamate infusion, which is more precise. The limitations of our trial include the small sample size and the limited duration of exposure to the vitamin D receptor activator. This study was not powered to provide definite answers to our questions; the study was designed simply to detect a signal if paricalcitol mediates its effects by hemodynamic or nonhemodynamic pathways.

**Perspectives**

This study was not able to show an improvement in endothelial function but a reduction in inflammation and albuminuria within 1 month after treatment with paricalcitol in patients with CKD despite use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. These benefits were not attributable to improvement in ambulatory BP, fall in GFR, or improvement in PTH. Randomized, controlled trials with paricalcitol are under way to demonstrate whether paricalcitol will have antiproteinuric or cardioprotective
effects in patients with CKD. In 1 such trial, reduction in albuminuria from baseline to 24 weeks is the primary end point (www.clinicaltrials.gov identifier NCT00421733), whereas in another the change in left ventricular mass index assessed by cardiac MRI over 48 weeks is the primary end point (www.clinicaltrials.gov identifier NCT00497146). Both of these trials were done in patients with CKD and should provide better evidence (or lack thereof) for cardiovascular and renal protection.

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Disclosures

R.A. serves on the speaker bureau of Abbott Pharmaceuticals and on the steering committee of clinical trials using paricalcitol supported by Abbott Pharmaceuticals. The remaining authors report no conflicts.

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