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Original Article

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Osteoporosis and Associated Factors in Renal Transplant Patients

Ahmet Karataş[1], Ebru Çanakçı[2], Emre Erdem[3], Yeliz Kasko Arıcı[4], Mervegül Kaya[5]

[1]Division of Nephrology, Department of Internal Medicine, Ordu University School of Medicine, Ordu, Turkey
[2]Department of Anesthesiology and Reanimation, Ordu University School of Medicine, Ordu, Turkey
[3]D-MED Dialysis Center Private Sector, Samsun, Turkey
[4]Department of Biostatistics and Medical Informatics, Ordu University School of Medicine, Ordu, Turkey
[5]Department of Family Medicine, Ordu University School of Medicine, Ordu, Turkey

ABSTRACT

Objective: The study aims to draw attention to the bone disease that occurs in the post-transplantation period in renal transplant patients, to investigate the factors that facilitate the formation of bone disease, and to assess the problems that may be associated with bone disease.

Methods: In addition to routine biochemical parameters, hormone tests and bone mineral density were measured in 85 patients who underwent renal transplantation. Total steroid dose (milligrams) of all patients until the dual-energy X-ray absorptiometry measurement was calculated. The patients were divided into 3 groups as normal, osteopenia, and osteoporosis according to the T score based on World Health Organization criteria.

Results: The mean age of the patients was 47.29 ± 13.32 years, and 59 (69.4%) patients were male. Transplantation time (Tx time) was statistically significantly higher in osteoporosis patients than in both the normal bone mineral density and osteopenia groups (P = .020). The mean total steroid dose of the patients in the osteoporosis group was higher than the patients in the normal bone mineral density group (P = .044). But when transplantation time (Tx time) was used as a covariate variable in analysis of variance, this difference among the bone mineral density groups was not statistically significant (P = .238). Alkaline phosphatase was statistically significantly higher in osteoporosis patients (P = .016). The 25-hydroxy vitamin D level of the patients in the osteoporosis group was statistically lower than in the normal bone mineral density group (P = .029).

Conclusion: Low 25-hydroxy vitamin D level, high alkaline phosphatase, and menopause are the risk factors for osteoporosis in renal transplant patients.

Keywords: Bone mineral density, corticosteroids, osteoporosis, renal transplantation

Corresponding author: Ahmet Karataş ✉ karatas55@hotmail.com

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INTRODUCTION

World Health Organization (WHO) defines osteoporosis as an increase in the risk of fracture due to low bone mass and deterioration in bone tissue.[1] Bone and mineral disorders are common in kidney transplant recipients. The causes of bone disorders after transplantation are renal osteodystrophy before transplantation, immunosuppressive drugs used after transplantation (glucocorticoids and calcineurin inhibitors), parathyroid hormone (PTH), changes in vitamin D, and fibroblast growth factor 23.[2,3] The period in which bone loss is most pronounced after renal transplantation is the first 6-12 months.[4]

Both bone mineral density (BMD) and markers of the bone cycle may return to pre-transplant levels in parallel with improved renal functions after renal transplantation.[5] Recent studies have shown that the incidence of hip fractures is reduced, possibly due to a decrease in steroid use.[6] The presence of very few centers with expertise in processing and analyzing bone biopsy samples and the reluctance of patients to make bone

biopsies almost impossible even though bone biopsy is the gold standard for post-transplant bone disease diagnosis in kidney transplant recipients.[7] Dual-energy x-ray absorptiometry (DEXA) test provides an accurate, non-invasive, and cost-effective BMD estimation and can help to estimate the risk of fracture in kidney transplant recipients.[8]

This study aims to draw attention to the bone disease that occurs in the post-transplantation period in renal transplant patients, to investigate the factors that facilitate the formation of bone disease, and to examine the problems that may be associated with bone disease.

METHODS

Our study was conducted with 85 renal transplant cases followed up in nephrology outpatient clinic dated from February 01, 2019, to August 31, 2019. The study design was a designed prospective clinical observational study. The approval was obtained from Ordu University Clinical Research Ethics Committee dated January 10, 2019, and numbered 2019/07. Volunteer consent was obtained from those who accepted to participate in our study. Blood samples were taken from each patient in the morning after 12 hours of fasting. Demographic characteristics of each case such as age, weight, and height were recorded, and body mass indexes (BMIs) were calculated. Routine biochemical examinations of each case were recorded. The estimated glomerular filtration rate value of the patients was calculated using the Kidney Disease Epidemiology Collaboration creatinine equation.[9] Patients with parathyroidectomy, history of hip fracture, hip prosthesis, and known malignancy were excluded from the study.

Donor type (living/deceased) and type of transplantation of all patients were recorded. The immunosuppressive drug regimen used by the cases were divided into 3 groups: the first group was tacrolimus, mycophenolate mofetil, and prednisolone, the second group was cyclosporin A, mycophenolate mofetil, prednisolone, and the third group was azathioprine, mycophenolate sodium, mammalian target of rapamycin inhibitors (sirolimus and everolimus). In addition, the use of pulse steroids, polyclonal antibodies, anti-thymocyte globulin (ATG), a monoclonal antibody (basiliximab) for rejection treatment after renal transplantation (renal Tx), and other drugs used by all cases were recorded. Total steroid dose (milligrams) of all patients until the DEXA measurement was calculated. Menopausal status was questioned in female patients. In addition, the etiology and duration of chronic kidney disease (CKD), hemodialysis before renal Tx, and/or peritoneal dialysis times were recorded.

MAIN POINTS

- Bone and mineral disorders are common in kidney transplant recipients.
- Dual-energy x-ray absorptiometry (DEXA) test provides an accurate, non-invasive, and cost effective BMD estimation and can help to estimate the risk of fracture in kidney transplant recipients.
- In our study, alkaline phosphatase was highly elevated in osteoporosis patients. The 25-hydroxy vitamin D level of the patients in the osteoporosis group was statistically lower than in the normal bone mineral density group. We also found a high risk of osteoporosis in postmenopausal kidney transplant recipients in this study.
- It is important to measure BMD, monitor vitamin D and ALP levels in the post-transplant period.

The devices (Cell-Dyn Ruby; Abbott, Lake Bluff, USA and Roche Cobas; C-501; Indianapolis, USA) were used for hemogram and routine biochemical analyses (serum blood urea nitrogen, creatinine, albumin, potassium, calcium, C-reactive protein, alkaline phophatase (ALP), and uric acid). The device (Roche Cobas E-601; Indianapolis, USA) was used for hormone analyses (vitamin D, ferritin, and PTH) in our Training and Research Hospital central laboratory.

BMD measurements were performed with DEXA method (Hologic SQ-15882, Bedford, USA). Lumbar spine and femur measurements were performed for all patients. The patients were divided into 3 groups as normal, osteopenia, and osteoporosis according to the T score based on WHO criteria. Classification for lumbar spine and femur T scores was made based on the lowest T score. T score was evaluated as normal ≥ -1.0, osteopenia between -1.0 and -2.5, and osteoporosis ≤ -2.5.[10]

Statistical Analysis

All data analyses were performed using SPSS v26 (IBM Corp., Armonk, NY, USA) statistical software package. The continuous data were tested for normality using the Shapiro–Wilk's test and for homogeneity of variance using Levene's test prior to the statistical analyses. The one-way analysis of variance (ANOVA) or Kruskal–Wallis test with Tukey's or Dunn's multiple comparisons was used to assess the differences among more than 2 groups. Analysis of variance was performed to the total steroid dose by considering the Tx time as a covariate variable. The chi-square test was used to compare between females and males percentage. All comparisons were two-tailed, and a *P*-value less than 5% was considered statistically significant.

RESULTS

The study was conducted with 85 renal transplant patients. The study consists of 26 (30.6%) female and 59 (69.4%) male patients. The mean age of all patients was 47.29 ± 13.32 years, and the mean age in the normal, osteopenia, and osteoporosis groups was 42.8 ± 15.75, 46.80 ± 12.49, and 51.04 ± 12.77 years, respectively. There was no difference between the mean age and the percentage of females and males in the study groups according to the one-way ANOVA and chi-square test, respectively ($P > .05$) (Figure 1).

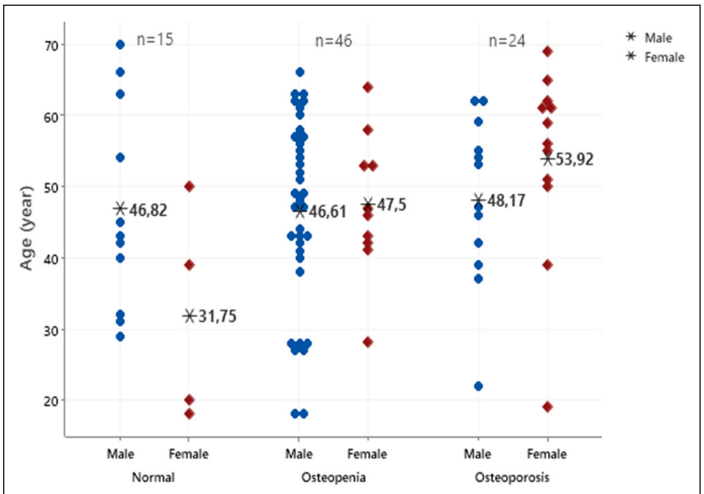

Figure 1. Individual value plot of age for patients in the study groups.

Table 1. Descriptive Statistics of BMD Scores According to NHANES III Reference Database

	Mean ± SD (Min–Max)
T score hip	−1.708 ± 0.99693 (−4.9 to 0.7)
T score lumbar	−1.4364 ± 1.35792 (−4.7 to 2.7)
Z score lumbar	−1.0649 ± 1.47982 (−4.0 to 3.5)
Z score hip	−0.9904 ± 0.96052 (−3.1 to 1.1)
BMD total hip	0.72569 ± 0.137693 (0.302 to 1.006)
BMD total lumbar	0.91696 ± 0.205635 (0.535 to 1.930)

BMD, bone mineral density; SD, standard deviation.

According to our BMD results, 15 (17.6 %) patients had normal BMD, while 46 (54.1%) patients had osteopenia and 24 (28.2%) patients had osteoporosis.

The descriptive statistics of BMD scores according to National Health and Nutrition Examination Survey (NHANES) III reference database are shown in Table 1.

The proportion of patients who used and did not use ATG due to rejection after renal Tx did not differ significantly according to the study groups ($P > .05$). Patients who used and did not use steroids varied significantly according to the BMD groups ($P < .01$). The proportion of patients who used steroids after renal Tx was 37.5% in the osteoporosis group, whereas only 13.3% and 6.5% of the patients in the normal and osteopenia groups used steroids after renal Tx (Table 2).

There was no significant difference between immunosuppressive drug regimens according to BMD groups ($P > .05$). There was no significant difference between the groups in cases using vitamin D and phosphorus binding drugs ($P > .05$).

There was no significant difference between groups according to BMI and CKD etiology ($P > .05$).

There was no significant change in BMI according to the groups ($P > .05$). The BMI of patients with menopause were 16.7%, 55.6%, and 58.6% in the normal, osteopenia, and osteoporosis groups, respectively. The chi-square test confirmed that the ratio of patients with menopause varied significantly according to the groups ($P = .030$) (Table 3).

Table 2. Distribution of Steroid and ATG Use Status After Donor Type and Renal Tx According to Study Groups

	Diagnosis				
	Normal	Osteopenia	Osteoporosis	Total	*P*
Tx donor type					
Living	11 (73.3)	38 (82.6)	21 (87.5)	70 (82.4)	.541
Deceased	4 (26.7)	8 (17.4)	3 (12.5)	15 (17.6)	
Post-Tx steroid					
No	13 (86.7)	43 (93.5)	15 (62.5)	71 (83.5)	.006**
Yes	2 (13.3)	3 (6.5)	9 (37.5)	14 (16.5)	
Post-Tx ATG					
No	13 (86.7)	45 (97.8)	20 (83.3)	78 (91.8)	.070
Yes	2 (13.3)	1 (2.2)	4 (16.7)	7 (8.2)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	

**$P < .01$.
ATG, anti-thymocyte globulin.

Table 3. Distribution of Drug Use Status, BMI, CKD Type, and Menopausal Status According to Study Groups

	Diagnosis				
	Normal	**Osteopenia**	**Osteoporosis**	**Total**	*P*
Immunosuppressive					
TACROMMFGC	12 (80.0)	37 (80.4)	21 (87.5)	70 (82.4)	.934
CYCMMFGC	2 (13.3)	5 (10.9)	2 (8.3)	9 (10.6)	
Others	1 (6.7)	4 (8.7)	1 (4.2)	6 (7.1)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	
Calcium use					
No	14 (93.3)	40 (87.0)	20 (83.3)	74 (87.1)	.639
Yes	1 (6.7)	6 (13.0)	4 (16.7)	11 (12.9)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	
DVIT use					
No	11 (73.3)	29 (63.0)	18 (75.0)	58 (68.2)	.529
Yes	4 (26.7)	17 (37.0)	6 (25.0)	27 (31.8)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	
Phosphate binder use					
No	13 (86.7)	39 (84.8)	20 (83.3)	72 (84.7)	.961
Yes	2 (13.3)	7 (15.2)	4 (16.7)	13 (15.3)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	
Menopause					
No	5 (83.3)	4 (44.4)	3 (21.4)	12 (41.4)	.030*
Yes	1 (16.7)	5 (55.6)	11 (78.6)	17 (58.6)	
Total	6 (100.0)	9 (100.0)	14 (100.0)	29 (100.0)	
CKD etiology					
DM	0 (0.0)	7 (16.3)	4 (17.4)	11 (13.6)	.213
HT	11 (73.3)	21 (48.8)	13 (56.5)	45 (55.6)	
Glomerulonephritis	0 (0.0)	4 (9.3)	1 (4.3)	5 (6.2)	
Others	4 (26.7)	11 (25.6)	5 (21.7)	20 (24.7)	
Total	15 (100.0)	43 (100.0)	23 (100.0)	81 (100.0)	
BMI					
Normal	6 (40.0)	15 (32.6)	12 (50.0)	33 (38.8)	.057
Overweight	8 (53.3)	18 (39.1)	5 (20.8)	31 (36.5)	
Obese	1 (6.7)	13 (28.3)	5 (20.8)	19 (22.4)	
Morbid obese	0 (0.0)	0 (0.0)	2 (8.3)	2 (2.4)	
Total	15 (100.0)	46 (100.0)	24 (100.0)	85 (100.0)	

TACROMMFGC, tacrolimus, mycophenolate mofetil, prednisolone; CYCMMFGC, cyclosporin A, mycophenolate mofetil, prednisolone; Others, azathioprine, mycophenolate sodium, mammalian target of rapamycin inhibitors, sirolimus, everolimus.; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HT, hypertension.
*$P < 0.05$.

The descriptive statistical values and comparison results of the laboratory variables considered in the study according to the groups are given in Table 4.

The mean total steroid dose was 14 505.42 ± 6642.30 mg in the normal group, 17 484.08 ± 7045.46 mg in the osteopenia group, and 21 223.46 ± 9833.42 mg in the osteoporosis group. The total steroid dose of the patients in the osteopenia group was not different from that in both the normal and osteoporosis groups ($P > .05$), but the mean total steroid dose of the patients in the osteoporosis group was higher than in the normal group ($P = .044$). But when Tx time was used as a covariate variable in ANOVA, this difference among the BMD groups was not statistically significant ($P = .238$). Tx time was statistically significantly higher in osteoporosis patients (88.75 ± 47.05 months) than in both the normal (52.00 ± 37.72 months) and osteopenia (58.91 ± 48.43 months) groups ($P = .020$). Similarly, ALP was statistically significantly higher in osteoporosis patients (102.09 ± 34.36 U/L) than in both the normal (83.07 ± 46.82 U/L) and osteopenia (80.57 ± 31.88 U/L) groups ($P = .016$). The level of 25-hydroxy vitamin D (25-OHD) decreased in the total steroid dose and, unlike ALP, in the osteoporosis group. The 25-OHD level of the patients in the osteoporosis group (15.17 ± 8.20 ng/mL) was statistically lower than in the normal group (22.50 ± 9.92 ng/mL) ($P = .029$). The 25-OHD levels of the patients in the osteopenia group (20.76 ± 9.57 ng/mL) did not differ significantly from those in both the normal (22.50 ± 9.92 ng/mL) and osteoporosis groups (15.17 ± 8.20 ng/mL) ($P > .05$) (Figure 2). There was no significant difference between BMD groups in terms of other variables ($P > .05$).

DISCUSSION

It was found that most of the patients had low BMD (osteopenia and osteoporosis) in this study which was conducted with a researcher to evaluate the changes in bone in renal transplant patients. Low vitamin D level, high ALP levels, and menopause condition have been identified as risk factors for osteoporosis

Table 4. Descriptive Statistical Values and Comparison Results of Study Variables by Groups

	Normal (n = 15)		Osteopenia (n = 46)		Osteoporosis (n = 24)		
	Mean	SD	Mean	SD	Mean	SD	*P*
CKD time (month)	112.20	70.05	104.93	58.96	122.79	62.81	.522
HD time (month)	68.71	49.59	39.13	53.90	42.75	36.02	.358
PD time (month)	48.00	43.27	36.00	50.91	60.50	84.15	.916
BMI (weight (kg)/height (m^2))	26.78	2.88	27.48	3.31	27.40	8.07	.895
Biochemistry							
BUN (mg/dL)	21.43	10.26	21.80	12.64	21.75	8.39	.994
Creatinine (mg/dL)	1.45	.65	1.49	.81	1.27	.61	.492
eGFR (mL/min/1.73 m^2)	65.23	29.40	64.19	26.52	65.87	24.43	.967
Calcium (mg/dL)	9.40	.73	9.66	0.64	9.43	.76	.269
Phosphorus (mg/dL)	.39	3.26	0.74	3.30	.74	.909	
Albumin (g/dL)	4.54	.36	4.53	0.33	4.34	.49	.118
Uric acid (mg/dL)	5.84	1.77	5.95	1.28	5.96	1.79	.965
C reactive protein (mg/dL)	0.83	0.90	0.92	1.34	1.29	2.74	.650
Ferritin (ng/dL)	521.43	627.55	310.60	396.60	518.06	644.71	.191
Parathyroid hormone (pg/mL)	84.18	42.27	111.72	117.76	94.05	53.06	.550
UACR (mg/g)	104.51	206.99	317.00	582.08	460.90	1042.49	.313
Hba1C	5.67	.80	5.77	.81	6.29	1.76	.146
Hemogram							
WBC (µL)	8020.00	1998.36	8201.98	2532.29	8326.25	2956.05	.937
Hemoglobin (g/dL)	13.79	2.19	13.58	1.97	12.67	1.65	.115
Platelets ($\times 10^3$, µL)	205	470	237.8	775.6	231.8	811.9	.335

BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; UACR, Urine albumin-creatinine ratio; WBC, white blood cells.

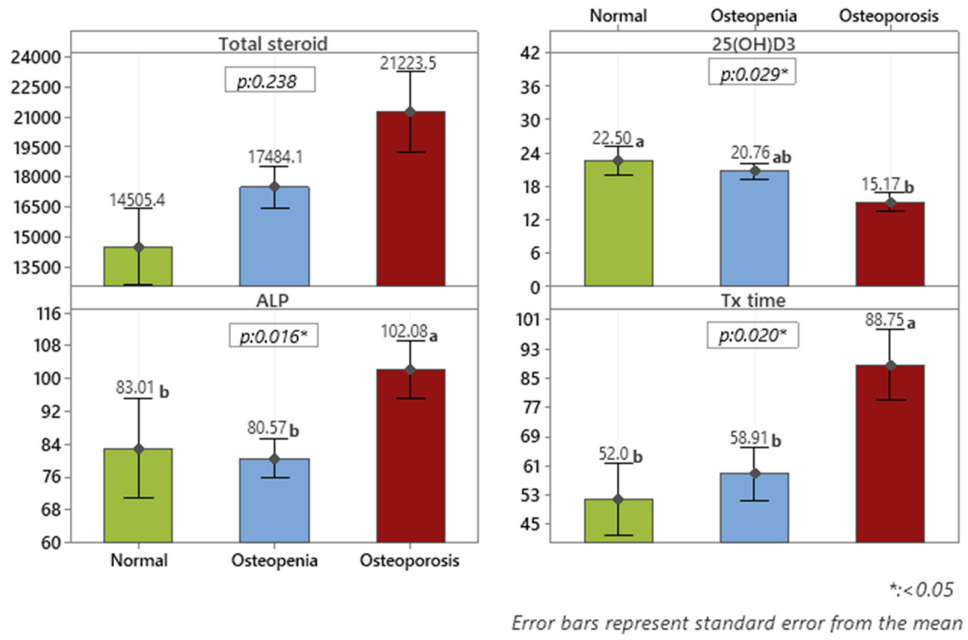

Figure 2. Interval plot of total steroid, Tx time, ALP, and 25(OH)D3 for patients in the study groups. 25-OHD3, 25-hydroxy vitamin D3; ALP, alkaline phosphatase.

in renal Tx patients in this study. Although we found the total steroid dose was high in osteoporosis patients, it was not statistically significant when Tx times were equalized. In other words, although the total steroid dose after renal Tx was clinically significant in terms of osteoporosis, it was not statistically significant.

Segaud et al[11] showed in their study that 106 (40.9%) of 259 renal Tx patients had osteoporosis and 111 (42.8%) had osteopenia. The rate of osteoporosis was reported to be 27.5%, and the rate of osteopenia was 52.5% in the study conducted by Marcén et al.[12] Many studies have shown that BMD decreased after renal transplantation.[13,14] A decrease in BMD was shown after renal transplantation in our study. The present study is consistent with the literature in this respect.

Studies on the relationship between age and BMD after kidney transplantation are quite different. Some studies have suggested that advanced age causes bone loss, while many studies have claimed that there is no relationship between age and decrease in BMD.[15-18] Similarly, its effect on bone density differs in gender. Gupta et al[19] confirmed that bone density decreased in women, and Huang and Lai[20] also confirmed that osteopenia and osteoporosis were less common in men, while there was no correlation between gender and bone density in many studies.[14-16,20] Khosravi et al[17] showed that both age and gender had no effect on bone density in renal transplantation patients. Alis et al[21] claimed in their study that osteoporosis after renal Tx had no relationship with age and gender. There was no relationship between the bone density with both age and gender in our study. In other words, the present study revealed that age and gender were not associated with a decrease in bone density in accordance with the general results in the literature.

The role of glucocorticoids in the pathogenesis of bone loss is to cause early and rapid bone loss by suppressing the bone formation and stimulating osteoporosis.[22] Dempster et al[23] conducted one of the first studies in the literature on this subject. They claimed that corticosteroids lead to prolonged bone formation and increased bone resorption. Some studies have shown that increased cumulative cyclosporin and steroid doses have a negative effect on bone density, whereas in some studies, tacrolimus, another calcineurin inhibitor, has been claimed to have a protective effect on bone density.[24,25] Segaud et al[11] have claimed that the main factor in bone loss after renal transplantation is the use of corticosteroids . Nishioka et al[26] have found that BMD decrease develops in the period from 4 to 8 months after transplantation, and the corticosteroid dose returns to pre-transplant levels after 12-24 months with a decrease to 4 mg at the end of the first month. Casez et al[27] have claimed that the cumulative steroid dose after renal transplantation is associated with BMD changes . A high cumulative corticosteroid dose was not seen as a risk factor for osteoporosis development in our study. The present study is incompatible with the literature in this respect. This may be due to the relatively small number of our patients.

In addition to this, it was found in the present study that the use of pulse steroid therapy increased the risk of osteoporosis in patients due to rejection in the post-transplant period. The present study is the first study in the literature in this respect.

Low serum 25-OHD levels after solid organ transplantation are common both in the early postoperative period and in the long term.[28] The circulating 25-(OH) vitamin D (calcidiol) levels of the renal transplant patient must be evaluated in terms of vitamin D deficiency, and vitamin D deficiency must be treated according to the Kidney Disease Outcomes Quality Initiative (KDIGO) 2009 guideline.[29] Ugur et al[30] have shown that BMD is maintained in renal transplant patients with normal vitamin D levels. Sikgenc et al[31] have claimed that vitamin D is not associated with bone density when the patients with renal transplantation are evaluated with 2 separate measurements at 6-month intervals. Falkiewicz et al[32] have claimed that high vitamin D levels have a positive effect on BMD after 1-24 months of renal transplantation. Osteoporosis was found to be associated with low vitamin D in our study. It can be said that the low rate of exposure to sunlight in our geography explains the relatively high rate compared to the literature. This can also be considered as a factor contributing to the clinical situation resulting in low vitamin D level and triggering osteoporosis.

High ALP level after renal transplantation has been claimed as a risk factor for osteoporosis development. Jerman et al[33] have shown in their study that the risk of osteoporosis increases with high ALP within 1-10 years of post-transplantation. Some studies have claimed that ALP is not associated with bone density. Sikgenc et al[31] claimed that ALP levels were not associated with bone density. High ALP levels were found as a risk factor for osteoporosis in our study in parallel with the general approach in the literature.

Osteoporosis and associated hip fractures are common especially in elderly postmenopausal women.[34] Around 200 million women worldwide suffer from osteoporosis.[35] Segaud et al[11] found the rate of osteoporosis in postmenopausal women to be 28.8%. Brandenburg et al[36] claimed that low estradiol and high luteinizing hormone levels were correlated with the degree of annual BMD loss in postmenopausal women. The ratio of patients with menopause varied significantly according to the groups in our study. In other words, the rate of osteoporosis was found to be significantly higher in postmenopausal women than in the group with normal BMD (58.6%). In our study, the risk of osteoporosis was found to be high in postmenopausal women. Our study results are consistent with the literature findings.

The present study had some limitations. The lack of pre-transplant BMD measurements of the cases is the first limitation. The second limiting factor is the inability to obtain long-term post-treatment results of the cases. Last, the use of total ALP instead of bone-specific ALP can be considered as a limitation of the present study.

In the post-transplant patient follow-up, if women are in the postmenopausal period, if low vitamin D level and high ALP are detected, they should be evaluated in terms of osteoporosis risk. It is important for nephrologists to develop strategies to provide a more comfortable life in kidney recipients by evaluating the risks of osteoporosis, which is a common problem in the post-transplantation period in light of new studies. There is a need for a wider population and multicenter trials on this subject. The present study is believed to shed light on long-term studies with a larger population.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Studies Ethics Committee of Ordu University (Approval Date: January 10, 2019; Approval Number: 2019/07).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept - A.K.; Design - A.K., E.Ç., E.E.; Data Collection and/or Processing - A.K., E.Ç., E.E., Y.K.A., M.K.; Analysis and/or Interpretation - E.E., Y.K.A.; Literature Search - A.K., E.Ç., M.K.; Writing - A.K.; Critical Revision - A.K., E.Ç., E.E.

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REFERENCES

1. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int*. 2016;27(4):1281-1386. [CrossRef]
2. Bouquegneau A, Salam S, Delanaye P,Eastell R, Khwaja A. Bone disease after kidney transplantation. *Clin J Am Soc Nephrol*. 2016;11(7):1282-1296. [CrossRef]
3. Vangala C, Pan J, Cotton RT, Ramanathan V. Mineral and bone disorders after kidney transplantation. *Front Med*. 2018;5:211. [CrossRef]
4. Brandenburg VM, Westenfeld R, Ketteler M. The fate of bone after renal transplantation. *J Nephrol*. 2004;17(2):190-204.
5. Carlini RG, Rojas E, Weisinger JR,Lopez M, Martinis R, Arminio A. Bone disease in patients with long-term renal transplantation and normal renal function. *Am J Transplant*. 2000;36(1):160-166.
6. Nair SS, Lenihan CR, Montez-Rath ME, Lowenberg DW, Chertow GW, Winkelmayer WC. Temporal trends in the incidence, treatment and outcomes of hip fracture after first kidney transplantation in the United States. *Am J Transplant*. 2014;14(4):943-951. [CrossRef]
7. Evenepoel P, Behets GJS, Laurent MR, D'Haese PCD. Update on the role of bone biopsy in the management of patients with CKD–MBD. *J Nephrol*. 2017;30(5):645-652. [CrossRef]
8. Akaberi S, Simonsen O, Lindergård B, Nyberg G. Can DXA predict fractures in renal transplant patients? *Am J Transplant*. 2008;8(12):2647-2651. [CrossRef]

9. National Kidney Foundation. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kid Int Suppl*. 2013;3(1):136-150.
10. World Health Organization Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group.*World Health Org Tech Rep Ser*. 1994;843:1-129.
11. Segaud N, Legroux I, Hazzan M, Noel C, Cortet B. Changes in bone mineral density after kidney transplantation: 2-year assessment of a French cohort. *Osteoporos Int*. 2018;29(5):1165-1175. [CrossRef]
12. Marcén R, Caballero C, Uriol O, et al. Prevalence of osteoporosis, osteopenia, and vertebral fractures in long-term renal transplant recipients. *Transplant Proc*. 2007;39(7):2256-2258. [CrossRef]
13. Marcén R, Caballero C, Pascual J, et al. Lumbar bone mineral density in renal transplant patients on neoral and tacrolimus: a four-year prospective study. *Transplantation*. 2006;81(6):826-831. [CrossRef]
14. Karatas A, Erdem E, Kaya C, et al. Risk factors for osteoporosis in renal transplant recipients. *Turk Neph Dial Transpl*. 2012;21(3) :267-272. [CrossRef]
15. Ahmadpoor P, Reisi S, Makhdoomi K, Ghafari A, Sepehrvand N, Rahimi E. Osteoporosis and related risk factors in renal transplant recipients. *Transplant Proc*. 2009;41(7):2820-2822. [CrossRef]
16. Unal A, Kocyigit I, Sipahioglu MH, et al. Loss of bone mineral density in renal transplantation recipients. *Transplant Proc*. 2010;42(9):3550-3553. [CrossRef]
17. Khosravi M, Soltanian N, Monfared A, Ghanbari A, Ramezandade E, Leyli EK. Bone mineral density and related factors in renal transplant recipients, in the north of Iran. *Iran J Kidney Dis*. 2020;14:405-411.
18. Zhang Q, Cao K, Hu X, et al. Investigation of bone loss, and its related factors in renal transplant recipients. *Zhonghua Yi Xue Za Zhi*. 2015;95:2062-2065.
19. Gupta AK, Huang M, Prasad GV. Determinants of bone mineral density in stable kidney transplant recipients. *J Nephrol*. 2012;25(3):373-383. [CrossRef]
20. Huang WH, Lai PC. Age at transplant—one of the factors affecting bone mineral density in kidney recipients: a single-center retrospective study. *Ren Fail*. 2011;33(8):776-780. [CrossRef]
21. Alis G, Alis M, Erturk T, Karayagiz AH, Berber I, Cakir U. Evaluation of bone disease in kidney transplant recipients. *Transplant Proc*. 2017;49(3):509-511. [CrossRef]
22. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine*. 2018;61(1):7-16. [CrossRef]
23. Dempster DW, Arlot MA, Meunier PJ. Mean wall thickness and formation periods of trabecular bone packets in corticosteroid-induced osteoporosis. *Calcif Tissue Int*. 1983;35(4-5):410-417. [CrossRef]
24. Goffin E, Devogelaer J-P, Lalaoui A, et al. Tacrolimus and low-dose steroid immunosuppression preserves bone mass after renal transplantation. *Transpl Int*. 2002;15(2-3):73-80. [CrossRef]
25. Almond MK, Kwan JT, Evans K, Cunningham J. Loss of regional bone mineral density in the first 12 months following renal transplantation. *Nephron*. 1994;66(1):52-57. [CrossRef]
26. Nishioka S, Sofue T, Inui M, et al. Mineral and bone disorder is temporary in patients treated with early rapid cortico steroid reduction after kidney transplantation: a single-center experience. *Transplant Proc*. 2014;46(2):514-520. [CrossRef]
27. Casez JP, Lippuner K, Horber FF, Montandon A, Jaeger P. Changes in bone mineral density over 18 months following kidney transplantation: the respective roles of prednisone and parathyroid hormone. *Nephrol Dial Transplant*. 2002;17(7):1318-1326. [CrossRef]
28. Stein EM, Shane E. Vitamin D in organ transplantation. *Osteoporos Int*. 2011;22(7):2107-2118. [CrossRef]
29. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(Suppl 3):S1-S155. [CrossRef]
30. Ugur A, Guvener N, Işiklar I, Turan M, Erdal R, Haberal M. Osteoporosis after renal transplantation: single center experience. *Transplantation*. 2001;71(5):645-649. [CrossRef]
31. Sikgenc MM, Paydas S, Balal M, et al. Bone disease in renal transplantation and pleotropic effects of vitamin D therapy. *Transplant Proc*. 2010;42(7):2518-2526. [CrossRef]
32. Falkiewicz K, Boratyńska M, Zmonarski SC, et al. Evolution of bone disease at 2 years after transplantation: a single-center study. *Transplant Proc*. 2009;41(8):3063-3066. [CrossRef]
33. Jerman A, Lindic J, Skoberne A, et al. Prevalence and risk factors for nonvertebral bone fractures in kidney transplant recipients: a single-center retrospective analysis. *Clin Nephrol*. 2017;88(13):101-108. [CrossRef]
34. Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med*. 2016;374(3):254-262. [CrossRef]
35. International Osteoporosis Foundation. The facts about osteoporosis and its impact. *International Osteoporosis Foundation Website*. Available at: http://www.osteofound.org/press_centre/fact_sheet.html, Acccessed July 26, 2005.
36. Brandenburg VM, Ketteler M, Heussen N, et al. Lumbar bone mineral density in verylong-termrenaltransplantrecipients: impact of circulating sex hormones. *Osteoporos Int*. 2005;16(12):1611-1620. [CrossRef]