Treatment with Vitamin D and Calcium Reduces Bone Loss after Renal Transplantation: A Randomized Study

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Abstract. A decrease in bone mineral density (BMD) is a major complication of renal transplantation (RTx), predominantly occurring within the first 6 mo after RTx. The most important causative factor is the use of corticosteroids, but persisting hyperparathyroidism and abnormalities in vitamin D metabolism play a role too. This study examines the effect of treatment with calcium and active vitamin D on the loss of BMD in the first 6 mo after RTx. A total of 111 renal transplant recipients (65 men, 46 women; age, 47 ± 13 yr) were randomized to either treatment with active vitamin D (0.25 µg/d) plus calcium (1000 mg/d) (CaD group), or to no treatment (NoT group). Immunosuppressive therapy consisted of cyclosporine, prednisone, and mycophenolate mofetil. Laboratory parameters and BMD (lumbar spine and hip) were measured at 0, 1 (laboratory only), 3, and 6 mo after RTx. Lumbar BMD was nearly normal at the time of RTx. In both groups, a significant decrease in lumbar BMD was observed during the first 3 mo (CaD, −3.3 ± 4.3%; P < 0.0001; NoT, −4.1 ± 4.8%; P < 0.0001). Between the third day and sixth month, lumbar BMD slightly recovered in the CaD group, but it decreased further in the NoT group (total loss 0 to 6 mo: CaD, −2.6 ± 5.0% [P < 0.001]; NoT, −5.0 ± 4.7% [P < 0.0001]). As a result, the amount of bone loss at 6 mo was significantly lower in the CaD group (P = 0.02). Loss of BMD at the different femoral sites was also significantly reduced in the CaD group. Apart from a trend toward more frequent hypercalcemia in the CaD group, no clinical or biochemical differences existed between the groups. Treatment with a low dose of active vitamin D and calcium partially prevents bone loss at the lumbar spine and proximal femur during the first 6 mo after RTx.

After renal transplantation (RTx), an important loss of bone mineral density is observed (1–3), which contributes to an increased incidence of fractures (4,5). The exact mechanism of this increased bone loss is unknown, but several factors might play a role: the use of corticosteroids and possibly cyclosporine, persisting hyperparathyroidism, and disturbances in vitamin D metabolism (6–8).

Few data are available regarding possible preventive therapies (9). Bisphosphonates are currently the most promising agents in the prevention of corticosteroid-induced osteoporosis (10). However, they are contraindicated in patients with moderate to severe renal insufficiency, mainly because of the lack of data regarding the safety of bisphosphonates in patients with renal osteodystrophy. There are serious concerns, especially for patients with preexisting low bone turnover disease (diabetes mellitus, aluminum exposure), where bisphosphonates could further slow down the rate of bone turnover and thus increase the fracture rate (11).

Another option for the prevention of corticosteroid osteoporosis is treatment with calcium and (active) vitamin D. Several studies have documented the efficacy of such a treatment in non-transplant patients with corticosteroid-induced osteoporosis (12,13) as well as in patients after cardiac (14,15) and liver (16) transplantation.

Recent data from our center also support the use of active vitamin D immediately after RTx. In a prospective study, we have demonstrated that vitamin D metabolism is disturbed after RTx. In almost 50% of the patients, blood levels of 1,25 dihydroxy vitamin D were below normal until 6 mo after RTx (3).

In this study, renal transplant recipients were randomized to treatment with calcium and active vitamin D or to no treatment during the first 6 mo after RTx. The data indicate that treatment attenuates bone loss after RTx.

Materials and Methods

Patients

Adult recipients (≥18 yr) of a first or second renal transplant were eligible for this study. We excluded patients who had received corticosteroid treatment within 3 mo before RTx, patients after total parathyroidectomy, and patients treated with bisphosphonates, fluoride, calcitonin, or anabolic steroids at any time before RTx. Patients with hypercalcaemia (adjusted [Ca], >2.80 mmol/L) that persisted during the first 2 wk after RTx were also excluded. Patients treated for hyperparathyroidism with calcium and/or vitamin D at the time of RTx as well as patients with diabetes mellitus or patients treated for hypothyroidism were eligible for the study. The study was approved.
by the hospital committee for studies in humans. All participants gave written informed consent.

**Study Design**

Patients were randomly assigned to either treatment with 0.25 μg of 1α-hydroxy vitamin D (Eialpha; Leo Pharmaceuticals, Weesp, The Netherlands) plus calcium lactogluconate containing 1000 mg of elemental calcium (Calcium Sandoz Fortissium; Novartis Pharma, Arnhem, The Netherlands) or to no treatment. Treatment was started after graft function was obtained, but not later than 1 mo after RTx. If severe hypercalcemia occurred (adjusted [Ca], >2.80 mmol/L), the study medication had to be interrupted and eventually stopped definitively. If hypercalcemia persisted after stopping the medication or if hypercalcemia occurred in the control group, bisphosphonates could be prescribed to reduce serum calcium. In case of a need for diuretic therapy, loop diuretics were used to prevent hypercalcemia associated with the use of thiazide diuretics.

Routine laboratory measurements (serum creatinine, calcium, phosphorus, albumin, alkaline phosphatase) were performed during regular follow-up, at least monthly. Intact parathyroid hormone (iPTH) and 25 hydroxy vitamin D were measured just before RTx and at 1, 3, and 6 mo after RTx. Twenty-four–hour urine collections were analyzed for creatinine, calcium, sodium, and protein excretion at 3 and 6 mo after RTx. Bone mineral density was assessed within 2 wk after RTx and again at 3 and 6 mo after RTx.

**Immunosuppression**

During the first 6 mo after RTx, immunosuppressive therapy consisted of cyclosporine (CsA), prednisone, and mycophenolate mofetil (MMF), except for recipients of a graft from an HLA-identical living related donor. The latter patients were treated with CsA and prednisone during the first 3 mo, after which CsA was replaced by azathioprine. The dose of prednisone was 100 mg/d intravenously for the first 3 d and 0.35 mg/kg per d for the first month; the dose was then gradually tapered to 0.10 mg/kg per d at 3 mo. CsA was dosed to a level of 150 to 300 ng/ml during the first 3 mo and 150 ng/ml thereafter. MMF was prescribed in a fixed dose of 1000 mg twice daily. Rejection treatment consisted of 1000 mg of intravenous methylprednisolone for 3 consecutive days. Steroid-resistant rejections were treated with antithymocyte globulin or an extended course of azathioprine. The dose of prednisone was 100 mg/d intravenously for the first 3 d and 0.35 mg/kg per d for the first month; the dose was then gradually tapered to 0.10 mg/kg per d at 3 mo. CsA was dosed to a level of 150 to 300 ng/ml during the first 3 mo and 150 ng/ml thereafter. MMF was prescribed in a fixed dose of 1000 mg twice daily. Rejection treatment consisted of 1000 mg of intravenous methylprednisolone for 3 consecutive days. Steroid-resistant rejections were treated with antithymocyte globulin or an extended course of oral high-dose prednisone (1500 mg within 2 wk).

**Laboratory Measurements**

Routine biochemical measurements were performed in the central clinical chemistry laboratory, using a Hitachi 747 automated analyzer (Hitachi Inc., Tokyo, Japan). 25 hydroxy vitamin D was assessed using an HPLC method (17). The normal value range is 10 to 34 ng/ml. Intact PTH was measured using a commercial assay (Nichols, San Juan Capistrano, CA). The normal value range is 1.0 to 6.5 pmol/L.

**Bone Densitometry**

Bone mineral density (BMD) of the lumbar spine (L1 to L4) and the right proximal femur was measured with dual energy x-ray absorptiometry using the Hologic QDR 1000 or QDR 4500 densitometer (Hologic Inc., Waltham, MA). The coefficient of variation (CV) of daily measurements of the lumbar spine phantom was 0.4%. The CV of lumbar spine measurements in healthy controls was 1.0% in our laboratory (data not published). All bone mineral density measurements in one patient were performed using the same densitometer. Z and T scores were calculated using the Hologic reference database.

**Radiography**

A radiograph of the lumbar spine was obtained at entry into the study. If patients had symptoms suggestive of a vertebral fracture during the study, this radiograph was repeated. If a vertebral fracture was diagnosed, the densitometry result of this vertebra was excluded from the analysis.

In case of other musculoskeletal complaints, additional investigations were performed according to the judgment of the physician.

**Power Calculation and Randomization Procedure**

Assuming a reduction of the estimated bone loss from 8.8% (1) to 3.5% during the first 6 mo after RTx and a power of 0.80 and an α of 0.05, it was calculated that at least 31 patients should be included in each group. Because of the expected higher incidence of hypercalcemia in the treated group, randomization was performed in a 3:2 ratio for treated versus nontreated patients to obtain enough patients for evaluation of the treatment effect. Patients were randomly assigned to one of the treatment groups, with stratification for sex, menopausal status, and corticosteroid use before 3 mo before RTx. Randomization was carried out by opening a sealed envelope with the lowest available study number.

**Calculations and Statistical Analyses**

The serum total calcium concentrations were adjusted for albumin following the equation:

\[
\text{adjusted calcium (mmol/L)} = \text{calcium} - (0.025 \times \text{albumin}) + 1 \text{ mmol/L}.
\]

The creatinine clearance was estimated using the Cockcroft-Gault equation (19) and was calculated from 24-h urine collections.

Analyses were performed according to the intention-to-treat principle. Comparison of continuous variables was performed using the Wilcoxon rank sum test. Spearman’s rank test was used for correlation analyses. Categorical variables were analyzed with Fisher’s exact test.

Calculations were performed using the SAS system (version 6.12; SAS institute, Cary, NC). Results are expressed as mean ± SD unless stated otherwise. \( P < 0.05 \) was considered statistically significant.

**Results**

**Patients**

One hundred thirteen renal graft recipients transplanted in our hospital between January 1998 and April 2000 participated in this study. Two patients who lost their graft before a second BMD measurement was obtained were excluded from the analysis. Demographic characteristics of the remaining 111 patients are given in Table 1. Patients were included on average 14 ± 6 d after RTx (range, 7 to 30 d). Sixty-five patients were allocated to treatment with vitamin D and calcium (CaD group), and 46 patients to no treatment (NoT group). No differences between both groups existed.

**Renal Function**

Immediate graft function was obtained in 98 patients. Delayed graft function occurred in 13 patients (8 in the CaD group, 5 in the NoT group; NS); eventually, all grafts functioned well within 3 wk. During the study period, graft failure due to chronic allograft nephropathy occurred in one patient in the CaD group. No patient death occurred. Two patients in the NoT group developed a proteinuria of >1 g/d, presumably also due to chronic allograft nephropathy.
免疫抑制和排斥

初始免疫抑制性治疗由CsA、MMF和泼尼松在100名患者中采用，持续6个月。有8名来自HLA同一的活体相关供体的受者，分别在CaD组（3名）和NoT组（5名）中接受CsA和泼尼松（NS）治疗。CaD组1名、NoT组1名受者在研究期间接受CsA、泼尼松和硫嘌呤治疗。在4名受者中，CsA被停止是因为难以忍受的副作用，同时继续MMF和泼尼松治疗（CaD组3名，NoT组1名；NS）。CaD组1名、NoT组1名受者在研究期间停止MMF，继续CsA和泼尼松治疗。NoT组1名受者在研究期间停止CsA和MMF，改为硫嘌呤，继续泼尼松。没有受者出现未计划的改变。

累积口服泼尼松剂量在两个患者组内相似（Table 2）。急性排斥的发病率也在两个组内相似（CaD组23%，NoT组24%；NS）。大多数排斥受者接受了治疗。

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CaD</th>
<th>NoT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>65</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46±12</td>
<td>49±14</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>40/25</td>
<td>25/21</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-/postmenopausal women</td>
<td>14/11</td>
<td>10/11</td>
<td>NS</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>72±12</td>
<td>72±13</td>
<td>NS</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>174±10</td>
<td>171±8</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24±3</td>
<td>24±4</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Treated hypothyroidism</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Subtotal parathyroidectomy before RTx</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Renal replacement therapy: hemodialysis/CAPD/no dialysis</td>
<td>32/30/3</td>
<td>24/17/5</td>
<td>NS</td>
</tr>
<tr>
<td>Time on dialysis (mo)</td>
<td>31±22</td>
<td>30±24</td>
<td>NS</td>
</tr>
<tr>
<td>Number of transplants (1/&gt;1)</td>
<td>60/5</td>
<td>43/3</td>
<td>NS</td>
</tr>
<tr>
<td>Corticosteroid use before 3 mo before RTx</td>
<td>10</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Cadaveric/living donor</td>
<td>49/16</td>
<td>27/19</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate/delayed graft function</td>
<td>57/8</td>
<td>41/5</td>
<td>NS</td>
</tr>
</tbody>
</table>

a CaD, vitamin D plus calcium group; NoT, no treatment.
b Excluding patients transplanted before renal replacement therapy was started.

cumulative oral prednisone dose was similar in either patient group (Table 2). The incidence of acute rejections was also similar in both groups (23% in the CaD group, 24% in the NoT group; NS). Rejections in most patients were treated

Table 2. Clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>CaD</th>
<th>NoT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>65</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Graft failure</td>
<td>1/65</td>
<td>0/46</td>
<td>NS</td>
</tr>
<tr>
<td>Patient death</td>
<td>0/65</td>
<td>0/46</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinued study medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient withdrawal</td>
<td>1/7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypercalcemia</td>
<td>6/7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with acute rejection (n)</td>
<td>15/65</td>
<td>11/46</td>
<td>NS</td>
</tr>
<tr>
<td>steroid-sensitive rejection</td>
<td>8/15</td>
<td>8/11</td>
<td></td>
</tr>
<tr>
<td>steroid-resistant rejection</td>
<td>7/15</td>
<td>3/11</td>
<td></td>
</tr>
<tr>
<td>Oral prednisone dose month 0 to 3 (mg)</td>
<td>1425±487</td>
<td>1424±293</td>
<td>NS</td>
</tr>
<tr>
<td>Oral prednisone dose month 3 to 6 (mg)</td>
<td>876±243</td>
<td>915±293</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercalcemiaab</td>
<td>6/65</td>
<td>2/46</td>
<td>NS</td>
</tr>
<tr>
<td>stop study medication</td>
<td>2/6</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>addition of bisphosphonates</td>
<td>4/6</td>
<td>1/2</td>
<td></td>
</tr>
</tbody>
</table>

a na, not applicable.
b Adjusted serum calcium, >2.80 mmol/L.
successively with intravenous methylprednisolone. Additional treatment with anti-T cell antibodies was given in seven patients in the CaD group and in three patients in the NoT group (NS; Table 2).

**Biochemical Measurements**

Biochemical data are summarized in Table 3. The iPTH level rapidly decreased within the first month after RTx. A small further decline occurred between 1 and 3 mo. Thereafter, the iPTH level stabilized, albeit at slightly elevated levels in both groups. There were no differences in iPTH and adjusted calcium levels between the treated and the control group at any time point. In both groups, alkaline phosphatase increased significantly within the normal range from baseline to 3 mo after RTx.

**Bone Mineral Density Measurements**

At study entry, lumbar BMD was numerically lower in the CaD group, and the difference in Z score reached statistical significance (Table 4). In the first 3 mo after RTx, lumbar BMD decreased by $-3.3 \pm 4.3\%$ in the CaD group ($P < 0.0001$) and $-4.1 \pm 4.8\%$ in the NoT group ($P < 0.0001$; NS between groups). In the following months, there was a recovery of lumbar BMD in the CaD group ($+0.7 \pm 4.5\%$; ns) and a further decrease in the NoT group ($-0.9 \pm 3.3\%$; NS), resulting in a significant difference ($P = 0.02$) in the amount of loss in lumbar BMD between the groups at 6 mo after RTx (CaD, $-2.6 \pm 5.0\%$ [$P < 0.0001$]; NoT, $-5.0 \pm 4.7\%$ [$P < 0.0001$]; Figure 1).

In the CaD group, baseline BMD in the femoral neck and the trochanteric region were significantly lower than in the NoT group (Table 4). At the femoral neck, a significantly larger loss of BMD was found in the NoT group during the first 6 mo (CaD, $-0.22 \pm 6.0\%$ [NS]; NoT, $-4.0 \pm 6.0\%$ [$P < 0.0001$; between groups, $P < 0.001$]). At the trochanteric region, the amount of bone loss was also significantly higher in the NoT group (CaD, $-2.2 \pm 5.6\%$ [$P < 0.01$]; NoT, $-4.3 \pm 5.7\%$ [$P < 0.0001$]; between groups, $P < 0.05$). In Ward’s triangle, BMD did not change significantly over time in either group. In the total proximal femur, there was a nonsignificant loss of BMD in the CaD group during the first 6 mo after RTx ($-0.97 \pm 4.9\%$; ns), whereas the loss of BMD in the NoT group was significantly larger ($-3.0 \pm 4.2\%$; $P < 0.0001$; between groups, $P < 0.01$).

As noted before, there was an unexpected difference in BMD between the groups at the time of RTx. To exclude that this difference in baseline BMD could have biased the data, we have performed a second analysis. For this analysis, patients in the CaD group were matched for BMD with patients from the NoT group. When comparing these newly formed groups, no more differences in baseline BMD were apparent. During the first 6 mo after RTx, lumbar BMD decreased by $-2.5 \pm 5.2\%$ in the CaD group and by $-5.0 \pm 4.7\%$ in the NoT group ($P < 0.05$). At the femoral neck, the loss in BMD was $-0.8 \pm 5.2\%$ in the CaD group (NS) and $-4.0 \pm 6.0\%$ in the NoT group ($P < 0.01$).
Side Effects and Other Events

Severe hypercalcemia (adjusted serum calcium, $>2.80$ mmol/L on more than one occasion) was slightly more frequent in the CaD group (six patients) than in the NoT group (two patients), but this was NS (Table 2). Nearly all patients who developed hypercalcemia already had a high-normal serum calcium at inclusion in the study. Urinary calcium excretion was similar at 3 mo in the two groups, but it was slightly higher in the CaD group at 6 mo after RTx (Table 3). One patient in the CaD group had a renal calculus shortly after stopping treatment with calcium and vitamin D due to hypercalcemia. Multiple vertebral fractures occurred in two patients in the NoT group. One patient in the CaD group suffered from avascular necrosis of the right hip.

Discussion

Our study clearly demonstrates that treatment with active vitamin D and calcium during the first 6 mo after renal trans-
plantation reduces bone loss in the lumbar spine and the trochanteric region and almost completely prevents bone loss in the femoral neck. Theoretically, the results could have been biased by the slight but significant differences in baseline BMD between the groups. However, additional analysis of the data indicated that these differences could not explain the results.

Our findings are in agreement with our observation that vitamin D metabolism is disturbed in the majority of renal transplant recipients in the first months after renal transplantation. In more than 50% of patients, levels of active vitamin D remain below the lowest threshold of normal in this period, which may be an important factor in causing a decreased bone mineralization (3).

We have used a fixed dose of 1α-hydroxy vitamin D and have not measured 1,25 dihydroxy vitamin D levels. Thus, we cannot exclude that higher doses of active vitamin D may have been needed to obtain even better results. Future studies must answer this question. However, increasing the dose of active vitamin D will increase the incidence of hypercalcemia, and thus may not be feasible. In this study, hypercalcemia occurred in 9% of treated patients and treatment had to be stopped in 6%.

The use of corticosteroids is regarded to be the most important causative factor in posttransplant osteoporosis. Several strategies have proved efficacy in the treatment of corticosteroid-induced osteoporosis in nonrenal patients, including calcium combined with active vitamin D (12,13), calcitonin (12), and bisphosphonates (10,20). In recipients of heart and liver transplants, calcitriol and bisphosphonates were both effective in reducing bone loss during the first postoperative year (14–16,21).

Few studies have addressed the accelerated bone loss during the first 6 mo after renal transplantation, and most data are reported in abstract form only. Our conclusion on the efficacy of a regimen containing calcium and vitamin D is supported by data of a nonrandomized study of Talalaj et al. (22), who reported that treatment with 25 hydroxy vitamin D in an initial dose of 40 μg/d plus calcium carbonate 3000 mg/d partially prevented bone loss during the first year after renal transplantation. Preliminary data from a randomized trial are also suggestive for a beneficial effect of cholecalciferol (23).

Calcitonin or bisphosphonates could be alternative treatment options. In a randomized trial comparing 200 U/d nasal calcitonin with placebo during the first year after RTx, calcitonin largely prevented bone loss (24). In a small randomized trial, two intravenous doses of pamidronate given at the time of renal transplantation and again 1 mo later, prevented bone loss at the femoral neck and possibly the lumbar spine during the first year after renal transplantation (25). However, this study has been criticized because of statistical shortcomings, and the conclusions have been partially withdrawn by the authors (26). In a recently published randomized trial, ibandronate given intravenously immediately before and at 3, 6, and 9 mo after transplantation prevented bone loss in the lumbar spine and the proximal femur nearly completely during the first year after transplantation (27).

Data concerning other options such as treatment with hormone replacement therapy, with anabolic steroids, or with fluoride in patients after renal transplantation are lacking. Currently, bisphosphonates are the most promising agents for the treatment of osteoporosis, with proven efficacy in patients with postmenopausal (28,29) and corticosteroid-induced (30,31) osteoporosis. Although the two studies mentioned above suggest that bisphosphonates are also effective in preventing bone loss after renal transplantation, there is much concern about the long-term efficacy and safety of these agents in patients with renal insufficiency. Bisphosphonates will accumulate in bone in patients with renal insufficiency, eventually resulting in a defective mineralization, thus paradoxically increasing the fracture risk.

The use of bisphosphonates is even more complex in patients with renal osteodystrophy. Renal osteodystrophy is not one entity, but encompasses several bone abnormalities with either high bone turnover (hyperparathyroidism), low bone turnover (osteomalacia and adynamic bone disease), or a mixed osteodystrophy with characteristics of high and low bone turnover. The effect of bisphosphonates may differ, depending on the underlying abnormality; beneficial effects may be expected in patients with predominantly high bone turnover (32), whereas problems may be worsened in patients with adynamic bone disease. Thus, it seems unwise to administer bisphosphonates to patients after renal transplantation without proper knowledge of bone morphology (11).

In conclusion, our data provide compelling evidence that treatment with low dose of active vitamin D and calcium is safe and partially prevents rapid bone loss during the first 6 mo after RTx. Future studies are needed to assess the efficacy of even higher doses of active vitamin D and to delineate any additional benefits of bisphosphonates.

Acknowledgments

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Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/