Bone Mineral Density in Kidney Transplant Recipients and Patients on Hemodialysis

A Comparison With Healthy Individuals

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Introduction. We measured bone mineral density (BMD) before and after transplantation to determine the frequency and severity of preoperative and postoperative osteoporosis and compare them with the BMD in healthy individuals.

Materials and Methods. We determined the BMD at the lumbar spine and femoral levels in 22 men and 18 women who were on long-term dialysis in Yazd, Iran, and a group of kidney transplant recipients including 43 men and 18 women. They were compared with each other and healthy individuals studied in a recent study in Iran. Factors potentially associated with alterations of the BMD were studied in each group.

Results. The frequency of osteoporosis in the vertebrae and femoral neck was higher in the kidney transplant recipients than the healthy population (21.3% versus 4.9%; $P = .001$; odds ratio, 5 and 9.8% versus 2.4%; $P = .02$; odds ratio, 5.4, respectively) but not significantly different from those in the patients on dialysis (17.9% and 17.5%, respectively). In transplantation group, multivariate analysis showed that there was a significant negative correlation between the lumbar BMD and the cumulative prednisolone dose ($r = -0.36$, $P = .003$). No correlation was found between BMD of lumbar or femoral neck and the body mass index, age, and cumulative cyclosporine level.

Conclusions. Osteoporosis is more frequent in patients on dialysis and kidney transplant recipient than in general population. However, there is no difference in osteoporosis frequency between transplanted patients and those on dialysis. In the lumbar spine, a higher cumulative prednisolone dose results in decreased BMD among kidney transplant recipients.

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INTRODUCTION

Patients with end-stage renal disease (ESRD) are predisposed to many risk factors of osteoporosis prior to transplantation, including low dietary calcium intake, reduced exercise, heparin therapy, low body weight, amenorrhea, premature menopause, and renal osteodystrophy.[1,2] Although transplantation may correct many of the biochemical imbalances associated with ESRD such as secondary hyperparathyroidism, immunosuppressants, though essential for preventing transplant rejection, offer continuing insult to the bones.[3,4] However, surprisingly, this is not a universal finding.[5] There is no consensus at present as to which risk factors are most strongly associated with reduced bone mineral density (BMD). Although prednisolone

is a likely candidate,[3,6] BMD is also influenced by several variables including genetic, environmental, and ethnic factors.[7,8] Little is known about the BMD in patients on dialysis and transplant recipients when compared to the general population in patients, especially in the people of southwest region of Asia. Fortunately, we have promising knowledge on BMD in healthy population in Iran.[9] We designed this cross-sectional study to assess the frequency of osteoporosis in kidney transplant recipients and patients on dialysis in Yazd, a city in the center of Iran, and to evaluate predictors of osteoporosis in kidney transplant recipients in this region.

MATERIALS AND METHODS

Patients on Hemodialysis

The population on dialysis consisted of 40 patients who were on maintenance hemodialysis and continues ambulatory peritoneal dialysis (CAPD) in Shahid Rahnemoun hospital, Yazd, Iran, in 2005. The patients on dialysis had a mean age of 38.0 ± 10.6 years (range, 20 to 50 years), and 18 of them (45.0%) were women. Patients who were on levothyroxine sodium and smokers were excluded. Five of the women (27.8%) were in their postmenopausal period or had amenorrhea for more than 3 months.

Transplant Recipients

There were 61 kidney allograft recipients under regular posttransplant follow-up for 3 to 96 months in Yazd, Iran. Their data were collected between 2005 and 2006. The mean age of the kidney allograft recipients was 39.0 ± 11.8 years (range, 18 to 66 years). Eighteen of them (29.5%) were women, 8 of whom (44.4%) were in their postmenopausal period or had amenorrhea for more than 3 months. The exclusion criteria were smoking, receiving levothyroxine, and kidney transplant for the second or third time. In 12 patients (19.7%), the cause of ESRD was diabetes mellitus. All of the kidney transplant recipients were on a triple immunosuppression regimen consisting of prednisolone, cyclosporine, and mycophenolate mofetil or azathioprine. Cumulative doses of immunosuppressive drugs were calculated according to the hospital and outpatient records, and for prednisolone, any pulse of intravenous methylprednisolone given during transplant rejection episodes were included. Methylprednisolone was regarded as being equipotent with oral prednisolone. None of the patients had ever been treated with bisphosphonates.

Bone Mineral Density

To establish whether there was a significant reduction in the BMD of kidney transplant recipients and patients on dialysis, we compared the absolute BMD (g/cm^2) at the lumbar spine and the femoral neck with the BMD at the same sites in 553 healthy subjects in Tehran, Iran measured by Larijani and coworkers.[9] Bone mineral density was measured by dual x-ray absorptiometry using Lunar DPX-MD device (Lunar Corporation, Madison, Wisconsin, USA).

The dual x-ray absorptiometry device was calibrated daily and weekly using appropriate phantom methods. To assess BMD, the second to the fourth lumbar vertebrae and the femur (neck, trochanter, and the whole femur) were used. Bone density was calculated based on g/cm^2, and it was also expressed in standard deviation units as T-scores (comparison with the mean bone density in young adults) when defining osteoporosis with reference to the World Health Organization criteria.[10] Otherwise, the Z-scores (comparison with age-matched mean) were used. According to the World Health Organization categories, BMD in any adult that is between 1 and 2.5 standard deviations below the mean is defined as osteopenia, and a value more than 2.5 standard deviations below the mean is defined as osteoporosis.[10]

The patients consented in written form to participate in the study, and our protocol was approved by the ethics committee of the faculty of medicine, Yazd University of Medical Sciences.

Statistical Analyses

Serum level of alkaline phosphatase, duration of dialysis, time since transplantation, plasma cyclosporine level, and cumulative cyclosporine dose were positively skewed, and therefore, their natural log was transformed for statistical analyses. Univariate linear regression analysis (pearson correlation) was used to identify factors associated with bone loss. The chi-square test was used to associate differences in dichotomous variables. The unpaired Student *t* test was used

to compare differences between transplant and dialysis variables. The one-sample *t* test was used to compare differences between healthy population and patients with renal replacement therapies. Multiple regression analysis was used to assess the correlations between age, sex, body mass index (BMI), time since transplantation, cumulative cyclosporine dose, and prednisolone exposure and the spinal and femoral BMDs. We calculated odds ratios for the presence of lumbar and femoral osteoporosis for transplant recipients against the patients on dialysis or healthy individuals. Results were expressed as means ± standard errors. Values were given with 95% confidence intervals (CIs). A *P* value less than .05 was regarded significant.

RESULTS

Tables 1 and 2 demonstrate the characteristics of the participants in our study and the healthy individuals studied by Larijani and colleagues.[9] Osteoporosis in the lumbar vertebrae was detected in 13 of 61 (21.3%) kidney transplant recipients and 7 of 39 (17.9%) patients on dialysis. Among 553 healthy individuals, 27 (4.9%) had been reported to have osteoporosis in this area. Osteoporosis in the femoral neck was documented in 6 of 61 (9.8%) and 7 of 40 (17.5%) kidney transplant recipients and patients on dialysis, respectively. In comparison, 13 healthy individuals (2.4%) had osteoporosis in this area. Table 3 shows the respective odds ratios.

Table 4 shows BMD values in the patients on dialysis and the kidney transplant recipients. After controlling of the effects of age, sex, and BMI by multiple linear regression analysis, the BMD of the femur in transplant recipients was still significantly higher compared with that in patients on dialysis (P = .01).

In the transplant group, the BMD at the lumbar spine, but not at the femur, correlated with serum levels of calcium (r = -0.29, P = .02). Kidney function (measured by serum levels of creatinine, phosphorus, alkaline phosphatase, and cyclosporine) were not associated with BMD of the spine and the femur.

Because cumulative prednisolone exposure has been implicated in posttransplantation bone loss,[4,6] we examined the relationship between cumulative prednisolone dose and the BMD of the lumbar

Table 2. Treatment and Laboratory Characteristics of Kidney Allograft Recipients and Patients on Dialysis*

Characteristic	Value
Transplant recipients	
Months since transplantation	25.0 ± 21.8 (3 to 96)
Serum calcium, mg/dL	9.4 ± 0.9 (7 to 12)
Serum phosphorus, mg/dL	3.9 ± 0.8 (1.8 to 6.0)
Serum alkaline phosphatase, U/L	241.0 ± 247.9 (73 to 1806)
Serum cyclosporine, ng/mL	206.0 ± 74.3 (70 to 394)
Cumulative prednisolone, g	7.1 ± 4.9 (2.3 to 34)
Cumulative cyclosporine, g	170.0 ± 121.9 (33 to 697)
Third Immunosuppressive	
Mycophenolate mofetil	53 (86.9)
Azathioprine	6 (9.8)
Patients on dialysis	
Serum calcium, mg/dL	8.4 ± 1.3 (5.8 to 12.2)
Serum phosphorus, mg/dL	5.8 ± 1.4 (3.1 to 9.8)
Serum alkaline phosphatase, U/L	249.0 ± 261.9 (27 to 1280)
Dialysis modality	
Hemodialysis	27 (67.5)
Peritoneal dialysis	13 (32.5)

*Values in parentheses are the minimums and maximums except for the third immunosuppressive and the dialysis modality (percentages).

Table 1. Characteristics of Kidney Allograft Recipients, Patients on Dialysis, and Healthy Individuals*

Characteristic	Transplant Recipients	Patients on Dialysis	Healthy Individuals	*P*
Number of patients	61	40	553	…
Mean age, y	39.0 ± 11.8	38.0 ± 10.6	44.0 ± 12.6	<.001†
Age group				
< 50 years	47 (77.0)	31 (77.5)	359 (64.9)	
≥ 50 years	14 (23.0)	9 (22.5)	194 (35.1)	.05
Sex				
Male	43 (70.5)	22 (55.0)	188 (34.0)	
Female	18 (29.5)	18 (45.0)	365 (66.0)	< .001†
Body mass index, kg/m^2	25.0 ± 4.0	24.0 ± 3.9	24.0 ± 4.1	.07†
Postmenopausal women	8 (13.1)	5 (12.5)	118 (21.3)	.42
Dialysis duration, mo	1.0 ± 13.8	21.0 ± 31.8	…	.83

*Values in parentheses are percents. Ellipses indicate not applicable.
†Healthy individuals were compared with the total patients of other two groups (one-sample t test).

Table 3. Odds Ratios, 95% Confidence Intervals, and P Values for Osteoporosis Between Groups

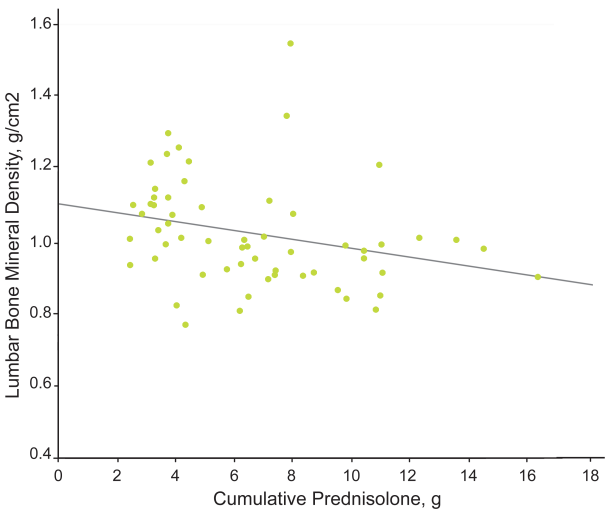
	Transplant Recipients Versus Healthy Individuals		Patients on Dialysis Versus Healthy Individuals		Transplant Recipients Versus Patients on Dialysis	
Osteoporosis	**Odds Ratio (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***
Lumbar vertebrae	5.0 (1.8 to 14.0)	.001	4.1 (1.4 to 11.7)	.004	1.2 (0.4 to 3.4)	.68
Femoral neck	5.4 (1.1 to 25.0)	.02	10.0 (2.4 to 47.0)	< .001	0.5 (0.1 to 1.6)	.26

Table 4. Bone Mineral Density (BMD) in Kidney Allograft Recipients and Patients on Dialysis*

BMD	Transplant Recipients	Patients on Dialysis	*P*
Lumbar vertebrae			
BMD, g/cm^2	1.07 ± 0.19	1.02 ± 0.14	.12
T score, SD	-1.21 ± 1.55	-1.51 ± 1.21	.26
Z score, SD	-0.88 ± 1.61	-1.19 ± 1.19	.28
Femoral neck			
BMD, g/cm^2	0.83 ± 0.16	0.90 ± 0.15	.02
T score, SD	-1.55 ± 1.22	-1.03 ± 1.17	.04
Z score, SD	-1.14 ± 1.10	-0.65 ± 1.06	.03

*Values are means ± standard deviations. BMD indicates bone mineral density and SD, standard deviation.

spine in the kidney transplant recipients; a strong association was found between these two variables (r = -0.36, *P* = .003; Figure). Albeit less strongly, the BMD of the lumbar spine correlated with the time since transplantation (r = -0.33, *P* = .006), cumulative cyclosporine exposure (r = -0.26, *P* = .02), and BMI (r = 0.24, *P* =.03). Age (r = -0.06, *P* = .66) and sex (r = -0.02, *P* = 0.83) were not related with the lumbar BMD. Multivariate analysis showed that only cumulative doses of prednisolone remained independently associated with the BMD of the lumbar spine (*P* = 0.01). Finally, no correlation was found between the femoral BMD and the time since transplantation, cumulative cyclosporine level, prednisolone exposure, BMI, age, or sex.



Correlation of bone mineral density for the lumbar vertebrae and the cumulative prednisolone dose among kidney transplant recipients (r = -0.36; *P* = .003).

DISCUSSION

The most important finding of this cross-sectional study was that severe osteoporosis was very common in the patients on dialysis and kidney transplant recipients compared to the healthy population.[9] In concert with these findings, osteoporosis after transplantation compared with that in the general population has been reported worldwide.[11-13] We showed that the frequency of lumbar spine osteoporosis was 5 times and 4 times higher among the patients on dialysis and kidney transplant recipients than the healthy population, respectively. For femoral neck osteoporosis, these rates were 5.5 times and 10 times, respectively. These results are in agreement with those of other studies.[1,11-13]

It is surprising that not only the frequency of osteoporosis was not significantly different between transplanted and dialysis group, but also 10% lower femoral neck BMD was found in the kidney transplant recipients. Our findings, are supported by some other studies,[4,5,14,15] while conflict with the study by Ramsey-Goldman and colleagues.[16] For instance, Julian and colleagues reported a 9% loss in the vertebral BMD, but a 4% rise in the radius BMD (*cortical bone*) in 20 patients following kidney transplantation.[4] Grotz and associates[6] reported that reduction of BMD after transplantation is highest within the first posttransplant year, but slightly

increased lumbar BMD was shown during the 3rd to the 10th postoperative years.

In the transplant recipients of our study, the cumulative steroid dose was the only significant predictor of low vertebral BMD which could not be explained by differences in the BMI, sex, time since transplantation, or cumulative cyclosporine exposure. Our data support the findings of other studies that indicate the major role of steroids in posttransplant osteoporosis.[4,5,17,18] However, we could not show the glucocorticoid-induced osteopenia on the femoral neck BMD. In contrast, the increasing of femoral BMD was shown after transplantation. This finding might be due to the weaker effect of prednisolone on the cortical bone, and consequently, a gain of BMD pertaining to transplantation at the cortical bone.

We failed to show the potential negative effect of cyclosporine and cyclosporine level on BMD. Parallel with our results, some previous reports did not find an association between cyclosporine levels or doses and BMD after kidney transplantation either.[19] However, cyclosporine has been shown to cause a duration-dependent high-turnover osteoporosis in animals.[20] We could not find any correlation between BMD and age, BMI, sex, or time since transplantation in the transplanted group. However, some studies has shown low BMI is a predictor of loss of BMD.[5,15]

A significant shortcoming in this study was that we could not prospectively assess the effect of transplantation. The cross-sectional design does not allow us to accurately assess the impact of transplantation and immunosuppression on BMD in each subject. A longitudinal study will provide insight into intra-individual changes in BMD. Furthermore, our group of transplant patients had a wide range of follow-up which is a considerable limitation of our study. Nevertheless, findings of this research can provide the basic knowledge and background among the physicians in Iran and help us design prospective nationwide studies on the issue.

CONCLUSIONS

We reported that severe osteoporosis is very common in patients with end-stage renal disease who enjoy either dialysis or transplantation as their renal replacement therapy. There seems to be no doubt that the use of glucocorticoids plays an important role in the loss of bone mass and defective mineralization seen in these patients. However, persistence of pre-existing osteoporosis during dialysis period may also be considered as the predominant risk factor of bone loss after kidney transplantation. We recommend screening and preventive intervention for osteoporosis in patients on hemodialysis who are candidates for transplantation.

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CONFLICT OF INTEREST

None declared.

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