Bone Density Reduction and Its Associated Factors in Kidney Transplant Recipients: A Cross-Sectional Study

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ABSTRACT

Background: Decreased bone mineral density (BMD) is one of the complications of kidney transplantation, which is associated with many factors. However, the findings of relevant studies are inconsistent and contradictory.

Objective: To investigate the prevalence of BMD reduction and its associated factors in kidney transplant recipients.

Methods: All kidney transplant recipients (n=69), referred to Shahid Mostafa Khomeini Hospital in Ilam, southwest of Iran, were included in this study between 2016 and 2018. The BMD of the lumbar spine and femoral neck was examined using dual-energy X-ray absorptiometry. According to the Z-score and T-score, the patients were divided into two age groups: <50 years and >50 years. All patients' demographic characteristics, background variables, and laboratory parameters were evaluated. Descriptive statistics were measured, and binary and multinomial logistic regression analyses were performed.

Results: The overall prevalence of osteoporosis in the femur and lumbar spine was 38% and 32%, respectively. In patients aged <50 years, femoral head osteoporosis showed a significant relationship with the vitamin D level and sex. In patients aged >50 years, advancing age and duration of prednisolone consumption were associated with an increased risk of osteoporosis and osteopenia at the femoral neck (P<0.05). Besides, the duration of prednisolone use was associated with osteoporosis at the lumbar spine (RRR=1.02, P<0.05).

Conclusion: Various factors, including prednisolone consumption, affect BMD reduction in kidney transplant recipients. Regular monitoring of BMD, maximum reduction of prednisolone dose, training on the use of effective supplements, and other preventive and supportive measures can be helpful for this group.

KEYWORDS: Bone mineral density; Kidney transplantation; Osteoporosis; Osteopenia; Prednisolone

INTRODUCTION

The number of kidney transplants is showing an upward trend due to the increasing prevalence of chronic kidney diseases. The use of novel medications for patients undergoing kidney transplantation improves their life expectancy; however, it may increase the risk of non-renal complications [1]. Bone involvement is a common complication, which decreases the bone mineral density (BMD) and increases the risk of fracture [2]. Frequently, bone loss associated with most fractures occurs in the first year after transplantation; nevertheless, these patients remain at risk over time [3]. In women, bone loss begins before menopause, while in men, it starts from the third to the fifth decade of life [4].

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Several studies have shown that the prevalence of osteopenia and osteoporosis after kidney transplantation is up to 50% and 15-56%, respectively [5, 6]. Post-transplantation bone loss is related to various factors, including genetics, sex, race, calcium intake, sun exposure, physical activity, and use of glucocorticoids or other drugs, such as cyclosporine and tacrolimus [6-8]. However, there are no apparent causes for post-transplantation bone loss, and the results of previous studies are inconsistent [9]. Therefore, the present study aimed to investigate the prevalence of BMD and its associated factors in kidney transplant recipients.

MATERIALS AND METHODS

This cross-sectional, analytical study was performed on 69 kidney transplant recipients who had undergone kidney transplantation in the last five to 30 months and presented to the nephrology clinic of Shahid Mostafa Khomeini Hospital in Ilam, southwest of Iran, during 2016-2018. The exclusion criteria were as follows: use of anticoagulants or bisphosphonates; history of femoral fractures; other bone diseases; undergoing transplantation in the last three months; and malignant diseases.

The BMD was assessed at the lumbar spine and femoral neck, using dual-energy X-ray absorptiometry (DEXA). In this study, according to the World Health Organization (WHO) definition, osteoporosis was defined as a T-score equal to or less than -2.5 standard deviations (SD) below the mean maximum density at the age of >50 years. Osteopenia was also defined as a T-score between -2.5 SD and -1 SD. On the other hand, a T-score equal to or above -1 SD was considered normal. At the age of <50 years, a Z-score equal to or less than -2 SD below the mean maximum density was considered as osteoporosis, and a Z-score between 0 and -1.92 SD was considered normal.

Ethical Considerations

This research was approved by the Medical Ethics Committee of Ilam University Medical Science (MEDILAM.REC.1399.130).

Statistical Analysis

Data analysis was performed using logistic regression analysis and polynomial logistic regression methods. For data analysis, STATA version 10 was used; a P-value <0.05 was considered statistically significant. All variables with P-values <0.05 in the univariate analysis were included in the multivariate binary and polynomial logistic regression models.

RESULTS

A total of 69 patients were included in this study. Overall, 32% (22 patients) were female and others (68%) were male. The mean age of the patients was 47.3 years (SD=1.8); the youngest patient was 17 years old, and the oldest one was 74 years old. Based on the results, the prevalence of osteoporosis at the femoral neck and lumbar spine was 41% and 38.5% in patients aged <50 years and 33.4% and 23.3% in patients aged ≥50 years, respectively. The mean time since transplantation in patients aged <50 years and ≥50 years was 87.5 and 102 months, respectively. Other characteristics of the patients are summarized in Table 1.

The results of the univariate logistic regression analysis showed a significant relationship between sex, duration of prednisolone use, serum creatinine level, vitamin D level, glomerular filtration rate (GFR), and femoral neck osteoporosis in patients aged <50 years. However, none of the variables showed a significant relationship with lumbar spine osteoporosis. Moreover, the results of multivariate logistic regression analysis showed that in patients aged <50 years, vitamin D was a protective factor for bone loss and femoral neck osteoporosis. Overall, vitamin D levels of 15-30 ng/mL decreased the risk of bone loss and femoral neck osteoporosis compared to vitamin D levels <15 ng/mL (OR: 0.07, 95% CI: 0.01 to 0.59) (Table 2).

In patients aged ≥50 years, the results of the univariate polynomial logistic regression analysis showed that osteopenia-osteoporosis at the femoral neck was associated with age, cyclosporine use, type of transplantation, and duration of post-transplantation prednisolone

Table 1: Distribution of demographic and clinical qualitative and quantities variables among the patient groups.

Parameters mean±SE; n (%)		Age <50 years (n=39)	Age ≥ 50 years (n=30)
Age, years		36.2±1.4	61.9±1.3
Sex (%)			
Male		25 (64.1)	22 (73.3)
Female		14 (35.9)	8 (26.7)
Body mass index, kg/m2		24.8±0.7	23.7±0.5
Diabetes (%)			
No		38 (97.4)	26 (86.7)
Yes		1 (2.6)	4 (13.3)
Prednisolone use (%)			
No		7 (18)	2 (6.7)
Yes		32(82)	28 (93.3)
Length of use of prednisolone (month)		87.5±8.9	102±15.9
Drug (%)			
Tacrolimus		17 (43.6)	17 (56.6)
Cyclosporin		19 (48.7)	11 (36.7)
Sirolimus		3 (7.7)	2 (6.7)
Receipt of a kidney donor (%)			
Deceased		6 (15.4)	8 (26.7)
Living		33 (84.6)	22 (73.3)
Time post-transplantation (month)		87.5±8.9	102.1±15.9
Dialysis duration before transplant		14.6±2.3	14.6±1.5
Serum Vitamin D, ng/mL (%)			
<15		11 (28.2)	6 (20)
15-30		21 (53.9)	15 (50)
>30		7 (17.9)	9 (30)
Serum PTH, mg/dL		78.7±8.7	97.6±12.4
Serum Ca2+, mg/dL		9.3±0.1	9.3±0.1
Serum Phosphorus, mg/dL		3.7±0.1	4±0.2
Serum Creatinine, mg/dL		1.5±0.1	1.4±0.1
Estimated GFR*, mL/min/1.73 m^2		66.2±3.4	55.2±2.7
Normal BMD (%)	Femur	23 (59)	4 (13.3)
	Lumbar	24 (61.5)	8 (26.7)
Osteopenia (%)	Femur	-	16 (53.4)
	Lumbar	-	15 (50)
Osteoporosis (%)	Femur	16 (41)	10 (33.4)
	Lumbar	15 (38.5)	7 (23.3)

*Chronic Kidney Disease Equation Epidemiology Collaboration formula
PTH: parathyroid hormone, GFR: glomerular filtration rate, BMD: bone mineral density

Table 2: Logistic regression analysis for significant risk factors of efmoral neck osteoporosis in multivariable analysis (age <50 years).

Parameters	Odds Ratio (CI 95%)	SE (OR)	P-value
Sex			
Male	1*		
Female	7.38 (0.77–70.9)	8.52	0.08
Length of use of prednisolone	0.99 (0.98–1.01)	0.01	0.64
Serum Vitamin D(ng/mL)			
<15	1		
15-30	0.07 (0.01–0.59)	0.08	0.01**
>30	0.89 (0.11–18.94)	0.85	0.81
Serum Creatinine	2.06 (0.04–107.31)	4.16	0.45
Estimated GFR***	0.99 (0.91–1.08)	0.04	0.91

*: Reference category
**: Significant
***: Chronic Kidney Disease Equation Epidemiology Collaboration formula
CI: confidence interval, GFR: glomerular filtration rate

use. There was also a relationship between osteopenia-osteoporosis at the lumbar spine and type of transplantation, duration of prednisolone use, vitamin D level, and the estimated GFR. Moreover, the results of multivariate analysis showed a significant relationship between osteopenia/osteoporosis at the femoral neck and age and duration of post-transplantation prednisolone use. Each additional month of prednisolone use caused a 10% increase in the risk of osteopenia and 0.08% increase in the risk of osteoporosis at the femoral neck compared to normal-BMD patients (Table 3). A one-year increase in age increased the risk of osteoporosis and osteopenia at the femoral neck by 1.59 and 1.49 folds compared to patients with a normal BMD, respectively (Table 3).

The present results showed that the duration of post-transplantation prednisolone use significantly increased the risk of osteoporosis at the lumbar spine compared to the normal BMD group (RRR=1.02, 95% CI: 1.00 to 1.04, P=0.05) (Table 4).

DISCUSSION

This study investigated the prevalence of BMD and its associated factors in kidney transplant recipients between 2016 and 2018. In recent years, many studies with different sample sizes and statistical models have been conducted on BMD; however, the results of these studies are inconsistent. In the present study, the overall prevalence of osteoporosis at the femur and lumbar spine was 38% and 32%, respectively. Sixteen patients (53%) had osteopenia at the femoral neck, and 15 patients (50%) had osteopenia at the lumbar spine.

In some previous studies, age was introduced as an independent risk factor for osteoporosis in kidney transplant recipients [10, 11]. The present results showed that patients aged >50 years were at a high risk of osteopenia/osteoporosis at the femoral neck; this finding is consistent with the results of previous research [12, 13]. On the other hand, similar to a previous study, no significant relationship was found between age and osteoporosis at the femoral neck and lumbar spine [14]. The results showed that women were seven times more likely to develop osteoporosis at the femoral neck compared to men; however, it was not statistically significant (P=0.08). In Ahmadpoor *et al*. [8] study, consistent with this finding, there was no such association, but other studies found a significant between sex and osteoporosis at the femoral neck and lumbar spine [12, 15].

Vitamin D deficiency has been associated with poor outcomes in kidney transplant recipients

Table 3: Polynomial logistic regression analysis for significant risk factors of femoral neck osteopenia and osteoporosis in multivariable analysis (age ≥ 50years).

Parameters	(normal BMD)	RRR* (osteopenia) (95%CI)	P-value	RRR (osteoporosis) (95%CI)	P-value
Age, years	1**	1.49 (1.01–2.28)	0.05***	1.59 (1.02–2.49)	0.04***
Drug	1	-		-	
Tacrolimus		1	-	1	-
Cyclosporin		0.32 (0.01–12.39)	0.55	0.03 (0.001–2.66)	0.13
Sirolimus		0.01 (0.01–10.23)	0.99	No data	-
Receipt of a kidney donor	1	-		-	
Deceased		1		1	
Living		0.33 (0.01–17.88)	0.59	0.19 (0.02–14.82)	0.46
Length of use of prednisolone	1	1.1 (1.01–1.17)	0.05***	1.08 (1–1.18)	0.04***

*: Relative risk ratio
**: Reference category
***: Significant
CI: confidence interval, BMD: bone mineral density

[16]. In this study, 25% of patients were deficient in vitamin D (<15 ng/mL). A significant relationship was found between vitamin D levels (15-30 ng/mL) and osteoporosis at the femoral neck. Overall, a vitamin D level of 15-30 ng/mL can be an important protective factor for femoral osteoporosis in people aged <50 years compared to vitamin D levels <15 ng/mL; in other words, people with vitamin D levels of 15-30 ng/mL are 90% less likely to develop femoral osteoporosis compared to those with vitamin D levels <15 ng/mL. Although this finding is inconsistent with the results of some previous studies [12, 14], some other studies on the general population have demonstrated that a low serum vitamin D level can be associated with decreased BMD and increased bone loss [17]. The present finding might be attributed to vitamin D supplementation in patients younger than 50 years.

Glucocorticoids are generally necessary to avoid renal rejection after transplantation. They mainly increase bone reabsorption, reduce bone formation, and decrease bone density [18]. The current findings showed that in patients aged >50 years, the duration of prednisolone use after transplantation was associated with osteoporosis at the neck, femur, and lumbar spine. The risk of osteopenia and osteoporosis at the femoral neck increased by 10% and 8% with a one-month increase in prednisolone use compared to normal BMD patients. Moreover, a one-month increase in prednisolone use was associated with a 2% increase in the risk of osteoporosis at the lumbar spine. The present findings are in line with the results of other studies, which showed that glucocorticoids play a major role in secondary osteoporosis following transplantation (17, 18). In this regard, a study by Khosravi et al. showed that the cumulative dose of prednisolone was higher in osteoporotic patients compared to the normal BMD group (14); similar results were reported by Ellis et al. [19]. However, the use of glucocorticoids should be limited as much as possible in the post-transplantation period.

In the present study, we could not find a significant relationship between post-transplantation osteopenia/osteoporosis and other variables. Although GFR was significantly associated with osteoporosis at the femur and lumbar spine in the univariate analysis, it was not found to be significant in the multivariate analysis. One of the most influential variables in osteopenia/osteoporosis was body mass index (BMI). In this study, although a higher BMI was a protective factor for osteoporosis at the femoral neck and lumbar spine, this re

Table 4: Polynomial logistic regression analysis for significant risk factors of lumbar spine osteopenia and osteoporosis in multivariable analysis (age ≥ 50years).

Parameters	(normal BMD)	RRR* (osteopenia) (95%CI)	P-value	RRR (osteoporosis) (95%CI)	P-value
Length of use of predni-solone	1**	1.01 (0.99–1.03)	0.20	1.02 (1.00–1.04)	0.05***
Receipt of a kidney donor	1	-		-	-
Deceased		1		1	-
Living		3.72 (0.36–38.88)	0. 27	5.38 (1.25–115)	0.25
Serum Vitamin D****	1	0.95 (0.85–1.06)	0.30	0.95 (0.85–1.06)	0.32
Estimated GFR	1	0.96 (0.88–1.04)	0.31	0.99 (0.91–1.10)	0.99

*: Relative risk ratio
**: Reference category
***: Significant
****: Because of the small sample size, Vitamin D was introduced into the model quantitatively
CI: confidence interval, BMD: bone mineral density, GFR: glomerular filtration rate

lationship was not significant. Similarly, in a study by Naylor et al., a higher BMI was not associated with the osteoporosis risk [20]. Nonetheless, several studies have shown that a lower BMI is an important risk factor for the occurrence of a low BMD; these results do not support the findings of the present study and the study by Ahmadpour et al. [8].

In conclusion, the long-term use of corticosteroids, such as prednisolone, was associated with a higher risk of osteopenia and osteoporosis in patients aged ≥50 years. Due to the inevitability of corticosteroid use for kidney transplant recipients, regular monitoring of BMD, maximum reduction of prednisolone dose, education on the use of supplements (e.g., vitamin D and calcium), and other preventive and supportive measures are essential for this group.

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