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Factors influencing vertebral bone density after renal transplantation

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Abstract To improve our understanding of the mechanisms underlying osteoporosis following renal transplantation, we compared bone mineral density (BMD) in 158 transplant recipients and in 293 patients undergoing maintenance hemodialysis with age- and sex-matched normal controls. Observations in graft recipients were made up to several years following transplantation. Dual-energy X-ray absorptiometry was used to measure BMD. Correlations with clinical variables including serum concentration of parathyroid hormone (PTH) and steroid therapy were evaluated. Lumbar BMD was lower in transplant patients than in dialysis patients at all ages, and continued to decrease with increasing interval posttransplant until the second year after transplantation. Persistent hyperparathyroidism and daily prednisolone dosage were both associated with decreased BMD. Age and creatinine clearance were independent long-term predictors of BMD by multiple regression analysis. Treatment of renal graft recipients with calcium and vitamin D supplements or calcitonin may be indicated in the early months after transplantation.

Key words Bone mineral density · Hyperparathyroidism · Osteoporosis · Renal transplantation · Steroid therapy

Introduction

Despite the ability of renal transplantation to reverse many of the underlying defects in bone metabolism that occur with chronic renal failure and dialysis, osteoporosis remains a frequent and serious complication affecting renal transplant patients. Short-term studies of bone mass following kidney transplantation have indicated rapid bone loss within the first year [1–3]. Treatment with prednisolone [2] and persistent hyperparathyroidism [3] predominate among multiple factors associated with bone loss. On the other hand, there have been a few reports on the long-term course of bone mineral density (BMD). Grotz noted that the bone mass decreased within the first two years posttransplant because of high-dose prednisolone, but subsequently increased thereafter, though not reaching preoperative values.

We designed a cross-sectional study to determine the influence of immunosuppressive therapy, the predictive factor, and the time-course of BMD after kidney transplantation. The data were then compared with those recorded in hemodialysis (HD) patients.

Patients and methods

A total of 158 renal transplant recipients (101 male and 57 female) seen at various time intervals after kidney transplantation and a total of 293 uremic patients (170 male and 123 female) undergoing maintenance HD were evaluated by densitometry between 1997 and 1998. All recipients underwent kidney transplantation at the Osaka University hospital between 1973 and 1998. BMD was measured by dual-energy X-ray absorptiometry (DEXA, Hologic QDR-2000) for the lumbar spine and the distal radius. Lumbar bone density values represented the average of three vertebrae, L2–4. BMD measurements were expressed in grams per square

Table 1 Clinical characteristics and bone mineral density. Normal ranges: intact parathyroid hormone *(i-PTH)* 10–65 pg/ml, hypersensitive *(HS)* PTH 74–273 pg/ml

	Men			Women		
	Kidney recipients (n = 101)	Hemodialysis patients (n = 170)	P	Kidney recipients (n = 57)	Hemodialysis patients (n = 123)	P
Age (years)	42.1 ± 10.0	48.9 ± 7.8	< 0.0001	41.3 ± 11.1	49.0 ± 8.1	< 0.0001
Time on dialysis (years)	3.30 ± 3.39	8.40 ± 6.23	< 0.0001	3.75 ± 3.78	8.79 ± 6.06	< 0.0001
i-PTH (pg/ml)	107.9 ± 102.9	441.4 ± 551.9	< 0.0001	128.6 ± 173.3	372.0 ± 501.6	0.0021
HS-PTH (pg/ml)	1943 ± 2592	21539 ± 32276	< 0.0001	1934 ± 2495	18668 ± 20262	< 0.0001
Total calcium (mEq/ml)	4.62 ± 0.28	4.69 ± 0.76	0.4514	4.64 ± 0.35	4.67 ± 0.61	0.7711
Phosphorus (mg/ml)	2.98 ± 0.65	5.63 ± 1.34	< 0.0001	3.19 ± 0.73	5.76 ± 1.13	< 0.0001
Lumbar BMD (g/cm^2)	0.908 ± 0.145	1.007 ± 0.163	< 0.0001	0.872 ± 0.123	0.918 ± 0.146	0.0431
Distal radius BMD (g/cm^2)	0.540 ± 0.075	0.543 ± 0.118	0.860	0.488 ± 0.137	0.441 ± 0.066	0.0024

centimeter and as a percentage of values from a sex- and age-matched normal Japanese control population. At the time of bone examination, serum levels of creatinine, calcium, phosphate, intact parathyroid hormone (i-PTH), hypersensitive PTH (HS-PTH) and creatinine clearance were determined.

To evaluate the long-term bone status of transplant recipients, recipients were divided into two subgroups according to time since kidney transplantation.

In the statistical analysis, Student's t-test and Chi-square tests were used for group comparison. Correlation coefficients were calculated to assess possible relationships between variables. Multiple regression and multiple stepwise linear regression were performed using lumbar bone density as the dependent variable.

Results

Kidney transplant recipients were younger than HD patients (41.8 ± 3.5 vs 48.9 ± 7.9 years, $P < 0.0001$). The kidney recipients had been treated with dialysis for 3.5 ± 3.5 years before transplantation, while time on dialysis for HD patients was 8.6 ± 6.2 years (a significant difference). Serum concentrations of i-PTH or HS-PTH levels were significantly higher in HD patients than in recipients. Lumbar BMD (g/cm^2) was lower in transplant recipients than in HD patients for each age group (Table 1). These differences were significant for men at 20–29 and at 40–49 years of age and for women aged 20–29 years. Distal radius BMD (g/cm^2) in transplant recipients was the same as or higher than in HD patients in each age group; these differences were not significant except for women aged 30–39 years (Fig. 1).

Expressed as a percentage of the value in age- and sex-matched populations, relative lumbar BMD (%) and distal radius BMD (%) within the first postoperative year were significantly higher than in other recipients evaluated 1–5 years after transplantation. The lowest lumbar BMD values were observed between 13 and 24 months after transplantation. Beyond the third year, lumbar BMD increased slightly, while distal radius BMD showed little change (Fig. 2). Prednisolone dosage 0–12 months after renal transplantation was significantly higher than after 2 posttransplant years (Fig. 2).

By simple linear regression analysis in the whole group, there was a significant but weak negative correlation between relative lumbar BMD and daily prednisolone dosage. In the subgroup of recipients investigated within 5 years posttransplant there was a significant but weak negative correlation between distal radius BMD and cumulative prednisolone dose. In the subgroup of recipients investigated 5 years or more after the transplant operation a significant weakly negative correlation was found between lumbar BMD and daily prednisolone dosage (Table 2).

By multiple regression analysis (Table 3) in the whole group, age, serum creatinine and creatinine clearance (CCR) were the only independent predictors of lumbar BMD. Distal radius BMD did not correlate with graft function, biochemical parameters or any other parameters. In the subgroup of recipients seen within 5 postoperative years, HS-PTH was a predictor of lumbar and distal radius BMD. In the subgroup of recipients seen after 5 postoperative years, CCR was the only independent predictor of lumbar BMD (Table 3). A significant correlation was seen between the serum HS-PTH level and CCR (or serum creatinine), as shown in Fig. 3.

Discussion

While successful renal transplantation usually corrects the mineral metabolism disturbances that lead to renal osteodystrophy, a significant bone loss still occurs within the first year after kidney transplantation [1–3], and the same tendency is seen following heart [4] and liver [5] transplantation. After transplantation, immunosuppressive therapy, especially steroid therapy, has a deleterious effect on bone metabolism. Other negative factors may include impaired renal function and pre-existing secondary hyperparathyroidism taking a long time to normalize. We performed a cross-sectional study to analyze

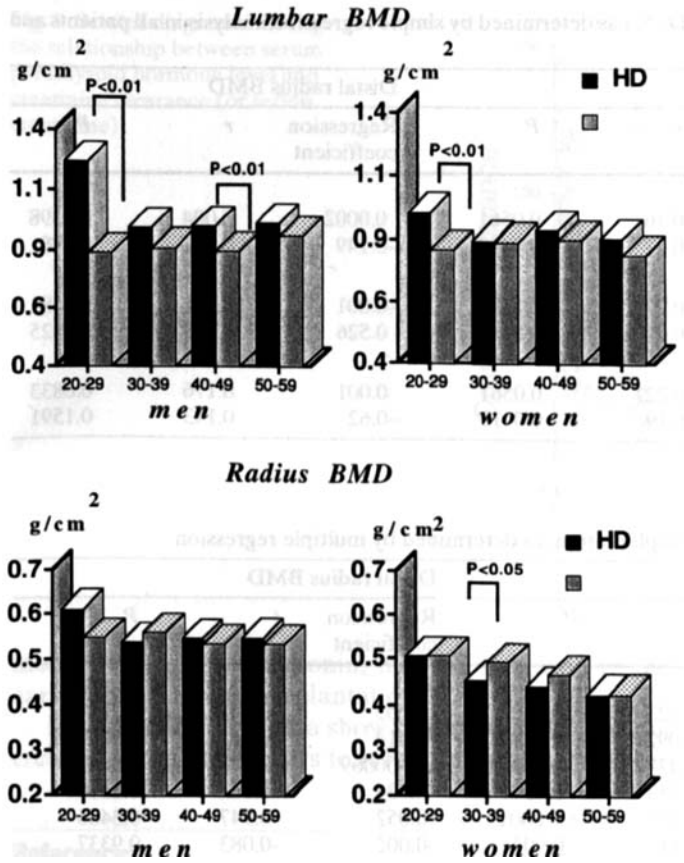

Fig. 1 Bone mineral density (BMD) of graft recipients and HD patients in different sex and age groups

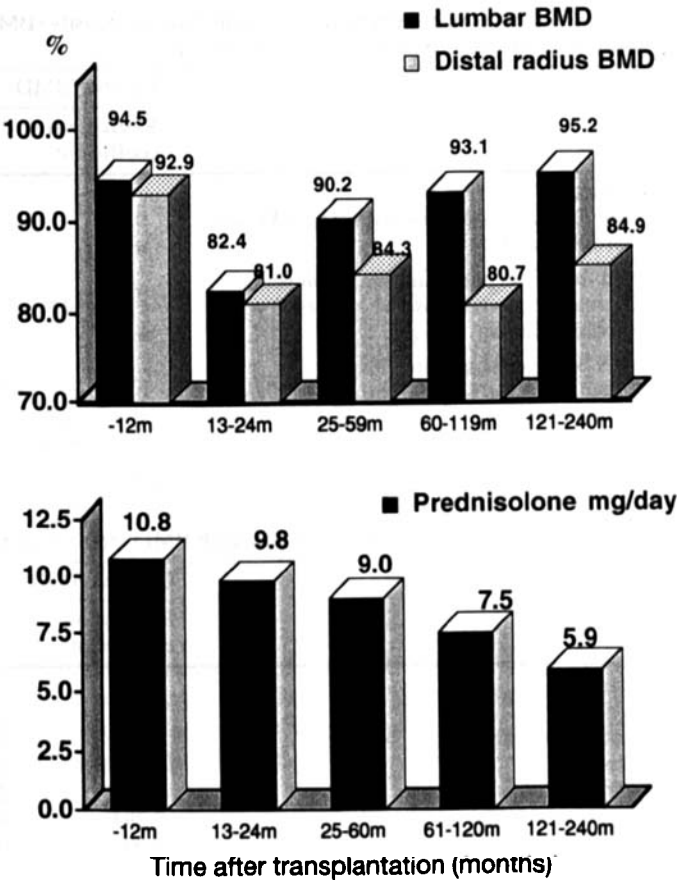

Fig. 2 Mean BMD and mean daily prednisolone dose in different time periods after transplantation

the distribution of BMD values at different times over 20 years after transplantation. We compared BMD in our allograft recipients with bone density in HD patients.

In our study the lowest mean lumbar BMD was reached 13–24 months after transplantation, while lumbar BMD slowly increased and distal radius BMD did stabilized beyond 24 posttransplant months. Distal radius BMD did not show a time-dependent change in the posttransplant period, but lumbar BMD did, indicating that lumbar BMD is a more sensitive and stable indicator for monitoring osteodystrophy in the posttransplant period. In accordance with our findings, many studies have shown a progressive decrease in BMD during the first 2 years posttransplant [1–3]. Some authors have implicated prednisolone as one of the main factors in BMD loss after renal transplantation. We could not observe any statistical link of BMD and cumulative prednisolone dose, but observed a weak negative correlation between relative lumbar BMD and daily prednisolone dosage.

Our findings confirm the prevalence of hyperparathyroidism in HD patients, and of persistent secondary hyperparathyroidism in transplant recipients. However, serum PTH levels in recipients were significantly lower than those in HD patients. Our results for lumbar BMD also contrast with those reported by Julian [1] in the short term after transplantation caused by resolution of mild secondary hyperparathyroidism. Multiple regression analysis revealed that persistent hyperparathyroidism was a significant factor underlying the loss of bone mass during the first 5 years after transplantation. Therefore, in addition to the use of high-dose prednisolone therapy, residual abnormality of parathyroid function also exacerbates short-term loss of BMD following transplantation.

Over a longer term, our cross-sectional data suggested that after 3 years posttransplant distal radius BMD no longer changes and that lumbar BMD might recover slightly, while remaining below reference values obtained in a normal population. We found that CCR was the only independent predictor of long-term lumbar BMD. The dose of prednisolone in our recipients had decreased to 8.5 ± 3.0 mg/day by 2 years after transplantation. The findings agree with previous observations that low prednisolone doses have less

Table 2 Factors correlating with relative bone mineral density (BMD, %) as determined by simple regression analysis in all patients and in two subgroups according to timeafter transplantation

	Lumbar BMD			Distal radius BMD		
	Regression coefficient	r	P	Regression coefficient	r	P
All patients						
Cumulative steroid dose within first 2 years	0.001	0.16	0.0561	0.0002	0.004	0.9598
Steroid dose/day	–0.996	0.17	0.0419	–0.149	0.036	0.678
Within the first 5 posttransplantation years						
Cumulative steroid dose within first 2 years	–0.0004843	0.079	0.6289	–0.001	0.341	0.0481
Steroid dose/day	0.226	0.027	0.8663	0.526	0.103	0.5625
After 5 posttransplantation years						
Cumulative steroid dose within first 2 years	0.002	0.221	0.0561	0.001	0.176	0.0833
Steroid dose/day	–1.168	0.19	0.0419	–0.62	0.143	0.1591

Table 3 Factors independently correlating with BMD after renal transplantation, as determined by multiple regression

	Lumbar BMD			Distal radius BMD		
	Regression coefficient	t	P	Regression coefficient	t	P
All patients						
Age	0.419	2.623	0.0103	–0.055	–0.361	0.719
Time on dialysis	0.377	1.092	0.2779	–0.314	–1.001	0.32
After TPL	–0.000435	–0.437	0.6629	0.000069	0.075	0.9403
S-Cr	6.933	2.153	0.0341	–4.734	–1.564	0.1217
CCR	0.294	4.979	< 0.0001	0.052	0.947	0.3466
i-PTH	0.003	0.117	0.907	–0.002	–0.083	0.9337
Hypersensitive PTH	–0.001	–1.164	0.2476	0.000069	0.075	0.9405
Total calcium	1.209	0.23	0.8184	2.081	0.405	0.6868
Phosphorus	2.25	1.012	0.3143	3.396	1.667	0.0994
Cumulative steroid dose within first 2 years	0.000236	0.398	0.6915	0.000198	0.357	0.722
Steroid dose/day	–0.99	–1.642	0.1042	0.032	0.058	0.9543
Multiple correlation	$R = 0.636$	$F = 5.301$	($P < 0.0001$)	$R = 0.407$	$F = 1.479$	($P = 0.1553$)
Recipients within the first 5 posttransplantation years						
Age	0.578	2.413	0.0246	–0.137	–0.556	0.5845
S-Cr	15.96	3.204	0.0041	–0.324	–0.061	0.9516
CCR	0.284	2.774	0.0111	0.015	0.142	0.8887
Hypersensitive PTH	–0.002	–2.406	0.025	–0.002	–2.673	0.0146
Multiple correlation	$R = 0.658$	$F = 4.204$	($P = 0.011$)	$R = 0.619$	$F = 3.108$	($P = 0.038$)
Recipients after 5 posttransplantation years						
Age	0.293	1.629	0.108	–0.027	–0.173	0.8629
S-Cr	5.203	1.63	0.1078	–3.674	–1.304	0.1967
CCR	0.298	4.244	< 0.0001	0.064	1.049	0.2982
Hypersensitive PTH	–0.001	–1.345	0.1831	0.000331	0.596	0.5534
Multiple correlation	$R = 0.572$	$F = 8.387$	($P < 0.0001$)	$R = 0.32$	$F = 1.877$	($P = 0.125$)

marked adverse effects on trabecular bone than higher doses. Raisz [6] has postulated a threshold dose of 7.5 mg/day prednisolone for osteoporotic effects. Because of decreases in dose with time, the osteoporotic effects of prednisolone after renal transplantation are essentially limited to the first 2 years after grafting.

There was a significantly correlation between serum PTH levels and graft function. A significant correlation was seen between lumbar BMD and CCR. The BMD in our patients could theoretically be related to hyperparathyroidism, but we did not find any correlation between PTH levels and BMD. The reason may be that the reversal of hyperparathyroidism in recipients occurs over a period of time that is different for each patient, presumably depending on factors such as gland size and previous level of hyperparathyroidism.

To prevent exacerbation of bone lesions, specific therapy including oral calcium and vitamin D supple-

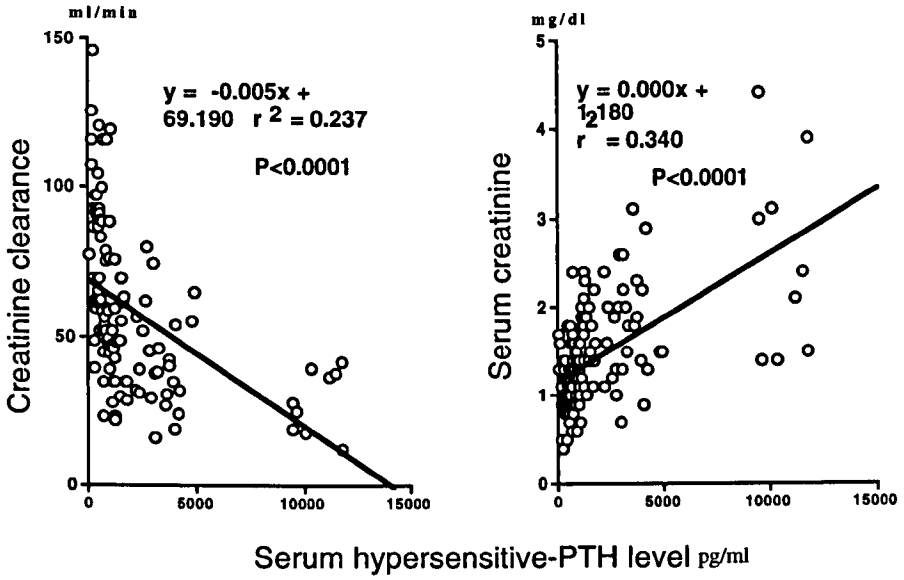

Fig.3 Scatter diagram showing the relationship between serum parathyroid hormone level and creatinine clearance (or serum creatinine)

ments, or possibly calcitonin, may be indicated in the early months after transplantation.

In conclusion, our data show that bone mass was decreased during the 2 years following transplantation because of high-dose prednisolone therapy and persistent hyperparathyroidism. Beyond 3 years, bone mass recovered slightly and CCR was a significant long-term predictor of lumbar BMD.

References

1. Julian BA, Laskow DA, Dubovsky J, Dubosky EV, Curitis JJ, Quarles LD (1991) Rapid loss of vertebral mineral density after renal transplantation. N Engl J Med 352: 544–550
2. Grotz WH, Mundinger FA, Gugel B, Exner VM, Kirste G, Schollmeyer PJ (1995) Bone mineral density after kidney transplantation: a cross-sectional study in 190 graft recipients up to 20 years after transplantation. 59: 982–986
3. Grotz WH, Mundinger FA, Rasenack J, Speidal L, Olschewsk L, Exner VM, Schollmeyer PJ (1995) Bone loss after kidney transplantation : a longitudinal study in 115 graft recipients. Nephrol Dial Transplant 10: 2096–2100
4. Shane E, Rivas M, Silverberg S, Kim J, Staron R, Bilezikian J Osteoporosis after cardiac transplantation. Am J Med 94: 257–264
5. Macdonald J, Dunstan C, Dilworth P, Sherbon K, Shell AG, Evans RA, McCaughan GW (1991) Bone loss after liver transplantation. Hepatology 14: 613–619
6. Lukert B, Raisz L (1990) Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 112: 352–355