Analysis of Fracture Prevalence in Kidney-Pancreas Allograft Recipients

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Abstract. Fractures occur in 11 to 26% of renal allograft recipients after transplantation despite improvements in bone and mineral disorders. This high fracture rate is likely a consequence of accelerated osteopenia. The cause of posttransplant bone loss is multifactorial, and patients with insulin-dependent diabetes mellitus and renal failure may have additional fracture risks such as low turnover bone disease. This retrospective cohort study was undertaken to determine the long-term incidence and the potential risk factors of posttransplant fractures in patients with insulin-dependent diabetes mellitus undergoing combined kidney-pancreas allograft transplantation. Thirty-five patients with insulin-dependent diabetes mellitus who received a combined kidney-pancreas allograft between 1987 and 1992 were evaluated. Thirty-five kidney allograft recipients matched for age, gender, and the date of transplant were also reviewed. The fracture incidence in the kidney-pancreas group was 49% after transplantation. The rate of first fracture after kidney-pancreas transplantation was 12.1% per patient year, resulting in a 5-yr fracture-free rate of 48%. The initial fracture occurred at a mean of 31.06 ± 19.9 mo. Steroid exposure was found to increase the risk of fracture, and analysis by means of a Cox regression model estimated that an increase in cumulative steroid exposure of 10 mg/kg at any given month increased the hazard of sustaining a fracture by 9% (95% confidence interval for hazard ratio, 1.01 to 1.18; P = 0.031). This analysis suggests that kidney-pancreas recipients are at significant risk of sustaining a fracture within a few years after transplantation. (J Am Soc Nephrol 9: 677–683, 1998)

Successful renal transplantation corrects many of the disorders of mineral metabolism associated with chronic renal failure. The presence of a functional kidney normalizes serum phosphorus and calcium regulation, leads to increased synthesis of calcitriol, and generally reverses secondary hyperparathyroidism (1–3). However, despite the correction of many of the mineral and bone abnormalities associated with end-stage renal disease, osteopenia and the incidence of fracture greatly increase after renal transplantation. The incidence of fracture has been reported to range from 11 to 26% after successful transplantation (4,5). This increase in fracture incidence is believed to be secondary to the rapid development of osteopenia after transplantation. An accelerated loss of trabecular bone during the first 6 mo after renal transplantation has been documented by several investigators (6–9). This early rapid decrease of bone mineral density is usually followed by a period of continued slow demineralization over the first year and a half (6). However, in long-term cross-sectional studies, a stabilization of (8) or a secondary increase in (8,10) bone mineral density has also been described.

The use of corticosteroids both for rejection therapy and maintenance immunosuppression has been implicated as the major risk for osteopenia and fractures in transplant recipients (6–9,11). This association is supported by the early rapid bone loss that occurs at a time when patients have the largest corticosteroid exposure. The use of cyclosporine has resulted in the administration of lower doses of glucocorticoids and improved survival of renal allografts; however, severe osteopenia continues to occur. The persistence of osteopenia with cyclosporine-based regimens may be due to direct effects of cyclosporine on bone, which may accelerate bone loss (12,13). In addition, renal transplant recipients may be particularly vulnerable to posttransplantation bone loss because of preexisting bone and mineral disorders, persistent hyperparathyroidism, renal dysfunction, and chronic graft rejection.

Diabetes mellitus is a common cause of renal failure accounting for approximately 38% of patients with end-stage renal disease. Approximately 25% of all transplant recipients have insulin-dependent diabetes mellitus (IDDM) as their original disease (14). Most studies on posttransplant bone disease have focused on patients who do not have diabetes. In a previous review of long-term follow-up of kidney-pancreas patients, we observed a 36% incidence of fracture (15). Patients who have IDDM with or without chronic renal failure are predisposed to low-turnover bone disease and osteopenia, presumably secondary to factors such as hypocalcemia, insulin insufficiency, hypomagnesemia, relative hypoparathyroidism,
and a propensity for metabolic acidosis (16–21). Those patients with diabetes mellitus have a higher incidence of fractures than the nondiabetic population (22). Patients with diabetes mellitus can present with osteoporotic bone changes early in the course of their disease, even at the time of diagnosis (23,24). It has been suggested that the bone defect of IDDM may be related to a decrease in bone formation during the growth period rather than bone loss per se. (23,24). In patients with chronic renal failure and diabetes, an increased incidence of adynamic bone disease is observed (20), and adynamic bone has been suggested to be a risk factor for fracture after transplantation (25).

To determine whether the correction of hyperglycemia with a combined kidney-pancreas allograft reduces the risk of post-transplant fracture, a retrospective analysis was performed. Thus, we analyzed the long-term incidence of posttransplant fracture in a group of diabetic patients undergoing kidney-pancreas transplantation and compared it with a kidney-alone transplant group.

Materials and Methods

Patients

This study included 35 patients who underwent a combined kidney-pancreas transplant between February 1987 and February 1992 at the University of Chicago and who met the following criteria: age > 18 yr, first transplant, IDDM, and adequate organ function for at least 1 yr. Dialysis information was available for all patients. Of the 35 patients, 17 received 11.4 ± 7.4 mo of hemodialysis, 10 received 19.1 ± 11.4 mo of peritoneal dialysis, and eight received no renal replacement therapy before transplantation. Mean age ± SD of onset of diabetes was 12.7 ± 8.7 (range, 3 to 38). None had a parathyroidectomy before transplantation, although one female subject underwent the surgery 12 mo after transplantation. Bladder drainage of exocrine secretions was performed in 32 kidney-pancreas recipients and enteric drainage was performed in three recipients.

A group of 35 kidney allograft recipients matched for age and gender, transplanted during the same time period, were identified. The cause of end-stage renal disease for this population was chronic glomerulonephritis in 14 patients, hypertension in nine patients, diabetic nephropathy in seven patients, lupus nephritis in three patients, reflux nephropathy in one patient, and polycystic kidney disease in one patient. Among kidney recipients, 29 patients had been treated with hemodialysis for 37.8 ± 36.4 mo, five patients with peritoneal dialysis for 15 ± 6.1 mo before transplantation, and one patient received no renal replacement therapy. Mean age ± SD of onset of diabetes was 25.8 ± 11.3 yr (range, 13 to 42 yr) for the kidney allograft recipients with diabetic nephropathy. One kidney-only patient had a parathyroidectomy before transplantation.

Study Design

The records of all patients who met the inclusion criteria were reviewed. The baseline clinical data collected from hospital and physician records included race, type of pancreatic drainage, and the number of rejection episodes until the time of first fracture, graft loss, death, or last follow-up (whichever occurred first). The posttransplant fracture date, number of pretransplant and posttransplant fractures, and the total number of fractures were confirmed by reviewing radiology files and through patient interviews.

Immunosuppressive Therapy

Thirty-one of 35 kidney-pancreas recipients and 31 of 35 kidney recipients received OKT3, antilymphocyte globulin, or antithymocyte globulin induction. All patients took cyclosporine, prednisone, and azathioprine for maintenance immunosuppression. The initial prednisone dose was 1 mg/kg body wt per d during the first week after surgery, after which it was gradually reduced to 0.2 mg/kg per d by 4 mo. Cyclosporine was started at a dose of 6 mg/kg to maintain a trough level of 350 to 400 ng/ml for the first 3 mo after transplantation. The daily dose was then gradually reduced to establish a trough level of 150 to 200 ng/ml 4 mo after transplantation and to maintain a trough level of 100 to 150 ng/ml after 1 yr. Azathioprine was started at 2.5 mg/kg per d. In the absence of side effects, the azathioprine dose was not changed. Episodes of acute graft rejection diagnosed by biopsy were treated with pulse steroids. Corticosteroid rejection therapy consisted of 500 mg of methylprednisolone administered intravenously daily for 3 d, combined with a prednisone taper to the prerejection dose over a 2-wk period. OKT3 or lymphocyte immunoglobulin, anti-thymocyte globulin (equine) was used to treat steroid refractory rejections. Immunosuppression regimens were unchanged during the study period.

Statistical Analyses

Analyses were performed from the time of transplant until first fracture. Patients who died, experienced graft loss, were lost to follow-up, or completed the study without a fracture were censored at that time. The fracture-free survivor curves were estimated separately for the two transplant groups, using the Kaplan–Meier method. The log-rank test was used to compare the two groups, first by including all patients, and then by analyzing only patients who had diabetes mellitus. Because none of the kidney allograft recipients sustained fractures during the follow-up period, we were unable to model the difference between the two groups controlling for covariates. However, for the kidney-pancreas recipients, a Cox regression model was fit to the time to first fracture (26). Covariates considered for inclusion in the model included gender, age at the time of transplant, year of transplant (1987 to 1992), age at onset of diabetes mellitus (range, 3 to 38 yr), and years with diabetes mellitus before transplant (range, 12 to 35 yr). Cumulative steroid and cyclosporine doses were also included as time-varying covariates. The cumulative steroid dose was calculated by converting the dose of methylprednisolone to an equivalent dose of prednisone by multiplying it by 1.25. The daily immunosuppression doses (divided by the patient’s body weight) were summed over time to obtain a cumulative prednisone dose in milligrams per kilogram. The type of pancreatic drainage was not analyzed as a covariate because only three patients had enteric drainage of exocrine secretions. Estimated hazard ratios from a Cox model, together with approximate 95% confidence intervals (CI), are reported.

Results

The demographics and clinical characteristics of the study population are listed in Tables 1 and 2, respectively. Because each kidney-pancreas patient was matched with a kidney transplant patient of the same age and sex, the male/female ratio and age distribution are the same in the kidney-pancreas and kidney groups. Nearly all of those with a combined kidney-pancreas transplant were white and all had IDDM. Ninety-one percent of kidney-pancreas recipients had one or more rejection episodes, and four patients had experienced a fracture before transplantation. None had previously received steroid therapy. The mean
Table 1. Patient demographic data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Kidney-Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Males/females</td>
<td>22/13</td>
<td>22/13</td>
</tr>
<tr>
<td>Age</td>
<td>35.5 ± 8.7</td>
<td>35.0 ± 10.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (100)</td>
<td>7 (20)</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>32 (91)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>African-American</td>
<td>2 (6)</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>peritoneal dialysis</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>duration (mo)</td>
<td>19.1 ± 11.4</td>
<td>15.6 ± 6.1</td>
</tr>
<tr>
<td>hemodialysis</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>duration (mo)</td>
<td>11.4 ± 7.4</td>
<td>37.8 ± 36.4</td>
</tr>
<tr>
<td>No pretransplant dialysis</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>49 ± 28</td>
<td>41 ± 28</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± SD or number. Percentages are given in parentheses.

Table 2. Clinical data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Kidney-Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 rejection (%)</td>
<td>32 (91)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Previous transplant (%)</td>
<td>0</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Previous steroid use (%)</td>
<td>0</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Failed graft</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

cumulative steroid dose was 4.6 g (range, 1.8 to 8.3 g) at 1 mo and 11.6 g at 1 yr (range, 6.1 to 18.8 g) after transplantation. The mean cumulative cyclosporine dose was 14.5 g (range, 9.1 to 23.5 g) at 1 mo and 143.8 g at 1 yr (range, 94.9 to 217.2 g). The median serum bicarbonate concentration after transplantation was 23.4 mEq/L (range, 18.0 to 27.8 mEq/L) for those who had a fracture and 23.4 mEq/L (range, 18.8 to 28.4 mEq/L) for those who did not. The mean follow-up time in the kidney-pancreas group was 49 ± 28 mo. Seventeen patients sustained a total of 25 fractures during this time. Of these 17 patients, 10 patients (59%) suffered one fracture, whereas four patients (23%) experienced two fractures and three patients (18%) experienced three fractures. The most common sites of fracture were the feet (n = 19), followed by hips (n = 4), hands (n = 2), tibia (n = 1), and ribs (n = 1). The fracture-free survival curve for this group is shown in Figure 1. Fracture-free survival was estimated to be 91% at 1 yr, 71% at 3 yr, and 48% at 5 yr, with a 95% CI (based on Greenwood's formula) of 0.76 to 0.97, 0.53 to 0.83, and 0.29 to 0.65, respectively. The mean time until the first fracture was 2.6 ± 1.7 yr. The rate of first fracture was 12.1% per year, with a median time until first fracture of 4.8 yr (95% CI, 2.7 to 6.9 yr).

More than half of the kidney recipients were black, 37% experienced a rejection (Table 2), and 51% had been exposed to steroids before transplantation. One kidney allograft recipient experienced a fracture before transplantation. The mean (±SD) follow-up time in the kidney group was 41 ± 28 mo. None of these patients sustained a fracture during this period. Ninety-five percent lower confidence bounds for the fracture-free survival rate (computed using the binomial distribution) are 90% at 1 yr and 85% at 3 yr.

The fracture-free survival for the two transplant groups was compared using the log-rank test. Using all 35 patients in both

Figure 1. Estimated fracture-free survival curve for kidney-pancreas transplant recipients.
groups, the \( P \) value obtained was 0.0002, confirming that the difference in the observed fracture rate between the two groups was not merely due to the longer follow-up period of the kidney-pancreas patients. Because diabetes mellitus is a risk factor for fracture, we also compared the time until fracture for patients with kidney-pancreas allografts with the seven diabetic kidney recipients. The resulting \( P \) value was 0.127, which, although not significant by conventional standards, suggests that the difference between the two groups may not be due solely to the difference in the proportion of diabetics in the kidney-only group.

Table 3 presents estimated hazard ratios from a Cox proportional hazards model fit to the data for the kidney-pancreas group. At any point during the follow-up period, the hazard of first fracture is estimated to be 9% higher (95% CI is 1 to 18% higher) for each additional 10 mg/kg in the cumulative prednisone dose (or, equivalently, a 700-mg increase for an individual who weighs 70 kg). Those with greater cumulative cyclosporine exposure were also estimated to have an increased risk of fracture, although the effect was not statistically significant (95% CI, 2% decrease to 15% increase for each additional 100 mg/kg). The data provide stronger evidence for a relationship between steroid exposure and fracture than for a relationship between cumulative cyclosporine dose and fracture. The risk of fracture was estimated to be 62% less for men than women.

Interestingly, the relationship between age at time of transplant and time until first fracture seemed to be nonlinear. This finding is illustrated in Figure 2, which plots time of follow-up versus age at transplant. The shortest time until first fracture occurred among patients between 30 and 40 yr old, whereas both the youngest and especially the oldest patients remained fracture-free much longer.

Finally, year of transplant (1987 to 1992), age of onset of diabetes mellitus, and years with diabetes mellitus before transplant were each added to the model one at a time. None was related to the time until first fracture (\( P > 0.2 \)), and in no case did the added covariate change the conclusions with respect to the other covariates.

**Discussion**

Successful renal transplantation quickly reverses many of the bone and mineral abnormalities associated with end-stage renal disease; however, the incidence of fracture increases after renal transplantation (4,5). It has been suggested that adynamic bone disease is an additional risk factor associated with increased fracture rate after renal transplantation (25). The observation is of particular importance for diabetic patients, because they have an increased incidence of adynamic bone disease (16–21). Whether diabetic renal transplant recipients actually have an increased risk of fracture after transplantation has yet to be determined. In this study, we assessed the incidence of fracture in insulin-dependent chronic renal failure patients undergoing their first kidney-pancreas transplantation. A surprisingly high incidence of postransplant fractures was observed in the diabetic patients undergoing combined kidney-pancreas transplantation during a 4-yr average follow-up period (49%). This fracture rate was much higher than the 11 to 26% incidence previously reported for patients receiving single-organ renal allografts (4,5). The fracture rate was also markedly higher than the 0% reported in our group of kidney allograft recipients. The discrepancy between the kidney transplant fracture rate quoted in the literature and that reported in our study may be due either to sampling error or perhaps to beneficial effects associated with the evolving changes in immunosuppressive therapy. The study that reported an 11% fracture incidence described patients transplanted between 1974 and 1993 (4), whereas the other focused on those receiving kidneys between 1964 and 1976 (5). Both studies reported on patients who were likely exposed to more steroid therapy than our cohort.

Similar to the nontransplant diabetic population, the kidney-pancreas recipients most commonly experienced fractures in the feet, *i.e.*, cortical bones (27). This finding suggests that factors associated with the kidney-pancreas transplantation process accelerated the underlying bone disease in patients with IDDM. Paradoxically, most of the reported bone mineral density findings demonstrate a loss of trabecular bone. Diabetic patients are different from those without diabetes mellitus in that they are predisposed to low-turnover bone disease and osteopenia, and are at risk for stress fractures in their feet secondary to peripheral neuropathy. However, although osteoporosis may be present, the actual degree of bone loss may be small (28). Hyperglycemia and insulin deficiency both may cause low-turnover bone disease by inhibiting parathyroid hormone release (29). This idea is further supported by the observation that insulin therapy normalizes low parathyroid hormone levels and bone formation rate in diabetic rats (30).

Although the mechanism by which patients with IDDM develop osteopenia is unknown, factors including hypocalcemia due to abnormalities in calcium absorption and vitamin D metabolism, insulin deficiency, hypomagnesemia, hypoparathyroidism, negative protein balance, decreased physical activity, impaired gonadal function, and metabolic acidosis have been implicated (21,28). Whether exposure to excess insulin levels (which occurs in patients taking exogenous insulin as well as those with a pancreas transplant) may play a role is an unexplored possibility. However, the findings that insulin may decrease bone loss in IDDM compared with oral agents (24) and that insulin stimulates bone formation and may contribute to increased bone mineral content (28) seem to oppose this.
Peripheral neuropathy may contribute to foot fractures by allowing repetitive stresses to accumulate without normal pain response and by applying stresses in a harmful manner (31). This study was unable to distinguish whether diabetes mellitus or the kidney-pancreas transplant process itself was the primary risk for fracture because the kidney-alone cohort contained only seven patients with diabetes mellitus. A comparison of IDDM patients who undergo kidney-pancreas and kidney transplantation would be useful to define whether the risk of fracture is inherent in the specific type of transplant.

In addition to the conditions that place patients with IDDM at increased risk for fracture, there are aspects inherent in kidney-pancreas transplantation that may accelerate bone disease. For example, steroids used for immunosuppression cause osteopenia by inhibiting osteoblastic activity and collagen synthesis (32,33), as well as by accelerating bone resorption and lowering intestinal calcium absorption (34). The present study provides moderate evidence for a positive relationship between the risk of fracture and cumulative steroid dose in the kidney-pancreas group.

In addition to steroids, cyclosporine may contribute to bone loss. Our data, although consistent with the possibility that cyclosporine may play a role in posttransplant osteoporosis, did not show a statistically significant effect. In rats, cyclosporine increases bone remodeling, causing reductions in cancellous bone volume. There is no effect on serum levels of calcium, 1,25-dihydroxycholecalciferol, or parathyroid hormone (12). In vitro, cyclosporine inhibits bone resorption in a dose-dependent manner during incubations with parathyroid hormone, 1,25-dihydroxycholecalciferol, and interleukin-1 (35). Interestingly, combined cyclosporine and steroid use in rats minimizes the adverse effects of either agent alone (13). In humans, the effect of cyclosporine on bone mineral density is unclear, and at least one investigator was unable to demonstrate an association (36). Although not statistically significant, this study suggests that cyclosporine may contribute to an increase in fractures.

The nonlinear relationship observed between time until first fracture and age at time of transplant is puzzling and may be due in part to random error and/or a selection effect, whereby older patients who are more frail are less likely to be transplanted with synchronous kidney-pancreas allografts. That controlling for age at onset of diabetes mellitus and time with diabetes mellitus before transplant does not alter this nonlinear relationship helps to eliminate potential explanations based on these variables.

Other factors associated with a successful kidney-pancreas transplantation may contribute to the increased fracture rate. Increased physical activity associated with a heightened sense of well being (15) and underlying peripheral neuropathy may predispose to stress fracture. Bladder drainage of the pancreas may lead to severe metabolic acidosis causing increased bone resorption and negative calcium balance. Neither of these complications was present in our patient population. Our patients replaced bicarbonate loss with the chronic use of sodium bicarbonate. However, whether the normalization of serum bicarbonate levels through the administration of sodium bicarbonate is as effective at reducing bone loss as has been shown with potassium phosphate is presently unknown (37). It would be instructive to compare a group of patients with bladder drainage to a group with enteric drainage using a population larger than that included here.

The retrospective design of our study has several limitations, including the absence of data concerning bone mineral density determinations, parathyroid hormone, vitamin D levels, and urinary excretion of calcium and phosphorous. This format also makes the identification of a comparable control group difficult. During the period studied at our institution, young
patients with IDDM were preferentially directed toward combined kidney-pancreas transplantation. Although the kidney group is not a direct comparison group, its inclusion serves to demonstrate that potential differences exist between kidney-pancreas and kidney transplant protocols, as well as important demographic features such as race and mode of pretransplant dialysis therapy. The kidney-alone group, which was matched for age and gender, had a markedly lower fracture rate than the kidney-pancreas group. In addition to the difference in diabetes history, those receiving combined allografts were more commonly white, exposed to higher cyclosporine and steroid doses (Table 4), and had a significantly earlier onset of diabetes mellitus than those receiving a kidney allograft alone (12.7 ± 8.7 versus 25.8 ± 11.3; \( P = 0.002 \)). Whether race is an additional risk factor for this population requires further study. The role of age of onset of diabetes mellitus is unclear. There was considerable variation in the age of onset of diabetes mellitus and no evidence of an association between age of onset and the likelihood of fracture within the kidney-pancreas group. Despite these limitations, kidney-pancreas recipients might be a high-risk group for bone fracture after transplantation.

In conclusion, kidney-pancreas allograft recipients, a subset of solid organ transplant patients, seem to be at increased risk for fracture compared with recipients of kidneys alone. The positive relationship between fracture and cumulative steroid dose suggests that osteopenia is likely a major underlying cause. At present, those undergoing the combined procedure are frequently white and exposed to more rejections and increased doses of cyclosporine and steroids compared with kidney allograft recipients. It will be important to evaluate these patients with bone mineral densitometry and bone biopsies to understand the natural history of bone disease after transplantation and to develop strategies to prevent this debilitating complication.

Acknowledgments
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References
19. Nishitani H, Miti T, Morii H, Nishizawa Y, Ishimura E, Hagiwara S, Nakatsuka K, Yamakawa M: Decreased bone mineral...


