

Bone Mineral Density After Simultaneous Kidney–Pancreas Transplantation: Four Years Follow-up of 57 Recipients

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ABSTRACT

Bone disease and an high risk of fractures are major problems in transplantation. Among diabetic patients undergoing simultaneous kidney–pancreas (SKP) transplantation, there are few studies assessing long-term effects on bone mass. The aim of this study was to evaluate bone mineral density (BMD) over 4 years follow-up after SKP transplantation. Fifty-seven patients had 22.8 ± 5.3 years of prior diabetes, 65% were female, and the overall mean age was 24.3 ± 5.93 years. At the time of transplantation, the lumbar spine and femoral neck T-scores were -1.75 ± 1.05 and -1.95 ± 0.73 , respectively; 28% of subjects had evidence of osteoporosis. One year after transplantation, 77.6% of patients displayed improved lumbar T-scores to -1.33 ± 0.94 ($P = .044$) with stable femoral neck T-scores. Bone densitometry enhanced gradually through the 4 years follow-up: lumbar T-score to -1.04 ± 0.67 ($P = .004$) and femoral neck T-score to -1.69 ± 0.49 ($P = .12$). At year 4, no osteoporosis cases were detected but 86.7% of patients did not receive steroids in the immunosuppressive regimen. The graft function remained stable (serum creatinine, 1.2 mg/dL; fasting glucose, 87.7 mg/dL). During the follow-up, BMD improved more significantly at cortical sites. Our study reports a reduced prevalence of fractures (8.7%) compared with the literature, which could be related to a steroid-sparing protocol and/or aggressively treatment of osteoporosis.

SIMULTANEOUS kidney–pancreas (SPK) transplantation is the treatment of choice for patients with end-stage renal disease secondary to diabetic nephropathy. Despite advances in patient and graft survival after SKP transplantation, bone disease is one of the most common complications.¹ Bone loss and consequent fracture are prevalent.^{2–4} The incidence of fractures in kidney transplant patients has been reported to be as high as 45% at 1 year posttransplantation.^{5–7} Among SKP transplants the risk of fracture is even greater compared with kidney recipients. The increased prevalence of fractures may incapacitate some patients affecting quality of life.⁸ In some solid organ transplants, there is a significant amount of evidence that steroids are the main cause of posttransplant bone loss, especially the rapid loss that occurs in the first 6–12 months. In SKP other factors may contribute such as the diabetic state and consequent nephropathy.^{9–11} Data characterizing bone loss after SKP transplantation, particularly in long-term are scarce. Some studies have demonstrated a rapid loss of bone density over the first 6 months, with trabecular bone being the most affected. After this

period it tends to stabilize or even recover.^{4,10} The optimal strategy to prevent or improve management of bone loss in transplantation patients, particularly after SKP, is controversial. The aim of our study was to evaluate BMD over 4 years follow-up among 57 patients who underwent SKP transplantation.

METHODS

Eighty-eight patients with diabetic nephropathy underwent SKP transplantation between 2000 and 2008. A retrospective study was performed in a cohort of 57 subjects with functioning kidney and pancreas grafts excluding patients with recent procedures, insufficient x-ray densitometry data, or kidney or pancreas graft loss.

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Graft function was determined by measuring serum creatinine, fasting glycemia, and glycosylated hemoglobin (HbA_{1C}). Bone mineral density determined by X-ray densitometry had results expressed as T-scores and BMD (g/cm²). Patients underwent a BMD measurement at the time of transplantation and then annually. The normal references values of BMD were those defined by the World Health Organization.

The data were analysed with SPSS 12.0 (SPSS, Inc, Chicago, Ill). Results were expressed as mean values and standard deviations. The univariate analysis used Student's t- and chi-square tests. Statistical significance was considered when $P < .05$.

RESULTS

We analyzed 57 transplanted patients among whom 65% ($n = 37$) were women. At the time of transplantation, the overall mean age was 24.3 ± 5.93 years; the duration of diabetes, 22.8 ± 5.30 years; and renal replacement therapy (hemodialysis or peritoneal dialysis), 36.4 ± 29.4 months (Table 1). Induction immunosuppressive therapy included steroids, tacrolimus, mycophenolate mofetil, and antithymocyte globulin. At transplantation, the lumbar spine T-score was -1.75 ± 1.05 with a BMD of 0.87 ± 0.12 g/cm²; the femoral neck T-score -1.95 ± 0.73 with a BMD of 0.71 ± 0.12 g/cm². The BMD revealed osteoporosis in 28% of patients and osteopenia in 36.8%. Table 2 summarizes laboratory data at the time of transplantation and during the follow-up period.

One year after transplantation, there was an improvement in lumbar spine T-score (-1.33 ± 0.94 ; $P = .044$) among 77.5% of the patients including 66% women. No significant differences were observed related to gender, age, time on dialysis, body mass index, parathormone (PTH), creatinine, dose of prednisone, dose of oral calcium carbonate and vitamin D analogs or biphosphonate therapy. The dose of oral calcium per day in this group was greater (1.25 g/d) then among the other patients (0.33 g/d), although the difference has not significant. No change in the femur T-score (-1.92 ± 0.73) occurred during the first year. At 1 year, the mean dose of prednisone was 4.3 mg/d.

BMD at the lumbar spine and femoral neck improved gradually over the 4 years of follow-up (Fig 1). In the fourth year the lumbar spine T-score improved to -1.04 ± 0.67 ($P = .004$) and the femoral neck T-score to -1.69 ± 0.49 ($P = .12$). At this time, no cases of osteoporosis were diagnosed. The patients maintained good kidney (serum creatinine = 1.2 mg/dL) and pancreatic graft function (fasting glucose = 87.7 mg/dL; HbA_{1C} = $4.6 \pm 0.3\%$). At the end of the fourth year, 86.7% of patients were not prescribed steroids

Table 1. Demographic Characteristics at Time of SKP Transplantation

	Mean ($\pm$ SD)
Age (y)	24.3 ($\pm$ 5.93)
Duration of diabetes mellitus (y)	22.8 ($\pm$ 5.30)
Time on dialysis (mos)	36.4 ($\pm$ 29.4)
Body mass index (kg/m ²)	22.3 ($\pm$ 2.79)

SD, standard deviation.

Table 2. Laboratory Data During Follow-up

	Year 0	Year 1	Year 2	Year 3	Year 4
Body mass index (kg/m ²)	22.3	22.7	22.7	23.5	23.5
Creatinine (mg/dL)	1.2	1.1	1.2	1.3	1.2
Phosphorous (mmol/L)	1.04	1.03	1.05	1.01	0.98
Calcium (mmol/L)	2.31	2.34	2.36	2.34	2.32
Fasting glucose (mg/dL)	87.1	79.4	78.6	80.2	87.7
Prednisone (mg/d)	20	4.3	2.3	1.5	1.3
Calcium carbonate (g/d)	0.89	1.18	0.71	1.5	0.95
Biphosphonates (n)	7	17	12	15	11

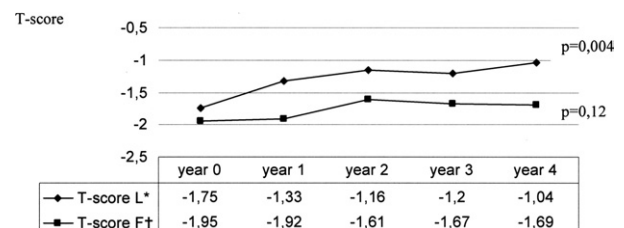
and in the others it had been tapered to a minimum of 5 mg/d prednisone.

During this period 5 symptomatic fractures occurred in 4 patients; all of which occurred in small peripheral bones. At the time of transplantation, the fracture patients, showed T-scores in the lumbar and femoral neck of -2.5 ± 0.9 and -2.1 ± 0.5 , respectively.

DISCUSSION

SKP transplantation is the first option for patients with diabetes mellitus and end-stage nephropathy. Bone disease is one of the most common complications of transplantation.¹ Among SKP transplants data are scarce characterizing posttransplant bone loss, particularly after the first year.^{4,8-10} Our results demonstrate a progressive improvement in BMD after transplantation. This recovery was more pronounced in the lumbar spine than the femoral neck cortical bone, results that were consistent with other studies,^{4,8,10} which documented a predominant cortical osteopenia with consequent increased risk of peripheral fractures. Longitudinal studies have shown that the majority of bone loss occurs in the first 6–18 months.⁴⁻⁸ In our study no data were collected during the first 6 months posttransplant.

Preventing long-term complications of SKP transplantation, such as bone disease, has become an essential part of posttransplant care. In kidney recipients the presence of renal osteodystrophy contributes to low BMD.¹² The diabetic condition adds to the risk of renal bone disease. Diabetes significantly decreases bone mass, particularly at cortical sites. Controversy exists regarding prevention and management of transplantation osteoporosis in the renal population.^{11,13} The diabetic state and end-stage nephropa-



*lumbar spine
† femoral neck

Figure 1. Evolution of BMD in the 4 years after SKP transplantation.

thy are corrected with successful SKP transplantation.^{11,13–15} Numerous studies have demonstrated significant evidence that steroids are a major contributor to posttransplant bone loss, especially the rapid loss that occurs in the first 6–12 months.^{9,16} A rapid reduction of steroids dose is a general practice in our transplant unit. This therapeutic approach did not increase acute rejection episodes. An average of 4.3 mg/d of prednisone, the dose at 1 year, was tapered over time. At the end of the first year, about 26% of patients had no steroids in the immunosuppressive therapy, which may be the main reason for the improved BMD. These results are consistent with those showing that steroid sparing protocols prevent bone loss.^{16,17} Other therapies believed efficient for prevention and/or treatment of bone reduction include calcium carbonate, vitamin D analogs and bisphosphonates. Our patients were treated with these drugs during the 4 years an approach that was possible due to the good kidney graft function.^{14,18–20}

Limitations of the study are related to the interpretation of BMD in end-stage renal disease, and the lack of evaluations during the first 6 months posttransplant, which is an essential period to treat and prevent bone loss.

Transplanted patients display an increased risk of fractures. The 6 to 45% prevalence among kidney transplant alone patients is increased 40%–50%, 5%–10% per year among diabetic patients who receive SKP transplantations.^{6,7,18} Documented risk factors for fractures include age, body mass index, dialysis time, diabetes, steroids, and other immunosuppressive drugs. In SPK transplantation, diabetic blindness and neuropathy are associated risk factors for falls and fractures.²¹ Only 5 patients (8.7%) experienced symptomatic fractures in our unit, a lower prevalence than that described in the literature. At the initial evaluation, osteoporosis was diagnosed in 28% and osteopenia in 37% of our patients. During the 4 years follow-up no patient displayed criteria of osteoporosis, an improvement related to the strategy of early steroid reduction and to intensive therapy with bisphosphonate vitamin D analog or calcium carbonate.

In conclusion, posttransplant bone disease is a common complication frequently associated with osteoporosis. Our patients experienced a lower prevalence of fractures than that in the literature. Using a steroid sparing immunosuppressive protocol and active treatment of osteoporosis may be a good approach to reduce bone loss. More randomized trials are needed to define the best option to manage bone disease after SKP transplantation.

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