Factors Associated With Lumbar and Femoral Bone Mineral Density in Kidney Transplants Candidates

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Introduction. Data on risk factors associated with low bone mineral density are limited in patients with end-stage renal disease. This study evaluated the factors deemed associated with lumbar and femoral Z and T scores.

Materials and Methods. Clinical and demographic data of 98 patients waiting for kidney transplantation were collected, as well as lumbar and femoral bone densitometries, before transplantation. Osteoporosis and osteopenia and factors associated with bone mineral density were assessed.

Results. According to the femoral T score, 38.8% (95% confidence interval [CI], 29.1% to 48.4%), 44.9% (95% CI, 35.1% to 54.7%), and 16.3% (95% CI, 9.0% to 23.6%) of the patients had normal bone density, osteopenia, and osteoporosis, respectively. According to the lumbar T score, 54.1% (95% CI, 44.2% to 63.9%), 33.7% (95% CI, 24.3% to 44.0%), and 12.2% (95% CI, 5.8% to 18.7%) of the patients had normal density, osteopenia, and osteoporosis, respectively. Age, serum levels of creatinine and parathyroid hormone, and use of calcitriol and calcium carbonate were associated with femoral densitometry scores. Serum total protein level, Rh-negative status, and B blood type were associated with the lumbar scores.

Conclusions. Parathyroid hormone contributed to bone loss in our kidney transplant candidates, and B and Rh-negative blood types were associated with a higher risk of lumbar osteoporosis while total protein was negatively associated with the risk of bone loss. Calcitriol might improve femoral mineral density, but calcium carbonate was negatively associated with femoral bone density. Age and higher creatinine levels were associated with higher femoral bone densities.

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INTRODUCTION

An important task of the kidney is to maintain phosphorus homeostasis. In patients suffering from late stages of chronic kidney disease (CKD), the physiological phosphorus balance turns into pathological positive phosphate balance.[1-3] The hyperphosphatemia leads to crucial pathophysiology, such as cardiovascular problems, contributing to significant mortality rates seen in CKD.[3-5] Studies have shown that kidney dysfunction might considerably increase risk of osteoporosis and bone fracture compared to healthy population.[3,6-15] This is becoming more important as patients are now living longer, and by aging, they become more prone to bone fracture.[7]

The prevalence of osteoporosis and osteopenia

is unclear among Iranians with kidney disease. Moreover, the associations of serum vitamin D with femur density, controlling for the role of parathyroid hormone (evaluated only in few studies on health populations, but not patients with kidney disease), are not extensively studied.[16] Therefore, measuring the levels of factors such as vitamin D and parathyroid hormone and their associations in patients with end-stage renal disease (ESRD) can help to comprehend their role.[2] Hence, this study was conducted to evaluate the association between bone density and prevalence of osteoporosis and osteopenia in candidates for kidney transplantation and the associations between the bone densities with numerous demographic, medication-related, and biochemical components.

MATERIALS AND METHODS

This cross-sectional study was performed on 98 candidates for kidney transplantation enrolled subsequently and prospectively during 2014 and 2015. The inclusion criteria were having ESRD, currently being on hemodialysis, and scheduled kidney transplantation. The study protocol was approved by the research ethics committee of the university in accordance with the Helsinki declaration, and signed consents were obtained from the patients.

Before transplantation, a complete set of tests was carried out. This, together with the results of previous laboratory tests existing in patient files plus directly surveying the patients, were used to obtain the following information: birth date, sex, dairy and protein consumption instances per day (asked from patients, not standardized according to amount but only as the number of meals including dairy and protein per day), education level, employment, marital status, number of deliveries in women, place of birth, ABO blood type, Rh blood type, any underlying diseases (such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and infection), duration of the disease according to the date of first diagnosis, the medications and dosages for the underlying disease, the presence of anemia and medication dosages for treating the existing anemia, previous history of hemodialysis (absent [pre-emptive kidney transplantation] or present, its duration between the starting date and the transplantation, and the number of hemodialysis sessions per week), medications received till the transplantation date, laboratory tests preceding kidney transplantation (fast blood glucose, blood hemoglobin, and serum levels of calcium, phosphorus, parathyroid hormone, vitamin D, creatinine, uric acid, magnesium, alkaline phosphatase, total protein, and albumin).

Patients' height and weight were directly measured. Before the transplantation, they underwent L1-L4 anteroposterior lumbar spine densitometry at 98% to 99% accuracy, and hip densitometry at 97% to 98% accuracy, by dual-energy x-ray absorptiometry scan using a well maintained weekly-calibrated Lunar DPXMD densitometer (Lunar 7164, GE, Madison, WI, USA). The T and Z scores were calculated for the femur and lumbar areas in each patient.[17] Osteoporosis was characterized by having T scores equal to or lower than -2.5, while osteopenia was defined as T scores between -2.5 and -1.0. T scores above -1.0 were considered normal.[17,18]

Descriptive statistics and 95% confidence intervals (CIs) were computed for the variables involved. Correlations between the independent and dependent variables were established using the Spearman correlation coefficient, in order to mark the independent variables more likely to play a role (determined as *P* values equal to or less than 0.2). A multiple linear regression analysis was used to examine the associations between the selected independent variables and the femoral T score. Additionally, a step-wise backward-selection multiple linear regression was conducted to select automatically the independent variables with the highest relevance. The same 2 procedures were repeated for the femoral Z score as well as the lumbar T and Z scores. The level of significance was set at .05.

RESULTS

Thirty-eight women and 62 men were included in the study, with an average age of 42.16 ± 12.72 years (range, 17 to 68). Of those, 64 had hypertension, 8 were receiving insulin, 3 had obstructive problems, and none had any infection. Medications calcium carbonate, being taken by 64; magnesium hydroxide, by 1; calcitriol, by 87; sevelamer, by 28; Erythropoietin, by 69; Vitamin D, by 10; and calcium-vitamin D, by 16. Five patients had fasting blood glucose values greater than 125 mg/dL.

Of the patients, 16 were preemptive transplant candidates. The average hemodialysis time was 17.23 ± 18.42 months (maximum, 108 months). Of the patients undergoing hemodialysis, 6 were treated twice per week and the rest were treated 3 times per week.

The laboratory tests and bone densitometry results are summarized in Tables 1 and 2. There were significant and positive correlations between Z and T scores; the correlations were excellent in the same bony site, while they were moderate or weak between femoral and lumbar sites (Table 3). According to the femoral T score, 38.8% (95% CI, 29.1% to 48.4%), 44.9% (95% CI, 35.1% to 54.7%), and 16.3% (95% CI, 9.0% to 23.6%) of the patients had normal bone density, osteopenia, and osteoporosis, respectively. According to the lumbar T score, 54.1% (95% CI, 44.2% to 63.9%), 33.7% (95% CI, 24.3% to 44.0%), and 12.2% (95% CI, 5.8% to 18.7%) of the patients had normal density, osteopenia, and osteoporosis, respectively.

The regression analysis detected parathyroid hormone and serum creatinine as predictors of for femoral T score (P = .006; Table 4), and also age, calcitriol, and calcium carbonate as predictors for femoral Z score (P = .002; Table 4). The sole predictor for lumbar T score was Rh (P = .02; Table 4), and parathyroid hormone and blood type B were predictors of lumbar Z score (P < .001; Table 4).

Table 3. Correlations Between T and Z Scores of Lumbar And Femoral Sites

	Coefficient (*P*)		
Bone Score	**Femur Z**	**Femur T**	**Lumbar Z**
Femur Z	…	…	…
Femur T	0.901 (< .001)	…	…
Lumbar Z	0.585 (< .001)	0.488 (< .001)	…
Lumbar T	0.604 (< .001)	0.590 (< .001)	0.911 (< .001)

DISCUSSION

In the present study, we observed a rather similar prevalence of osteoporosis when evaluating lumbar versus femoral areas. In a study on postmenopausal women, osteoporosis was seen in 26.4% of the lumbar spines and 13.2% of the femurs, showing the higher vulnerability of the more cancellous lumbar bones to osteoporosis among postmenopausal women.[19] This study identified a rather broad range of different predictors for the T and Z scores of the lumbar and femoral bones. In the case of the femur, parathyroid hormone and serum creatinine were associated with both

Table 1. Blood Tests Results Before Kidney Transplantation

Blood Parameter	Mean Value	Range	95% Confidence Interval
Calcium, mg/dL	8.83 ± 0.86	6.3 to 10.4	8.7 to 9.0
Phosphorus, mg/dL	5.84 ± 1.68	2.7 to 11.0	5.5 to 6.2
Parathyroid hormone, pg/mL	341.40 ± 293.72	7.5 to 1737.0	283.2 to 399.6
Vitamin D, mg/dL	26.52 ± 20.93	3.0 to 91.3	22.4 to 30.7
Hemoglobin, %	11.35 ± 1.77	6.6 to 14.7	11.0 to 11.7
Creatinine, mg/dL	7.45 ± 2.24	3.1 to 14.5	7.0 to 7.9
Uric acid, mg/dL	7.31 ± 8.59	3.0 to 85.0	5.6 to 9.0
Fasting blood glucose, mg/dL	92.69 ± 19.93	50.0 to 198.0	88.5 to 96.9
Magnesium, mg/dL	20.78 ± 40.93	1.7 to 94.0	12.7 to 28.9
Alkaline phosphatase, U/mL	304.66 ± 164.11	8.7 to 998.0	272.2 to 337.2
Hemoglobin A1c, %	5.39 ± 0.77	4.2 to 8.2	5.2 to 5.5
Total protein, mg/dL	6.88 ± 0.99	3.0 to 8.9	6.7 to 7.1
Albumin, mg/dL	5.68 ± 7.00	3.0 to 40.0	4.3 to 7.1

Table 2. Bone Densitometry Results Before Kidney Transplantation

Bone Score	Mean Value	Range	95% Confidence Interval
Femur			
Z	8.83 ± 0.86	6.3 to 10.4	8.7 to 9.0
T	5.84 ± 1.68	2.7 to 11.0	5.5 to 6.2
Lumbar			
Z	341.40 ± 293.72	7.5 to 1737.0	283.2 to 399.6
T	26.52 ± 20.93	3.0 to 91.3	22.4 to 30.7

Table 4. Multiple Linear Regression Analyses

Predictor	Coefficient	Standard Error	Standardized Coefficient	*P*	95% Confidence Interval
Femur T					
Age	-0.009	0.010	-0.102	.352	-0.029 to 0.010
Calcitriol	0.465	0.354	0.142	.193	-0.241 to 1.170
Parathyroid hormone	-0.001	0.000	-0.263	.013	-0.002 to 0.000
Serum creatinine	0.142	0.056	0.275	.013	0.031 to 0.254
Calcium carbonate	-0.484	0.256	-0.202	.062	-0.993 to 0.025
Femur Z					
Age	0.023	0.009	0.280	.012	0.005 to 0.041
Calcitriol	0.657	0.322	0.222	.045	0.016 to 1.299
Parathyroid hormone	-0.001	0.000	-0.308	.004	-0.002 to 0.000
Serum creatinine	0.145	0.051	0.307	.006	0.044 to 0.246
Calcium carbonate	-0.504	0.233	-0.232	.034	-0.969 to -0.040
Rh	0.427	0.632	0.071	.501	-0.831 to 1.686
Lumbar T					
Calcitriol	0.359	0.420	0.092	.396	-0.477 to 1.195
Parathyroid hormone	-0.001	0.001	-0.178	.166	-0.002 to 0.000
Rh	2.011	0.846	0.254	.020	0.326 to 3.695
Alkaline phosphatase	-0.001	0.001	-0.174	.175	-0.004 to 0.001
Blood group B	-1.158	0.332	-0.381	.001	-1.800 to -0.515

scores, while age, calcitriol, and calcium were only predictors of the Z score. The gold standard method of noninvasive bone densitometry is dual-energy x-ray absorptiometry which is safe and reliable.[17,18,20] Similar to this study, other studies on CKD patients as well showed levels of loss of bone density.[3,10-15]

Parathyroid hormone is a well-known factor capable of reducing bone density by releasing calcium ions into the blood system, and its negative association with bone density is anticipated.[2,3,16,21-26] However, the negative link observed between the calcium carbonate supplemental consumption and Z scores was surprising, as binding of calcium with systemic phosphorus can neutralize the pathological positive phosphate balance and indirectly improve bone density. Similar unexpected results were observed in the case of total protein and creatinine, where higher rates of these factors were associated with higher bone densities. Future studies are needed in this regard. Unlike calcium, calcitriol was positively associated with improved bone density. It is suggested that low levels of endogenous vitamin D may reduce bone density and increase fracture risk; however, the underlying mechanisms such as the existence of associations between serum vitamin D levels and volumetric bone mineral density or proximal femur dimensions are not clearly understood.[16] Parathyroid hormone regulates bone turnover and systemic vitamin D and can be associated with cortical measures,[7,16,24-26] although some studies have not found an association between either of the factors parathyroid hormone, vitamin D, and cortical measures.[16,23]

A major source of hyperphosphatemia in CKD and ESRD is skeletal remodeling disorders associated with excess bone resorption relative to bone formation.[5,27] In many hyperphosphatemia syndromes, the skeleton remains healthy and contributes to the balance of phosphorus through depositing the extra phosphorus, resulting in bone mass increase.[5,27] However, in 2 scenarios (immobilization and CKD) bones lose their capacity to overtake phosphorus, and instead start to release more phosphorus to the blood system via an increased resorption rate.[5,27] The complex alterations occurred to the skeletal function in CKD worsen the condition, marking the skeleton no more as a buffer for systemic phosphorus excess, but as a contributing factor to the hyperphosphatemia in CKD, at the expense of a new phosphorus reservoir, the soft tissue including the cardiovascular system.[5,27]

It has been suggested that the kidney plays an important role in mediating the final hydroxylation step of 25-hydroxyvitamin D to calcitriol, and hence its malfunction might be associated with deficiency of 1,25-dihydroxyvitamin D.[2,22] Calcitriol deficiency itself can lead to secondary hyperparathyroidism

and a pathologic positive balance of phosphates.[2,21]

In this study, negative Rh was associated with reduced lumbar T score. There is no similar study in this regard. The only far-connected study was one that showed a higher prevalence of negative Rh blood type in osteochondrosis compared with controls.[28] It is also speculated that the blood type A might have a higher risk of osteoporosis while type O might have the smallest rate of osteoporosis because that intestinal alkaline phosphatase enzyme might be able to facilitate calcium absorption.[19,29] In this study, we observed no significant link between the blood type A or O and bone density. The only association was observed in terms of the blood type B, which was negatively correlated with the lumbar Z score. Choi and coworkers[29] studied the ABO blood types and bone density in 39 recovering male alcohol-dependents, comparing them according to being blood type O or other than O. They observed a significantly higher bone density in blood type O patients compared to other 3 blood types.[29] Kaur[19] evaluated the relationship between the ABO blood groups and the risk of osteoporosis among postmenopausal women of North India and reported that osteoporosis was more prevalent at the lumbar spines (L1 to L4) of people with blood group A (31.6%), followed by those with blood group B (29.7%), AB (28.6%), and then blood group O (15.0%). However, their findings in the case of femoral osteoporosis differed, showing the greatest prevalence of osteoporosis in blood type AB (21.4%) followed by A (17.5%), B (12.1%), and then O blood types (5.0%).[19]

It has been suggested that demographics and body mass index can affect the bone density in a normal population.[17] Nevertheless, this study did not find any significant role for age or sex in the population of kidney transplant patients.

Our results showed that not only the T and Z scores differ considerably, but also their risk factors differ. This was in agreement with recent studies suggesting the fundamental difference between the two scores because of the used formulas and underlying populations.[17,30] It is suggested that T and Z scores are similar in young adults, since the relevant reference populations should be the same.[17,31,32] However, in the case of premenopausal women and men aged between 20 and 50 years, the Z score should not be used instead of T score.[17,31,32] Recently, the Z score has been recommended to be used for diagnosing low bone mass in various age and sex groups, children, men younger than 50 years, and premenopausal women.[17,31] Interpreting the Z scores needs to take into consideration numerous factors such as demographics, ethnic background, bone marrow density, and even the manufacturer of the used dual-energy x-ray absorptiometry device.[17,18,30] Furthermore, the evaluated skeletal site can affect the Z score,[17] which might explain the observed differences between femoral and lumbar Z scores in this study. However, the Z score is not standardized and lacks a unique definition and formula and hence might become unreliable depending on the demographic texture of the evaluated population.[17,30,31]

CONCLUSIONS

Within the limitations of this cross-sectional study, it could be concluded with a 95% degree of confidence that only 29.1% to 48.4% of the femurs might have normal bone density among ESRD patients, while 35.1% to 54.7% of them might be osteopenic and 9.0% to 23.6% of them might be osteoporotic. In the case of the lumbar site, 44.2% to 63.9% might be normal while 24.3% to 44.0% might be osteopenic and 5.8% to 18.7% of lumbar bones might be osteoporotic. Parathyroid hormone was a major factor contributing to bone loss in both skeletal areas. Rh-negativity and B blood type were associated with a higher risk of lumbar osteoporosis, while total protein was negatively associated with the risk of bone loss. The consumption of calcitriol might improve femoral mineral density, but the consumption of calcium carbonate was found to be negatively associated with femoral bone density. Older ages and higher creatinine levels were associated with higher femoral bone densities in kidney transplant patients.

CONFLICT OF INTEREST

None declared.

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