Vitamin D, Parathyroid Hormone, and Bone Mineral Density Status in Kidney Transplant Recipients

Shokoufeh Savaj, Farinaz J Ghods

Firoozgar Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Introduction. Bone disease and bone fractures are common among kidney transplant recipients. The aim of this study was to investigate the prevalence of vitamin D deficiency, hyperparathyroidism, and osteoporosis kidney transplant patients.

Materials and Methods. A total of 113 kidney transplant recipients (58 women and 55 men) were selected consecutively from the transplant clinic between January and April 2010. A serum sample from each patient was analyzed for creatinine, calcium, phosphorus, 25-hydroxyvitamin D, and intact parathyroid hormone levels. Bone mineral density was measured by the dual energy x-ray absorptiometry method and classified according to the classification of the World Health Organization. Risk factors of bone mineral density outcomes were evaluated in univariable and multivariable analyses.

Results. Forty-five percent of the patients had vitamin D deficiency and 76.2% had hyperparathyroidism. There was a significant correlation between vitamin D deficiency and high serum parathyroid hormone (P = .04) and serum creatinine levels (P = .001). However, there were no significant associations of serum calcium and phosphorus with vitamin D or parathyroid hormone levels. The osteoporosis and osteopenia were reported in 12.4% and 52.2% of the recipients in the lumbar spine and 45.1% and 36.3% of the patients in the femoral neck, respectively. Multivariable analyses showed that there were significant correlations between patients' age and body mass index and femoral neck osteoporosis. Risk factors for lumbar spine osteoporosis were end-stage renal disease duration, serum calcium, and body mass index.

Conclusions. Vitamin D deficiency, hyperparathyroidism, and osteoporosis are very common in our kidney transplant recipients. Early diagnosis and treatment of these abnormalities should be included in the posttransplant follow-up of patients in order to prevent severe bone diseases and bone fractures.

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INTRODUCTION

Kidney transplant recipients represent a complex of different bone diseases, which are the causes musculoskeletal complains and bone fractures. They are at risk of vitamin D deficiency due to avoidance of sun exposure and impaired nutritional intake. Immunosuppressive drugs, hyperparathyroidism, chronic illnesses, and end-stage renal disease itself expose them to osteoporosis. Given the improvement in long-term graft survival, attention

to posttransplant bone disease is gaining importance. In this study, we evaluated different aspects on bone diseases, including vitamin D deficiency, hyperparathyroidism, and osteoporosis and its related risk factors in our kidney transplant patients.

MATERIALS AND METHODS

This study was carried out on 113 kidney transplant recipients (58 women and 55 men) with a mean age of 46.1 ± 13.6 years. All of them received a kidney allograft from living donors. They were selected consecutively from transplant clinic between January and April 2010. Patients with a prior history of parathyroidectomy and a posttransplant time less than 1 year were excluded from the study. None of the patients had received any treatment for bone disease after transplantation.

Data for age, sex, body mass index (BMI), time on dialysis, time posttransplant, and immunosuppressive medications were collected from the patients' medical records. A serum sample from each patient was analyzed for creatinine, calcium, phosphorus, 25-hydroxyvitamin D, and intact parathyroid hormone (PTH) levels. Vitamin D and PTH were measured by the Chemiluminescence (Roche, Basel, Switzerland). A 25-hydroxyvitamin D level less than 20 ng/mL was defined as vitamin D deficiency,[1] and a level between 20 ng/mL and 30 ng/mL, as vitamin D insufficiency. Hyperparathyroidism was defined as an intact PTH level greater than 70 pg/mL.[2] Bone mineral density (BMD) was measured by the dual energy x-ray absorptiometry method (Norland Model XR 600, Norland, Wisconsin, USA) and classified according to the World Health Organization classification.[3] Osteopenia was defined as a T score between -1.0 and -2.5 and osteoporosis as a T score less than -2.5.

Data analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 16.1, SPSS Inc, Chicago, Ill, USA). The Student *t* test, 1-way analysis of variance, and Pearson correlation were used for the comparisons of continuous variables and their correlations. The chi-square test was used for comparisons between categorical variables. For significant risk factors of osteoporosis in univariable analysis, multivariable logistic model was built using the stepwise forward elimination of nonsignificant factors. *P* values less than .05 were considered significant.

RESULTS

The time on dialysis was 147.1 ± 92.8 months and the posttransplant time was 106.4 ± 77.0 months. Most of the kidney allograft recipients (91%) were on 3 immunosuppressive medications, including cyclosporine, 3 mg/kg to 5 mg/kg; mycophenolate mefotil; and low-dose prednisolone, 5 mg/d, and 9% of the patients were on a steroid-free regimen.

Vitamin D deficiency was reported in 45% of the recipients and vitamin D insufficiency in 49.5%, while 5.5% had normal levels of 25-hydroxyvitamin D. Hyperparathyroidism was detected in 76.2%, which was accompanied by vitamin D deficiency in 33.6% of the recipients (Figure 1). There were significant correlations between high serum levels of PTH and vitamin D level (mean 25-hydroxyvitamin D level, 25.2 ± 20.0 ng/mL in low-PTH group versus 19.4 ± 8.3 ng/mL in high-PTH group; $P = .04$) and serum creatinine level (r = 0.38, $P = .00l$). However, there were no significant correlations between serum calcium and phosphorus levels and vitamin D or PTH levels.

Osteoporosis and osteopenia were reported in 14 and 59 recipients in the lumbar spine (lumbar BMD, 0.96 ± 0.20 g/cm^2; mean lumbar Z score, -1.05 ± 1.09; and mean lumbar T score, -1.3 ± 1.1) and in 51 and 41 recipients in the femoral neck (femoral BMD, 0.79 ± 0.16 g/cm^2; mean femoral Z score, -0.97 ± 1.2; mean femoral T score, -2.0 ± 1.4; Figure 2), respectively. There was a good correlation between femoral neck BMD and lumbar BMD (r = 0.55, $P < .001$). The number of recipients with femoral neck osteoporosis was significantly higher than the lumbar spine (51 versus 14, $P = .04$).

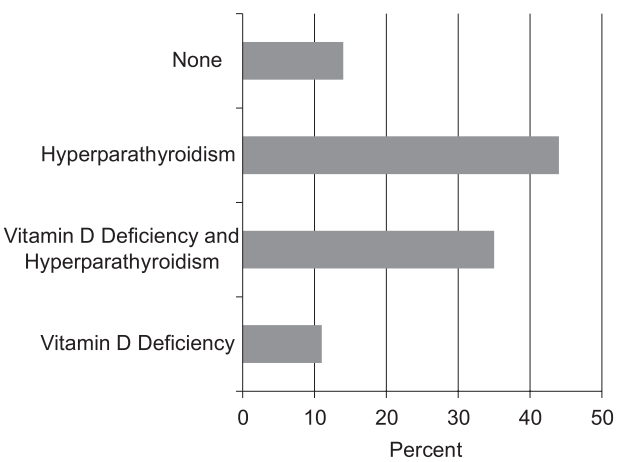

Figure 1. Vitamin D deficiency and hyperparathyroidism.

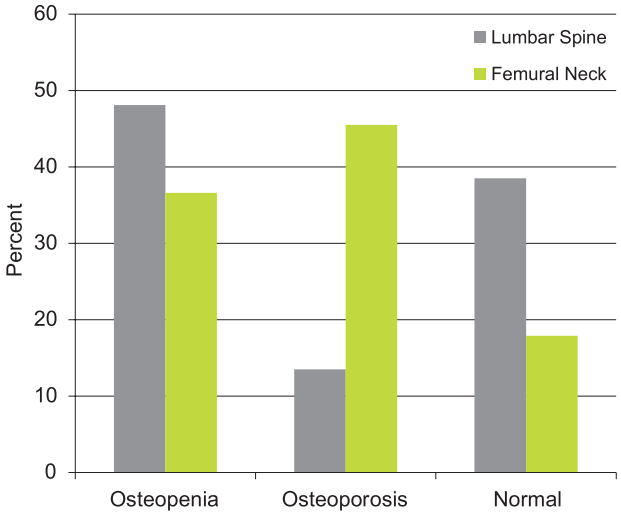

Figure 2. Osteoporosis and osteopenia in the lumbar spine and femoral neck.

In univariable analyses, serum calcium and phosphorus levels, PTH, end-stage renal disease duration, gender, and BMI in were associated with lumbar spine osteoporosis. However, in multivariable analysis, only a lower BMI, longer duration of end-stage renal disease, and lower serum calcium were found to significantly increase the risk of osteoporosis. Risk factors of osteoporosis in for femoral neck osteoporosis in both models were age and lower BMI (Tables 1 and 2).

DISCUSSION

This study in a large group of living-donor kidney transplant recipients showed 45.5% femoral neck and 12.5% lumbar spine osteoporosis. Forty-five percent of patients had vitamin D deficiency and 76.2% had hyperparathyroidism. We had a higher rate of osteoporosis in the femoral neck.

Kidney transplant recipients are involved in complex bone diseases before transplant. In the first 6 to 18 months after transplantation, there is rapid bone loss with the range of 5% to 8% at the hip and 4% to 9 % at the lumbar spine.[4] Fracture prevalence rate varies from 7% to 11% in nondiabetic kidney transplant recipients,[5] and there is 34% greater risk of hip fracture in kidney transplant population in comparison with patients on continued dialysis.[6] Diverse group of risk factors has been reported. Glucocorticoids induce bone loss by suppression of osteoblast-mediated bone formation, inhibition of osteoblast function, osteoclastogenesis, gonadal inhibition, and reduction of intestinal and renal calcium.[7]

Table 2. Logistic Regression Analysis for Significant Risk Factors of Osteoporosis in Multivariable Analysis*

Parameter	Odds Ratio	95% Confidence Interval	*P*
Femoral neck osteoporosis			
Body mass index	0.801	0.731 to 0.871	< .001
Age	1.087	1.067 to 1.107	.001
Lumbar osteoporosis			
Body mass index	0.717	0.578 to 0.856	.02
ESRD duration	1.007	1.003 to 1.011	.05
Serum calcium	1.790	1.78 to 1.8	.01

*R^2 = 0.347 for femoral neck and R^2 = 0.446 for lumbar spine risk factors. Hosmer-Lemeshow test *P* > .05. ESRD indicates end-stage renal disease.

Table 1. Risk Factors for Femoral Neck and Lumbar Spine Osteoporosis in Univariable Analysis

Parameter	Osteoporotic Femoral Neck			Osteoporotic Lumbar Spine		
	Yes (n = 51)	No (n = 61)	*P*	Yes (n = 14)	No (n = 98)	*P*
Age, y	52.9 ± 11.9	41.8 ± 11.9	< .001	47.8 ± 14.0	46.1 ± 13.0	.66
Gender						
Male	25	30		3	52	
Female	26	31	.56	11	46	.04
Body mass index, kg/m^2	24.5 ± 3.6	26.5 ± 4.4	.01	23.0 ± 2.3	26.1 ± 4.3	.01
Serum calcium, mg/dL	9.29 ± 0.48	9.262 ± 0.41	.41	8.87 ± 0.16	9.30 ± 0.45	.002
Serum phosphorus, mg/dL	4.2 ± 0.7	4.1 ± 0.75	.70	4.6 ± 0.5	4.1 ± 0.71	.02
Serum parathyroid hormone, pg/mL	192.8 ± 189.9	154.0 ± 214.1	.30	346.4 ± 379.5	151.6 ± 154.6	.001
Serum 25-hydroxyvitamin D, ng/mL	20.1 ± 8.7	20.9 ± 15.3	.74	22.4 ± 2.3	20.4 ± 13.6	.59
Serum creatinine (mg/dl)	1.34 ± 0.6	1.28 ± 0.39	.56	1.28 ± 0.56	1.32 ± 0.49	.84
Glomerular filtration rate, mL/min/1.73 m2*	61.3 ± 20.7	65.1 ± 16.7	.28	61.9 ± 22.8	63.6 ± 18.1	.76
Transplant duration, mo	111.4 ± 77.6	102.7 ± 77.4	.56	119.5 ± 88.9	105.6 ± 76.3	.52
Dialysis duration, mo	152.0 ± 88.2	141.8 ± 97.4	.56	199.1 ± 101.2	140.6 ± 90.4	.03
Prednisolone administration	45	55	.51	12	88	.66

*Chronic Kidney Disease Equation Epidemiology Collaboration formula[17]

Cyclosporine A increases bone turnover; however, kidney transplant recipients who receive cyclosporine without steroids do not lose bone.[8] There are limited data about other immunosuppressive drugs. Secondary hyperparathyroidism and vitamin D deficiency are associated with bone loss in the general population. Hyperparathyroidism is a well-recognized problem in the end-stage renal disease patients. The intact PTH often decreases after a successful transplantation; however, in cases with severe hyperparathyroidism, it may remain elevated. Time on dialysis, vitamin D level, and recipient's glomerular filtration rate have been introduced as risk factors of posttransplant hyperparathyroidism.[9] In our study, hyperparathyroidism was accompanied by vitamin D deficiency in 33.6%. There was also a significant correlation between hyperparathyroidism and serum creatinine ($P = .02$). Our study showed that 93.6% of recipients had low vitamin D level. In 2004, a survey on 1210 randomly selected subjects in Tehran showed prevalence of severe, moderate, and mild Vitamin D deficiency was 9.5%, 57.6%, and 14.2%, respectively.[10] It shows not only vitamin D deficiency is prevalent in our population but also transplant population have higher prevalence rate. Other studies reported ranges from 51% to 97% vitamin D insufficiency and 26% to 33% of severe vitamin D deficiency in the kidney transplant population. Most of studies could not show any correlation between vitamin D level and osteoporosis same as our study.[11-14]

Since the ethnicity has a direct effect on BMD, we looked if the low BMD in our patient population could be explained by lower bone mass in Iranian population or it is the result patient's comorbid disease. In a multicenter osteoporosis study in Iran, in a randomly chosen sample of 5201 healthy Iranian subjects (2340 men; mean age, 42.7 ± 13.8 years) lumbar and femoral BMD were 1.119 ± 0.171 g/cm^2 and 0.955 ± 0.140 g/cm^2 in the women and 1.181 ± 0.153 g/cm^2 and 1.096 ± 0.159 g/cm^2 the in men, respectively. They showed that Iranian peak bone mass values are comparable with that of Western countries and are generally higher than that of Eastern Asian and Middle Eastern countries.[15] Therefore, bone mass in our kidney transplant population is lower in the ethnic characteristics.

Low BMI is a traditional risk factor for osteoporosis. In our study, it was a risk factor for osteoporosis in both sites of femoral neck and lumbar spine in multivariable analysis. In the study of Gupta and colleagues in 415 kidney transplant recipients, there were independent associations of reduced BMD with gender and low BMI at all sites.[16] In our study, we could not find the prednisolone effect on patients, because majority of them were receiving prednisolone. Low serum calcium and end-stage renal disease duration were risk factors in the lumbar spine osteoporosis. We could not find a gender effect in multivariable analysis; however, we had a significant rate of osteoporosis in female's lumbar spine in univariable analysis. Age was a significant risk factor for femoral neck osteoporosis.

CONCLUSIONS

This study supports that improvement in patient survival demands a consideration on patient's bone disease and risk factors. We conclude that vitamin D deficiency, hyperparathyroidism, and osteoporosis are very common in kidney transplant recipients. Early diagnosis and treatment of these abnormalities should be included in the posttransplant follow-up of patients in order to prevent severe bone loss and bone fractures.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Firouzgar Hospital, Behafarin St, Karim Khan Ave, Valiasr Sq,
Postal code: 1593748711, Tehran, Iran
Tel: +98 21 2290 0008
Fax: +98 21 2227 6951
E-mail: ssavaj@tums.ac.ir

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