Brazilian Journal of Medical and Biological Research (2006) 39: 137-147
ISSN 0100-879X

Prevalence of low trauma fractures in long-term kidney transplant patients with preserved renal function

J.W.R. Braga Júnior[1], R.M.S. Neves[1], M.M. Pinheiro[1], A. Frisoli Júnior[1], C.H.M. Castro[1], V.L. Szejnfeld[1] and A.B. Carvalho[2]

[1]Disciplina de Reumatologia, [2]Disciplina de Nefrologia, Departamento de Medicina Interna, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brasil

Correspondence
V.L. Szejnfeld
Disciplina de Reumatologia
Departamento de Medicina Interna
EPM, UNIFESP
Rua Botucatu, 740
04023-900 São Paulo, SP
Brasil
Fax: +55-11-5579-6665
E-mail: vera@reumato.epm.br

Publication supported by FAPESP.

Received September 29, 2004
Accepted June 27, 2005

Abstract

We evaluated the prevalence of low bone mineral density (BMD) and osteoporotic fractures in kidney transplantation (KT) patients and determined risk factors associated with osteoporotic fractures. The study was conducted on 191 patients (94 men and 97 women) with first KT for 3 years or more presenting stable and preserved renal function (serum creatinine levels lower than 2.5 mg/dl). KT patients were on immunosuppressive therapy and the cumulative doses of these drugs were also evaluated. BMD was determined by dual-energy X-ray absorptiometry at multiple sites (spine, femur and total body). Quantitative ultrasound of the calcaneus (broadband ultrasound attenuation, speed of sound, and stiffness index, SI) was also performed. Twenty-four percent (46) of all patients had either vertebral (29/46) or appendicular (17/46) fractures. We found osteoporosis and osteopenia in 8.5-13.4 and 30.9-35.1% of KT patients, respectively. Women had more fractures than men. In women, prevalent fractures were associated with diabetes mellitus [OR = 11.5, 95% CI (2.4-55.7)], time since menopause [OR = 3.7, 95% CI (1.2-11.9)], femoral neck BMD [OR = 1.99, 95% CI (1.4-2.8)], cumulative dose of steroids [OR = 1.1, 95% CI (1.02-1.12)] and low SI [OR = 1.1, 95% CI (1.0-1.2)]. In men, fractures were associated with lower lumbar spine BMD [OR = 1.75, 95% CI (1.1-2.7)], lower SI [OR = 1.1, 95% CI (1.03-1.13)], duration of dialysis [OR = 1.3, 95% CI (1.13-2.7)], and lower body mass index [OR = 1.24, 95% CI (1.1-1.4). Our results demonstrate high prevalence of low BMD and osteoporotic fractures in patients receiving a successful kidney transplant and indicate the need for specific intervention to prevent osteoporosis in this population.

Key words
• Kidney transplantation
• Bone density
• Quantitative ultrasound
• Osteoporosis
• Fracture

Introduction

End-stage renal disease (ESRD) is associated with multiple skeletal and mineral metabolism disorders, leading to bone disease generically called "renal osteodystrophy" (1). Many mechanisms are involved in its pathophysiology including calcitriol deficiency, hypocalcemia, hyperphosphatemia, secondary hyperparathyroidism, metabolic

acidosis, uremia, and aluminum deposition (2). Age, gender, duration of dialysis, low calcium intake, and drugs such as phosphate binders may also play an important role in bone disease associated with ESRD (1,2).

Kidney transplantation (KT) is the treatment of choice for ESRD and its demand has grown tremendously due to the small number of short-term complications, mainly rejection episodes, and the increased long-term survival rates and quality of life when compared with patients treated with hemodialysis. Although most metabolic disturbances are reversible after transplantation, restoration of glomerular filtration and improvement of calcitriol production do not reverse renal bone disease. Many studies have shown that bone disease may persist during the first years following transplantation or even become worse due, in part, to the need for immunosuppressive therapy such as glucocorticosteroid, cyclosporine A and tacrolimus (FK506), which are important to prevent transplant rejection (3-5). Cyclosporine A and tacrolimus are relatively new immunosuppressive agents that, despite their well-documented steroid-sparing effect, are associated with several clinical complications. Particularly, the musculoskeletal system is often affected (6).

KT affects bone integrity and increases the risk of fragility fractures. However, not every patient displays sustained bone loss after KT. Due to post-transplantation bone disease, a rapid reduction of bone mineral density (BMD) develops that can exceed 10% in the first 12 months. Subsequently, the bone loss slows down or even a secondary increase occurs (7). Three patterns of BMD profiles have been observed after transplantation: a) steady decrease, b) decrease over 6 months and partial correction, and c) decrease over 6 months and total correction.

The most important and disabling clinical outcome of post-transplantation bone disease is fragility fracture (8-12). KT is associated with early rapid bone loss and subsequent sustained bone loss, consequently increasing fracture risk (3,4,13). Low BMD is one of the most important risk factors for fractures (14). However, fractures have been documented to occur not only in patients with low BMD but also in patients with normal BMD (8), suggesting that other factors may also play an important role to determine fractures in this population. Besides BMD, bone architecture, geometrical properties of the bone and risk of falls are also significant determinants of fracture risk. Age, ethnic origin, history of previous fracture, female sex and low weight, important risk factors for fracture previously reported in the general population (15), have also been observed in ESRD patients (16), and recently in KT patients (17).

Bone architecture can theoretically be assessed by quantitative ultrasound (QUS). QUS is a new, simple, portable, inexpensive, radiation-free method that evaluates bone structure and predicts fracture independently of BMD. It has been suggested as an alternative approach to BMD measurement to assess skeletal fragility and bone quality (18). Only a few studies have analyzed QUS parameters in KT patients and its usefulness in this set of patients has not been established.

In the present study, we evaluated the prevalence of low trauma fractures and low bone mass in KT patients presenting stable and preserved renal function. A search was also made for clinical risk factors potentially associated with osteoporotic fractures in this population. We describe here important clinical and densitometric determinants of fracture risk in KT recipients with preserved renal function.

Patients and Methods

Patients

Five hundred KT patients were selected from our transplant unit database in May

2000. These patients were Brazilian men and women living in the São Paulo metropolitan area, Brazil, under regular follow-up at the Renal Transplant Center of São Paulo Hospital, São Paulo, SP, Brazil. After approval from the local Ethics Committee, 207 patients were invited by telephone to participate in the present study. Only first-KT recipients were selected. Patients were selected at random from those with a kidney transplant performed at least three years before, and stable graft function (serum creatinine 2.5 mg/dL or less). All patients gave written informed consent to participate. Of a total of 207 patients invited, 191 concluded the study. Six patients did not accept to participate in the study protocol and 10 others did not attend the first appointment. Mean age was 44.8 ± 0.8 years and average time since transplantation was 87 ± 3.7 months. The cause of renal failure was unknown in 80 patients (41.9%) whereas chronic glomerulonephritis, hypertension, diabetes mellitus, polycystic kidney disease, and obstructive nephropathy were responsible for renal failure in 65 (34%), 18 (9.4%), 11 (5.7%), 5 (2.6%), and 4 (2.1%) cases, respectively. Other causes of renal failure were observed in 8 patients.

Patients were 94 males (20 of them had diabetes mellitus) and 97 females (30 of them were postmenopausal and 14 had diabetes mellitus). The medical charts of all patients were analyzed and the following information was obtained: demographic data, duration of pretransplant dialysis, time since transplantation, serum creatinine, value of glomerular function predicted by the equation of Cocroft and Gault, and cumulative drug dosage (steroids, cyclosporine A and azathioprine).

Exclusion criteria were prolonged immobilization, systemic illness or malignancy, as well as the use of drugs that affect bone metabolism (bisphosphonates, calcitonin, fluoride, selective estrogen receptor modulators, etc.), except immunosuppressive agents and corticosteroids. Calcium supplement use and hormone replacement therapy were not exclusion criteria for this study.

Fracture ascertainment

Patients were asked about symptomatic low-trauma fractures during the interview. None of them had symptomatic vertebral fractures. Traumatic fracture was excluded. Plain radiographs of the thoracic and lumbar spine were obtained for all patients using standard protocols to determine prevalent vertebral deformities. Vertebral deformity was defined by a quantitative method according to Eastell's criteria (19).

Bone mineral density measurements

Dual-energy X-ray absorptiometry was performed in all patients using a Lunar DPX device (Lunar Corp., Madison, WI, USA) and lumbar spine (LS) and femoral neck (FN) BMD was measured. These measurements were performed at the Osteoporosis Unit, Rheumatology Division, São Paulo Hospital, over a 5-month period. Daily calibration measurements using a phantom were performed according to manufacturer instructions. Coefficients of variation for BMD measurements were 1.9% for LS and 3.6% for FN. Prevalence of low bone mass in men and women was defined according to the World Health Organization (WHO) recommendations (20).

Quantitative ultrasound measurements

Bilateral heel QUS measurements were carried out using the Achilles + equipment (Lunar). During the passage of the ultrasound wave through the bone, its characteristic frequency spectrum is altered. These changes reflect the QUS parameters analyzed, i.e., broadband ultrasound attenuation (BUA), speed of sound (SOS) and stiffness index (SI). SI is a mathematical combi-

nation of BUA and SOS values [SI = 0.67 x BUA + 0.28 x SOS - 420]. T and Z scores for SI were calculated by comparison to a system-inherent white reference population for the same gender and age. The QUS normal reference curve for the Brazilian population is not significantly different from the American reference range (21), and so the latter was used in our study. The inter-foot coefficient of variation for QUS parameters was investigated and no statistically significant difference was found between left and right calcaneus measurements. For logistic regression analysis, right heel measurements were used. Precision errors determined as root mean squared coefficient of variation were 1.01% for BUA, 0.23% for SOS and 1.25% for SI (21).

Statistical analysis

Data are reported as means ± SEM. The SEM was chosen because it represents 68% of the population and ranges are presented when needed. The significance of the differences between groups (men versus women, men with fractures versus men with no fractures, women with fractures versus women with no fractures) was tested by the unpaired Student *t*-test, chi-square test or Pearson's correlation analysis when appropriate. Logistic regression analysis was performed to determine the factors that were better associated with fractures in our population. Since gender plays a critical role in bone mass and metabolism determination, separate analyses were performed for males and females. Variables significantly associated with fracture by chi-square analysis were tested by logistic regression analysis. For all analyses, the level of significance was set at $P < 0.05$.

Results

Characteristics of the kidney transplantation population

Table 1 shows descriptive characteristics of KT patients according to gender. Ninety-seven patients were females and 94 were males (mean age: 43.2 ± 1.0 and 46.6 ± 1.2 years, respectively). Males were significantly older, heavier and taller than females ($P < 0.05$). Since anthropomorphic characteris-

Table 1. Anthropomorphic and clinical data for 191 kidney transplant recipients according to gender.

	Total (N = 191)	Males (N = 94)	Females (N = 97)
Age (years)	44.8 ± 0.78 (20-70)	46.6 ± 1.16 (20-70)	43.2 ± 1* (23-68)
Weight (kg)	68.62 ± 1.11 (42-126)	73.87 ± 1.46 (47-120)	63.53 ± 1.48* (42-126)
Height (m)	1.63 ± 0.002 (1.39-1.85)	1.66 ± 0.007 (1.41-1.85)	1.54 ± 0.007* (1.39-1.68)
BMI (kg/m^2)	26.55 ± 0.38 (17.5-49.8)	26.61 ± 0.47 (17-44)	26.5 ± 0.57 (18-49)
Duration of dialysis (months)	46.48 ± 3.03 (3-204)	41.74 ± 3.79 (5-204)	51.08 ± 4.66 (3-193)
Time since transplantation (months)	86.96 ± 3.71 (36-231)	91.68 ± 5.51 (36-231)	82.39 ± 4.97 (36-231)
Creatinine (mg/dL)	1.62 ± 0.03 (0.9-2.5)	1.67 ± 0.03 (1-2.5)	1.57 ± 0.04 (0.9-2.5)
Cumulative dose of steroids (g)	29.93 ± 1.47 (0-114.33)	33.73 ± 2.41 (0-114)	26.25 ± 1.64* (3-91)
Cumulative dose of cyclosporin (g)	482.8 ± 26.4 (0-1516.4)	507.48 ± 42.5 (0-1516)	460.78 ± 31.96 (0-1158)
Cumulative dose of azathioprine (g)	224.2 ± 15.32 (0-1087.9)	259.9 ± 24.95 (0-1087)	191.1 ± 17.59* (0-858)

Data are reported as means ± SEM with range within parentheses. BMI = body mass index.
*P < 0.05 compared to males (Student *t*-test).

tics and bone measurements were also statistically different between men and women (Tables 1 and 2), males and females were evaluated separately. Diabetes mellitus was present in 34 patients (20 males and 14 females) and 30 of 97 women were postmenopausal. None of the postmenopausal women were taking hormone replacement therapy.

The transplanted kidney was from a living donor in 104 patients and from a cadaver in 87 patients. Most of the living transplants were from genetically related donors (94.2%) while 5.8% were from non-genetically related donors. Most of the non-genetically related transplants were from spouses (66.7%).

Anthropomorphic data, clinical aspects and immunosuppressive therapy used for patients with or without fractures after KT, according to gender, are shown in Table 3. KT female patients with fractures were significantly older and had used significantly higher cumulative doses of steroids than women with no fracture. KT men with fractures were significantly thinner and shorter

Table 2. Bone mineral density (BMD) and quantitative ultrasound (QUS) parameters for 191 kidney transplant recipients according to gender.

	Total (N = 191)	Men (N = 94)	Women (N = 97)
LS BMD (g/cm^2)	1.119 ± 0.013 (0.710-1.920)	1.096 ± 0.017 (0.710-1.480)	1.141 ± 0.021 (0.740-1.920)
FN BMD (g/cm^2)	0.886 ± 0.014 (0.600-1.425)	0.919 ± 0.016 (0.900-1.262)	0.864 ± 0.016* (0.600-1.425)
QUS			
Right heel			
BUA (dB/MHz)	109.1 ± 0.81 (64-140)	110.66 ± 1.21 (78-140)	107.59 ± 1.08* (64-128)
SOS (m/s)	1542 ± 2.52 (1457-1652)	1531 ± 11.62 (1457-1652)	1542 ± 3.40 (473-1647)
SI (%)	84.55 ± 1.11 (36-127)	85.55 ± 1.70 (44-127)	83.58 ± 1.47 (36-119)
Left heel			
BUA (dB/MHz)	108.1 ± 0.74 (62-140)	109.77 ± 1.20 (62-140)	106.66 ± 0.89* (88-136)
SOS (m/s)	1540.61 ± 2.61 (1404-1729)	1541.74 ± 3.44 (1471-1627)	1540 ± 3.95 (1404-1729)
SI (%)	83.48 ± 1.09 (38-150)	84.76 ± 1.59 (55-121)	82.32 ± 1.51 (38-150)

Data are reported as means ± SEM with range within parentheses. LS = lumbar spine; FN = femoral neck; BUA = broadband ultrasound attenuation; SOS = speed of sound; SI = stiffness index.
*P ≤ 0.05 compared to males (Student *t*-test).

Table 3. Anthropomorphic parameters and clinical data for 191 male and female kidney transplant recipients according to fracture status.

	Men		Women	
	Fracture (N = 20)	Non-fracture (N = 74)	Fracture (N = 26)	Non-fracture (N = 71)
Age (years)	47.15 ± 2.44	46.46 ± 1.33	46.69 ± 1.93	41.93 ± 1.13*
Weight (kg)	64.80 ± 2.41	76.32 ± 1.63*	66.88 ± 3.05	62.31 ± 1.69
Height (m)	1.61 ± 0.011	1.67 ± 0.008*	1.54 ± 0.011	1.54 ± 0.008
BMI (kg/m^2)	24.75 ± 1.01	27.15 ± 0.52*	28.16 ± 1.23	25.89 ± 0.63
Creatinine (mg/dL)	1.77 ± 0.09	1.64 ± 0.03	1.67 ± 0.08	1.53 ± 0.04
Duration of dialysis (months)	61.10 ± 11.24	36.51 ± 3.55*	55.80 ± 9.11	49.35 ± 5.44
Time since transplantation (months)	83 ± 12.4	94.07 ± 6.17	93.65 ± 11.38	78.26 ± 5.33
Cumulative dose of steroids (g)	32.04 ± 5.4	34.19 ± 2.71	33.15 ± 3.99	23.73 ± 1.62*
Cumulative dose of cyclosporin A (g)	351.81 ± 65.38	549.56 ± 50.09*	546.61 ± 64.12	429.35 ± 36.39
Cumulative dose of azathioprine (g)	227.19 ± 57.24	268.73 ± 27.78	226.30 ± 44.59	178.33 ± 17.64

Data are reported as means ± SEM. BMI = body mass index.
*P < 0.05 compared to same sex with fracture (Student *t*-test).

and had lower BMI values than those without fractures. On the other hand, no statistically significant difference in age was found in this subset of the KT population studied. Significantly longer duration of pre-KT dialysis was observed in KT men with fractures compared to those without fractures ($P < 0.05$).

LS and FN BMD values were significantly lower in KT male and female patients with fractures compared to controls with no fractures (Table 4). Even after adjustments for age and menopausal status, BMD values were still significantly lower in women with fractures than in women with no fractures. QUS values tended to be lower in men and women with fractures compared to their non-fracture controls, although the difference was not statistically significant (Table 4).

Bone mineral density and quantitative ultrasound measurements

BMD and QUS measurements for KT patients are shown in Table 2. Male patients had significantly higher FN BMD and BUA values than female patients. When BMD was classified according to the WHO criteria for skeletal fragility and risk of fracture, we found osteoporosis in 8.5-13.4% of KT patients and osteopenia in 30.9-35.1%, depending on gender or skeletal site examined. The prevalence of osteoporosis and osteopenia at the FN and LS did not differ significantly between men and women (Table 5).

Fracture data

Table 6 shows the prevalence of fragility fracture in our population. Forty-six KT patients (24%) presented low-impact fractures in our survey (20 men and 26 women, of whom 14 were postmenopausal). None of the postmenopausal women were under hormone replacement therapy. A history of peripheral fracture after low trauma was observed in 14 patients (mean time from trauma to KT: 8 years; range: 6 months to 12 years). Vertebral fractures were found in 29 patients (63% of the total cases with fractures, 17 men and 12 women). Three patients had peripheral and vertebral fractures simultaneously.

Diabetes mellitus was observed in 9 female KT patients with vertebral (N = 3) or peripheral (N = 6) fractures, but only in 3

Table 4. Bone mineral density (BMD) and quantitative ultrasound (QUS) parameters for 191 kidney transplant recipients according to fracture status and gender.

	Men		Women	
	Fracture (N = 20)	Non-fracture (N = 74)	Fracture (N = 26)	Non-fracture (N = 71)
LS BMD (g/cm^2)	0.983 ± 0.039	1.128 ± 0.017*	1.059 ± 0.03	1.171 ± 0.025*
FN BMD (g/cm^2)	0.849 ± 0.029	0.938 ± 0.018*	0.808 ± 0.025	0.896 ± 0.018*
QUS				
Right heel				
BUA (dB/MHz)	107.95 ± 2.90	111.4 ± 1.31	107.19 ± 2.13	107.74 ± 1.25
SOS (m/s)	1532 ± 8.13	1530 ± 14.67	1533 ± 7.42	1546 ± 3.71
SI (%)	81.35 ± 3.82	86.71 ± 1.89	80.5 ± 3.16	84.72 ± 1.64
Left heel				
BUA (dB/MHz)	107.10 ± 2.12	110.50 ± 1.41	106.26 ± 2.06	106.81 ± 0.96
SOS (m/s)	1531.55 ± 6.1	1544.53 ± 4.01	1530.46 ± 7.08	1544.04 ± 4.69
SI (%)	80.15 ± 2.86	86.02 ± 1.87	79.3 ± 3.19	83.44 ± 1.69

Data are reported as means ± SEM. LS = lumbar spine; FN = femoral neck; BUA = broadband ultrasound attenuation; SOS = speed of sound; SI = stiffness index.
*$P < 0.05$ compared to same sex with fracture (Student *t*-test).

males with fracture (vertebral = 2; non-vertebral = 1).

Risk factors for fracture

Backward conditional logistic regression analysis was performed including all variables that showed significance in the chi-squared analysis in order to identify potential risk factors for fractures in this population. Again, men and women were analyzed separately. Renal function assessed by creatinine levels and predicted creatinine clearance was not associated with BMD measurements or with the presence of fractures. As shown in Table 7, presence of diabetes mellitus [OR = 11.5, 95% CI (2.4-55.7)], menopausal status [OR = 3.7, 95% CI (1.2-11.9)] and FN BMD [OR = 1.99, 95% CI (1.4-2.8)] were the most important determinants of fracture risk in KT female patients. Less important but still significant risk factors for fracture in KT women were cumulative dose of steroids [OR = 1.1, 95% CI (1.02-1.12)] and low SI [OR = 1.1, 95% CI (1.0-1.2)]. Lower LS BMD [OR = 1.75, 95% CI (1.1-2.7)], lower SI [OR = 1.1, 95% CI (1.03-1.13)], longer duration of dialysis [OR = 1.3, 95% CI (1.13- 2.7)], and lower BMI values [OR = 1.24, 95% CI (1.1-1.4) were the factors that associated best with the presence of fractures in KT men.

Discussion

KT is a successful treatment for ESRD and results in better quality of life. In Brazil, the rate of KT reaches 3000 per year (22) with increasing long-term survival rates probably associated with the routine use of cyclophilin-binding agents (5). On the other hand, the use of immunosuppressants, especially glucocorticosteroids, causes multiple skeletal complications, including osteoporosis and increased fracture risk.

The current study was designed to estimate the prevalence of low-trauma fracture and osteoporosis in KT long-term recipients. Prevalent vertebral deformity and/or previous low-trauma fracture were found in 46 (of 191) KT patients (24%), with the

Table 5. Prevalence of low bone mass (osteopenia and osteoporosis) in 191 kidney transplant recipients according to gender and skeletal site.

Skeletal site	Normal	Osteopenia	Osteoporosis
Lumbar spine			
Men	52 (55.3%)	30 (31.9%)	12 (12.8%)
Women	55 (56.7%)	32 (32.9%)	10 (10.3%)
Femoral neck			
Men	53 (56.4%)	33 (35.1%)	8 (8.5%)
Women	54 (55.6%)	30 (30.9%)	13 (13.4%)
LS + FN			
Men	42 (44.6%)	17 (18%)	2 (2.1%)
Women	44 (45.3%)	16 (16.4%)	4 (4.1%)

Data are reported as number and percent. LS = lumbar spine; FN = femoral neck.

Table 6. Prevalence of fractures in 191 kidney transplant recipients according to gender and skeletal site.

Male	Male	Female	Total
Vertebral fracture	17 (85%)	12 (46%)	29 (63%)
Non-vertebral fracture	2 (10%)	12 (46%)	14 (30.4%)
Vertebral + non-vertebral fractures	1 (5%)	2 (7.7%)	3 (6.5%)
Total	20 (100%)	26 (100%)	46 (100%)

Data are reported as number and percent.

Table 7. Logistic regression analysis and age-adjusted odds ratio for factors associated with higher fracture risk for 191 kidney transplant recipients according to gender.

	OR (95% CI)
Women	
Diabetes mellitus	11.5 (2.4-55.7)
Menopausal status	3.7 (1.2-11.9)
Femoral neck BMD	1.99 (1.4-2.8)
Stiffness index	1.1 (1.0-1.2)
Cumulative dose of steroids	1.1 (1.02-1.12)
Men	
Lumbar spine BMD	1.75 (1.1-2.7)
Stiffness index	1.1 (1.03-1.13)
Dialysis time	1.3 (1.13-2.7)
Body mass index	1.24 (1.1-1.4)
Cumulative dose of cyclosporin A	0.4 (0.3-0.8)

BMD = bone mineral density; OR = odds ratio; 95% CI = 95% confidence interval. $P < 0.05$ for all factors.

difference between genders being not statistically significant. These data show that KT patients presented significantly higher fracture prevalence than that observed for the general population. Others have found similar fracture rates in KT patients (0-38.5%) (8-12,23-25). Some of this variability in fracture prevalence among KT patients might be related to the design of the study, the population assessed and the criteria used to define fracture, particularly vertebral deformity.

Vertebral deformities were observed in 29 of 46 patients with fractures (63% of the total number of fractures). This observation is consistent with some other studies (8,10,23-25) that have demonstrated a higher prevalence of vertebral than non-vertebral fractures in this set of patients. Patel et al. (25), using a different method to identify vertebral fracture, reported a prevalence of vertebral deformities in KT patients similar to ours, while other investigators have observed a lower prevalence of vertebral fractures than that described in the present study (9,26,27). These conflicting findings probably reflect methodological differences (inclusion criteria, selection bias) and management discrepancies (dialysis and transplantation) among centers. Moreover, ethnic and geographic factors may also play an important role in low-trauma fracture occurrence. Melton III et al. (28) observed that the prevalence of vertebral fractures ranges from 8 to 25% in healthy women, depending on the classification criteria applied. Differently from the vertebral fracture data, our non-vertebral fracture findings are similar to those reported in the literature. Again, the diagnostic criteria for appendicular fractures are universal and do not depend much upon the diagnostic methodology used.

It is also interesting to observe that the average cumulative dose of corticosteroid used in our patients was significantly higher than that described for other populations, especially in North America (8). At our center, KT patients use immunosuppressive therapy that includes prednisone, a calcineurin inhibitor (cyclosporine or tacrolimus) and an antimetabolite (azathioprine or mycophenolate mofetil). At the time the patients selected underwent KT, neither tacrolimus nor mycophenolate mofetil or induction therapy with polyclonal or monoclonal antibody preparations were easily available in Brazil. The immunosuppressive protocol consisted mainly of prednisone, cyclosporine and azathioprine. This may explain the higher glucocorticoid doses needed to avoid rejection in our patients. One year after KT, the average daily dosage of prednisone for our patients was 6.95 mg, high enough to have a negative impact on bone homeostasis. At pharmacological doses, glucocorticosteroids inhibit osteoblastogenesis and bone formation and increase osteoblast apoptosis, leading to bone loss and fragility fractures. The higher corticosteroid doses used by our patients could theoretically explain the higher prevalence of osteoporosis and fragility fractures in our sample.

The prevalence of low bone mass following KT varies according to the population studied; it tends, however, to be more pronounced than that observed in the general population (25). The KT men and women studied here showed a similar bone loss prevalence and had fractures with BMD values than those reported in the literature for the general population (9,10,23,25), a fact suggesting that factors other than BMD are involved in fracture risk determination in KT recipients. This observation also suggests that the WHO criteria used to determine fracture risk should be revised to better classify fracture risk in the KT population (10,14,29). Another strategy to improve the evaluation of fracture risk in KT patients would be to establish absolute BMD values below which fracture risk is significantly higher. The singular bone disease following KT could also explain the prevalence of fractures with higher BMD values in this population. Most patients developed bone

disease related to renal failure before KT (dialysis stage) and after it (immunosuppressive therapy). Thus, they could have a bone disease pathologically different from primary osteoporosis. Parker et al. (24), studying bone histomorphometry in 38 KT women, observed that only 2 of them had normal results even when evaluated 8 years after KT.

Most investigators studying skeletal fragility in KT patients have analyzed men and women together. In our study, men and women were assessed separately and classified according to fracture status. In women, diabetes mellitus, menopausal status, FN BMD, cumulative dose of steroids, and low SI were the most important determinants of fracture risk. As observed in another study (26), diabetes mellitus is a very important risk factor for fractures in KT women (OR = 11.5, 95% CI = 2.4-55.7). A dynamic bone disease and bone formation impairment related to peripheral resistance to PTH, have both been observed in diabetic patients, leading to higher fracture risk in this population (17). Moreover, other risk factors (steroids, physical activity, IGF-1, stress fractures, atherosclerosis) (24,30) could theoretically have synergistic effects on bone loss in this subgroup of patients. Menopause is one of the main risk factors for fractures in healthy women, as well as in KT patients (25). Interestingly, Ramsey-Goldman et al. (12) reported no statistically significant differences in fracture prevalence between pre- and postmenopausal KT women, but they only investigated symptomatic vertebral fractures.

In KT men, longer time of dialysis, lower LS BMD, lower SI, and lower BMI were the factors most significantly associated with fractures. A longer duration of dialysis influenced the occurrence of fractures, suggesting that pre-transplantation bone disease is an important determinant of future fractures. Lower SI and bone density were associated with fracture risk, as also reported by Pichette et al. (10) and Parker et al. (24), who have described vertebral fractures in men and have shown a significant correlation between lower LS BMD, lower SOS and fractures.

As previously noted by other authors, there was a statistically significant correlation between QUS measurements obtained from the left and right heels (r = 0.84), excluding the need for duplicate bilateral QUS testing in routine practice (31,32).

Even though KT recipients had a higher fracture prevalence than that reported for the general population, the odds ratio described in the present study are comparable to those found in patients with postmenopausal osteoporosis or osteoporosis related to the aging process (33). These findings suggest that bone mass measurements and specific clinical factors can predict fractures in KT patients with the same performance as that described for the general population.

Most of our patients had received a transplant from living donor (54%) and one could question whether our sample is representative of the Brazilian KT population. According to data from the Brazilian National System of Transplants, most of the organ transplantation in our country is still from living donors. Similar to our findings, repartition transplantation from living donors versus transplantation from cadaveric donors for kidney transplantation in Brazil in the years of 2003 and 2004 was 58.9 and 41.1% and 47.2 and 52.8%, respectively (24). At most Brazilian transplantation centers there still is a significantly high rate of allocation failure for organs from cadaveric donors, a fact that helps to explain the higher repartition rate for living donor transplants compared to cadaveric donors.

The present study has some limitations that need to be pointed out. The cross-sectional study design may have caused inherent flaws in the data collection and prevented the authors from determining the correct time when the vertebral deformities occurred. Important details regarding rejection episodes, oral calcium intake and mineral

calcium metabolism before and after KT were also not assessed in this study and may have had a significant impact on fracture determination.

We observed a high prevalence of low-impact fractures in a young population of kidney transplantation patients. Higher fracture prevalence was found in postmenopausal or diabetic women and in men with a longer time of dialysis, lower FN BMD and lower BMI. In addition, BMD and QUS measurements showed a comparable performance in distinguishing male and female patients with fractures from those without after kidney transplantation. Longitudinal studies are needed to better quantify the influence of these factors on fracture risk in this population.

References

1. Malluche H & Faugere MC (1990). Renal bone disease 1990: an unmet challenge for the nephrologist. *Kidney International*, 38: 193-211.
2. Hruska K (2000). Pathophysiology of renal osteodystrophy. *Pediatric Nephrology*, 14: 636-640.
3. Almond MK, Kwan JT, Evans K et al. (1994). Loss of regional bone mineral density in the first 12 months following renal transplantation. *Nephron*, 66: 52-57.
4. Horber FF, Casez JP, Steiger U et al. (1994). Changes in bone mass early after kidney transplantation. *Journal of Bone and Mineral Research*, 9: 1-9.
5. Suthanthiran M, Morris RE & Strom TB (1996). Immunosuppressants: cellular and molecular mechanisms of action. *American Journal of Kidney Diseases*, 28: 159-172.
6. Epstein S (1996). Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. *Journal of Bone and Mineral Research*, 11: 1-7.
7. Brandenburg V, Westenfeld R & Ketteler M (2004). The fate of bone after renal transplantation. *Journal of Nephrology*, 17: 190-204.
8. Grotz WH, Mundinger FA, Gugel B et al. (1994). Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation*, 58: 912-915.
9. Nisbeth U, Lindh E, Ljunghall S et al. (1994). Fracture frequency after kidney transplantation. *Transplantation Proceedings*, 26: 1764.
10. Pichette V, Bonnardeaux A, Prudhomme L et al. (1996). Long-term bone loss in kidney transplant recipients: a cross-sectional and longitudinal study. *American Journal of Kidney Diseases*, 28: 105-114.
11. Chiu MY, Sprague SM, Bruce DS et al. (1998). Analysis of fracture prevalence in kidney-pancreas allograft recipients. *Journal of the American Society of Nephrology*, 9: 677-683.
12. Ramsey-Goldman R, Dunn JE, Dunlop DD et al. (1999). Increased risk of fracture in patients receiving solid organ transplants. *Journal of Bone and Mineral Research*, 14: 456-463.
13. Julian BA, Laskow DA, Dubovsky J et al. (1991). Rapid loss of vertebral mineral density after renal transplantation. *New England Journal of Medicine*, 325: 544-550.
14. Kanis JA, Melton III LJ, Christiansen C et al. (1994). The diagnosis of osteoporosis. *Journal of Bone and Mineral Research*, 9: 1137-1141.
15. Cummings SR (1985). Are patients with hip fractures more osteoporotic? Review of the evidence. *American Journal of Medicine*, 78: 487-494.
16. Stehman-Breen CO, Sherrard DJ, Alem AM et al. (2000). Risk factors for hip fracture among patients with end-stage renal disease. *Kidney International*, 58: 2200-2205.
17. Abbott KC, Oglesby RJ, Hypolite IO et al. (2001). Hospitalizations for fractures after renal transplantation in the United States. *Annals of Epidemiology*, 11: 450-457.
18. Hans D, Dargent-Molina P, Schott AM et al. (1996). Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet*, 348: 511-514.
19. Eastell R, Cedel SL, Wahner HW et al. (1991). Classification of vertebral fractures. *Journal of Bone and Mineral Research*, 6: 207-215.
20. Consensus Development Conference Panel (1993). Diagnosis, prophylaxis, and treatment of osteoporosis. *American Journal of Medicine*, 94: 646-650.
21. Heldan de Moura CC, Medeiros PM & Lucia SV (2000). Quantitative ultrasound of the calcaneus in Brazilian Caucasian women: normative data are similar to the manufacturer's normal range. *Osteoporosis International*, 11: 923-928.
22. Associação Brasileira de Transplante de Órgaos. The Brazilian Association for Organ Transplants web page. [http://www.abto.org.br/]. Accessed March 16, 2005.
23. Nam JH, Moon JI, Chung SS et al. (2000). Prevalence and risk factors for vertebral fractures in renal transplants. *Transplantation Proceedings*, 32: 1877.
24. Parker CR, Freemont AJ, Blackwell PJ et al. (1999). Cross-sectional analysis of renal transplantation osteoporosis. *Journal of Bone and Mineral Research*, 14: 1943-1951.
25. Patel S, Kwan JT, McCloskey E et al. (2001). Prevalence and causes of low bone density and fractures in kidney transplant patients. *Journal of Bone and Mineral Research*, 16: 1863-1870.
26. Nisbeth U, Lindh E, Ljunghall S et al. (1999). Increased fracture rate in diabetes mellitus and females after renal transplantation. *Transplantation*, 67: 1218-1222.
27. Brandenburg VM, Ketteler M, Fassbender WJ et al. (2002). Development of lumbar bone mineral density in the late course after kidney transplantation. *American Journal of Kidney Diseases*, 40: 1066-1074.
28. Melton III LJ, Atkinson EJ, O'Fallon WM et al. (1993). Long-term fracture prediction by bone mineral assessed at different skeletal sites. *Journal of Bone and Mineral Research*, 8: 1227-1233.
29. Riggs BL, Wahner HW, Seeman E et al. (1982). Changes in bone mineral density of the proximal femur and spine with aging: differ-

ences between the postmenopausal and senile osteoporosis syndromes. *Journal of Clinical Investigation*, 70: 716-723.
30. Grotz WH, Mundinger FA, Rasenack J et al. (1995). Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. *Nephrology*, *Dialysis*, *Transplantation*, 10: 2096-2100.
31. Kosch M, Hausberg M, Link T et al. (2000). Measurement of skeletal status after renal transplantation by quantitative ultrasound. *Clinical Nephrology*, 54: 15-21.
32. Mondry A, Hetzel GR, Willers R et al. (2001). Quantitative heel ultrasound in assessment of bone structure in renal transplant recipients. *American Journal of Kidney Diseases*, 37: 932-937.
33. Pinheiro MM, Castro CH, Frisoli Jr A et al. (2003). Discriminatory ability of quantitative ultrasound measurements is similar to dual-energy X-ray absorptiometry in a Brazilian women population with osteoporotic fracture. *Calcified Tissue International*, 73: 555-564.