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Paricalcitol Versus Ergocalciferol for Secondary Hyperparathyroidism in CKD Stages 3 and 4: A Randomized Controlled Trial

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Background: The efficacy of 25-hydroxyvitamin D (25(OH)D) supplementation versus vitamin D receptor activators for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) stages 3 or 4 and vitamin D deficiency is unclear.

Study Design: Randomized controlled trial.

Setting & Participants: 80 patients with CKD stages 3 or 4, 25(OH)D level <30 ng/mL, and SHPT in a single medical center.

Intervention: Ergocalciferol, 50,000 units, titrated to achieve serum levels ≥30 ng/mL versus paricalcitol, 1 or 2 μg/d, for 16 weeks.

Outcomes: The occurrence of 2 consecutive parathyroid hormone (PTH) levels decreased by at least 30% from baseline. All analyses were intention to treat.

Results: Baseline characteristics in the 2 groups were similar. 21 patients (53%) on paricalcitol and 7 patients (18%) on ergocalciferol treatment achieved the primary outcome measure (P = 0.002). After 16 weeks, PTH levels did not decrease significantly in patients receiving ergocalciferol, but were decreased significantly in those treated with paricalcitol (mean estimate of between-group difference over 16 weeks of therapy, 43.9 pg/mL; 95% CI, 11.2-76.6; P = 0.009). Serum 25(OH)D levels increased significantly after 16 weeks in only the ergocalciferol group, but not the paricalcitol group (mean estimate of between-group difference over 16 weeks of therapy, 7.08 ng/mL; 95% CI, 4.32-9.85; P < 0.001). Episodes of hyperphosphatemia and hypercalcemia were not significantly different between the 2 groups.

Limitations: Lack of blinding and use of surrogate end points.

Conclusions: Paricalcitol is more effective than ergocalciferol at decreasing PTH levels in patients with CKD stages 3 or 4 with vitamin D deficiency and SHPT.

INDEX WORDS: Parathyroid hormone; vitamin D; ergocalciferol; paricalcitol; clinical trial.

Secondary hyperparathyroidism (SHPT) is a common finding in patients with chronic kidney disease (CKD) of all stages.1 Its clinical importance has been emphasized by numerous studies showing an association between higher parathyroid hormone (PTH) levels and adverse clinical outcomes in patients with both end-stage renal disease2-5 and non–dialysis-dependent CKD.6 The pathogenesis of SHPT is complex.7,9 and among the various causes responsible for its development, abnormal vitamin D metabolism features prominently.1,10,11 Insufficient and deficient serum levels of 25-hydroxyvitamin D (25(OH)D) are common in the general population12 and patients with CKD1,13 and have been linked to elevated PTH levels irrespective of kidney function.14 This association is compounded in patients with CKD by abnormal 1α hydroxylation caused by decreased functioning kidney mass and elevated fibroblast growth factor 23 levels,15 leading to a progressive decrease in serum levels of 1,25-dihydroxyvitamin D (1,25(OH)2D).1,16 which is the active moiety responsible for the physiologic actions of vitamin D, and deficiencies of which also have in turn been linked to higher mortality in patients with end-stage renal dis-
ease.\textsuperscript{13} Such a complex pathophysiologic process offers opportunities for therapy by intervening at various points along the chain of events leading to SHPT. Given the compromised ability of patients with advanced CKD to renally convert 25(OH)D to 1,25(OH)\textsubscript{2}D, vitamin D–based interventions traditionally have been focused on active vitamin D (calcitriol)\textsuperscript{17} and its various analogues,\textsuperscript{18} which provided vitamin D receptor activation with reduced rates of metabolic complications, such as hypercalcemia or hyperphosphatemia.\textsuperscript{19–21} and also have been associated with lower mortality in patients with CKD of all stages.\textsuperscript{22,23} The more recent understanding of vitamin D effects mediated by tissue-level (paracrine) conversion of 25(OH)D to 1,25(OH)\textsubscript{2}D\textsuperscript{24} has resulted in a re-evaluation of the tenet that patients with little or no kidney function cannot effectively use 25(OH)D. Because supplementation of 25(OH)D with oral supplements such as cholecalciferol or ergocalciferol is inexpensive and safe, there has been increasing interest in using these agents as first-line treatment of SHPT in patients with CKD and 25(OH)D insufficiency or deficiency.\textsuperscript{25} The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines made an opinion-based recommendation to correct low 25(OH)D levels as a first step toward treating SHPT in patients with nondialysis-dependent CKD, with subsequent application of vitamin D receptor activators (VDRAs) if this approach fails.\textsuperscript{26} The effectiveness of this strategy has been uncertain due to many open questions about what the optimal agent (ergocalciferol vs cholecalciferol) and optimal dose and dosing interval are and, most importantly, due to a lack of conclusive evidence regarding the efficacy of these agents vis a vis VDRAs in suppressing SHPT.\textsuperscript{25} Perhaps the biggest impediment to determining a most effective and safe vitamin D–based intervention for SHPT is the lack of prospective clinical trials comparing head-to-head the effects of 25(OH)D supplementation with VDRAs. We conducted a single-center randomized controlled study to compare the effects of ergocalciferol with those of paricalcitol in treating SHPT in patients with stage 3 or 4 CKD.

**METHODS**

**Study Design**

This was an open label, single center, randomized, active comparator, controlled study comparing the effects of vitamin D replacement with oral ergocalciferol versus paricalcitol on PTH levels in patients with stage 3 or 4 CKD and vitamin D deficiency or insufficiency. The study was approved by the Institutional Review Board at the Salem Veterans Affairs Medical Center. Study participants were enrolled from patients at the Salem Veterans Affairs Medical Center between August 2009 and September 2010. The main inclusion criteria were estimated glomerular filtration rate of 15-60 mL/min/1.73 m\textsuperscript{2} according to the isotope-dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, serum intact PTH (iPTH) level >75 pg/mL, and serum 25(OH)D level <30 ng/mL. Detailed inclusion and exclusion criteria are shown in Item S1. Patients were prescreened by reviewing electronic medical records, and those deemed eligible were invited to participate. After informed consent, patients who agreed to participate underwent 2 screening evaluations, as shown in Fig 1. Patients who satisfied all the inclusion and none of the exclusion criteria at the end of the screening period were block randomly assigned 1:1 after stratification by race and CKD stage to either oral paricalcitol (Zemplar; Abbott Laboratories, www.abbott.com) or ergocalciferol using a computer-generated allocation sequence that was delivered to the person performing the treatment allocation in sequentially numbered sealed envelopes. Patients randomly assigned to paricalcitol treatment received 1 μg once daily if serum iPTH level was <500 pg/mL or 2 μg once daily if iPTH level was $\geq$500 pg/mL without further titration for a total duration of 16 weeks. Because none of the enrolled patients had a PTH level >500 pg/mL, all patients in this arm received 1 μg of paricalcitol daily. Patients randomly assigned to ergocalciferol received medication dosed according to their baseline 25(OH)D level, as recommended by KDOQI,\textsuperscript{26} but with modifications to facilitate the correction of 25(OH)D levels that were measured every 4 weeks (Item S2). Adherence to the prescribed medication regimens was monitored by performing pill counts every 4 weeks.

**Measurements**

After treatment allocation, patients were assessed every 4 weeks with recording of any adverse events, assessment of medication adherence, and measurement of serum iPTH, 25(OH)D, calcium (corrected for serum albumin level\textsuperscript{27}), phosphorus, and urine calcium-creatinine ratio (Fig 1). Serum iPTH initially was measured using a Beckman Coulter Access2 immunoassay (Beckman

![Figure 1. Study time line. Arrows represent patient visits.](image-url)
Coulter Inc, www.beckman.com), which was changed due to a system update in the clinical laboratory at Salem Veterans Affairs Medical Center in April 2010 to an Advia Centaur XP chemiluminescent assay (Siemens Healthcare Diagnostics, www.medical.siemens.com). As a result, 12 of 80 patients (15%) had at least one follow-up iPTH measurement performed with a method different from that used for baseline iPTH measurement. Exclusion of these 12 patients from analyses did not result in significant changes in results; hence, data considering all 80 patients are presented. Serum 25(OH)D was measured using a commercial immunochemiluminometric assay reporting total (vitamin D3 + D2) serum 25(OH)D levels (Diasorin LIAISON; Laboratory Corp of America, www.labcorp.com).

End Points

The primary efficacy end point of the study was defined as achievement of 2 consecutive decreases from baseline iPTH levels (defined as the average of 2 iPTH levels measured during screening) ≥30%. Secondary efficacy end points included absolute change in serum iPTH and bone-specific alkaline phosphatase (ALP) compared with baseline levels. Another secondary end point was change in serum 25(OH)D levels, to provide a means to ensure that ergocalciferol therapy corrected such levels and patients on paricalcitol treatment would not be exposed to significant vitamin D effects through either surreptitious medication exposure or sunshine exposure. Non–bone-mineral-metabolism–related secondary end points were measured at baseline and the end of the study and consisted of various cardiovascular disease–related markers, including serum levels of C-reactive protein, homocysteine, total, high- and low-density lipoprotein cholesterol, B-type natriuretic peptide, aortic pulse wave velocity, and percentage of total-body fat. Pulse wave velocity was measured by applanation tonometry (Sphygmocor; AtCor Medical Inc, www.atcormedical.com) and percentage of body fat was measured using both near-infrared interactance (Funtrex 6100; www.funtrex.com) and bioimpedance analysis (Bodystat Quadscan4000; Bodystat Ltd, www.bodystat.com). Because results of these latter 2 measurements showed a high degree of correlation, only results of bioimpedance analysis are presented. The primary safety end points were incidence of hypercalcemia and hyperphosphatemia, defined as increases in serum albumin-corrected calcium level >1.5 mg/dL compared with baseline or to an absolute value ≥10.7 mg/dL, and increases in serum phosphorus level to >4.8 mg/dL. If corrected calcium level was >10.7 mg/dL, paricalcitol or ergocalciferol treatment was stopped and corrected calcium levels were followed up weekly until normalization. Paricalcitol or ergocalciferol treatment could be restarted at a lower dose when serum calcium level was <10.7 mg/dL. If serum phosphorus level was >4.8 mg/dL, interventions including phosphorus binders could be implemented at the discretion of the investigators and titrated to normalization of serum phosphorus levels.

Statistical Considerations

It was hypothesized that paricalcitol would achieve a 30% decrease in serum iPTH levels on 2 consecutive occasions in 80% of patients, and ergocalciferol would achieve the same in 40% of patients. A sample size of 34 patients in each group (total, 68 patients) would allow detection of such a 40% difference in the primary efficacy end point with 90% power at a 0.05 significance level. A 15% attrition rate was assumed, resulting in a prespecified number of 80 patients to be enrolled in the study. Fisher exact test was used to compare between-group proportions of categorical primary or secondary efficacy and safety end points. Between-group differences at baseline and the end of the study for continuous variables were compared by unpaired t tests or nonparametric tests, as appropriate, and within-group differences were compared by paired t tests. To compare within- and between-group differences for variables measured every 4 weeks (serum iPTH, 25(OH)D, calcium, phosphorus, and urine calcium-creatinine ratio), linear mixed-effects models were fitted using maximum likelihood estimation and allowing for a random intercept at the individual level. All analyses were intention to treat, with patients who discontinued treatment contributing data up to the time of treatment discontinuation and considered to belong to the group to which they originally were randomly assigned. Patients who dropped out without contributing data were considered treatment nonresponders. All analyses were performed using Stata, version 11 (Stata Corp, www.stata.com).

RESULTS

Study participant flow is shown in Fig 2. Of 595 patients whose electronic charts were reviewed, 192 were deemed eligible and 108 agreed to participate in the study and underwent screening. Twenty-one patients failed screening and 7 patients withdrew consent during the screening period. Of 80 patients who were randomly assigned to one of the treatment arms, 76 completed 16 weeks of therapy (36 in the paricalcitol group and 40 in the ergocalciferol group). Of the 4 patients who dropped out, only one did so due to an adverse event (at the advice of the principal investigator after exacerbation of a pre-existing skin condition), and 3 more dropped out due to the inconvenience of adhering to the study protocol. No patient crossed over to the other treatment group. Baseline characteristics of patients randomly assigned to receive paricalcitol and ergocalciferol are listed in Table

Figure 2. Flow chart of patient selection.
None of the patient characteristics was significantly different between the 2 groups except for urine calcium-creatinine ratio, which was slightly higher in patients assigned to ergocalciferol treatment.

The primary efficacy end point of 2 consecutive decreases in serum iPTH levels of at least 30% compared with baseline was achieved by 21 patients (53%) receiving paricalcitol and 7 patients (18%) receiving ergocalciferol (Fig 3; $P = 0.002$). Mean serum iPTH levels decreased significantly after initiation of treatment with paricalcitol ($P < 0.001$), but not in patients treated with ergocalciferol ($P = 0.6$; Fig 4; Table 2), with a significant between-treatment-group difference seen in the mixed-effect model. At the end of the study, iPTH levels were significantly lower in patients treated with paricalcitol versus ergocalciferol: $119 \pm 64$ versus $166 \pm 85$ pg/mL ($P = 0.009$). Serum 25(OH)D levels increased significantly in patients treated with ergocalciferol ($P < 0.001$), and although they also increased slightly in patients treated with paricalcitol ($P = 0.04$; Fig S1), the magnitude of this increase was trivial and there was a significant intergroup difference in the mixed-effect model ($P < 0.001$; Table 2). At the end of the study, 25(OH)D levels were significantly lower in patients treated with paricalcitol versus ergocalciferol: $18 \pm 7$ versus $29 \pm 9$ ng/mL ($P < 0.001$). Changes in serum calcium and phosphorus and urine calcium-creatinine ratio values over 16 weeks were not significantly different in either treatment group (Table 2; Figs S2, S3, and S4), although urine calcium-creatinine ratio became marginally higher in patients treated with paricalcitol compared with ergocalciferol ($P = 0.06$ for between-group comparison; Table 2). Episodes of hyperphosphatemia occurred on 26 occasions (9.7%) in patients using paricalcitol and on 29 occasions (10.9%) in patients using ergocalciferol ($P = 0.9$). Phosphorus binder treatment was started in 9 patients (6 in the paricalcitol group [16%] and 3 in the ergocalciferol group [8%]; $P = 0.3$). Hypercalcemia was recorded on a single occasion in each group ($P = 0.9$). Episodes of hypercalciuria (defined as spot urine calcium-creatinine ratio $>0.2$) also were rare and not significantly different between the 2 groups: 0.8% versus 1.1% in the paricalcitol and ergocalciferol groups, respectively ($P = 0.9$). Clinical adverse and severe adverse events occurred with similar frequency in the 2 treatment groups (data not shown).

Levels of various secondary end points at baseline and after 16 weeks of treatment with paricalcitol or ergocalciferol are listed in Table 3. Serum bone-specific ALP levels decreased significantly after 16 weeks of treatment in only the paricalcitol group. None of the various cardiovascular end points was affected significantly by either treatment regimen except for a small within-group decrease in low-density lipoprotein cholesterol level in the paricalcitol group, but the difference between the 2 treatment groups was not significant ($P = 0.6$; Table 3). Results were similar when analyzing data from only the 68 patients with iPTH measurements performed with a single method: the primary efficacy end point was achieved in 16 patients (47%) randomly assigned to paricalcitol and 5 patients (15%) randomly assigned to ergocalcif-

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**Table 1.** Baseline Characteristics of Patients Randomly Assigned to Paricalcitol or Ergocalciferol

<table>
<thead>
<tr>
<th></th>
<th>Paricalcitol (n = 40)</th>
<th>Ergocalciferol (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69.3 ± 10.6</td>
<td>67.6 ± 9.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>White</td>
<td>24 (60)</td>
<td>25 (62)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16 (40)</td>
<td>15 (38)</td>
<td></td>
</tr>
<tr>
<td>Sex (men)</td>
<td>39 (98)</td>
<td>40 (100)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cause of CKD</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (37)</td>
<td>20 (50)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (27)</td>
<td>7 (17)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>6 (15)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (12)</td>
<td>8 (20)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (60)</td>
<td>31 (77)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior exposure to</td>
<td>14 (35)</td>
<td>10 (25)</td>
<td>0.7</td>
</tr>
<tr>
<td>active vitamin D</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Prior exposure to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phosphorus binders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>32.1 ± 11.2</td>
<td>30.9 ± 11.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Serum iPTH (pg/mL)</td>
<td>168 ± 62</td>
<td>175 ± 88</td>
<td>0.7</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/mL)</td>
<td>16.3 ± 6.7</td>
<td>17.2 ± 5.9</td>
<td>0.6</td>
</tr>
<tr>
<td>bALP (µg/L)</td>
<td>12.6 ± 3.6</td>
<td>14.9 ± 7.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.29 ± 0.40</td>
<td>9.31 ± 0.33</td>
<td>0.8</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>3.74 ± 0.71</td>
<td>3.96 ± 0.79</td>
<td>0.2</td>
</tr>
<tr>
<td>Spot urine calcium-creatinine ratio</td>
<td>0.03 [0.01-0.13]</td>
<td>0.04 [0.01-0.18]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Note:** Continuous data are presented as mean ± standard deviation or median [range]; categorical data, as number (percentage). Baseline values for biochemical parameters were defined as the average of the 2 values measured at a 7- to 14-day interval during screening evaluations. Comparisons between the 2 groups were made by unpaired t-tests, rank-sum tests, χ² tests, or Fisher exact tests. Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², × 0.01667; serum iPTH in pg/mL to pmol/L, × 10.1661; serum 25(OH)D in ng/mL to nmol/L, × 2.496; serum calcium in mg/dL to mmol/L, × 0.2495; serum phosphorus in mg/dL to mmol/L, × 0.3229.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; bALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone.
erol ($P = 0.008$). Results also were unchanged when including in analyses only patients in the ergocalciferol group who achieved at least one serum 25(OH)D level $> 30$ ng/mL ($n = 34$ [43%]; data not shown).

**DISCUSSION**

We describe results of a single-center randomized controlled trial comparing the effects of oral paricalcitol and ergocalciferol on treating SHPT in patients with CKD stages 3 or 4 and vitamin D insufficiency or deficiency. Our results suggest that fixed-dose paricalcitol is more effective than ergocalciferol as a treatment for SHPT.

SHPT is a common and early complication of CKD. Various aspects of disordered vitamin D metabolism have been linked to the development of SHPT, including low 25(OH)D levels, diminished 1,25(OH)2D production as a result of low $1 \alpha$ hydroxylation caused by decreased kidney mass and elevated fibroblast growth factor 23 levels, and decreased vitamin D receptor expression. Low 1,25(OH)2D levels are a characteristic of patients with CKD. Therefore, traditionally, treatment of SHPT in this patient population consisted of administering calcitriol or one of its synthetic analogues (VDRA) with more selective PTH-lowering characteristics and less side effects of hypercalcemia and hyperphosphatemia. Their clinical use also has been bolstered by an association with lower mortality in numerous observational studies of patients with end-stage renal disease and non–dialysis-dependent CKD. The discovery that 25(OH)D can be converted to 1,25(OH)2D at the tissue level in a paracrine manner and thus inducing vitamin D receptor stimulation despite low circulating 1,25(OH)2D levels has lead to re-examination of strategies aimed at replenishing low 25(OH)D levels as a means to treat SHPT in patients with CKD. The KDOQI guidelines from 2003 recommended routine screening of 25(OH)D levels for patients with SHPT and advocated the correction of vitamin D insufficiency or deficiency using ergocalciferol according to a standard weekly-to-monthly dosed protocol, with subsequent application of VDRAs in case 25(OH)D level normalization did not effectively decrease PTH levels. This recommendation was based on the opinion of an expert panel, and the efficacy of 25(OH)D supplementation to suppress SHPT has remained in question because results of the numerous small observational and interventional studies that examined the ability of various ergocalciferol- or cholecalciferol-based treatment regimens to decrease PTH levels has not been uniform.

A recent meta-analysis of such studies indicated that 25(OH)D supplementation could decrease PTH levels.

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**Figure 3.** Proportion of patients with 2 consecutive serum parathyroid hormone levels decreased by $\geq 30\%$ after treatment with paricalcitol and ergocalciferol. $P$ value represents comparison by Fisher exact test.

**Figure 4.** Mean serum intact parathyroid hormone (PTH) levels (95% confidence interval) at baseline and during 16 weeks of therapy in patients treated with paricalcitol and ergocalciferol. $P$ value represents the average between-group difference from a mixed-effect model. Numbers represent the number of participants providing data at each visit in each treatment group.
Table 2. Within-Group Changes and Between-Group Comparisons of Various Bone-Mineral Metabolism Markers

<table>
<thead>
<tr>
<th></th>
<th>Paricalcitol</th>
<th>Ergocalciferol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iPTH (pg/mL)</td>
<td>-9.9 (-13.9 to -5.8)</td>
<td>-1.1 (-5.8 to 3.6)</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/mL)</td>
<td>0.32 (0.02 to 0.63)</td>
<td>2.70 (2.17 to 3.24)</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>0.02 (-0.005 to 0.04)</td>
<td>0.005 (-0.02 to 0.03)</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>0.03 (-0.01 to 0.08)</td>
<td>-0.04 (-0.09 to 0.03)</td>
</tr>
<tr>
<td>Urine calcium-creatinine ratio</td>
<td>0.002 (-0.001 to 0.005)</td>
<td>0.001 (-0.003 to 0.005)</td>
</tr>
</tbody>
</table>

Note: Results estimated from mixed-effects models using maximum likelihood estimation and allowing for a random intercept at the individual level. Within-group changes of each parameter represent average changes (slopes) over a 4-week period. Between-group comparisons represent average treatment effect of ergocalciferol versus paricalcitol during the entire 16 weeks of the study. Conversion factors for units: serum iPTH in pg/mL to pmol/L, 2.496 for serum calcium in mg/dL to mmol/L, ×0.2495; serum phosphorus in mg/dL to mmol/L, ×0.3229; serum 25(OH)D in ng/mL to nmol/L, ×2.496; serum calcium in mg/dL to mmol/L, ×0.2495; serum phosphorus in mg/dL to mmol/L, ×0.3229.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; iPTH, intact parathyroid hormone.

Table 3. Baseline and End-of-Treatment Values for Various Secondary End Point Measures

<table>
<thead>
<tr>
<th></th>
<th>Paricalcitol</th>
<th>Ergocalciferol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0</td>
<td>Wk 16</td>
<td>Wk 0</td>
</tr>
<tr>
<td>bALP (µg/L)</td>
<td>12.64 ± 5.99</td>
<td>10.64 ± 3.90</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>167 ± 437</td>
<td>158 ± 36</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>95 ± 38</td>
<td>81 ± 34</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>40 ± 13</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Serum homocysteine (mg/L)</td>
<td>20.0 [17.7-22.5]</td>
<td>19.3 [17.0-21.8]</td>
</tr>
<tr>
<td>Serum BNP (pg/mL)</td>
<td>67 [53-84]</td>
<td>65 [51-82]</td>
</tr>
<tr>
<td>Serum hs-CRP (mg/L)</td>
<td>3.8 [2.2-6.0]</td>
<td>4.0 [2.2-6.6]</td>
</tr>
<tr>
<td>Pulse wave velocity (m/s)</td>
<td>13.5 ± 3.9</td>
<td>13.3 ± 2.9</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>32.2 ± 6.5</td>
<td>31.6 ± 6.1</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± standard deviation or median [range]. Baseline values were defined as the average of 2 values measured at a 7- to 14-day interval during screening evaluations. Within-group comparisons were made by paired t tests, and between-group comparisons were made by unpaired t tests or nonparametric tests, as appropriate. Conversion factors for units: total, LDL, and HDL cholesterol in mg/dL to mmol/L, ×0.02586; serum homocysteine in mg/dL to μmol/L, ×7.397; serum hs-CRP in mg/L to μg/L, ×1.000; no conversion necessary for serum BNP in pg/mL and ng/L.

Abbreviations: bALP, bone-specific alkaline phosphatase; BNP, B-type natriuretic peptide; HDL, high-density lipoprotein, LDL, low-density lipoprotein, hs-CRP, high-sensitivity C-reactive protein.

*P < 0.01 for comparisons of week-16 values between the paricalcitol and ergocalciferol groups.
ate and advanced non–dialysis-dependent CKD over 3 months and found a significant decrease in PTH levels in patients treated with doxercalciferol, but not those treated with cholecalciferol. Despite significant intragroup differences, the difference between the 2 treatments was not statistically significant compared with each other, thus not allowing for unequivocal conclusions regarding the superiority of one over the other. The lack of statistically significant difference could have been the result of the small sample size of this study; hence, results from larger studies would have to be considered before declaring the 2 treatment strategies equally effective. Although our study cannot in itself be considered large, the number of participants enrolled was based on prespecified sample size calculations and proved to be sufficient to detect significant differences between the paricalcitol- and ergocalciferol-based regimens, not only in their effect to decrease PTH levels within the individual treatment groups, but also comparing effects of the 2 regimens head to head.

Our study suggests that paricalcitol is superior to ergocalciferol in treating SHPT in non–dialysis-dependent patients with CKD, but it leaves open the question regarding other clinical benefits of these treatment strategies. That treatment with paricalcitol in our study also resulted in differential lowering of serum bone-specific ALP levels suggests a likely benefit over ergocalciferol in the treatment of high-turnover bone disease; but definitive evidence toward such a benefit requires studies examining bone biopsies. Observational studies have linked low levels of both 25(OH)D and 1,25(OH)2D to increased mortality, which could be mediated through SHPT, elevated ALP levels (which has been linked to mortality independent of SHPT), or one of the many other complex physiologic roles of vitamin D which, if disturbed, could lead to adverse outcomes independent of elevated PTH levels. A more robust PTH- and ALP-lowering effect by paricalcitol over ergocalciferol thus theoretically could translate to better clinical outcomes, but such a hypothesis would have to be tested carefully due to the unknown impact on such outcomes of the ancillary biochemical effects (such as increases in serum calcium and phosphorus and urinary calcium values) inherent of more effective vitamin D receptor stimulation. The lesser hypercalcemic and hyperphosphatemic effects of the VDRA, such as paricalcitol over calcitriol, again could prove beneficial, but the lack of any kind of clinical trials examining hard clinical end points allows for only speculation in this regard.

Results of our study need to be interpreted with due consideration of its limitations. We examined almost exclusively men at a single institution, which limits the generalizability of our results. Interventions were not blinded, which could have introduced bias. This is less likely in a study with an objective end point like ours, but we cannot rule out the possibility that knowledge of the intervention may have affected patients’ adherence to the intervention or physicians’ responses to ancillary treatments, such as administration of phosphate binders. As with any randomized controlled trial, the external validity of our study also is limited by our trial design. We used an ergocalciferol-based treatment regimen advocated by the KDOQI, with adjustments to attempt correction of 25(OH)D levels to 30 ng/mL, which allows us to conclude the superiority of paricalcitol only against treatment regimens of 25(OH)D supplementation of the same nature. The recent meta-analysis of 25(OH)D supplementation studies suggested that effects of 25(OH)D supplementation are influenced by the applied type of replacement regimen, with the KDOQI-advocated dosing schedule appearing less effective and resulting in a lower magnitude of PTH suppression. We thus cannot exclude the possibility that correction of 25(OH)D insufficiency or deficiency by using alternative agents, alternative dosing schedules, or alternative 25(OH)D target levels could be equally effective as paricalcitol in suppressing SHPT. By the same token, paricalcitol-based regimens that are titrated to achieve prespecified goals could prove even more effective compared with the fixed-dosing regimen used by us. Any or all of these alternative strategies would have to be tested in future clinical trials to define the ideal approach to SHPT therapy. The prespecified primary end point of this study (decreasing PTH level) is a surrogate end point of correcting high bone turnover. Correction of 25(OH)D in itself could be considered a surrogate outcome measure of various potential clinical outcomes. Although paricalcitol was more effective at decreasing PTH levels in our study, it is possible that correction of 25(OH)D in itself could have benefits independent of PTH lowering. Any clinical benefits of either therapeutic strategy would have to be tested in future clinical trials.

Paricalcitol is significantly more effective in treating the SHPT of vitamin D–deficient patients with CKD stage 3 or 4 compared with ergocalciferol dosed according to a modified KDOQI treatment regimen.

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SUPPLEMENTARY MATERIAL

Figure S1: Mean serum 25(OH)D levels at baseline and during 16 weeks of therapy in patients treated with paricalcitol and with ergocalciferol.

Figure S2: Mean serum calcium levels at baseline and during 16 weeks of therapy in patients treated with paricalcitol and with ergocalciferol.

Figure S3: Mean serum phosphorus levels at baseline and during 16 weeks of therapy in patients treated with paricalcitol and with ergocalciferol.

Figure S4: Mean spot urine calcium-creatinine ratio levels at baseline and during 16 weeks of therapy in patients treated with paricalcitol and with ergocalciferol.

Item S1: Detailed inclusion and exclusion criteria.

Item S2: Ergocalciferol dosing protocol.

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REFERENCES


38. Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in nondia-


42. Moe SM, Saifullah A, LaClair RE, Usman SA, Yu Z. A randomized trial of cholecalciferol versus doxercalciferol for low-


