Long-term follow-up study on bone mineral density and fractures after simultaneous pancreas-kidney transplantation

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Background. In type 1 diabetic patients with end-stage renal failure, low bone mass is prevalent and the incidence of fractures high after simultaneous pancreas kidney transplantation (SPK). Data are scarce on preexisting skeletal morbidity or the long-term effects of SPK on bone mass and risk of fractures.

Methods. We conducted a prospective study addressing these issues in 19 consecutive SPK recipients before and at 3, 6, and 12 months, and 2.5 to 4 years after establishment of graft function.

Results. Prior to transplantation, 13 patients (68%) had hyperparathyroidism, 7 of whom had osteoporosis. Mean bone mineral density (BMD) was significantly lower at the femoral neck than at the lumbar spine (T-scores \(-2.0 \pm 0.89\) vs. \(-0.66 \pm 0.84\)). There was a significant decrease in BMD at both lumbar spine and femoral neck at 6 months post-transplantation \((-6.0 \pm 5.4\%\) and \(-6.9 \pm 4.3\%,\) respectively). No further loss was observed in the following 6 months. At 1 year post-transplantation, 9 patients had osteoporosis associated with hyperparathyroidism in 8, and none had sustained a clinical fracture. A significant albeit small increase in BMD was observed 6 months after start of alfacalcidol 0.25 \(\mu g/\)day. At end-evaluation, osteoporosis and hyperparathyroidism persisted in the patients in whom it was documented at 1 year. Five patients who had lower BMD at the femoral neck pretransplantation sustained a clinical fracture.

Conclusion. Cortical osteoporosis is prevalent in SPK recipients at the time of transplantation, progresses early post-transplantation, and is associated with relatively high incidence of fractures. Reversal of persistent hyperparathyroidism with the use of alfacalcidol may contribute to a decrease in skeletal morbidity.

Simultaneous pancreas-kidney (SPK) transplantation is currently established as the treatment of choice for patients with type 1 diabetes mellitus and end-stage diabetic nephropathy, successfully restoring normoglycemia and providing adequate renal function [1, 2]. Technical success rates have improved over the last decade, resulting in prolonged graft survival, thereby also increasing potential morbidity from other complications of the transplant process. There had recently been increased interest in addressing long-term morbidity aiming at reducing it in SPK transplant recipients. In keeping with other organ transplantation, bone loss and consequent increase in fracture rate is prevalent after SPK transplantation because of the compulsory immunosuppressive regimen, including glucocorticoids [3, 4]. We have indeed shown in a cross-sectional study, conducted more than one year after SPK, that osteoporosis is prevalent after successful transplantation, and that it is associated with a high incidence of mainly nonvertebral fractures in up to 45% of patients [5]. Intriguingly, and contrary to expectation if solely due to use of high dose glucocorticoids, osteoporosis was predominant at cortical sites. The risk of fracture is apparently also greater in SPK transplant recipients compared with kidney transplant recipients [4, 6].

In most solid organ transplant recipients, the use of glucocorticoids is thought to be the main cause of bone loss [7]. In simultaneous pancreas-kidney transplant recipients, however, other factors may well play a more prominent role. First, preexisting type 1 diabetes mellitus has been shown to be associated with low turnover bone disease and osteopenia [8–10]. Second, diabetic nephropathy and subsequent progressive renal failure is likely to be associated with secondary hyperparathyroidism, which also leads to bone loss [11–13].

In SPK recipients, data are scarce on preexisting skeletal pathology, and on the time course and characterization of bone loss following transplantation, particularly in the long-term. The aim of our study was 2-fold: first, to characterize skeletal morbidity before transplantation, and second, to determine changes occurring in the years following establishment of graft function. Pathophysiological processes involved are discussed, and clinical implications of our findings are outlined.
METHODS

Patients

We studied 22 consecutive patients with type 1 diabetes mellitus and end-stage renal failure who underwent simultaneous pancreas-kidney transplantation at the Leiden University Medical Center between 1995 and 1997. Three patients were excluded from the study, 2 because they had parathyroidectomy before transplantation, and 1 because of a nonfunctioning kidney graft and return to dialysis. Failure of the pancreas graft was not an exclusion criterion.

Study design

This was a prospective study in which patients were evaluated before the transplantation, as part of the pre-transplant work-up, and at regular intervals thereafter for 18 months post-transplant (3, 6, 12, and 18 months). A further single end-evaluation was undertaken 2½ to 4 years after transplantation. Each evaluation consisted of a full clinical examination, laboratory investigations, and bone mineral density (BMD) measurements. All clinical fractures were carefully documented and confirmed radiologically.

At the end of the first year post-transplantation, all patients were started on the synthetic analog of active vitamin D (alfacalcidol) at a fixed dose of 0.25 µg per day. Informed consent was obtained from all patients.

Transplantation procedure

Simultaneous pancreas-kidney transplantation was performed using the bladder-drainage technique with systemic insulin delivery. All patients received triple immunosuppressive therapy including glucocorticoids, microemulsion cyclosporine, and mycophenolate mofetil (2 g/day) or azathioprine (1.5–2.0 mg/kg/day; N = 7). Prednisone was started at a dose of 50 mg twice daily for the first 3 days, quickly tapered to 20 mg daily at 4 weeks, 15 mg daily at 3 months, and 10 mg daily from 9 months onwards. Cyclosporine was started at a dose of 8 to 10 mg/kg/day, aiming for trough serum levels of 300 ng/mL (range 250–350 ng/mL). The dosage was adjusted from 3 months post-transplant onward, to maintain a trough level of 150 ng/mL (range 100–200 ng/mL). No prophylactic therapy with poly- or monoclonal antibodies was given. Rejection episodes were treated with 3 1-g pulses of methylprednisolone (SoluMedrol®; Pharmacia, Woerden, The Netherlands), and steroid-resistant episodes with anti-thymocyte globulin (ATG; RIVM, Bilthoven, The Netherlands). In the event of a third rejection episode, treatment with methylprednisolone was repeated, sometimes followed by OKT3 rescue therapy, depending on the patients’ clinical condition. Immunosuppression was altered to cyclosporine and prednisone only in the event of loss of pancreatic graft function. All patients received individually tailored doses of bicarbonate to correct for their tendency to metabolic acidosis.

Laboratory investigations

Graft function was determined at each time point by measuring endogenous creatinine clearance and HbA1c concentrations. Serum calcium, albumin, creatinine, and alkaline phosphatase activity, and urine calcium and creatinine were measured by automated techniques. Serum calcium concentrations were adjusted to an albumin concentration of 42 g/L. Plasma parathyroid hormone (PTH) concentrations were measured by an immunoradiometric assay, detecting the intact molecule (Nichols Institute Diagnostics, Wijchen, The Netherlands), and serum 25-hydroxy vitamin D (25-OHD) and 1,25-dihydroxyvitamin D (1,25-(OH)2-D), and osteocalcin by commercial radioimmunoassays (Incstar/DiaSorin, Stillwater, MN, USA).

Bone densitometry

Bone mineral density measurements (BMD) were undertaken at the lumbar spine (L1-L4) and at the femoral neck using dual x-ray absorptiometry (Hologic QDR 1000 or Hologic QDR 4500; Hologic, Waltham, MA, USA). At some stage during follow-up our nuclear medicine department switched to measuring BMD exclusively using the Hologic QDR 4500 densitometer. A conversion formula obtained from double bone densitometry measurements on 300 patients on both the Hologic QDR 1000 and the Hologic QDR 4500 allowed us to follow-up changes in bone mineral density across this period (it must be noted that the conversion formula had to be applied in 3 patients only). The formula we used was:

\[
\text{At the lumbar spine: } \text{BMD}_{\text{HologicQDR1000}} = (\text{BMD}_{\text{HologicQDR4500}} - 0.0109)/0.9736
\]

\[
\text{At the femoral neck: } \text{BMD}_{\text{HologicQDR1000}} = (\text{BMD}_{\text{HologicQDR4500}} - 0.01195)/0.98025
\]

Changes in BMD (delta) were calculated using the absolute values for BMD (g/cm²). Further results are expressed as T- and Z-scores, respectively, denoting the number of standard deviations below the mean for young adults and age- and sex-matched controls. WHO criteria were used to define osteoporosis (T-score < −2.5) and osteopenia (T-score > −2.5, < −1) [14].
Table 1. Patients’ characteristics at the time of simultaneous pancreas-kidney transplantation (N = 19)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>68%</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>32%</td>
</tr>
<tr>
<td>Age years</td>
<td>39 ± 7.4</td>
<td></td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>23 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes years</td>
<td>25 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.6 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>47%</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>4</td>
<td>21%</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>6</td>
<td>32%</td>
</tr>
<tr>
<td>Duration of dialysis months</td>
<td>17 ± 12</td>
<td></td>
</tr>
</tbody>
</table>

*Only patients with dialysis were included.

Statistical analysis

Values are expressed as mean ± standard deviation except where otherwise indicated. Non-normally distributed variables such as PTH and osteocalcin were log-transformed before analysis. The SPSS for Windows software package (Chicago, IL, USA) was used for all statistical analysis. Fisher exact tests were used to compare nominal variables, and independent samples Student t tests for continuous variables. Paired Student t tests were applied to compare continuous variables before and after transplantation. Pearson’s correlation’s coefficient was used as necessary. A P value of < 0.05 was considered statistically significant.

RESULTS

Baseline evaluation

Patients. There were 13 (68%) men and 6 (32%) women with a mean age of 39 ± 7.4 years. Five of the 6 female patients were premenopausal, 3 of whom were on oral contraceptives. The 1 postmenopausal female patient was not treated with hormone replacement therapy. None of the male patients had hypogonadism. Ten patients (53%) were on dialysis. Mean creatinine clearance of the other 9 patients was 18 ± 7 mL/min. Pretransplant baseline patients’ characteristics are summarized in Table 1. Baseline evaluation was performed within 1 year prior to transplantation in all patients (mean 6.3 ± 2.8 months).

Laboratory investigations. Three patients had mildly elevated serum calcium concentrations, with adequately suppressed PTH values in 2, and a raised PTH in the third, indicating parathyroid autonomy. Serum phosphate concentration was increased in 14 patients. Serum osteocalcin concentrations were increased in 15 of the 16 patients in whom this parameter of bone formation was measured. A total of 13 patients (68%) had evidence for secondary hyperparathyroidism as defined before transplantation by PTH levels >10 pmol/L in the presence of low or normal serum calcium concentrations. 25-OH vitamin D measurements were decreased in 4 patients, who also all had elevated PTH levels. There was a significant relationship between PTH and osteocalcin concentrations (r = 0.60, P = 0.014).

Bone mineral density. Seven patients (37%) had cortical osteoporosis as evidenced by a femoral neck T-score below −2.5 SD before transplantation (mean T-score −2.0 ± 0.89 SD; mean Z-score −1.34 ± 0.91; Fig. 1). In contrast, none of the patients had osteoporosis at the lumbar spine prior to transplantation (mean T-score −0.66 ± 0.84 SD; mean Z-score −0.41 ± 0.93). Patients on dialysis before transplantation had significantly lower femoral neck T- and Z-scores than patients who did not dialyze (T-score −1.4 ± 0.8 vs. −2.6 ± 0.5; Z-score −0.7 ± 0.8 vs. −1.9 ± 0.6; both P = 0.001), but there was no difference in lumbar spine T- and Z-scores. There was no correlation of log-transformed PTH and osteocalcin concentrations with BMD measurements.

Accurate fracture data were not available pretransplantation.

Sequential changes within the first year post-transplantation

As per inclusion criteria, all 19 patients had sufficient kidney function throughout the first year after transplantation, with endogenous creatinine clearance ranging from 28 to 115 mL/min. Seventeen patients (89%) were normoglycemic and insulin-independent, indicating adequate function of the pancreatic graft. None of the patients received hormone replacement therapy after transplantation. Sixteen patients (84%) had a mean of 2 rejection episodes (range 1 to 4). All rejection episodes took place within the first 6 months post-transplantation. The effect of cumulative prednisone doses on various outcome variables could not be adequately assessed because...
the cumulative prednisone dosage was similar in the majority of the patients.

**Laboratory investigations.** Serum calcium concentrations were within the normal laboratory reference range in all but 2 patients, who had mildly elevated concentrations throughout the study. Serum phosphate concentrations normalized in due course in all patients, with 5 patients having mild transient hypophosphatemia early post-transplantation. Serum osteocalcin concentrations decreased in all patients during the first 3 months post-transplantation \((P < 0.001)\), and this decrease was sustained throughout the year. In contrast, alkaline phosphatase activity was within the normal range and did not change throughout the year. Mean PTH levels significantly decreased post-transplantation \((P = 0.001\) at 6 months), although 8 patients (42%) still demonstrated evidence for hyperparathyroidism at the 1-year time point. There was a significant correlation between serum PTH and osteocalcin concentrations \((r = 0.79; P < 0.001)\). Sequential changes in biochemical parameters of bone and mineral metabolism are summarized in Table 2.

**Bone mineral density.** There was a rapid decrease in mean BMD at both lumbar spine and femoral neck sites observed as early as 3 months, persisting at 6 months post-transplantation. No further bone loss was observed at either site from 6 months onward. Changes in BMD measurements after transplantation are illustrated in Figure 2. All but 1 patient experienced bone loss at the lumbar spine site within 3 months after transplantation, with a maximum loss of 10% (mean change \(-5.1 \pm 3.3\%\); \(P < 0.001)\). Mean bone loss at the femoral neck was \(3.7 \pm 3.8\%\) at the 3-month evaluation \((P = 0.001)\). In the majority of patients (63%) the lumbar spine BMD decreased further between 3 and 6 months post-transplantation to \(94 \pm 4.3\%\) of baseline. Similarly, all patients showed a decrease in BMD at the femoral neck during the first 6 months after transplantation (mean loss \(6.9 \pm 5.4\%\); \(P < 0.001)\). Mean BMD remained stable at both the lumbar spine and the femoral neck between 6 months and 1 year after transplantation (mean change \(0.0 \pm 3.0\%, \text{NS}\), and \(-1.0 \pm 4.2\%, \text{respectively, NS}\)). Compared to baseline evaluation, 9 patients had osteoporosis at the femoral neck (47%), and only 1 patient (5%) at the lumbar spine at 1 year post-transplantation. There was no correlation between initial BMD and the amount or rate of bone loss.

None of the patients experienced clinical fractures during the first year after transplantation.

**Long-term follow-up**

Seventeen patients were evaluated 2\(1/2\) to 4 years after transplantation (mean \(40 \pm 6\) months). One patient developed bronchus carcinoma and widespread skeletal metastases and died 3 years after transplantation. The other chose to discontinue his participation in the study for personal reasons. Twelve patients had an additional evaluation at 18 months post-transplantation. Kidney graft function remained stable in all patients during follow-up (endogenous creatinine clearance range 29 to 99 mL/min). Two patients lost their pancreas graft function 1 and 3 years post-transplant, and had to return to

**Table 2. Biochemical parameters of bone and mineral metabolism in serum (mean ± SD)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior to SPK</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>30–48 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine mmol/L</td>
<td>649 ± 277</td>
<td>148 ± 36</td>
<td>144 ± 38</td>
<td>139 ± 42</td>
<td>143 ± 31</td>
<td>150 ± 61</td>
</tr>
<tr>
<td>Calcium mmol/L (^a)</td>
<td>2.38 ± 0.21</td>
<td>2.38 ± 0.12</td>
<td>2.36 ± 0.1</td>
<td>2.33 ± 0.1</td>
<td>2.29 ± 0.1</td>
<td>2.41 ± 0.1</td>
</tr>
<tr>
<td>Phosphate mmol/L</td>
<td>1.74 ± 0.47</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>NA</td>
</tr>
<tr>
<td>Alkaline phosphatase U/L</td>
<td>97 ± 39</td>
<td>101 ± 39</td>
<td>106 ± 34</td>
<td>98 ± 26</td>
<td>89 ± 32</td>
<td>77 ± 25</td>
</tr>
<tr>
<td>Osteocalcin μg/L</td>
<td>12.1 ± 6.6</td>
<td>3.7 ± 2.7</td>
<td>5.2 ± 3.2</td>
<td>5.8 ± 3.3</td>
<td>4.8 ± 2.7</td>
<td>NA</td>
</tr>
<tr>
<td>25-OHD nmol/L (^b)</td>
<td>49 ± 23</td>
<td>30 ± 17</td>
<td>35 ± 14</td>
<td>30 ± 16</td>
<td>51 ± 17</td>
<td>NA</td>
</tr>
<tr>
<td>1,25-(OH)(_2)-D pmol/L (^c)</td>
<td>30 ± 17</td>
<td>43 ± 21</td>
<td>58 ± 24</td>
<td>61 ± 28</td>
<td>55 ± 18</td>
<td>NA</td>
</tr>
<tr>
<td>Parathyroid hormone pmol/L</td>
<td>17 ± 13</td>
<td>11 ± 11</td>
<td>6.6 ± 3.5</td>
<td>10.9 ± 13</td>
<td>6.7 ± 7</td>
<td>10.0 ± 6.7</td>
</tr>
</tbody>
</table>

\(^a\)Calcium corrected for an albumin of 42 g/L.
\(^b\)25-OHD: 25-hydroxyvitamin D.
\(^c\)1,25-(OH)\(_2\)-D: 1,25-hydroxyvitamin D.
insulin injections. HbA1c measurements were in the normal range in 16 patients (84%). The 3 patients on insulin had HbA1c levels of 7.8% to 11.5%. From 1 year onward, all patients received alfacalcidol at a fixed dose of 0.25 μg per day.

**Laboratory investigations.** There was a significant increase in serum calcium concentration (+0.08 ± 0.02 mmol/L; *P* = 0.002) in the first 6 months following the start of treatment with alfacalcidol. This was not associated with a significant decrease in PTH. At end-evaluation, 10 patients (59%) had persistently elevated PTH levels.

**Bone mineral density.** A significant increase in BMD was observed at the lumbar spine in the first 6 months following start of alfacalcidol treatment (mean +1.7 ± 2.1%; *N* = 11; *P* = 0.028). BMD at the femoral neck also increased, albeit nonsignificantly.

At end-evaluation, overall mean BMD loss compared with baseline was 4.6 ± 5.7% at the lumbar spine, and 4.6 ± 4.7% at the femoral neck (*P* = 0.006 and *P* = 0.001, respectively). As a result of this, mean T-score at the lumbar spine was −1.0 ± 1.0 SD, and mean T-score at the femoral neck −2.3 ± 1.0 SD at end-evaluation. Mean Z-scores were −0.7 ± 1.2 SD at the lumbar spine, and −1.5 ± 1.1 SD at the femoral neck. Compared with baseline, 9 patients (47%) had osteoporosis at the predominantly cortical femoral neck site. Only 1 patient developed osteoporosis at the lumbar spine (5%). There were no differences in BMD observed between patients with or without pancreas graft function.

**Fractures.** Five patients (29%) sustained clinical fractures more than 1 year after transplantation (range 1.3–4.0 years). Most fractures occurred at peripheral sites (feet). Two patients had multiple peripheral fractures (clavicle/foot and humerus/foot). One patient had both a vertebral and a peripheral fracture (radius). Patients with fractures had a higher mean serum osteocalcin concentration at the pretransplant work-up (18.8 ± 7.1 μg/L vs. 9.1 ± 3.7 μg/L; *P* = 0.003). Patients with fractures also had significantly lower T-scores at the femoral neck site before transplantation (−2.6 ± 0.7 SD vs. −1.7 ± 0.9 SD; *P* = 0.033). These significantly lower T-scores persisted throughout the first year post-transplant. Patients who sustained fractures had significantly higher PTH and osteocalcin concentrations, and significantly lower T-scores at the femoral neck 1 year post-transplantation than their counterparts without fractures, although they did not demonstrate more accelerated bone loss. There were no differences in sex, age, rejection episodes, immunosuppressive regimens, or post-transplantation kidney and pancreas function between patients with or without fractures. Table 3 summarizes pre- and post-transplant factors in patients with and without fractures post-transplantation.

### Table 3. Characteristics of patients with and without fractures after transplantation

<table>
<thead>
<tr>
<th></th>
<th>No fracture (N = 13)</th>
<th>Fracture (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretransplant factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients on dialysis %</td>
<td>4 (31%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Parathyroid hormone pmol/L</td>
<td>15.2 ± 12</td>
<td>20.4 ± 15</td>
</tr>
<tr>
<td>Osteocalcin μg/L</td>
<td>9.1 ± 3.7</td>
<td>18.8 ± 7.1</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>8.9 ± 1.9</td>
<td>8.3 ± 1.1</td>
</tr>
<tr>
<td>BMD at femoral neck (T-score; SD)</td>
<td>−1.7 ± 0.9</td>
<td>−2.6 ± 0.7</td>
</tr>
<tr>
<td>BMD at lumbar spine (T-score; SD)</td>
<td>−0.5 ± 0.8</td>
<td>−1.0 ± 1.0</td>
</tr>
<tr>
<td><strong>Posttransplant factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance mL/min</td>
<td>65 ± 19</td>
<td>60 ± 27</td>
</tr>
<tr>
<td>Parathyroid hormone pmol/L</td>
<td>5.6 ± 2.7</td>
<td>20.7 ± 19</td>
</tr>
<tr>
<td>Osteocalcin μg/L</td>
<td>4.3 ± 1.7</td>
<td>8.3 ± 3.9</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>6.1 ± 1.8</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>BMD at femoral neck (T-score; SD)</td>
<td>−2.0 ± 0.9</td>
<td>−3.0 ± 0.7</td>
</tr>
<tr>
<td>BMD at lumbar spine (T-score; SD)</td>
<td>−1.2 ± 0.9</td>
<td>−1.5 ± 1.2</td>
</tr>
<tr>
<td>BMD loss at femoral neck %</td>
<td>5.4 ± 3.4</td>
<td>6.1 ± 5.9</td>
</tr>
<tr>
<td>BMD loss at lumbar spine %</td>
<td>6.0 ± 5.9</td>
<td>5.8 ± 5.9</td>
</tr>
</tbody>
</table>

* Except when otherwise indicated, all results are expressed as mean ± SD.

* *P* < 0.05.

**DISCUSSION**

To our knowledge, this is the first study reporting sequential changes in bone mineral density and risk of fracture in simultaneous pancreas-kidney transplant recipients from before transplantation up to 4 years after successful establishment of graft function. We have previously reported a high incidence of cortical osteoporosis and peripheral fractures in SPK transplant recipients in a cross-sectional study undertaken more than 1 year after transplantation [5]. Our data from the present study establish preexisting cortical osteoporosis at the time of transplantation, likely to be related to the diabetic state, as the major cause for the high skeletal morbidity in SPK transplant recipients although secondary hyperparathyroidism due to renal impairment also plays a contributory role. We also confirm the significant bone loss observed overall in solid organ transplant recipients, within the first 6 months post-transplantation. This loss is likely to be due to glucocorticoid use as part of the immunosuppressive regimen. However, contrary to expectation, we show no further bone loss past the first 6 months post-transplantation, and a significant, albeit marginal, increase in BMD following treatment with alfacalcidol. Of note is that, despite the early decrease in BMD patients sustained clinical fractures only a year after transplantation. The fact that the vast majority were peripheral fractures is not surprising considering the predominantly cortical osteoporosis.

Patients with type 1 diabetes mellitus have been shown to have a low bone mass, particularly at cortical sites [15–19]. In diabetic patients, low bone formation rates are believed to account for the low bone turnover state [8–10]. The development of diabetic nephropathy and progressive renal failure adds another dimension to the bone
pathology. Secondary hyperparathyroidism is common in patients with end-stage renal failure, and is associated with high bone turnover and a decrease in predominantly cortical bone mineral density [11–13]. In our study, secondary hyperparathyroidism was prevalent, and high bone turnover was suspected by the increased osteocalcin levels in the majority of patients. These findings somewhat contrast with the commonly described low turnover state characterizing patients with type 1 diabetes mellitus [8, 9]. Rix et al observed that bone mineral density decreased parallel to declining renal function, and that the decrease was most pronounced in the femoral neck. The combination of type 1 diabetes mellitus and impaired renal function was associated with lower bone mineral density measurements than those observed in patients with renal failure not due to diabetes [13]. As expected with the high prevalence of cortical osteoporosis, an increase in the risk of hip fracture was recently documented in a large registry study of patients with end-stage renal failure [20].

Post-transplantation bone disease has been well documented after solid organ transplantation [3]. Immunosuppressive agents together with persistent hyperparathyroidism are believed to be the main cause of bone loss in renal transplant recipients. It has clearly been shown that the use of high-dose glucocorticoids leads to rapid bone loss during the first months after transplantation, mainly affecting trabecular bone [21–23]. The effect of cyclosporine, azathioprine, and mycophenolate mofetil appears to be limited [3, 24]. In the present study, we demonstrate a pattern of accelerated trabecular and cortical bone loss during the first 6 months after simultaneous pancreas-kidney transplantation. These findings are consistent with those found in kidney transplant recipients in the early stages after transplantation, and are highly likely to be related to the high levels of immunosuppression required early after transplantation [23, 25, 26]. Our data on stabilization of bone mineral density after the first 6 months post-transplantation are in contrast with those of Julian et al, who observed a continuing decrease in bone mineral density up to 18 months in kidney transplant recipients [23]. Other studies have also demonstrated slow ongoing bone loss [27, 28], while Grotz et al found that the bone loss was limited to the first year in kidney transplant recipients [26].

Our patients were uniformly treated with a fixed dose of alfacalcidol of 0.25 μg per day from a year after transplantation onward. We observe a significant albeit small increase in bone mineral density in those patients in whom it was measured within 6 months of starting treatment (N = 11). We may have been too cautious in the design of our study by restricting the dose of alfacalcidol to 0.25 μg per day. The persistence of secondary hyperparathyroidism despite treatment with alfacalcidol indeed suggests that this dose may have been insufficient to normalize PTH secretion. Even so, the role of alfacalcidol in maintaining bone mineral density is difficult to accurately assess, as numbers are small, duration of evaluation short, and we have not studied a comparable group of patients not receiving this agent. A marked increase in the incidence of fractures is reported after solid organ transplantation, particularly in kidney transplant recipients with diabetes [4, 29, 30]. Pancreas-kidney transplant recipients are at increased risk of fracture compared with recipients of kidney transplants alone, with a recorded fracture prevalence of nearly 50% [6]. In a previously published cross-sectional study, we found a comparable, predominantly nonvertebral fracture rate of 45% more than 1 year after simultaneous pancreas-kidney transplantation [5]. In the present study, clinical fractures were sustained in about a third of patients over a mean follow-up period of 3.3 ± 0.5 years. Patients who have sustained a fracture indeed had a low bone mass predominantly at the cortical femoral neck site at the pretransplant work-up. The lower fracture rate we observe is possibly due to an underestimate of additional silent fractures, as only symptomatic clinical fractures were recorded.

All fractures were sustained more than 1 year after transplantation. The late timing of the fractures has significant implications for the clinical management of these patients, as more time may be available to implement preventive measures. The use of lowest possible dose of prednisone and adequate supplementation with calcium and vitamin D has been advocated as prevention for osteoporosis after organ transplantation [7, 22, 31]. Supplementation with both calcium and vitamin D is also recommended in glucocorticoid-induced osteoporosis [32, 33]. A recent study in kidney transplant recipients showed that treatment with low dose vitamin D and calcium partially prevents the initial rapid bone loss observed in the first 6 months after transplantation [34]. A beneficial effect of this therapeutic maneuver was observed at both lumbar spine and femoral neck sites. In our patients, alfacalcidol treatment appeared to result in a significant increase in lumbar spine bone density, but these findings should be interpreted with caution because of limited numbers and lack of a control group. Although bisphosphonates have been shown to be effective in preventing bone loss and increasing bone mass in glucocorticoid-induced osteoporosis [32], data on the use in solid organ transplantation are scarce [7, 35, 36]. Whether bisphosphonates would be beneficial in decreasing the risk of fracture in SPK transplant recipients remains to be explored.

**CONCLUSION**

We observe that skeletal morbidity is high in patients undergoing simultaneous pancreas-kidney transplantation. Cortical osteoporosis is prevalent due to the
preexisting diabetic state and secondary hyperparathyroidism, which persists after transplantation. Significant bone loss is observed within 6 months of transplantation at both trabecular and cortical sites, and the risk of fractures is significantly increased after the first year of transplantation. Our data hold important clinical implications in the management of SPK transplant recipients. The significant contributory role of secondary hyperparathyroidism in the pathophysiology of bone loss before and after transplantation suggests that adequate therapeutic interventions, mainly using active metabolites of vitamin D, should be implemented long before SPK transplantation is considered, and certainly continued thereafter. Whether additional treatment with bisphosphonates could further decrease skeletal morbidity remains to be established.

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