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Research Article

Decreased Bone Mineral Density in Patients Submitted to Kidney Transplantation Is Related to Age, Body Mass Index, Time on Dialysis, and Hyperparathyroidism

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Background. Renal transplantation (Tx) influences bone mineral density (BMD) by several mechanisms. The main objective of this study was to correlate BMD and risk factors associated with bone loss in patients submitted to kidney Tx. *Methods*. We evaluated 88 individuals after renal Tx (median time = 31.5 months since Tx). All of them sustained glomerular filtration rate ≥60 mL/min/1.73 m^2. BMD was measured by dual-energy X-ray absorptiometry (DXA, Prodigy-GE). Calcium, phosphate, albumin, creatinine, and intact parathormone (PTH) were measured at the same time. All statistical tests were two-sided and P value less than 0.05 were accepted as significant for all analyses in this study. *Results*. Serum PTH was raised in 42% patients, but corrected calcium was normal in 83 patients. No fragility fracture was reported, but the overall prevalence of osteoporosis was 27.6% and lower than expected BMD (Z-score ≤ −2.0 SD) was observed in 28.4%. Patients with lower than expected BMD had higher PTH levels. *Conclusions*. Older age, lower body mass index (BMI), longer time on dialysis, and elevated PTH levels were identified as the main factors associated with lower BMD.

1. Introduction

Chronic kidney disease is caused by several conditions and has become a prevalent comorbidity. Renal transplantation (Tx) is the treatment of choice for most patients with end-stage renal disease (ESRD) [1]. Advances in immunosuppressive agents and transplant techniques during the last decades have led to improved long-term graft and patient survival. This fact resulted in both increases in transplant numbers and an increased recognition of previously neglected long-term complications of Tx, such as osteoporosis and fractures. Osteoporosis is prevalent in more than half of solid organ recipients and vertebral fractures are found in almost a third of patients [2].

Particularly during the early post-Tx period, kidney recipients experience a rapid loss of bone mass [3]. Rates of bone loss are greatest during the first 6–18 months after renal Tx and range from 4 to 9% at the spine and 5 to 8% at the

Table 1: Daily pharmacological doses of posttransplantation immunosuppressive treatment of the 88 patients evaluated.

	Initial doses	Maintenance doses
Prednisone	0.5 mg/Kg/day (30–50 mg/day) for up to 90 days	5–7.5 mg/day
Mycophenolate mofetil	500 mg 3-4 times/day	500 mg 2-3 times/day
Tacrolimus	0.15–0.2 ng/kg/day to obtain serum levels of 10–15 ng/mL (day 1)	Serum levels 3–7 ng/mL (4th day on)

hip [4]. Different factors have been associated to this bone disease. Chronic kidney disease-mineral and bone disorder (CKD-MBD) begins during the early stages of the disease and usually worsens during dialysis. Both pretransplantation bone disease and immunosuppressive therapy result in rapid bone loss and increased fracture rates [4, 5]. It is expected that parathormone (PTH) levels reach 50% of their initial values on the fourteenth day after renal Tx and that hyperparathyroidism (HPT) reverses during the first year after kidney Tx. However, elevated PTH levels have been observed in more than 25% of patients one year after renal Tx despite good renal function [6]. Besides persistent HPT, other factors have also been implicated in bone loss related to kidney Tx, such as immunosuppressive therapy, hypophosphataemia, hypomagnesaemia, and vitamin D deficiency [1].

The aim of the present study is to evaluate bone mineral density (BMD) in patients after renal Tx and associated factors to the development and persistence of bone disorder.

2. Patients and Methods

This was a cross-sectional study of patients submitted to kidney Tx and regularly seen as outpatients at the Clementino Fraga Filho Hospital, Federal University of Rio de Janeiro. The study was approved by the ethical committee and all participants signed an informed consent. Inclusion criteria were age ≥ 20 years and glomerular filtration rate ≥60 mL/min/1.73 m^2. Exclusion criteria were previous parathyroidectomy, return to dialysis, active diseases that could influence bone metabolism (such as systemic lupus, rheumatoid arthritis, celiac disease, diabetes mellitus, and AIDS), and use of any antiresorptive or anabolic drug (calcitonin, bisphosphonates, teriparatide, strontium ranelate, or denosumab) to treat bone disease in the last twelve months. The eighty-eight selected patients, 36 women and 52 men, had no limitations for physical activities, had no difficulty for walking, and were not receiving calcium and/or vitamin D. Patients received 0.5 mg/Kg/day of prednisone until the third month after kidney Tx and then the dose was reduced to 5 mg/day. Table 1 reports the daily pharmacological medication dosages at the time of the present evaluation. Forty-three received the kidney from living donors and forty-five from deceased donors. The cause of renal failure, time on dialysis, and time since transplantation were considered.

Body mass index (BMI) was estimated by the ratio weight/height^2 and expressed as kg/m^2. BMD was evaluated by dual-energy X-ray absorptiometry (DXA) using a Prodigy-GE densitometer and analyzed by the same experienced physician. BMD was measured at lumbar spine (LS), femoral neck (FN), and total femur (TF) and expressed in absolute values (g/cm2) and in standard deviations (SD) from peak bone mass (T-score) and from expected BMD for age-matched population (Z-score). The reference standard from which T-score was calculated was the NHANES III and the Prodigy-GE densitometer databases, corrected for male sex when men were evaluated. In accordance with the World Health Organization and with the International Society of Clinical Densitometry (ISCD) official positions, the diagnosis of osteoporosis is based on a BMD T-score ≤ −2.5 SD at any site of the skeleton of postmenopausal women and men aged 50 years and older. Values of Z-scores ≤ −2.0 SD were considered lower than expected bone mass. The coefficient of variation (CV) for the BMD measurements in normal subjects at our institution is 1.5% at LS and 2.3% at FN.

In the same day, blood was drawn after overnight fast for determination of serum calcium, phosphate, creatinine, and albumin by standard colorimetric methods. Calcium levels were corrected for albumin concentration, according to the formula: corrected calcium (cCa) (mg/dL) = serum calcium (mg/dL) + 0.8 × [4.0 − serum albumin (g/dL)]. Glomerular filtration rate was estimated by the formula of Cockcroft and Gault (values corrected for body surface area): [140 − age (years)] × weight (Kg)/72 × serum creatinine (mg/dL). For women, the result is multiplied by 0.85. Serum samples were stored at −80°C until analysis of intact PTH by chemiluminescent enzyme immunometric assay (kit DSL; Diagnostic Corp., California, USA; range 11–67 pg/mL); inter- and intra-assay variations were 4.3% and 5.7%, respectively; PTH analyses were run in duplicate.

3. Statistical Analysis

Statistical analysis was performed using SPSS 13.0 for Windows Student Version. Mann Whitney test compared groups: men and women, living and deceased donor, and patients with Z-score at any site > −2.0 SD versus ≤ −2.0 SD. Univariate Pearson or Kendall.s Tau_b. correlation coefficients were used to test the overall correlation between densitometric parameters and BMI, time on dialysis, time since kidney transplantation, calcium, phosphorus, creatinine, and PTH. Finally, a stepwise multiple regression analysis was used to investigate relationships between independent variables and Z-scores. All statistical tests were two-sided and P values less than 0.05 were accepted as significant for all analyses in the study.

4. Results

Arterial hypertension was the main cause of renal failure (40%) followed by undefined etiology (22%), polycystic kidneys (7%), glomerulonephritis (6%), systemic lupus (4%),

Table 2: Comparisons between patients who received kidney transplant from living or deceased donors.

	Living donor ($n = 43$)	Deceased donor ($n = 45$)	P value
Sex			
Women	16	20	
Men	27	25	0.493
Age (years)	40.1 (31.3–46.7)	49 (39.6–54)	**0.004**
BMI (kg/m^2)	23.6 (22.3–26.5)	25.5 (22.7–28.3)	0.176
Time on dialysis (months)	20 (12–48)	90 (62.5–108)	<**0.001**
Time since Tx (months)	38 (13–84)	28 (18–39)	0.293
cCalcium (mg/dL)	9.2 (8.9–9.7)	9.5 (9.1–9.8)	0.343
Phosphorus (mg/dL)	2.9 (2.7–3.3)	3 (2.6–3.5)	0.627
Creatinine (mg/dL)	1.1 (1.3–1.7)	1.2 (1.1–1.5)	0.261
Albumin (g/dL)	4.3 (4.2–4.6)	4.3 (4.1–4.6)	0.839
PTH (pg/mL)	47.3 (37.6–72.7)	72.7 (38.7–126)	0.126
Lumbar spine Z-score	−1.3 (−1.9–0.1)	−0.7 (−1.5–0.2)	0.251
Femoral neck Z-score	−0.8 (−1.3–0.2)	−0.6 (−1.3–0.1)	0.726
Total femur Z-score	−0.6 (−1.4–0)	−0.8 (−1.4–−0.1)	0.917

BMI: body mass index; Tx: transplant; cCalcium (corrected for albumin); PTH: parathormone. Results in absolute numbers or median (interquartile interval).

obstructive uropathy (3%), IgA nephropathy (2%), drug-induced nephropathy (2%), virus B hepatitis (1%), and leptospirosis (1%).

Results are expressed as median values (interquartiles interval). Consider the whole population: age (years) 44.3 (37.2–52.5), time on dialysis (months) 60 (12–91.3), and time elapsed from transplantation to the study (months) 31.5 (15.8–62.5). The only sex difference was serum creatinine (mg/dL), higher in male, 1.4 (1.2–1.7), than in female patients, 1.1 (1–1.4), $P < 0.001$. Patients who received kidney transplant from living donors were younger and remained less time on dialysis. Comparisons are shown in Table 2. No patients had graft rejection.

Serum PTH was above normal levels in 42% of all patients, and cCalcium was normal in all but five patients (mildly hypercalcemic). However, median (quartile interval) of cCalcium, phosphorus, glomerular filtration rate, time on dialysis, and time since transplantation did not differ between patients with high or normal PTH. The only difference was a lower median LS Z-score (−1.6 SD) in patients with hyperparathyroidism compared to subjects with normal PTH values (−0.8 SD; $P < 0.05$).

No patient reported fragility fracture. Bone density T-score at lumbar spine and/or proximal femur was ≤ −2.5 SD in three of the twelve postmenopausal women and in five of the 17 men aged fifty years and older (age range 52–66.5 years, median 53.4 years). Thus, prevalence of osteoporosis in these patients was 27.6%. BMI tended to be lower in osteoporotic patients ($P = 0.089$).

Considering the whole group, twenty-five patients (28.4%) had a bone density Z-score ≤ −2.0 SD at lumbar spine and/or proximal femur. The only difference between these patients and those with a Z-score < −2 SD was serum PTH, higher in the former. These data are shown in Table 3.

The significant correlations identified after stepwise multiple regression analysis are shown in Table 4. An inverse correlation between serum PTH and Z-score at LS, FN, and TF was statistically significant only in women. Figure 1 illustrates this inverse correlation at LS.

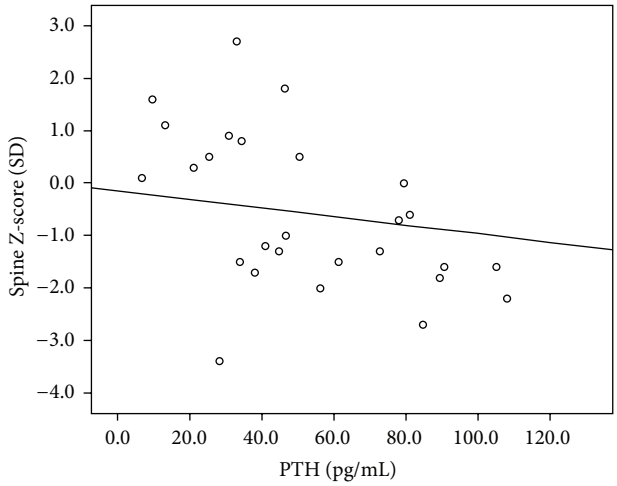

Figure 1: Correlation between serum PTH levels and lumbar spine Z-score in women ($r^2 = 0.442$, $P < 0.001$). PTH: parathormone; SD: standard deviation.

5. Discussion

The determinants of chronic renal disease in this study were similar to previously reported ones, because hypertension is the leading cause of ESRD in Brazil. Interestingly, the diagnosis of diabetes mellitus was not included as a cause of ESRD in this group, but probably it may corresponded to part of the undefined causes of chronic renal disease. Men and women did not differ in demographics and biochemical and densitometric parameters. The only exception was serum creatinine, higher in men but always compatible with a glomerular filtration rate ≥60 mL/min/1.73 m^2, possibly due to a

Table 3: Comparisons between patients with bone density Z-scores ≤ −2.0 SD at lumbar spine and/or proximal femur.

	Z-score ≤ −2.0 SD (n = 25)	Z-score > −2.0 SD (n = 63)	P value
Sex			
Women	8	28	0.287
Men	17	35	
Age (years)	44.5 (34.6–52)	43.7 (37.4–53.9)	0.691
BMI (kg/m^2)	24.6 (19.7–28.3)	24.9 (22.8–26.7)	0.307
Time on dialysis (months)	78 (12–84)	60 (13–96)	0.880
Time since Tx (months)	29 (14–48)	32 (17.5–68.5)	0.598
Donor			
Living	14	29	0.402
Deceased	11	34	
cCalcium (mg/dL)	9.4 (9–9.8)	9.3 (8.9–9.7)	0.506
Phosphorus (mg/dL)	3 (2.8–3.2)	3 (2.6–3.6)	0.858
Creatinine (mg/dL)	1.4 (1.1–1.6)	1.2 (1.1–1.6)	0.552
Albumin (g/dL)	4.4 (4.3–4.6)	4.3 (4.1–4.6)	0.104
PTH (pg/dL)	83.3 (49.1–137.8)	48.2 (33.1–79.3)	**0.016**

BMI: body mass index; Tx: transplant; cCalcium (corrected for albumin); PTH: parathormone. Data expressed as absolute values or median (interquartile interval).

Table 4: Correlations between bone density Z-scores and age, body mass index (BMI), PTH, time on dialysis, and time from kidney transplantation to bone mineral density evaluation (Tx-BMD) in different subgroups populations.

Groups/sites	Lumbar spine Z-score	Femoral neck Z-score	Total femur Z-score
All patients	No correlation	No correlation	No correlation
Men	No correlation	No correlation	No correlation
Women	PTH and age (r^2 = 0.442 P < 0.001)	PTH (r^2 = 0.356 P < 0.001)	PTH (r^2 = 0.347 P < 0.001)
Deceased donor	Time on dialysis (r^2 = 0.118 P = 0.034)	No correlation	Time TPX-BMD (r^2 = 0.172 P = 0.010)
Living donor	Time on dialysis (r^2 = 0.167 P = 0.038)	Time on dialysis (r^2 = 0.270 P = 0.007)	Time on dialysis and BMI (r^2 = 0.412 P = 0.002)

Dependent variable: bone mineral density Z-scores.
Independent variables: sex, age, BMI, time on dialysis, time Tx-BMD, type of kidney donor, PTH, calcium, phosphorus, creatinine, and albumin.

greater muscle mass in males. Thus, a homogeneous group was evaluated, despite the different etiologies of ESRD.

As expected, older patients had lower BMD, since aging is related to bone loss. Data obtained from patients between 6 and 20 years after renal Tx (when bone loss is in a stable period) showed a mean annual decrease in lumbar T-scores of −0.6 ± 1.9%, a value similar to the observed decline in the general population with aging [7]. So, together, both conditions may predispose to a greater bone loss.

Among the general population, higher BMI have been shown to be protective against osteoporosis [8]. Sezer et al. reported lower post-Tx BMI in osteoporotic compared to osteopenic or normal subjects [9] and another recent trial revealed BMI to be an independent risk factor for a lower T-score at femoral neck [10]. A negative correlation between BMI and BMD was also reported in our group.

Longer time on dialysis is generally associated with longer time under the deleterious effects of uremia and secondary HPT. There seems to be no doubt that pre-Tx CKD-MBD plays an important role in the maintenance or development of post-Tx alterations of bone remodeling [11]. Thereby, our findings showed that longer time on dialysis is related to lower BMD after renal Tx and corroborates the importance of pre-Tx bone disease.

Even though patients who received kidney Tx from living donors were younger and remained less time on dialysis, no differences were found in other data, including BMD (Z-score). Therefore, donor source did not affect the current bone health of these individuals.

Metabolic bone disease after kidney transplantation has a complex pathophysiology and heterogeneous histology. Bone density loss remains a serious problem after renal Tx and is most pronounced during the first months of engraftment. Each patient may have multiple risk factors for bone loss, such as steroids usage, hypogonadism, persistent hyperparathyroidism, poor allograft function, metabolic acidosis, hypophosphatemia, vitamin D deficiency, aging, immobility, and chronic disease. The main alterations in bone remodeling after renal Tx probably consist of a decrease in bone formation and mineralization in the face of persistent bone resorption [11]. Almost all studies noticed a BMD loss at lumbar spine, if no bone sparing medication was used. In the first six months, median bone loss was 4.1% and persisted in the majority of cases at one year after engraftment, although

at a lower level (median 3.4%). At the femoral neck, bone loss was slightly less after six months (median 2.8%) but showed a tendency to increase further thereafter [12]. Controversial data exist concerning BMD development in long-term kidney transplant recipients. While some studies demonstrated no further significant bone loss after the first post-Tx year [13, 14], another study noticed an ongoing reduction in lumbar spine BMD of 1.7% per year [15]. On the other hand, a study found BMD stabilization beyond the second post-Tx year, followed by an improvement of 1-2% per year thereafter [16]. Our patients presented a median time elapsed from Tx to the study above 2 years (31.5 months), suggesting they already had most of their bone loss related to post-Tx period. The clinical impact of post-Tx osteopathy and bone loss is a marked increase in the fracture rate following kidney Tx, almost threefold higher in patients after renal Tx compared to subjects in hemodialysis [17]. When comparing to healthy controls, the rise in fracture incidence varies between fivefold and 34-fold, depending on sex and age of kidney recipients [18].

Posttransplantation immunosuppressive treatment may have a major impact on the pathogenesis of bone disease. Corticosteroids can be directly toxic to osteoblasts and lead to increased osteoclast activity [19]. During the first months after Tx, rapid bone loss secondary to steroid-induced acceleration in bone remodeling occurs. Steroids withdrawal three months after kidney Tx was associated with decreased risk of osteoporosis [20, 21] and steroid withdrawal one year after kidney Tx was associated with improved BMD [22]. None of our patients were receiving corticosteroids in high doses (>5 mg/day of prednisone), which could be related to bone loss. Moreover, our patients were using only mycophenolate mofetil and tacrolimus as posttransplantation immunosuppressive treatment and these medications do not affect BMD [19, 23].

Persistent HPT is a frequent finding in kidney graft recipients [24]. Torres et al. showed that only 23% of long-term recipients with serum creatinine below 2 mg/dL had PTH levels within the normal range [25]. We found 42% of the evaluated patients with elevated PTH levels, even though all of them had glomerular filtration rate ≥60 mL/min/1.73 m^2. The most important risk factors for ongoing hyperparathyroidism are dialysis duration, severity of secondary HPT prior to Tx, and development of monoclonal hyperplasia of the parathyroid glands (tertiary HPT) [26]. In five of our patients (5.7%), corrected calcium was elevated, suggesting autonomous or tertiary HPT. In the remaining patients with elevated serum PTH, corrected calcium was normal, suggesting secondary HPT. Additional factors that may contribute to elevated PTH levels are hypovitaminosis D and decreased calcium absorption caused by corticosteroids [3]. Many studies related persistent HPT to increased bone turnover and decreased BMD after Tx. In our trial, PTH levels were significantly higher in the twenty-four patients with lower than expected bone mass (Z-score ≤ −2.0 SD in lumbar spine and/or proximal femur) compared with the sixty-four patients with normal Z-score, suggesting the involvement of PTH in the reduction of BMD. In the female group (36 patients), the inverse correlation between PTH and Z-score confirmed this finding. Other authors also demonstrated similar results [19, 27, 28], highlighting the role of PTH in bone loss after renal Tx.

Organ transplantation is now a well-known condition associated with secondary osteoporosis. Current guidelines for bone disease in renal Tx recommend that patients should be regularly monitored for changes in their bone mass. BMD measurements by DXA scans should be obtained at the time of Tx as well as 1 and 2 years thereafter [29]. We observed a high prevalence of osteoporosis in postmenopausal women (25%) and in men aged fifty years and older (29.4%), with an overall prevalence of 27.6%. Patel et al. found a similar prevalence of osteoporosis in 165 transplant patients, ranging from 10 to 44% and depending on gender or measured site [30]. Although our patients did not report fragility fractures, we cannot exclude the prevalence of asymptomatic fractures (mainly vertebral ones), which could lead to even greater prevalence of osteoporosis in these patients. A cross-sectional study demonstrated an osteoporotic fracture prevalence of 17% in renal Tx recipients. A higher rate was found among recipients with diabetes type 1 (40%) and among females (23%) [31]. Thus, further studies evaluating vertebrae morphometry by X-ray or by DXA scans (vertebral fracture assessment or VFA) should be performed in order to clarify the real prevalence of asymptomatic vertebral fractures in this population, which indicates the need for pharmacological treatment.

Our study has some limitations. First, the transversal design prevented the evaluation of BMD pre-Tx and the rate of bone loss after engraftment. Timing of the DXA scans was variable (13–84 months) but all patients went through the worst period for bone heath, which is the first year after kidney Tx [11, 12]. Other limitations were the small size of the sample and the lack of data about other factors that may affect BMD, like 25(OH) vitamin D, which could be responsible for the elevation of PTH levels seen in some subjects.

Bone disease related to renal Tx is a common disorder and is associated with higher morbidity and mortality. Our study highlights older age, lower BMI, longer time on dialysis, and persistent HPT as important risk factors for this condition. Adequate screening, correction of modifiable predisposing conditions, and treatment of bone loss are essential for proper management of these patients, leading to longer survival and improved quality of life.

6. Conclusions

A high prevalence of bone involvement after renal Tx was observed in this study and the main influences on the reduction of BMD were age, BMI, dialysis duration, and PTH levels.

Conflict of Interests

The authors have declared that no conflict of interest exists.

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