Changes in Bone Mineral Density after Kidney Transplantation

Böbrek Nakli Sonrası Kemik Mineral Yoğunluğundaki Değişiklikler

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ABSTRACT

Aim: The aim of this study was to evaluate changes in lumbar and femoral bone mineral density (BMD) in the post-transplant period.

Material and Methods: A total of 69 consecutive adult (>18 years of age) patients who underwent kidney transplantation between Jan 2016 and Jul 2019 were included in this retrospective study. The demographic features and laboratory findings of the patients (serum corrected calcium, phosphorus, alkaline phosphatase, creatinine, eGFR, i-parathormone and 25(OH) D vitamin levels) were recorded. BMD was evaluated by dual energy X-ray absorptiometry (DEXA).

Results: According to the DEXA results, lumbar and femoral T scores were -1.1±1.3 and -1.1±1.1, respectively. Lumbar assessment revealed osteoporosis in 12 (17.4%) patients and osteopenia in 24 (34.8%) patients. Femoral assessment revealed osteoporosis in 7 (10.1%) patients and osteopenia in 29 (42.0%) patients. The first year, 1-2 year and >2 years follow up data revealed osteoporosis in 4.3%, 5.8% and 7.2% of patients in the lumbar region and in 2.9%, 2.9% and 4.3% of patients in the femoral region, respectively. There was no significant difference in cumulative steroid dose between patients with BMD loss in the lumbar (p=0.197) and femoral (p=0.971) region and patients with normal BMD measurement. In addition, no significant relation was observed between the induction therapy and loss of BMD in the lumbar region (p=0.671) and femur (p=0.126).

Conclusion: As a result, 25(OH) D vitamin deficiency is quite common in transplant patients and the loss of BMD is observed especially in the lumbar region in the first year after transplantation.

Keywords: Kidney transplantation; bone mineral density; lumbar region; femoral; vitamin D.

ÖZ

Amaç: Bu çalışmanın amacı böbrek nakil sonrası dönemde lomber ve femoral kemik mineral yoğunluğundaki (KMY) değişiklikleri değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Ocak 2016 ve Temmuz 2019 tarihleri arasında böbrek nakli yapılan ardışık 69 erişkin (>18 yaş) hasta dahil edildi. Hastaların demografik özellikleri ve laboratuvar bulguları (serum düzeltilmiş kalsiyumu, fosfor, alkalen fosfataz, kreatinin, eGFR, i-parathormon ve 25(OH) D vitamin düzeyi) ile ilgili veriler kaydedildi. KMY, dual enerji X-ray absorbsiyometri (DEXA) ile değerlendirildi.

Bulgular: DEXA sonuçlarına göre, lomber ve femoral T skorları sırasıyla -1,1±1,3 ve -1,1±1,1 idi. Lomber değerlendirmede 12 (%17,4) hastada osteoporoz ve 24 (%34,8) hastada osteopeni saptandı. Femoral değerlendirmede 7 (%10,1) hastada osteoporoz ve 29 (%42,0) hastada osteopeni saptandı. İlk yıl, 1-2 yıl ve >2 yıl takip verilerine göre, sırasıyla lomber bölgede hastaların %4,3, %5,8 ve %7,2'sinde, femurda hastaların %2,9, %2,9 ve %4,3'ünde osteoporoz saptandı. Lomber bölge (p=0,197) ve femurda (p=0,971) KMY kaybı tespit edilen hastalar ile KMY ölçümü normal olan hastalar arasında kümülatif steroid dozu açısından anlamlı bir fark yoktu. Ayrıca hastaların almış olduğu indüksiyon tedavisi ile lomber bölge (p=0,671) ve femurda (p=0,126) gelişen KMY kaybı arasında anlamlı bir ilişki görülmedi.

Sonuç: Sonuç olarak, nakil hastalarında 25(OH) D vitamini eksikliği oldukça yaygındır ve özellikle nakilden sonraki ilk yıl lomber bölgede belirgin olmak üzere KMY kaybı görülmektedir.

Anahtar kelimeler: Böbrek nakli; kemik mineral yoğunluğu; lomber bölge; femur; vitamin D.

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INTRODUCTION

Problems related to bone mineral density (BMD) is one of the complications associated with life-long immunosuppressive therapy in kidney transplant patients. This condition increases the length of hospital stay, treatment cost, and mortality and morbidity rates due to the increased fracture risk in kidney transplant recipients (1). Data from the two major studies on fracture and mortality rates in post-transplant patients revealed the incidence of fractures to be 3.4-3.8% and the 1-year mortality risk after fracture to be 9.0-11.0%, depending on the risk factors (2,3). Several factors have been implicated in the etiology of bone mineral disorders develop after kidney transplantation including immunosuppressive drugs along with duration of chronic renal failure, type and duration of dialysis, pre-transplant bone disease (secondary hyperparathyroidism, osteomalacia, mixed bone disease, adynamic bone disease), diabetes mellitus, smoking, physical inactivity, menopause, fracture history, malnutrition, post-transplant persistent hyperparathyroidism and 25(OH) vitamin D deficiency (4,5). Immunosuppressive drugs, especially corticosteroids, reduce the number and activity of osteoblasts, increase osteoclastic activity and suppress bone formation resulting in rapid bone loss and increasing fracture risk via dose-dependent inhibition of growth hormone release and insulin-like growth factor-1 synthesis. Moreover, these agents cause negative calcium balance by decreasing intestinal absorption and increasing renal excretion of calcium (6). Calcineurin inhibitors can also cause high bone turnover, especially leading to trabecular bone loss. The combined use of cyclosporine (CsA) and glucocorticoid leads to bone loss by inhibiting osteoblast differentiation and enhancement. Tacrolimus (Tac) has been shown to cause osteopenia in animals, but there is limited data regarding its effect on bones in humans (5,7,8). Sirolimus, rapamycin, mycophenolate mofetil and azathioprine treatments were shown to have minimal effect on bone mass, and in vitro studies, everolimus has been shown to prevent bone resorption by inhibiting osteoclast cathepsin-K expression (9,10).

There are studies showing that the risk of fractures increases as BMD decreases in transplant patients (11,12). In this study, our aim was to show BMD changes in lumbar and femoral region in the post-transplant period.

MATERIAL AND METHODS

A total of 69 consecutive patients older than >18 years of age, who underwent kidney transplantation between January 2016 and July 2019 were included in this retrospective study. The blood biochemistry analysis was performed in routine controls including corrected serum calcium, phosphorus, alkaline phosphatase, creatinine, eGFR, i-parathormone and 25(OH) D vitamin level.

The study protocol was approved by the Ufuk University Faculty of Medicine Clinical Trials Ethics Committee (dated 16.12.2019 and numbered 5) and was conducted in accordance with the principles of Helsinki Declaration. Informed consent was obtained from all participants after informing them to participate in this research.

The 25(OH) D vitamin levels of the participants were studied by High Performance Liquid Chromatography (HPLC) method and vitamin D status was categorized as vitamin D deficiency (<20 ng/mL), vitamin D insufficiency (20-30 ng/mL), and normal vitamin D levels (>30 ng/mL, 13).

Anti-thymocyte globulin (Grafalon Neovii), one of the antilymphocyte antibodies, was given in 100 mg/g dose for 3 days as induction therapy on demand. All patients were started on prednisolone (0.8 mg/kg/day, oral) after intravenous 1500 mg methyl-prednisolone treatment. Prednisolone was given as 30 mg/day, 20 mg/day and 5 mg/day, in the first month, in the second month and after the third month, respectively. In maintenance therapy, calcineurin inhibitor (Tac or Cs-A) and an antiproliferative agent (mycophenolate mofetil, maximum 2 g/day or mycophenolate sodium, maximum 1440 mg/g) were used in combination with prednisolone therapy. Cs-A (6 mg/kg/day, 2 oral doses daily) and Tac (0.1 mg/kg/day, 2 oral doses daily) blood levels were titrated as needed to achieve target levels. In case of acute organ rejection, renal biopsy was performed and treatment (pulse methyl-prednisolone, anti-thymocyte globulin, plasmapheresis and intravenous immunoglobulin treatments alone or in combination) was performed according to Banff criteria.

Bone mineral densitometry was evaluated by dual energy X-ray absorptiometry (DEXA). The shooting time and radiation dose were determined as 60 seconds and 42 μGy for lumbar region and femur. Results were determined as T score [defines the difference between the patient's BMD and the mean BMD of the standard young adult (20-30 years old) population as standard deviation (SD) and expresses peak bone mass] and Z score (standard deviation of difference of patient's BMD results with the mean BMD of controls in the same gender and age group). The T score ≤-2.5 SD was accepted as osteoporosis, and T score <-1.0 and >-2.5 SD was accepted as osteopenia.

Statistical Analysis

The Kolmogorov-Smirnov test was used to follow normal distribution of variables. For the variables assumed to be normally distributed, inter-group comparisons were made by Independent samples t-test, while Mann Whitney U test was used for non-normally distributed variables. Spearman's rank correlation analysis was used to test the relation between cumulative steroid dose and 25(OH) D vitamin levels and BMD measurements. Chi-square test was used to the test the relationships among the categorical variables. The p value <0.05 was considered as statistically significant. The statistical analyses were performed with SPSS v.22.

RESULTS

Overall, 24.6% (n=17) of the patients were female and 75.4% (n=52) were male. The mean age of the patients was 40.7±13.8 (range, 17.0 to 64.0) years, body mass index was 26.6±5.0 (range, 18.7 to 42.5) kg/m^2, and post-transplant follow-up duration was 20±12 (range, 1 to 41) months. The evaluation of patients' diseases underlying end-stage renal disease to be chronic glomerulonephritis in 23 (33.3%) patients, hypertension in 12 (17.4%) patients, diabetic nephropathy in 9 (13.0%) patients, secondary amyloidosis in 8 (11.6%) patients, chronic tubulointerstitial nephritis in 3 (4.3%) patients, nephrolithiasis in 2 (2.9%) patients, polycystic renal disease in 2 (2.9%) patients and vesicoureteral reflux in 1 (1.4%) patient. The etiology of end-stage renal disease was unknown in 9 (13.0%) patients. When classified according to the reference values, there were 3 (4.3%) patients with normal 25(OH) vitamin D

levels, 11 (15.9%) patients with 25(OH) vitamin D insufficiency and 55 (79.7%) patients with 25(OH) vitamin D deficiency. The type of dialysis, tissue compliance number, transplantation type, the features of immunosuppression induction and maintenance treatment, rejection development and laboratory values of the patients are demonstrated in Table 1.

The mean T score for the lumbar region was -1.1±1.3 (range, -3.3 to 2.1), while the mean T score for the femur was -1.1±1.1 (range, -3.4 to 1.3). In lumbar region evaluation, osteoporosis was detected in 12 (17.4%) patients and osteopenia was detected in 24 (34.8%) patients. Five (41.7%) of 12 patients who developed osteoporosis and 11 (45.8%) of 24 patients who developed osteopenia received induction therapy. Looking at the relationship between lumbar region BMD loss and induction therapy; loss of BMD was observed in 16 (55.2%) of the 29 patients given induction therapy, whereas BMD loss was observed in 20 (50.0%) of the 40 untreated patients (p=0.671). According to femur measurements, osteoporosis was detected in 7 (10.1%) patients and osteopenia in 29 (42.0%) patients. Three (42.9%) of 7 patients who developed osteoporosis and 9 (31.0%) of 29 patients who developed osteopenia received induction therapy. Considering the relationship between BMD loss and induction therapy in the femoral region; while BMD loss was observed in 12 (41.4%) of the 29 patients who received induction therapy, bone loss was observed in 24 (60.0%) of the 40 patients who did not receive induction therapy (p=0.126). There were 4 (5.8%) patients with osteoporosis in both regions and 14 (20.3%) patients with osteopenia. Overall, 24 (34.8%) patients had normal BMD. Fracture was noted in none of the patients during follow-up period (Table 2). Follow up data on BMD losses with respect to DEXA measurements of lumbar and femur area are shown in Table 3, Figure 1 and Figure 2. Follow up data on osteoporosis development in the first year, 1-2 years and >2 years revealed lumbar osteoporosis rates of 4.3%, 5.8% and 7.2%, respectively, and femoral osteoporosis rates of 2.9%, 2.9% and 4.3%, respectively. In addition, at the end of the first year, BMD loss in the lumbar region was higher than in the femur region, and the frequency of osteoporosis showed a cumulative increase in the post-transplant period.

Overall, 20 (29.0%) patients developed acute rejection and therefore received 1500 mg of methyl-prednisolone in addition to standard steroid treatment. When patients were evaluated in terms of the relationship between cumulative steroid dose and BMD; there was no significant difference in cumulative steroid dose between patients with BMD loss and with normal BMD measurement in the lumbar region (p=0.197). In the femur region, there was no significant difference in cumulative steroid dose between patients with BMD loss and patients with normal BMD measurement (p=0.971, Table 4).

The evaluation of relation between 25(OH) vitamin D levels and BMD of the patients revealed no significant difference in 25(OH) vitamin D levels between patients with BMD loss and normal BMD measurement (p=0.909) in the lumbar region. There was also no significant difference in 25(OH) Vitamin D levels in patients with BMD loss and in patients with normal BMD measurements in the femur region (p=0.177, Table 4).

Table 1. Demographic characteristics of patients, n=69

Gender, n (%)	
Female	17 (24.6)
Male	52 (75.4)
Age (year)	40.7±13.8
BMI (kg/m²)	26.6±5.0
Dialysis type, n (%)	
Preemptive	37 (53.6)
Hemodialysis	30 (43.5)
Peritoneal dialysis	2 (2.9)
Transplantation type, n (%)	
Live	66 (95.7)
Cadaveric	3 (4.3)
MM, n (%)	
0 MM	5 (7.2)
1 MM	4 (5.8)
2 MM	10 (14.5)
3 MM	24 (34.8)
4 MM	11 (15.9)
5 MM	8 (11.6)
6 MM	7 (10.1)
Immunosuppression, n (%)	
Tac+MMF	68 (98.6)
CsA+MMF	1 (1.4)
Induction treatment, n (%)	
ATG	28 (40.6)
Basiliximab	1 (1.4)
Non-inducted	40 (58)
Transplantation time (month)	20.0±12.0
Cumulative prednisolone dose (mg)	6450.0±2486.8
25(OH) vitamin D (ng/mL)	11.1±10.0
PTH (ng/L)	148.3±217.5
Ca (mg/dL)	9.3±0.4
P (mg/dL)	3.4±0.6
ALP (U/L)	76.0±27.2

BMI: Body Mass Index, MM: Miss-Match number, MMF: Mycophenolate mofetil, Tac: Tacrolimus, CsA: Cyclosporine-A, PTH: Parathyroid Hormone, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, ATG: Anti-thymocyte Globulin

Table 2. Patients' lumbar and femur BMD evaluations

		Lumbar			
		Normal	Osteopenia	Osteoporosis	Total
Femur	Normal	24 (34.8)	8 (11.6)	1 (1.4)	33 (47.8)
	Osteopenia	8 (11.6)	14 (20.3)	7 (10.1)	29 (42.0)
	Osteoporosis	1 (1.4)	2 (2.9)	4 (5.8)	7 (10.1)
	Total	33 (47.8)	24 (34.8)	12 (17.4)	69 (100)

BMD: Bone Mineral Density

Table 3. Lumbar and femur BMD evaluations according to follow-up duration

	Region	1-12 month	12-24 month	>24 month
Normal BMD	Lumbar	7 (38.9)	10 (41.7)	16 (59.3)
	Femur	9 (50.0)	10 (41.7)	14 (51.8)
Low BMD	Lumbar	11 (61.1)	14 (58.3)	11 (40.7)
	Femur	9 (50.0)	14 (58.3)	13 (48.2)
Osteopenia	Lumbar	8 (44.4)	10 (41.7)	6 (22.2)
	Femur	7 (38.9)	12 (50.0)	10 (37.0)
Osteoporosis	Lumbar	3 (16.7)	4 (16.6)	5 (18.5)
	Femur	2 (11.1)	2 (8.3)	3 (11.2)

BMD: Bone Mineral Density

Table 4. Effect of cumulative steroid dose and 25(OH) Vitamin D levels on BMD

		Normal BMD (n=33)		BMD Loss (n=36)		p
		Mean±SD	Median (Q₁-Q₃)	Mean±SD	Median (Q₁-Q₃)	
Cumulative Steroid Dose (mg)	Lumbar	6777±2232	6750 (5550 - 8250)	6125±1922	6075 (4275 - 7500)	0.197
	Femur	6427±2302	6450 (5100 - 8150)	6445±1901	6225 (5325 - 7725)	0.971
25(OH) Vit D (ng/mL)	Lumbar	13.8±11.4	12.3 (7.5 - 16.4)	14.1±8.6	11.1 (7.5 - 19.6)	0.909
	Femur	12.3±6.3	10.4 (7.5 - 15.5)	15.6±12.3	12.6 (7.3 - 21.5)	0.177

BMD: Bone Mineral Density, SD: Standard Deviation, Q_1: 1st Quartile, Q_3: 3rd Quartile
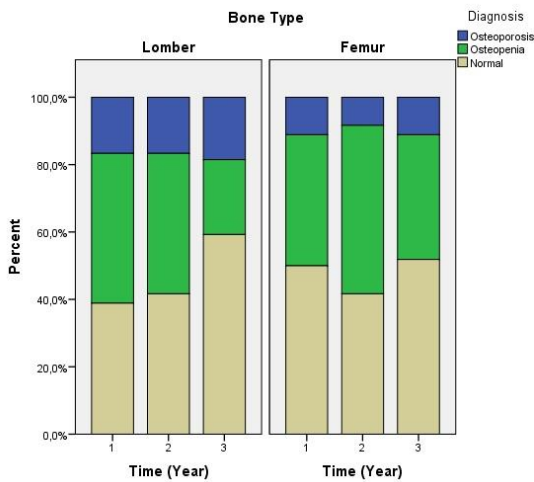
Figure 1. Evaluation of BMD in terms of normal, osteopenia and osteoporosis according to duration of follow-up
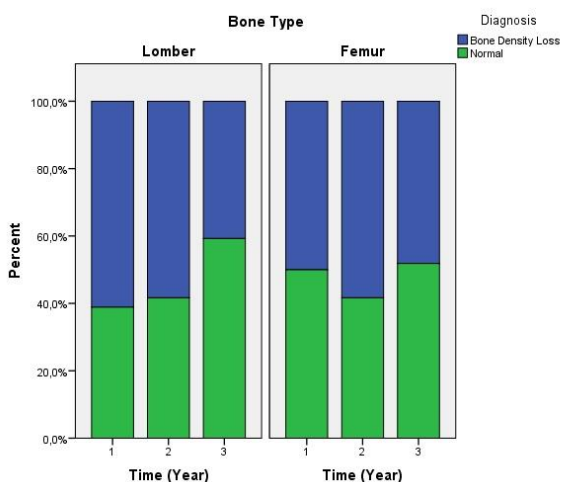
Figure 2. Evaluation of BMD changes of patients by years

In addition, there was no significant correlation between 25(OH) vitamin D levels and lumbar BMD measurement (r_s=0.036, p=0.771), and between 25(OH) vitamin D levels and femur BMD measurement (r_s=-0.015, p=0.905).

DISCUSSION

Our findings revealed more extensive BMD loss in the lumbar vs. femur region at the end of the first year than the following years and a cumulative increase in the frequency of osteoporosis in the post-transplantation period. The ratio of patients with adequate 25(OH) vitamin D levels was calculated as 4.3% (n=3). The majority of patients (79.7%, n=55) had 25(OH) vitamin D deficiency. There

was no relation between cumulative steroid dose and BMD loss. Also, no statistically significant relationship was shown between induction therapy and loss of BMD.

Although BMD loss is seen both in the lumbar region and in the femoral neck in the first 6 months of the transplantation, the most intense BMD loss is seen in the lumbar region. BMD loss in the femoral neck becomes prominent after 6 months by follow-up (14). Similar to our study, in the study of Julian et al. (15), 20 post-transplant patients were evaluated and BMD loss was shown to be more intense in the lumbar region in the first 6 months. This can be explained by the different bone structure of lumbar and femur regions. Lumbar region consists mainly of trabecular bone and is a region sensitive to steroid effect. For this reason, BMD loss in the first 6 months is the highest in this region, when glucocorticoid therapy is used at the maximum doses. Femoral neck, on the other hand, is sensitive to hyperparathyroidism as it contains cortical bone. The effects of high parathyroid hormone on femur are long-lasting, as it may take years for the recovery of parathyroid gland hyperplasia after transplantation (16).

Similar to our study, in the literature, it has been shown that BMD loss or osteoporosis during the post-transplantation period reached the highest level in the first 6 months, and continue at a lower rate in the 6-12 months. Although it varies according to the series, the BMD reduction rate in the post transplantation period has been shown to be 5.5-19.5% for the first 6-month and 2.6-8.2% for the second 6-month (17). In the study by Trabulus et al. (18), osteoporosis was reported in 15.3% of patients in the first year, in 37.5% between 1-3 years, and in 41.6% between 3-5 years.

Vitamin 25(OH) D levels, together with calcium and phosphorus metabolism, is one of the factors affecting development, structure and function of the musculoskeletal system. Moderate or severe 25(OH) D vitamin deficiency has been demonstrated in kidney transplant recipients. This situation varies according to seasons, countries and age. In the studies investigated 25(OH) D vitamin levels of the recipients, the ratio of patients with adequate vitamin 25(OH) D levels was reported to be 3-12%, similar to our findings (4.3%) (19,20).

In a study of 86 transplant patients followed for 38.3±14.8 years after transplantation, those who received >5600 mg steroids and those who received <3300 mg steroids were compared and it was shown that the cumulative steroid dose did not increase the risk of bone fracture (21). In a similar study, 59 patients (31 patients with osteoporosis, 28 patients without osteoporosis) were followed up for 8.5±3.1 years after transplantation, and authors reported no significant difference between patients with vs. without

osteoporosis in terms of cumulative steroid doses (11). However, data from the United States Renal Data System (USRDS) revealed that the fracture risk decreased by 31% without increasing acute rejection risk in patients who were discharged from hospital by discontinuing steroid treatment (22). Chandran et al. (23) showed a negative correlation between cumulative steroid doses and BMD in a 5-year study with 164 renal transplant patients. In a study of 68 transplant patients, >40% of patients were shown to have lumbar BMD loss in first 11 months and bone loss was closely related to the cumulative steroid dose (24).

The limitations of the current study are retrospective design, lack of detailed information on patients' mineral and bone disorders associated with chronic renal disease before transplantation, and lack of data on control BMD measurements after treatment.

CONCLUSION

In conclusion, 25(OH) vitamin D deficiency is commonly encountered in transplant patient population, while BMD loss is also evident, particularly within the first post-transplant year and in the lumbar region. However, no relationship has been demonstrated between induction therapy and loss of BMD. Conflicting data exists in the literature regarding the effects of cumulative steroid doses and immunosuppressive treatments on BMD. Further studies are needed to address BMD, potential treatments and treatment outcome in transplant patients.

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