Bone Mineral Density and Related Factors in Renal Transplant Recipients, in the North of Iran

Masoud Khosravi,[1] Nahid Soltanian,[1] Ali Monfared,[1]
Atefeh Ghanbari,[2] Elham Ramezanzade,[1]
Ehsan Kazemnezhad Leyli[3]

[1]Urology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2]Department of Nursing, School of Nursing and Midwifery, Social Determinants of Health Research Center, Guilan University of Medical Sciences, Rasht, Iran
[3]Department of Biostatistics, School of Nursing and Midwifery, Road Trauma Research Center, Guilan University of Medical Sciences, Rasht, Iran

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Introduction. Renal transplantation can lead to or be associated with Low bone mineral density (BMD). The aim of this study is evaluation of BMD and related factors in our renal transplant patients.
Methods. In this descriptive cross-sectional analytical study, 148 kidney transplant patients from university hospital, were enrolled. BMD of hip and lumbar spine was measured by dual-energy X-ray absorptiometry (DXA) and patients were divided into 3 groups: normal, osteopenia, and osteoporosis; according to T-score. Laboratory parameters and a series of variables were investigated, and the results were compared with BMD findings.
Results. In this study, 73 patients (49.3%) had osteopenia and 28 patients (18.9%) were osteoporotic. BMI was significantly lower in the osteoporosis group compared with the normal group ($P < .05$). Cumulative dose of prednisolone and calcium supplement were higher in osteoporotic group compared with normal group.
Conclusion. According to our results, osteoporotic and osteopenia groups have lower BMI that is associated with lower BMD. This can lead to increased risk of bone fractures in the future. Early discontinuation or reduction of prednisolone dose can improve BMD.

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INTRODUCTION

ESRD patients are known to have a spectrum of bone diseases, ranging from high to low-turnover bone disease.[1] Renal transplantation is the definitive treatment for many metabolic abnormalities of uremic patients.[2] After transplantation, disturbances of bone and mineral metabolism are among the long-term side effects of kidney recipients. These disorders cause significant morbidity in renal transplant patients.[3,4] Osteopenia-osteoporotic syndrome, along with bone fractures represent the bone complication most closely related to renal transplantation.[2,5,6] Specific factors that have been suggested to have a role in the pathogenesis of osteoporosis after transplantation include high daily and cumulative dosage of corticosteroids, cyclosporine, tacrolimus, persistent hyperparathyroidism, and preexisting bone disorders.[2,5,7] Steroid therapy is the most common cause of osteoporosis in kidney transplant patients.[8] Even low doses of steroids (5 or 7.5 mg/d) can reduce bone mass regardless of age, sex, and menopause.[9]

The most critical period of bone loss following transplantation appears to be the first 6 months, with the most dramatic reduction occurring in the first 3 months. Trabecular (cancellous) bone of the spine appears to be the most at risk, with vertebral fractures occurring most often. Therefore, kidney transplant should be followed by densitometric

methods and laboratory evaluations including: measurement of serum calcium, phosphorus, intact parathyroid hormone, and vitamin D metabolites.[10,11]

In this study, we aimed to investigate the risk factors of bone density reduction in renal transplant patients with a larger sample size than previous studies based on existing climatic conditions.

MATERIALS AND METHODS

This is a descriptive cross-sectional analytical study, taken from a medical dissertation, with regard to demographics conditions of renal transplant recipients, referring to university hospital of Guilan University of Medical Sciences, in Rasht. We enrolled 161 kidney recipients with transplant durations from 3 months to 204 months. Exclusion criteria included eGFR (lower than 30 mL/min/1.73m^2) (CKD-EPI Creatinine2009 Equation), acute graft rejection, malignant disease, history of hospitalization within 3 months prior to bone densitometry, use of bisphosphonate, and bone diseases caused by other medical problems.

BMD measurements of the lumbar spine and the femoral neck were obtained by dual-energy x-ray absorptiometry (DEXA) with a Hologic scanner (Discovery W) from April to September 2017. Vertebral bone density values represented the average of four vertebrae (the first to the fourth lumbar vertebrae). Hip-bone density was measured at the femoral neck level. Results were expressed as T-scores for sex-matched young adults. According to the T-score of the hip and spine, the patients were divided into three groups: normal, osteopenia, and osteoporotic. The definition of these groups, taken from the WHO definitions; was based on the following:

- Normal bone density: T-score equal to or above 1 standard deviation below the mean maximum density in youth (T-score equal to or above SD-1)
- Osteopenia: T-score between 1 and 2.5 standard deviations below the mean maximum density in youth (T-score between -1 SD to -2.5 SD)
- Osteoporosis: T-score equal to or less than 2.5 standard deviations below the mean maximum density in youth (T-score equal to or less than -5.5 SD)

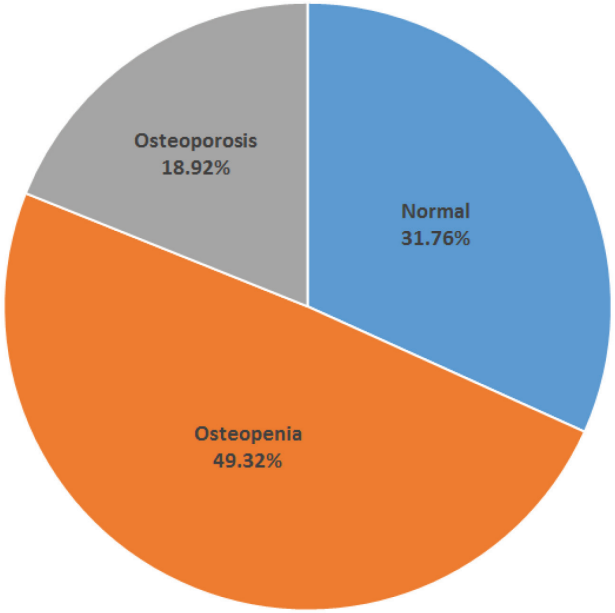
At the time of referral, patients were examined by a physician and their history was taken. General examinations and demographic characteristics of patients were recorded. Written consent was obtained from all patients and they were fully informed about the study. Patients information including demographic characteristics (age and sex), history and physical examination (BMI, pre-transplant dialysis duration, duration of transplantation, cumulative dose of prednisolone, and cyclosporine, calcium supplementation, vitamin D supplementation, MMF), laboratory tests (BUN, creatinine, calcium, phosphorus, iPTH (ELISA Method), and 25-hydroxy vitamin D levels), and bone densitometry results were recorded.

Statistical analyses were performed using SPSS software (version 16.0, SSPS Inc, Chicago, IL, USA). The Qualitative variables were represented using frequency and percentage. All quantitative variables were reported using mean ± SD (median). Normality of data was analyzed by the Shapiro-Wilk test. The significance between two categorical variables was assessed using Chi-square/Fisher's exact test. Normal continuous variables were analyzed by independent sample *t* or one-way analysis of variance (post hoc Tukey) tests. For non-normal variables Mann-Whitney U or Kruskal Wallis tests was done. A P value < .05 was considered to be statistically significant.

RESULTS

Among kidney transplant patients, 161 patients were assigned to this study. 12 patients were excluded from the study due to their eGFR being lower than 30 and one patient died. Finally, 148 patients were studied. Seventy-one of those who entered the study (48.0%) were women. The mean age of patients was 43.78 ± 12.67 years. The youngest patient was 17 and the oldest was 71 years old. Mean length of time on dialysis prior to renal transplantation was 14.18 ± 16.05 months. The average time elapsed since transplantation was 67.59 ± 42.66 months. One hundred and forty-six (98.7%) were taking cyclosporine and two (1.3%) patients received tacrolimus. All patients were taking prednisolone. Also, 139 patients (93.9%) received calcium and vitamin D. 110 patients (74.3%) were treated with MMF.

According to WHO definitions, 47 (31.76%) patients had normal bone density, 73 (49.32%) had osteopenia, and 28 (18.92%) had osteoporosis (Figure).



It shows 47 (31.76%) patients had normal bone density, 73 (49.32%) had osteopenia, and 28 (18.92%) had osteoporosis; according to WHO definitions.

Distribution of Demographic and Clinical Qualitative Variables among the Patient Groups is shown in Table 1. No difference was seen between these patient groups in terms of gender, use of Ca, vitamin D, cyclosporine, and MMF.

One-way ANOVA test was used for comparing mean age in the three groups of normal, osteopenia, and osteoporotic. This test did not show any statistically significant difference between groups ($P > .05$). But post hoc Tukey test showed a border line statistically significant difference between the mean age in the osteoporotic group with osteopenia and normal groups. The mean age in osteoporotic group was higher than the mean age in the other two groups (48.36 ± 15.02 vs. 42.86 ± 12.62, and 42.48 ± 10.77). Also, according to Kruskal Wallis test, BMI in three groups of normal, osteopenia and osteoporotic had a statistically significant difference ($P < .05$). In order to find more precise differences between groups, post hoc pairwise comparisons conducted by the Bonferroni correction. Only, BMI in two groups of normal and osteoporotic had a statistically significant difference ($P < .05$). There was no significant difference in cumulative dose of prednisolone (Table 2) between the three groups ($P > .05$). But the mean of cumulative dose of prednisolone in the osteoporotic group was higher than the normal group (20.75 ± 14.05 vs. 26.73 ± 14.07). The three groups of normal, osteopenia and osteoporotic were not statistically significant difference in terms of other biochemical and clinical factors (Table 2). Interestingly no bone fracture was found among our kidney transplant recipients.

DISCUSSION

Patient's unwillingness to have a BMD and lack of access to their medical history were the most

Table 1. Distribution of Demographic and Clinical Qualitative Variables among the Patient Groups

	Normal Group (n = 47)	Osteopenia Group (n = 73)	Osteoporotic Group (n = 28)	*P*
Gender				
Female	25 (53.2%)	32 (43.8%)	14 (50.0%)	> .05*
Male	22 (46.8%)	41 (56.2%)	14 (50.0%)	
Calcium				
Yes	44 (93.6%)	68 (93.2%)	27 (96.4%)	> .05**
No	3 (6.4%)	5 (6.8%)	1 (3.6%)	
Vit D				
Yes	44 (93.6%)	68 (93.2%)	27 (96.4%)	> .05**
No	3 (6.4%)	5 (6.8%)	1 (3.6%)	
Cyclosporine				
Yes	47 (100.0%)	71 (97.3%)	28 (100.0%)	> .05**
No	0 (0.0%)	2 (2.7%)	0 (0.0%)	
MMF				
Yes	37 (78.7%)	52 (71.2%)	21 (75.0%)	> .05*
No	10 (21.3%)	21 (28.8%)	7 (25.0%)	

*Pearson Chi-Square Test
**Fisher's Exact Test
MMF, mycophenolate mofetil

Table 2. Comparison of Demographic, Biochemical, and Clinical Quantitative Variables Among the Patient Groups

Variables	Normal Group Mean ± SD (Median)	Osteopenia Group Mean ± SD (Median)	Osteoporotic Group Mean ± SD (Median)	*P*
Age, y	42.48 ± 10.77 (43.00)	42.86 ± 12.62 (43.00)	48.36 ± 15.02 (51.00)	> .05*
BMI, kg/m^2	27.03 ± 6.37 (26.40)	24.88 ± 4.37 (24.85)	23.86 ± 4.42 (25.00)	< .05**
Dialysis Before Transplantation, mo	14.91 ± 19.42 (10.00)	13.19 ± 14.21 (10.00)	15.50 ± 14.75 (12.00)	> .05**
Post-Transplant Duration, mo	66.96 ± 46.90 (64.00)	64.81 ± 39.60 (64.00)	75.93 ± 43.47 (77.50)	> .05**
Cyclosporine (Cumulative Dose), g	370.04 ± 323.69 (291.00)	353.91 ± 249.52 (310.50)	364.29 ± 238.81 (325.88)	> .05**
Prednisolone (Cumulative Dose), g	20.75 ± 14.05 (18.82)	22.32 ± 15.35 (20.40)	26.73 ± 14.07 (28.95)	> .05**
BUN, mg/dL	20.30 ± 6.17 (19.00)	21.86 ± 8.72 (20.00)	22.54 ± 8.45 (19.00)	> .05**
Cr, mg/dL	1.29 ± 0.29 (1.20)	1.37 ± 0.38 (1.30)	1.33 ± 0.40 (1.30)	> .05**
GFR (CKD-EPI Creatinine 2009 Equation), mL/min/1.73 m^2	61.49 ± 14.60 (61.00)	59.21 ± 15.16 (59.00)	58.32 ± 12.87 (61.00)	> .05*
Calcium (Blood Level), mg/ dL	9.43 ± 0.40 (9.50)	9.44 ± 0.57 (9.40)	9.38 ± 0.50 (9.50)	> .05**
Phosphate (Blood Level), mg/dL	3.62 ± 0.62 (3.60)	3.53 ± 0.64 (3.60)	3.44 ± 0.53 (3.50)	> .05**
Vit D (Blood Level), ng/mL	33.77 ± 24.64 (35.00)	32.52 ± 15.06 (36.00)	35.67 ± 13.60 (34.00)	> .05**
iPTH (Blood Level), pg/ mL	82.00 ± 33.09 (79.00)	92.44 ± 53.92 (86.00)	118.70 ± 38.13 (118.50)	> .05**
Ca Dose, mg/d	659.57 ± 296.84 (500.00)	676.71 ± 305.74 (500.00)	767.86 ± 288.10 (1000.00)	> .05**
Vit D Dose, IU/d	264.89 ± 118.94 (200.00)	258.22 ± 130.23 (200.00)	307.86 ± 115.22 (400.00)	> .05**

*One-way ANOVA Test
**Kruskal Wallis test

important limitations in our cross-sectional study. For these reasons, 161 patients were selected. In some studies, risk factors related to the low BMD post-transplant were older age, postmenopausal status, and tertiary hyperparathyroidism.[12] While some studies have shown that increasing cumulative doses of cyclosporine and steroids have a negative effect on bone density,[13,14] tacrolimus has more protective effect on bone density.[14] Also, one study has shown the role of appropriate serum levels of calcitriol and PTH, good renal function, and tacrolimus treatment on preventing bone loss.[15] The results of this study showed that there was no relationship between age of patients and the study groups. Several previous studies have yielded similar results.[5,6,16] However, in the other studies, high age was identified as one of the causes of bone loss.[12,17,18] The difference between the results of our study and other studies may be due to differences in patients' conditions such as climatic conditions, socioeconomic status, and other factors that are not included in this study.

Our study showed that bone density was not relate to gender. This was similar to the results of Ahmadpour, Unal, and Tutal.[5,6,16] But Huang and Lai showed less osteopenia and osteoporosis in male patients.[19] Also, Gupta *et al.* showed association between female recipients and a decrease in bone density.[17]

Comparison of BMI between the groups showed that the mean BMI in the normal group was significantly higher than the Osteoporosis group. Several previous studies also suggested low BMI (< 21 kg/m^2) as a risk factor associated with decrease in bone density and increase in bone fracture rate especially in women.[5,16,17] Also, Durieux *et al.* showed that femoral neck bone density had a direct relationship with patients' weight.[20] However, in Ahmadpour's study, BMI was not related with bone density.[6] Therefore, the results of our study are consistent with most other studies, because they have shown that a higher BMI lowers the risk of osteoporosis. There is a strong relation between BMI and bone density, and several studies have shown that decrease in weight can lead to bone loss.[21,22]

In our study, the duration of hemodialysis before transplantation was not significantly different between the three groups. This is due to close mean duration of dialysis before transplantation in all groups (Table 2). The results of our study were in line with several studies.[5,6] However, Aroldi *et al.*, in a study on the effect of three different immunosuppressive regimens on bone density, found that spinal cord Z-score changes during this period were directly correlated with dialysis duration.[23]

According to the results of this study, there was no significant difference between the groups in terms of elapsed time of transplantation (the

results of the other study were in line with this result).[5,16] However, in Gupta *et al.* study suggested that elapsed time of transplantation may be an effective factor in decreasing femoral neck bone density. In the Lai study, bone mineral density was inversely correlated with the time elapsed since transplantation.[19]

The results of this study showed that the cumulative dose of cyclosporine used by patients was not significantly different in the study groups (Table 2). Other studies have yielded similar results.[5,6,16,17] Ellis *et al.* found that bone density (Z score) was inversely correlated with cumulative corticosteroid dose, but not with cumulative dose of cyclosporine.[24] In the Aroldi *et al.* study, the effect of three immunosuppressive regimens on bone density of 53 renal transplant patients was investigated. The first group consumed only cyclosporine, the second group received cyclosporine and steroids and the third group consumed cyclosporine, steroids and azathioprine. Spinal bone density was measured every 6 months for 18 months. As a result, at the end of the study, Z-score increased in the first group and decreased in the second and third groups.[23] In studies, calcineurin inhibitors; including cyclosporine and tacrolimus, have been associated with osteoporosis. However, the possible role of these drugs remains controversial. It should be kept in mind that evaluating the role of cyclosporine in kidney transplant patients is difficult because its effect on bone turnover may be obscured by glucocorticoids. Some studies have shown that in the absence of glucocorticoids, cyclosporine does not cause bone loss.[3,25]

According to the results of this study, clinically, the mean cumulative dose of prednisolone in the osteoporosis group was higher than in the normal group (Table 2). However, this difference was not statistically significant. Similar results were obtained in the other studies.[15,24] Overall, in many studies, the role of glucocorticoids in the development of secondary osteoporosis in renal transplant patients has been well documented and their use is an important pathogenic factor in the development and survival of post-transplant bone disease.[25,26] Our study also confirmed this result. In our study, use of MMF was not statistically significant between three groups. This is consistent with studies done by Unal, Gupta and Sessa.[2,5,17]

Frequency of calcium and vitamin D supplement consumption was not significantly different between groups. Also, no significant difference was observed in the dose of vitamin D supplementation. However, calcium supplementation was higher in the osteoporosis group than in the normal group. Similarly, in the Gupta *et al.* study, the frequency of calcium supplementation in patients with lower bone mineral density was significantly higher; but the frequency of vitamin D supplementation was not different between the groups.[17]

This study showed that the mean of BUN in the study groups was not significantly different from each other. Ugur *et al.* study showed that high BUN and low magnesium levels were associated with reduction in bone mineral density.[15] In general, this variable has not been studied in many studies and more accurate conclusions need further investigation in this field.

There was no significant difference between groups in our study regarding blood creatinine and GFR (Table 2). The results of the other studies were similar to our study.[5,17] There was a significant relationship between post-transplant creatinine and hip osteoporosis in Ahmadpour study.[6] In Huang's study, blood creatinine levels were also inversely correlated with bone mineral density.[19] The Falkiewicz *et al.* study showed that bone density decreased in the first year after transplantation and increased in the second year. Increased bone density was more pronounced in patients with higher levels of calcitriol at the beginning of the transplantation period, higher levels of iPTH in the first year after transplantation, and with higher GFR.[27] In our study, patients with a GFR of less than 30 were excluded from the study and this may be the reason for the difference in results with other studies. According to the results of our study, there was no meaningful relationship between calcium and phosphorus blood level in normal, osteopenia and osteoporosis groups. Gupta and Tutal's study also showed the same result.[16,17]

In this study comparison of vitamin D between groups showed no significant difference. Unal, Gupta and Durieux also reached to this result.[5,17,20] Finally, this study showed that there was no significant difference in blood levels of iPTH between study groups. In fact, blood tests for calcium and iPTH are not considered as the first -line tests for risk assessment of osteoporosis in high risk groups. The results of the Unal *et al.* study were

similar to our study.[5] However, Gupta *et al.* study, showed that hyperparathyroidism was associated with a decrease in femoral neck bone density.[17] In the Falkiewicz *et al.* study, follow-up of 90 kidney transplant patients for 2 years, it was observed that bone density decreased in the first year after transplantation and increased in the second year. iPTH is more prominent in the first year after transplantation.[27] Overall, several studies have linked hyperparathyroidism with increased bone turnover and decreased bone mineral density after renal transplantation. However, the association of hyperparathyroidism with decreased bone density is often prevalent in patients who have undergone transplantation for a short time. In long-term renal transplant patients have not shown any association between high PTH levels and bone density.[28] In our study, as the mean duration of transplantation was 67.59 months (over 5 years), the absence of a significant difference in mean levels of iPTH between groups was justified by later evidence.

CONCLUSION

In our study osteoporotic and osteopenic recipients had lower BMI that was associated with lower BMD, which could lead to increased risk of bone fractures in the future. Early discontinuation or reduction of prednisolone dose can improve BMD.

Take messages home of this study are:

1- Nephrologist must take care of their kidney transplant recipients regarding bone health, since bone health improves quality of life, by reducing osteoporosis risk, that can reduce the risk of bone fractures.[29]

2- Nephrologist must advise patients to use dairy products regularly, avoid immobility, smoking, and obesity.[29]

3- Nephrologist must consider DXA for assessing possibility of bone fracture in their high-risk patients.[30-2]

STATEMENT OF ETHICS

The study protocol was approved by the Guilan University of Medical Sciences Ethics Committees (No. IR.GUMS.REC.1394.432).

DECLARATION OF CONFLICT INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship of this publication.

AUTHORS CONTRIBUTIONS

Masoud Khosravi, design this study and provide most of the data, and wrote the manuscript.

Ali Monfared and Elham Ramezanzade, reviewed and finalized the manuscript.

Nahid Soltanian, collect data from clinical files and provide references.

Atefeh Ghanbari and Ehsan Kazemnezhad Leyli, statistical analysis was done by them.

All authors, Masoud Khosravi, Nahid Soltanian, Ali Monfared, Atefeh Ghanbari, Elham Ramezanzade, and Ehsan Kazemnezhad Leyli; reviewed and approved the manuscript.

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Abbreviations:
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry;
BMI, body mass index; MMF, mycophenolate mofetil; GFR, glomerular filtration rate;
ESRD, end stage renal disease; FGF 23, fibroblast growth factor; CyA, cyclosporine;
IS, immunosuppressive; BUN, blood urea nitrogen.

Correspondence to:
Masoud Khosravi, MD
Assistant Professor of Nephrology, Urology Research Center, Nephrology Department, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Razi Hospital, Sardar Jangal Street, Postal Code: 4144895655, Rasht, Iran
Tel: 0098 131 553 7500
E-mail: drmasoudkhosravi@gmail.com

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