Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism

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We compared the effects of calcitriol and doxercalciferol, in combination with either calcium carbonate or sevelamer, on bone, mineral, and fibroblast growth factor-23 (FGF-23) metabolism in patients with secondary hyperparathyroidism. A total of 60 pediatric patients treated with peritoneal dialysis were randomized to 8 months of therapy with either oral calcitriol or doxercalciferol, combined with either calcium carbonate or sevelamer. Bone formation rates decreased during therapy and final values were within the normal range in 72% of patients. A greater improvement in eroded surface was found in patients treated with doxercalciferol than in those given calcitriol. On initial bone biopsy, a mineralization defect was identified in the majority of patients which did not normalize with therapy. Serum phosphate concentrations were controlled equally well by both binders, but serum calcium levels increased during treatment with calcium carbonate, and serum parathyroid hormone levels were decreased by 35% in all groups. Baseline plasma FGF-23 values were significantly elevated and rose over fourfold with calcitriol and doxercalciferol, irrespective of phosphate binder. Thus, doxercalciferol is as effective as calcitriol in controlling serum parathyroid hormone (PTH) levels and lowers bone formation. However, this form of therapy may also lead to adynamic renal osteodystrophy, increased severity of growth retardation, hypercalcemia and/or hyperphosphatemia, and progressive vascular calcification. To minimize these side effects, vitamin D sterols, such as 19-nor-1,25 dihydroxyvitamin D2 (paricalcitol) and 1α-hydroxyvitamin D2 (doxercalciferol, 1αD2), and calcium-free phosphate binders, such as sevelamer hydrochloride and lanthanum carbonate, have been approved for clinical use in the United States.

Over the past decade, these new therapies have become integral to the management of chronic kidney disease (CKD) mineral and bone disorder. Indeed, both 1αD2 and paricalcitol suppress PTH secretion, whereas sevelamer and lanthanum are effective in controlling serum phosphate while preventing increases in serum calcium. Although the effects of sevelamer and lanthanum on skeletal histology have been evaluated, both in adult and pediatric dialysis patients, currently there are no studies in humans comparing differences in the effects of calcitriol and any of the new vitamin D sterols on the skeleton. Moreover, over the last few years, the role of fibroblast growth factor-23 (FGF-23) in the development and treatment of 2αHPT progression of renal disease, cardiovascular disease, overall risk of mortality, and bone metabolism in patients with CKD has been increasingly recognized. Therapy with 1,25(OH)2vitamin D appears to be the most potent stimulator of FGF-23 synthesis; however, there is limited knowledge of the response of FGF-23 to the treatment of 2αHPT and whether
the FGF-23 response differs between vitamin D sterols. Thus, this study was designed to prospectively compare the effects of 1αD2 and calcitriol therapy on the control of the biochemical and skeletal lesions of 2HPT and on circulating FGF-23 levels during treatment with either a calcium-based binder or sevelamer hydrochloride in pediatric patients treated with peritoneal dialysis.

RESULTS
Study participants: clinical characteristics and baseline vitamin D status
A total of 60 patients (30 males, 30 females) aged 13.9 ± 0.5 years were enrolled in the study (Table 1). These patients, their biochemical characteristics, and vitamin D sterol doses have been previously described.16 The average time on dialysis at initiation of study was 1.0 ± 0.2 years. Of these, 11 subjects had previously undergone renal transplantation and were receiving treatment with dialysis for at least 6 months before the beginning of the study; none of them were treated with immunosuppressive agents during the preceding 6 months. A total of 51 patients completed the study, whereas 9 terminated early (5 from group 1, 2 from group 2, 1 from group 3, and 1 from group 4), as per protocol, because of either renal transplantation (n = 5) or medication noncompliance (n = 4). Neither baseline biochemical nor bone parameters differed in the nine who were terminated early from those who completed the study. Baseline serum 25(OH)vitamin D levels were below 20 ng/ml in all four treatment groups, only one subject had a baseline value >30 ng/ml (Table 1).

Response of bone histology to therapy
Baseline static and dynamic bone variables did not differ between the four groups (Table 2). As per study design, all patients had either increased rates of bone formation and/or marrow fibrosis at the start of the study. Bone formation rate (BFR) declined equally in all four treatment groups throughout the course of the study, and values were in the normal range in 72% of the patients on follow-up bone biopsies. Only one patient developed adynamic bone. Eroded surface, which did not differ between the four groups at baseline, decreased in all patients treated with 1αD2 while

Table 1 | Demographic data

<table>
<thead>
<tr>
<th></th>
<th>1αD2+CaCO3 (n=16)</th>
<th>1αD2+sevelamer (n=14)</th>
<th>Calcitriol+CaCO3 (n=16)</th>
<th>Calcitriol+sevelamer (n=14)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.2 ± 0.9</td>
<td>14.5 ± 1.0</td>
<td>12.0 ± 3.0</td>
<td>15.0 ± 0.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>10/6</td>
<td>7/7</td>
<td>9/7</td>
<td>4/10</td>
</tr>
<tr>
<td>Time on dialysis (years)</td>
<td>0.8 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.5</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Etiology of ESRD (n)</td>
<td>Obstructive/dysplastic</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Glomerular</td>
<td>9</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Previous transplants (n)</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diabetic concentration (%)</td>
<td>2.5 ± 0.1</td>
<td>2.5 ± 0.1</td>
<td>2.5 ± 0.0</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Baseline 25(OH)vitamin D level (pg/ml)</td>
<td>15.7 ± 2.7</td>
<td>15.0 ± 2.7</td>
<td>17.1 ± 2.8</td>
<td>15.2 ± 1.9</td>
</tr>
</tbody>
</table>

Abbreviations: 1αD2, doxercalciferol; CaCO3, calcium carbonate; ESRD, end-stage renal disease; F, female; M, male.

Table 2 | Bone histomorphometry

<table>
<thead>
<tr>
<th></th>
<th>1αD2+CaCO3</th>
<th>1αD2+sevelamer</th>
<th>Calcitriol+CaCO3</th>
<th>Calcitriol+sevelamer</th>
<th>Normal values27,32</th>
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<td>Turnover</td>
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<tr>
<td>Bone formation rate/bone surface (BFR/BS; µm²/mm² per day)</td>
<td>124 ± 41</td>
<td>45 ± 22*</td>
<td>103 ± 41</td>
<td>53 ± 29*</td>
<td>152 ± 77</td>
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<tr>
<td>Eroded surface/bone surface (ES/BS; %)</td>
<td>10.3 ± 3.2</td>
<td>7.7 ± 3.5*</td>
<td>10.6 ± 2.7</td>
<td>7.3 ± 4.5*</td>
<td>10.3 ± 3.0</td>
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<td>Mineralization</td>
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<tr>
<td>Osteoid volume/bone volume (OV/BV; %)</td>
<td>15.3 ± 6.0</td>
<td>8.9 ± 4.3*</td>
<td>15.3 ± 6.1</td>
<td>10.8 ± 3.0*</td>
<td>17.6 ± 9.0</td>
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<tr>
<td>Osteoid surface/bone surface (OS/BS; %)</td>
<td>54.9 ± 16.3</td>
<td>54.8 ± 29.1</td>
<td>54.3 ± 12.4</td>
<td>44.3 ± 6.8*</td>
<td>56.3 ± 11.6</td>
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<td>Osteoid thickness (OTh; µm)</td>
<td>19.5 ± 4.0</td>
<td>14.9 ± 3.8*</td>
<td>21.1 ± 4.8</td>
<td>17.7 ± 2.7</td>
<td>22.0 ± 3.1</td>
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<tr>
<td>Osteoid maturation time (OMT; day)</td>
<td>19.6 ± 6.8</td>
<td>16.6 ± 7.8</td>
<td>19.7 ± 8.0</td>
<td>22.7 ± 9.9</td>
<td>18.4 ± 6.1</td>
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<tr>
<td>Mineralization lag time (MLT; day)</td>
<td>41.3 ± 25.2</td>
<td>75.5 ± 40.1*</td>
<td>46.8 ± 28.6</td>
<td>74.0 ± 43.4</td>
<td>36.4 ± 19.6</td>
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<tr>
<td>Volume</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Bone volume/tissue volume (BV/TV; %)</td>
<td>28.0 ± 7.2</td>
<td>26.0 ± 7.5</td>
<td>30.9 ± 6.3</td>
<td>28.2 ± 4.6</td>
<td>28.9 ± 8.0</td>
</tr>
</tbody>
</table>

Abbreviations: 1αD2, doxercalciferol; CaCO3, calcium carbonate.
*Significant change from baseline (P<0.05).
remaining unchanged in patients treated with calcitriol; this finding was irrespective of the type of phosphate binder therapy (Table 2).

Static indices of mineralization, including osteoid volume/bone volume, osteoid surface/bone surface, and osteoid thickness, did not differ at baseline between groups and values for each parameter declined in all four groups. A greater improvement in osteoid volume was observed in patients treated with calcium carbonate (CaCO₃), regardless of vitamin D sterol, than in patients treated with sevelamer (Table 2). Mineralization time, as measured by osteoid maturation time, was abnormal in the majority of patients at baseline and did not improve during therapy, whereas mineralization lag time increased. No differences in these parameters were observed amongst the four treatment groups either at baseline or after 8 months of treatment (Table 2).

Bone volume was normal or increased in all patients and did not change throughout the course of the study, regardless of therapy.

Response of serum biochemical parameters to therapy
As previously reported, initial serum calcium levels were similar between the four groups; however, values rose progressively in both groups treated with CaCO₃ while remaining unchanged in sevelamer-treated patients (Figure 1). By the end of the study, values in patients receiving CaCO₃ were higher than in either group of sevelamer-treated subjects (Figure 1). In total, 48 episodes of hypercalcemia (serum calcium ≥10.2 mg/dl) occurred in CaCO₃-treated subjects as compared with 17 episodes in those receiving sevelamer (P < 0.01). No differences in serum calcium levels or episodes of hypercalcemia were found between calcitriol and 1αD₂ therapies.

Overall, baseline serum phosphorus levels were 6.3 ± 0.1 mg/dl; values declined in the initial month of the trial and remained within target range in all groups throughout the study. Episodes of hyperphosphatemia did not differ between the groups during follow-up period (Figure 2). The dietary phosphorus intake throughout the study averaged 815 ± 43 mg per day and values were similar between groups. The calcium–phosphorus ion product was persistently below 55 mg²/dl² in all groups. Baseline serum bicarbonate levels did not differ between groups; however, final values were 24.8 ± 0.6 mEq/l and 22.5 ± 0.5 mEq/l in CaCO₃- and sevelamer-treated patients, respectively (P < 0.05).

Baseline PTH levels were 940 ± 55 pg/ml and values did not differ between groups. As previously demonstrated, PTH values decreased between months 3 through to 5 of therapy, reaching a plateau by month 6. By the end of the study, values had declined by an average of 34% (P < 0.01) in all treatment groups (Figure 3a and 3b). Initial serum alkaline phosphatase levels were 397 ± 36 IU/l, values did not differ between groups and declined similarly in all groups; final values were 259 ± 32 IU/l (P < 0.01 from baseline; nonsignificant between groups).

Median initial FGF-23 levels were 91 pg/ml (interquartile (IQ) range: 43–325) and 842 RU/ml (IQ range: 194–4186), as measured by the intact assay and C-terminal assays, respectively. Anuric subjects displayed higher baseline FGF-23 values than did patients with any degree of residual urine output; median baseline intact FGF-23 levels were 266 pg/ml (IQ range: 50–778) and 68 pg/ml (IQ range: 44–204) in anuric individuals and in those with residual renal function (P < 0.01), respectively, whereas baseline values by the C-terminal assay were 3389 RU/ml (IQ range: 1012–9623) and 318 RU/ml (IQ range: 194–4186; P < 0.01) in the two patient subsets, respectively. FGF-23 levels measured by the two different assays correlated throughout the course of treatment (r = 0.77, P < 0.01), levels did not differ between groups, and values increased by 428 ± 136% (intact assay) and 638 ± 178% (C-terminal assay; P < 0.01 from baseline,
both assays), irrespective of baseline FGF-23 value or residual renal function (Figure 4a and b). Similar increments in FGF-23 levels were observed between calcitriol and 1αD2 treatment groups, irrespective of phosphate binder therapy. No relationship was observed between the dose of vitamin D sterol and the magnitude of increase in FGF-23.

**Dosages of phosphate binders and active vitamin D sterols according to treatment group**

At the initiation of the trial, the average doses of CaCO3 were 4.3 ± 1.4 g/day and 3.4 ± 1.1 g/day in calcitriol- and 1αD2-treated patients, respectively (nonsignificant); doses of sevelamer were 4.7 ± 0.7 g/day and 5.9 ± 0.9 g/day in calcitriol and 1αD2 groups, respectively (nonsignificant). Final phosphate binder doses did not differ between groups and doses increased by an average of 54 ± 19% in all patients during the course of the study. Patients treated with CaCO3 ingested an average of 2.8 ± 0.1 g/day of elemental calcium from phosphate binders. Four sevelamer-treated patients ingested an average of 1.1 ± 0.1 g/day of elemental calcium during months 5 through to 8 of the study in order to maintain serum calcium levels above 8.2 mg/dl.

Vitamin D sterol doses increased monthly during the first 4 months and reached stable dosage in the last 4 months of the study (Figure 5). Patients treated with CaCO3 received an average dose of 4.8 ± 0.6 µg of 1αD2 or 1.4 ± 0.1 µg of calcitriol, and those given sevelamer received either
5.1 ± 0.5 µg of 1αD2 or 2.3 ± 0.1 µg of calcitriol. To compare maintenance doses of vitamin D between patients treated with different phosphate binders, 1αD2 dose was converted to a calcitriol-equivalent dose using the formula: calcitriol-equivalent dose = 1αD2 dose/5 (ref. 17). As previously reported,16 patients treated with sevelamer were found to have received higher calcitriol-equivalent doses of vitamin D sterols than those treated with CaCO3 during the last 4 months of therapy (P<0.05).

DISCUSSION
This trial, the first to compare the effects of calcitriol therapy with one of the new vitamin D sterols, 1αD2, in combination with either CaCO3 or sevelamer on bone histology, demonstrated equivalent improvement in the skeletal and biochemical lesions of 2HPT in all four treatment arms in pediatric patients treated with continuous cycling peritoneal dialysis. With a total of 51 patients completing 8 months of the trial, this study is one of few trials to achieve a sample size considered by current KDIGO (Kidney Disease: Improving Global Outcomes) recommendations as adequate to assess changes in bone histomorphometry, based on different therapeutic regimens.18 BFR, the primary end point, decreased during therapy in all treatment groups, and final values were within the normal range in 72% of the patients. A greater improvement in eroded surface was found in patients treated with 1αD2 than in those given calcitriol, regardless of the phosphate binder. A mineralization defect was identified in the majority of patients on initial bone biopsy and, although treatment with CaCO3 resulted in greater improvements in osteoid accumulation than did therapy with sevelamer, no treatment arm was able to normalize skeletal mineralization. Serum phosphate concentrations were controlled equally well by both binders; however, as previously shown, serum calcium concentrations increased during treatment with CaCO3, while remaining unchanged in those treated sevelamer.16 Serum PTH and alkaline phosphatase levels were suppressed to a similar degree in all groups despite differences in serum calcium levels, but patients treated with sevelamer received higher doses of vitamin D sterols. At baseline, plasma FGF-23 values were elevated; values rose by a similar degree in all four treatment groups during the follow-up period, irrespective of the type of vitamin D sterol therapy used and despite no increases in serum phosphate concentration.

Several studies have consistently demonstrated the effectiveness of calcitriol, paricalcitol, and 1αD2 in suppressing serum PTH levels,19–22 and recent studies have evaluated the effects of different phosphate binders and calcimimetic agents, when used in combination with active vitamin D sterols, on bone histology in adult dialysis patients with various subtypes of renal osteodystrophy.23,24 However, this is the first study to prospectively compare the specific effects of two different vitamin D sterols on the skeletal lesions of 2HPT. Increased levels of calcium were observed in patients treated with CaCO3, which may have contributed to declining PTH values; however, a similar degree of PTH reduction was observed in sevelamer-treated patients, despite stable serum calcium levels. These patients received higher doses of active vitamin D sterols, suggesting that sevelamer may enhance the margin of safety for the use of active vitamin D sterols. At doses that result in equivalent suppression of PTH, both oral 1αD2 and calcitriol, when given in intermittent, thrice-weekly dosing, suppressed bone formation to a similar degree. Interestingly, therapy with 1αD2 suppressed bone erosion to a greater degree than did calcitriol, regardless of the type of phosphate binder. The mechanism underlying this difference has yet to be explained, but may be due to differences in sterol bioavailability. Indeed, the biological actions of 1αD2 are largely dependent on the formation of 1,25(OH)2D3 after 25-hydroxylation by the liver, leading to sustained circulating levels of 1,25(OH)2D3, in contrast to the fluctuating values of 1,25(OH)2D3 associated with intermittent calcitriol administration.25,26 Although further studies are needed to compare the pharmacodynamic properties of these two sterols, differential activation of the receptor activator of nuclear factor-κB ligand/osteoprotegerin system and osteoclastogenesis may have a role.

The application of the TMV (turnover, mineralization, volume) classification of renal osteodystrophy to bone histomorphometric analyses, in accordance with current guidelines,18 identified a baseline mineralization defect in the vast majority of pediatric dialysis patients with 2HPT, which persisted despite normalization of BFR. Although increased circulating PTH levels, by activating osteoblast activity, stimulate the formation of unmineralized osteoid and thus increase the static amount of osteoid visualized on bone biopsy, patients in this study also displayed prolonged mineralization time periods. Osteoid volume and thickness improved as PTH levels declined; however, values remained above the upper limit of normal in all groups, while dynamic parameters of mineralization, including osteoid maturation time and mineralization lag time, remained abnormal and unchanged from baseline. The prevalence of mineralization defects in the current cohort contrasts markedly with the findings from a recent study in the adult dialysis population, in which mineralization defects were found to be rare.23 Although a low intake of dietary calcium may contribute to defective skeletal mineralization in the growing child, it is interesting to note that serum calcium levels were inversely related with indices of mineralization. However, even patients treated with calcium-based binders, who ingested quantities of elemental calcium far exceeding the daily-recommended intake, failed to normalize bone mineralization after 8 months of therapy. Thus, defective mineralization is a multifactorial process that may involve 25(OH)D/vitamin D deficiency and altered FGF-23 metabolism.27,28 Indeed, in this study, only one subject had a serum 25(OH)D vitamin D level >30 ng/ml; the remainder were either vitamin D insufficient or deficient according to the current diagnostic criteria.29,30 In light of data suggesting that treatment with
25(OH) vitamin D is effective in ameliorating defective mineralization in pediatric patients with predialysis CKD,\textsuperscript{31} such a degree of 25(OH) vitamin D deficiency may have had a critical role in the prevalence of mineralization defects in this study. Alternatively, alterations in bone FGF-23 and dentin matrix protein 1 (DMP-1) expression, both of which have been related to alterations in skeletal mineralization in children with CKD, may also contribute.\textsuperscript{28}

In the past, intermittent oral calcitriol therapy combined with calcium-based binders has been associated with over-suppression of bone turnover, despite the PTH levels that were consistent with 2HPT.\textsuperscript{5,32} In this study, BFRs normalized in the majority of patients and final PTH levels ranged from 357 to 610 pg/ml. Such values are consistent with current KDIGO PTH guidelines, which suggest that values as high as nine times the upper limit of the normal range may be associated with normal rates of bone formation in dialysis patients.\textsuperscript{18} The adjustment of vitamin D therapy according to concurrent target levels of serum calcium, phosphorus, and PTH, as performed in the current trial, provides evidence that bone turnover can be normalized while preventing the development of adynamic bone and its consequences of growth retardation,\textsuperscript{6} hypercalcemia, and progressive vascular calcification.\textsuperscript{7}

Consistent with previous studies,\textsuperscript{33,34} baseline plasma FGF-23 levels were markedly elevated in the current cohort of patients. Dietary phosphate, serum phosphate, and 1,25(OH)\textsubscript{2}D\textsubscript{3} are key regulators of FGF-23 production and several studies have demonstrated that different therapeutic regimens for the treatment of 2HPT lead to changes in circulating FGF-23 values. Indeed, FGF-23 levels decrease in response to sevelamer HCl treatment in all stages of CKD,\textsuperscript{35,36} as well as in response to calcimimetic therapy in CKD stage 5.\textsuperscript{37} In this study, increased values of FGF-23 were observed throughout the course of therapy in all treatment groups, despite stable serum phosphorus concentrations, likely reflecting the known effect of vitamin D sterols on FGF-23 secretion.\textsuperscript{38-41} The clinical implications of these increasing FGF-23 values remain to be established, as therapy with active vitamin D sterols provides a survival benefit that is independent of serum calcium, phosphorus, and PTH levels in dialysis patients.\textsuperscript{42-44} However, the increases in FGF-23 levels which accompany vitamin D sterol therapy, may prove detrimental to long-term survival; indeed, elevated FGF-23 values have been associated with left ventricular hypertrophy,\textsuperscript{45} vascular calcification,\textsuperscript{13} and an increased mortality rate\textsuperscript{12} in the adult dialysis population. This paradox highlights the needs for future prospective randomized trials, evaluating the end-organ effects of vitamin D sterol therapy and FGF-23 levels in patients treated with maintenance dialysis.

In conclusion, this study demonstrates that 1\textsubscript{2}D\textsubscript{2}, when used in combination with either CaCO\textsubscript{3} or sevelamer hydrochloride, is as effective as calcitriol in controlling serum PTH levels and suppressing BFR. Patients treated with sevelamer received higher doses of active vitamin D without inducing changes in serum calcium levels.\textsuperscript{16} Mineralization defects were highly prevalent in the pediatric dialysis population and these defects were not corrected with vitamin D sterol and phosphate binder therapies. Thus, altered skeletal mineralization in pediatric dialysis patients is a multifactorial process that may be complicated by alterations in FGF-23 metabolism and 25(OH) vitamin D deficiency. Therapy with both calcitriol and 1\textsubscript{2}D\textsubscript{3} resulted in similar increases in FGF-23, irrespective of phosphate binder medication. The implications of these increasing FGF-23 levels on bone and vascular disease in end-stage kidney disease remain to be established, but may have implications on skeletal mineralization,\textsuperscript{27} vascular calcification,\textsuperscript{13} and mortality.\textsuperscript{12}

\textbf{METHODS}

All potential study candidates were medically stable patients, aged 2-21 years, who were treated with continuous cycling peritoneal dialysis and had serum PTH levels > 400 pg/ml, as determined by a first-generation immunometric PTH assay (Nichols, San Clemente, CA, USA),\textsuperscript{47} as has been previously reported.\textsuperscript{10,16} After a 4-week withdrawal period from daily oral calcitriol therapy, study candidates were admitted to the UCLA General Clinical Research Center, and bone biopsies were obtained from the anterior iliac crest using a modified Bordier trephine after double tetracycline labeling. Potential subjects were eligible for randomization if they displayed bone histomorphometric evidence of 2HPT, as has been previously described.\textsuperscript{10,16} Exclusion criteria included previous history of poor medication compliance; parathyroidectomy within the past 12 months; concurrent treatment with immunosuppressive agents, growth hormone, or other bone pathology not related to 2HPT. Patients were removed from the study, per protocol, in the event of renal transplantation, medication noncompliance (defined as a serum phosphorus level > 7 mg/dl for 3 consecutive months), change in dialytic modality, and psychosocial factors, as determined by medical staff. This study was approved by the UCLA Human Subjects Protection Committee and consent forms were obtained from all patients and/or parents/guardians.

\textbf{Study design}

Using a 2 × 2 longitudinal factorial study design, a total of 60 patients with high-turnover bone disease were randomly allocated to one of four treatment regimens: group 1: 1\textsubscript{2}D\textsubscript{3} ± CaCO\textsubscript{3} (n = 16); group 2: 1\textsubscript{2}D\textsubscript{3} ± sevelamer (n = 14); group 3: calcitriol ± CaCO\textsubscript{3} (n = 16); and group 4: calcitriol ± sevelamer (n = 14). A flowchart of the overall study is displayed in Figure 6. Initial doses of vitamin D sterols were based on PTH levels; therapy was given thrice-weekly orally at bedtime.\textsuperscript{10,16} Doses were titrated upward every 4 weeks to achieve a target PTH level between 300 and 400 pg/ml, while maintaining serum calcium levels between 8.4 and 10.2 mg/dl and phosphorus between 4 and 6 mg/dl. Vitamin D dosages were kept constant when PTH levels fell below 500 pg/ml and serum calcium and phosphorus levels were within the target range; vitamin D sterol therapy was withheld for serum calcium values > 10.2 mg/dl and/or serum phosphorus levels > 6.0 mg/dl.

The initial dose of CaCO\textsubscript{3} was based on the previous regimen, whereas the initial dose of sevelamer was extrapolated from the CaCO\textsubscript{3} dosage;\textsuperscript{48} phosphate-binding therapy was titrated to maintain serum phosphorus between 4.0 and 6.0 mg/dl.\textsuperscript{10,16} In patients who were treated with sevelamer, 1000 mg of elemental calcium was added at bedtime if serum calcium levels were
25(OH)D values were measured by radioimmunoassay.49 The American Society of Bone and Mineral Research.51

The terminology established by the Nomenclature Committee of the previously described.27 As recommended by KIDGO,18 parameters quantitative histomorphometry analysis was performed as has been standard deviation of 1.1.32 To achieve a power of bone turnover, mineralization, and volume50 are reported with concentrations were determined by Technicon Autoanalyzer II (SEAL calcium, albumin, phosphorous, and alkaline phosphatase concentrations were determined according to ultrafiltration requirements. Serum levels of calcium, albumin, and phosphorus were obtained at baseline and biweekly throughout the study; serum alkaline phosphatase, PTH, and FGF-23 were determined monthly. Serum 25(OH)D values were measured only at baseline. Serum calcium, albumin, phosphorous, and alkaline phosphatase concentrations were determined by Technicon Autoanalyzer II (SEAL Analytical Mequon, WI, USA).10,16 Serum calcium levels were

were imputed by carrying forward the last observation. Baseline and final biochemical values were expressed as either mean ± s.e.m. or median (interquartile range). Comparisons of changes between groups were corrected for baseline for all parameters. Pearson correlation coefficients were used to assess the relationship between biochemical parameters. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC, USA) and all tests were two-sided with significance level of P<0.05.

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REFERENCES


