Annals of Nuclear Medicine Vol. 13, No. 3, 141–145, 1999

Factors affecting bone mineral density in renal transplant patients

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Bone disease is a major cause of morbidity in end stage renal failure. This study is aimed to assess the prevalence of abnormal bone mineral density (BMD), measured by dual photon absorptiometry (DPA) in the renal transplant population. Subjects consisted of 110 patients followed up after transplantation for between 1 and 17 years. Variables analyzed included age, sex, ethic origin, years and type of dialysis prior to transplantation, date of transplant, total steroid dose, number of rejection episodes, use of Cyclosporin, and biochemical/hormonal variables such as serum calcium, phosphate, magnesium, alkaline phosphatase, creatinine, FSH, LH and PTH.

Analysis of variance and chi square tests were performed to assess the differences between groups and Pearson correlation coefficients were obtained. The total steroid dose, year of birth, PTH level and duration since transplantation were correlated with BMD ($p < 0.05$). Despite the statistical significance, the degree of variability indicated by each of these variables was low revealed by multiple regression analysis. We conclude that although steroid therapy is a major contributor to the increase in osteoporosis in renal transplant patients, about two thirds of the parameters that can influence bone metabolism remain unexplained.

Key words: bone mineral density (BMD), renal disease, osteopenia, steroid therapy, renal transplantation

INTRODUCTION

BONE DISEASE is a major cause of morbidity in end stage renal failure,[1,2] clinical expression occurring in both dialysis and renal transplant populations. In the latter group, steroid therapy is often cited as an important contributor to osteoporosis and subsequent fractures.[3–5] Renal transplant patients are potentially subject to a number of risk factors such as prolonged immobilization hyper-parathyroidism vitamin D deficiency which causes bone loss in addition to normal aging. We attempted to determine if chronic steroid therapy encourages accelerated bone loss and accounts for the propensity of this population to osteopenia and spontaneous fracture. In this report, we describe the results of a survey of bone mineral density (BMD) in a renal transplant population, as measured by dual photon absorptiometry (DPA), and the relationship between BMD and a number of clinical and laboratory parameters known to influence bone metabolism.

Received August 20, 1998, revision accepted February 24, 1999.

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MATERIAL AND METHODS

Patients

The subjects consisted of 110 renal transplant patients followed up after transplantation between January, 1973 and January 1989. Nineteen percent (21/110) had been transplanted before 1980, 13.6% (15/110) had received a transplant between 1981 and 1983, 20.9% (23/110) between 1984 and 1986, and 46.3% (51/110) between 1987 and 1989. The patients underwent bone mineral density measurements and laboratory studies during routine outpatient visits for one full year. The patients were not selected according to any criteria other than routine clinic visits during that observation time. Subjects receiving anti-convulsant or calcium supplement therapy were excluded from the analyses.

Table 1 Fracture risks in relation to the BMD

	Spine		Hip	
	BMD g/cm^2	Fracture prevalence	BMD g/cm^2	Fracture prevalence
Normal	> 0.83	3%	> 1.00	3%
Mild	0.63–0.83	5%	0.80–0.99	5%
Moderate	0.52–0.67	10%	0.60–0.79	10%
Severe	< 0.51	15–50%	< 0.60	50–100%

Table 2 Demographics*
(n = 110; 64 males, 46 females)

Age	44
Years of Dialysis	1.7
Years Since Transplant	5
Steroid Therapy	
Total dose (mg)	19168
Average steroid/day (mg/day)	11.5
Creatinine (mmol/L)	142.8

*mean values

Bone Mineral Density Measurement

Bone mineral density (BMD) was measured by dual photon absorptiometry (Lunar DP3, Lunar Radiation Corporation, Madison, Wis.).[6] Results were expressed as absolute BMD values in grams per centimeter squared. These absolute values determined the fracture risk category (normal, mild, moderate or severe) according to the existing risk estimation tables (Table 1).[7]

Clinical and Laboratory Variables

Twenty variables were assessed to determine correlates of BMD. The nine demographic variables included: age, sex, ethnic background, years and type of dialysis prior to transplantation, date of transplant, total steroid dose, number of rejection episodes and use of Cyclosporin. The menopausal status of the female patients was defined biochemically, determined by high gonadotropin levels (FSH and LH greater than 25 I.U./L) and estradiol levels below 50 pmol/L; and clinically, with cessation of menses as determined by history.

The 10 biochemical/hormonal variables included serum calcium, phosphate, magnesium, alkaline phosphatase, creatinine, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol or free testosterone, prolactin and parathyroid (PTH intact molecule). All blood samples were drawn within one week of the bone mineral density assessment.

Statistical Analyses

Analyses of variance and chi square tests were performed to assess the differences between groups by using continuous and categorical variables, respectively. Pearson correlation coefficients were obtained in order to describe the strength of the relationship between BMD measurements and the baseline clinical, demographic, biochemical and hormonal variables. Multiple regression analyses were performed with both absolute BMD and the fracture risk category as the dependent variables, with PTH, date of transplant, date of birth and total steroid dose as predictors in order to explore possible functional relationships which could account for the differences in BMD or fracture risk. Analyses were done for both hip and spine BMD. All analyses were performed with the Statistical Analysis System Version 6 Software (SAS Institute, Cary, North Carolina, USA).

Table 3 Absolute BMD (g/cm^2)

Total group	Mean ± SD
Spine (L3–4)	1.14 ± 0.15
Femoral neck	0.84 ± 0.13
Wards triangle	0.72 ± 0.16
Trochanter	0.75 ± 0.15

Table 4 Predictors of fracture risk

	Hip	Spine
Total Steroid Dose	0.41*	0.38*
Year of Transplant	−0.40*	−0.33*
Year of Birth	−0.35*	−0.0004
PTH level	0.22*	0.002

*p significant (OS Pearson correlation coefficients)

RESULTS

The demographics are presented in Table 2. The mean duration of follow-up for the entire group was 5 years (± 0.40). Mean serum values for calcium, phosphate, magnesium, alkaline phosphatase and PTH, were all within the normal laboratory range.

The prevalence of "abnormal" BMD (as defined by the absolute values below which an individual's risk fracture is increased) differed depending on the site measured. Spine BMD (L3–4) were indicative of increased fracture risk in 39.5% of the population studied. Hip BMD measurements were performed at the 3 conventional locations: femoral neck, Ward's triangle and the greater trochanter. The proportion of patients with reduced BMD at these locations were 49%, 64% and 56% respectively. These proportions include all degrees of increased risk ranging from mild to severe. Twenty-five to 37% of these patients were categorized as being at moderate to severe risk of hip fracture, depending on the specific site of BMD measurement. The lowest BMD readings obtained were at Ward's triangle, the location which affects trabecular bone predominantly. The mean value for BMD in grams per centimeter squared (g/cm^2) at each location is shown in Table 3. Analyses performed with both the absolute and relative (i.e. fracture risk category) measures of BMD

Table 5 BMD values of the hip by year of birth

Year of birth	Average BMD (g/cm^2)
1960–69	0.83
1950–59	0.75
1940–49	0.72
1930–39	0.67
1920–29	0.56

Table 6 Steroid doses and fracture risk category (FRC)

FRC	Total steroid (mg)	Average steroid/day (mg)
Normal (n = 39)	12233	12
Mild (n = 31)	15039	10.9
Moderate (n = 29)	25439*	11.3
Severe (n = 11)	38472*	11.5

*$p < 0.001$ (vs. all other groups)

gave identical results.

Spontaneous fractures were defined retrospectively by reviewing the patients' charts and radiological documents. The history of no trauma preceding the event delegated the category of "spontaneous" fracture. Only events occurring post-transplantation were included. The cumulative incidence of spontaneous fractures in this group was 3%. This is a small number in absolute terms, but when compared to an age matched population,[8] this represents a two to four fold increase in the fracture rate.

Significant Correlations

The twenty demographic and laboratory variables were examined with the BMD as the dependent variable. Only 4 of these 20 variables were significantly correlated with the risk of a fracture of the hip or spine. These included the total steroid dose, year of transplant, year of birth, and parathyroid hormone level. The r values ranged between 0.22 and 0.41 ($p < 0.05$) for the hip, see Table 4. Each of these individual variables will be discussed below. The total steroid dose, and year of transplant, were, as expected, highly correlated ($r = 0.87$, $p < 0.0001$).

1) Year of Transplant

The year of transplant was a significant factor in predicting low BMD, in both relative and absolute measurements. BMD decreased as an inverse function of years since transplant. The group transplanted most recently (after 1987) had the highest hip BMD in g/cm^2 (mean = 0.78 ± 0.02) which was significantly different from all other groups transplanted earlier than 1987 (the mean of those groups ranged between 0.61 to 0.69 ± 0.02; $p < 0.01$). Of note is that each of these mean absolute values of BMD were below the fracture threshold (0.80 g/cm^2). Fifty percent of recent transplants were at increased risk of hip fracture, according to these BMD measurements. The results of spine BMD paralleled the abovementioned hip results, although absolute density values were higher.

Table 7 Steroid doses and year of transplant

Year of transplant	Total steroid (mg)	Average steroid/day (mg)
–1980 (n = 21)	63000*	12
1981–83 (n = 15)	25600*	11.1
1984–86 (n = 23)	9420*	11.3
1987– (n = 51)	5500*	11.7

*$p < 0.001$

2) Year of Birth (Table 5)

A significant relationship between age and BMD values (fracture risk) was demonstrated. The mean absolute BMD showed significant decline with respect to advancing age ($p < 0.03$). The oldest patients (age 60–70) had the lowest BMD (0.56 ± 0.01), and the youngest (age 20–29) had the highest BMD (0.83 ± 0.02) for hip BMD measurements.

Comparing this group to a normal age matched control population[8] revealed that lower BMDs were found in the young transplant patients. In the "normal" population, 1–3% of 30–40-year-old have hip BMD measurements less than 0.80 g/cm^2. In comparison, 62–66% of the renal transplant patients, in the same age group, have BMDs below that figure. Therefore, in this 30 to 40-year-old transplant group, the relative risk of having a significantly decreased BMD is 21 times greater than in an age matched population.

3) Steroid Therapy (Tables 6 and 7)

Patients with the lowest BMD (highest fracture risk), had the highest mean total steroid dose (greater than 25,000 mg). Lower total doses (less than 20,000 mg) were associated with higher BMD values ($p < 0.05$). In an attempt to determine if there were differences in maintenance steroid dose, the average steroid dose per day was calculated for each patient. There were no statistically significant differences between the different fracture risk groups or year of transplantation groups with respect to the mean average steroid dose per day (range 10.9–12.0 mg $\pm$ 0.5, $p = 0.52$).

4) Parathyroid Hormone Level

The mean PTH level was high (9.7 pmol/L $\pm$ 1.1) in the severe fracture risk group (n = 11) and was within the normal range in the other groups ($5–5.5 \pm 0.2$ pmol/L), ($p < 0.05$). In the current series of 110 patients, 22 patients had PTH levels higher than one standard deviation over the normal value of 5.0 pmol/L. Eight of the twenty-two were transplanted before 1983, and another eight patients between 1984 and 1987. Only one of the patients in the severe risk fracture category with high PTH had received a transplant after 1987.

Multiple regression analysis (MRA) was performed in

order to develop a risk profile/model for reduced BMD in the transplant population and to determine the relative contributions of specific variables in the equation. MRA with spine BMD measurements revealed that 18% of the variability ($R^2 = 0.18$, $p < 0.001$) was accounted for by the year of transplant and total steroid dose. These variables are so highly correlated ($r = 0.97$) that it is impossible to determine the relative contributions of each independently in practical terms.

MRA performed with hip BMD measurements revealed that 33% of the variability is explained by three independent variables: total steroid dose, year of birth and PTH level, so that while one third of the variability in hip BMD measurement can be accounted for, two thirds remains unexplained.

Non-significant Correlations

There were no sex differences demonstrable with respect to fracture risk. Renal function, as determined by serum creatinine, also did not predict BMD, nor did serum levels of calcium, phosphate, magnesium, alkaline phosphatase, FSH, LH, estrogen, testosterone or prolactin. Neither years, nor type of dialysis prior to transplantation was related to BMD. The average steroid dose, corrected for years since transplant, as previously mentioned, also did not correlate with BMD measurements.

DISCUSSION

This cross-sectional descriptive survey of a large number of unselected renal transplant recipients demonstrated a high prevalence of BMD below the fracture threshold, as measured by DPA, in the renal transplant population. We then explored the relationship of a number of demographic and laboratory variables to this non-invasive measurement of bone mineral density by dual photon absorptiometry. The findings here may therefore be clinically important with respect to the diagnosis and therapy of osteoporosis in transplant patients. Current literature[3,5,9–11] suggests that steroid therapy is a major contributor to the reduced BMD seen in the renal transplant population. It is imperative to note that fracture risk is not synonymous with fracture; so our finding of a significant proportion of transplant patients at risk, with only a small incidence of spontaneous fractures over the 16 year span is not surprising, but as previously stated, this low incidence is still very high relative to age match controls.

Despite finding significant correlations between BMD and variables commonly believed to be the major contributors to bone loss (steroid therapy, duration of steroid exposure and PTH) in the transplant population, the MRA revealed that only a limited amount of the variation in BMD at the various locations can be accounted for by long-term steroid use and hyperparathyroidism. This has not been reported elsewhere. Steroids do affect bone metabolism both directly and indirectly.[12,13] This is not disputed by our findings, but the extent to which and the manner in which, the use of steroids contributes to bone loss in the renal transplant population is uncertain, in light of our analysis.

Of interest were some of the non-significant correlations. Sex was not a predictor of abnormal BMD. This was surprising in view of the fact that, in the normal aging population, women have significantly lower BMDs than men. This difference is most prominent in the pre-menopausal period. Given that the majority of our female population is not peri-menopausal (as determined by menstrual history and hormonal FSH, LH levels) the sex difference was not evident.

In this study, we were unable to demonstrate an association between years of dialysis and BMD. The mean number of years of dialysis prior to transplantation was only 2.3 years. One could in fact postulate that this was not a long enough period to affect BMD in any appreciable manner. The current thinking with respect to dialysis associated bone disease has changed in the past few years. It is now recognized that a number of factors contribute to bone disease in the dialysis population, including heparin therapy, aluminum toxicity, hyperparathyroidism and vitamin D deficiency. Changes in practices based on a broader understanding of the multifactorial nature of bone disease in the dialysis population may positively affect the bone mass of patients before undergoing transplantation. That is, one of the variables not assessed in the current study is the state of bone prior to transplantation. This factor is undoubtedly an important one affecting post-transplant bone mineral density. As other types of metabolic bone disease (eg. osteomalacia and aplastic/low turn over disease) may be important, this area needs further exploration. Cross-sectional studies, because of their design, often raise more questions than they answer. The current study is no exception. Further prospective evaluation is necessary to identify other important factors which contribute to bone loss in the renal transplant population. Bone densitometry in current practice is used as a screening tool for osteoporosis, and for following the progression of bone loss or the effects of therapy. This study reveals a large at risk population of transplant recipients. Whether this increased risk does indeed translate into measurable outcome events, and is amenable to therapy, remains to be seen in a prospective longitudinal study.

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