Low-dose Pamidronate for Treatment of Early Bone Loss Following Kidney Transplantation

A Randomized Controlled Trial

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Introduction. Kidney transplantation is associated with rapid loss of bone mineral density (BMD) in the first months after transplantation. The effect of pamidronate on bone loss after transplantation was evaluated in a randomized controlled trial.

Materials and Methods. Forty patients were enrolled in this study (16 in the pamidronate group and 24 in the control group). Pamidrinate was administered as 30-mg intravenous infusion within 2 days after transplantation and 3 months later. All of the patients received calcium and vitamin D supplementation. Laboratory parameters and BMD (lumbar spine and femoral neck) were measured at baseline and 6 months after kidney transplantation.

Results. Bone mineral density at the initiation of study had no significant differences between the two groups. In each group, BMD of femoral neck and lumbar spine had no significant differences 6 months after transplantation in comparison to pretransplantation values. There was no significant difference in BMD changes after intervention between two groups. Parathyroid hormone level normalized in both of the pamidronate and control groups 6 months after kidney transplantation. Glomerular filtration rate at the end of study was not significantly different between the two groups.

Conclusions. Our study suggests that administration of calcium and vitamin D following transplantation may be beneficial to counterbalance the substantial bone loss occurring within 6 months after transplantation, and addition of pamidronate has no beneficial effect in BMD in this short interval after kidney transplantation.

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INTRODUCTION

Transplantation may be accompanied by complications. Posttransplant bone loss and fractures are major complications, which may occur after liver, heart, bone marrow, and especially, kidney transplantation.[1] Kidney transplantation has become the treatment of choice of patients with end-stage renal disease.[2] Similar to other types of transplantation, corticosteroid therapy in kidney transplantation is the major cause of osteoporosis.[3] Kidney recipients are even at increased risk of developing osteodystrophy associated bone abnormalities and hyperphosphatemia or vitamin D-induced hyperparathyroidism, which often lead to significant osteopenia and abnormal mineral metabolism.[4] In addition, cyclosporine therapy, immobilization, and hypogonadism are other factors which may contribute to bone loss.[5-8]

High-quality long-term survival following kidney transplantation needs prevention of bone

complications which can result in multiple fractures and serious disabilities.[9] Therefore, it is mandatory to find appropriate treatments which can improve bone condition in these patients. Active metabolites of vitamin D and bisphosphonates have been demonstrated to be effective in prevention of kidney transplantation-associated bone loss.[10,11] Some studies have documented the effectiveness of posttransplant treatment with vitamin D and calcium supplement in prevention of bone loss by facilitating calcium absorption and parathyroid hormone (PTH) suppression.[12-16] Bisphosphonates, like pamidronate, also improve bone density by reducing the number of osteoclasts and inhibiting their activity. They are considered as a safe and promising treatment.[4,17] Oral bisphosphonates may cause some gastrointestinal side effects, but intravenous forms are clinically more tolerable. Despite numerous studies regarding the best treatment options of posttransplant bone loss, controversy persists.[9] This study was performed to determine the effects of pamidronate therapy on kidney transplant recipients' bone mineral density (BMD).

MATERIAL AND METHODS

Participants

This study was approved by the ethics committee of Isfahan University of Medical Sciences (Ethics Committee approval number, 83473) and informed consent was obtained from all participants before enrollment in this trial. Forty patients included in this randomized controlled trial. Patients were included if they were older than 18 years old and had a living donor kidney transplant. Patients who had a history of previous parathyroidectomy, treatment with corticosteroids for more than 3 months before transplantation, or treatment with calcitonin and bisphosphonates were excluded. Posttransplant persistent hypercalcemia and posttransplant hemodynamic instability were considered as exclusion criteria, as well.

Study Design and Interventions

This study was a 6-month randomized clinical trial. Patients were randomly allocated into treatment group or control group. The treatment group received an intravenous infusion of 30 mg of pamidronate disodium (Mayne Pharma, Melbourne, Australia) within 2 days of transplantation and again 3 months after transplantation. Pamidronate was infused in 500 mL of normal saline in 2 hours. Pamidronate was not administered in the control group. All patients received oral calcium carbonate (Tehran Chemie Pharmaceutical Co, Tehran, Iran), 500 mg, and calcitriol (Zahravi Pharmaceutical Co, Tehran, Iran), 0.25 μg/d for 6 months. All of the patients received triple-agent immunosuppression with cyclosporine, mycophenolate mofetil, and corticosteroids. There was no significant difference between groups in cyclosporine levels, total intravenous corticosteroid dose, or cumulative dose of oral corticosteroids during the study period.

Any abnormality in serum level of calcium and phosphate were corrected. Serum parameters including calcium, phosphate, creatinine, and albumin were measured before the intervention and monthly thereafter. Serum PTH and alkaline phosphatase were measured every 3 months. Dual-energy radiographic absorptiometry (Lunar DPX-MD Bone Densitometer) of the lumbar spine (L2 to L4) and neck of the femur was performed before and 6 months after transplantation to evaluate BMD. The primary endpoint was BMD changes in the lumbar vertebrae, femur, or femur neck in 6 months. Fractures were screened clinically at baseline (previous fractures) and during the follow-up period (new fractures).

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 18.0, SPSS Inc, Chicago, Ill, USA). The 1-way analysis of variance, logistic regression, and *t* test were used when appropriate. *P* values less than .05 were considered significant.

RESULTS

Forty patients were enrolled in this study (16 in the pamidronate group and 24 in the control group). All 40 patients were alive throughout the study period. No significant difference was found between the two groups in baseline characteristics (Table 1). One woman (20%) in the pamidronate group and 4 women (100%) in the control group were in their menopausal age. However, it did not have any impact on the results because of small sample size of women in both groups.

The participants were compared at baseline and at the end of the study regarding serum

Table 1. Baseline Characteristics of Patients

Characteristic	Case Group (n = 16)	Control Group (n = 24)	*P*
Mean age, y	43.56 ± 15.76	46.54 ± 16.02	.56
Mean body mass index, kg/m^2	24.49 ± 4.86	22.90 ± 3.63	.31
Sex			
Male	11 (68%)	20 (83%)	
Female	5 (32%)	4 (17%)	.24
Etiology of kidney failure			
Primary kidney diseases*	4 (25%)	16 (66%)	
Hypertension	5 (32%)	3 (12%)	
Diabetes mellitus	2 (12%)	4 (16%)	
Obstructive nephropathy	1 (6%)	0 (0%)	
Unknown	4 (25%)	1 (6%)	.11

*Kidney diseases included different types of primary kidney disorders such as Alport syndrome, polycystic kidney disease, focal segmental glomerulonephritis, crescentic glomerulonephritis, and immunoglobulin A nephropathy.

biochemistry and BMD. At baseline and 6 months after transplantation, there was no significant difference between the two groups in serum levels of alkaline phosphatase, PTH,estimated glomerular filtration rate (based on Modification of Diet in Renal Disease equation), albumin, calcium, phosphate, and BMD (Table 2).

Pre- and postintervention serum alkaline phosphatase levels were higher than normal range in both groups. At the start of the study, PTH level was more than 3 times higher than the normal range; however, 6 months after the transplantation, it decreased to the normal range in both of the pamidronate and control patients. Serum albumin, calcium, and phosphate were within the normal range in both groups before and after the study.

Bone mineral density at the initiation of the study had no significant differences between the two groups. In each group, BMD of the femoral neck and lumbar spine had no significant difference 6 months after transplantation in comparison to pretransplant values. Bone mineral density changes after intervention was compared between two groups and there was no significant difference between the two groups (Table 3).

In a multivariate model, we estimated the odds ratio for positive BMD changes versus no change or negative changes by using the logistic regression analysis with adjustment for potential confounders. Age, sex, BMI, cumulated corticosteroid dose, smoking, glomerular filtration rate at the end of study, baseline PTH and PTH after 6 months were tested and there were no significant association between pamidronate treatment and BMD changes. The relative T score and Z score showed no significant differences either between the femoral neck and the lumbar spine in both groups (P = .63 and P = .39 in the pamidronate group, respectively; P = .56 and P = .20 in the

Table 3. Relative Bone Mineral Density (BMD) Changes in the Study Groups*

Relative BMD Change	Case Group (n = 16)	Control Group (n = 24)	*P*
Femoral neck			
T score	-0.53 ± 0.90	-0.31 ± 3.50	.81
Z score	-0.68 ± 1.31	0.78 ± 3.86	.18
Lumbar spine			
T score	-0.90 ± 3.17	-0.99 ± 3.75	.94
Z score	-1.22 ± 2.10	-0.45 ± 2.32	.32

*All values are presented as mean ± standard deviation.

Table 2. Pre- and Postintervention Measurements*

Parameter	Pre-intervention			Post -intervention		
	Case Group (n = 16)	Control Group (n = 24)	*P*	Case Group (n = 16)	Control Group (n = 24)	*P*
Blood chemistry						
Alkaline phosphatase, IU/L	218.18 ± 61.70	265.33 ± 177.47	.31	190.13 ± 72.45	214.17 ± 91.82	.39
Parathyroid hormone, pg/mL	210.86 ± 187.49	228.96 ± 304.15	.83	44.33 ± 35.3	63.55 ± 40.53	.13
GFR, mL/min	62.60 ± 11.93	52.65 ± 24.78	.10	67.83 ± 14.35	60.57 ± 16.43	.17
Calcium, mg/dl	9.08 ± 0.41	8.83 ± 0.44	.09	9.40 ± 0.65	9.39 ± 1.34	.98
Phosphate, mg/dl	2.94 ± 0.86	3.62 ± 1.79	.16	3.64 ± 0.67	4.15 ± 1.57	.22
Albumin, g/dl	3.66 ± 0.49	3.46 ± 0.46	.19	4.07 ± 0.55	4.23 ± 0.57	.39
Bone densitometry						
Femoral neck T score	-0.72 ± 1.88	-1.01 ± 1.45	.51	-1.61 ± 1.45	-1.40 ± 1.64	.19
Femoral neck Z score	-0.14 ± 1.82	-0.48 ± 1.36	.42	-0.85 ± 1.10	-0.52 ± 1.50	.13
Lumbar spine T score	-0.69 ± 1.29	-0.80 ± 1.29	.49	-1.04 ± 1.68	-1.15 ± 1.52	.64
Lumbar spine Z score	-0.28 ± 1.25	-0.40 ± 1.10	.66	-0.37 ± 1.52	-0.45 ± 1.45	.71

*All values are presented as mean ± standard deviation.

control group, respectively).

There was no history of fracture and no report of fractures during the study, neither in the pamidronate group nor in the control group. No serious adverse effect related to the study medications was reported. Glomerular filtration rate at the end of study was not significantly different between the two groups (Table 2).

DISCUSSION

Previous studies have shown that the bone loss rate after kidney transplantation is exceptionally high.[18] Bone loss is caused by uncoupled bone resorption and formation, and may lead to osteoporotic fractures, which reduce quality of life, increase morbidity and mortality, and impose financial burdens on healthcare system.[19,20] Savaj and Ghods showed vitamin D deficiency (45%) and hyperparathyroidism (76.2%) were very common in Iranian kidney transplant recipients.[21] Studies report high rates of post transplant fracture—about 45%—which is more than the fracture rate in patients on hemodialysis.[21] Given the importance of this problem, many studies have been performed to find out a solution, and different sorts of medications have been studied to achieve an effective method to prevent bone loss in the kidney transplant population.[9,22]

Guidelines for kidney transplantation recommend various treatments including vitamin D and calcium and antiresorptives. Antiresorptive medications, such as bisphosphonates, target several factors contributing to bone loss in kidney transplant patients and are advised for the kidney transplant population who are at increased risk of bone injury.[23,24] In the present study, influences of treatment with calcium and vitamin D were compared with the combination of calcium, vitamin D, and pamidronate to figure out whether pamidronate can provide any additional advantages in prevention of posttransplant bone loss. Although the sample size of the study was small and the follow-up was not long, this study documented significant fall in serum PTH level to the normal range in both groups; however, no significant change was found in calcium level. Several studies consider an important role for calcium and vitamin D therapy in bone loss prevention by improving calcium absorption and PTH suppression.[12-16] Another study on the kidney transplantation population by Torregrosa and coworkers also reported normalization of elevated serum PTH level after treatment with pamidronate.[4] This improvement could be caused by either better metabolic condition after transplantation or treatment with medications. Postintervention PTH levels were not significantly different in the two groups; hence, it implies that although patients' condition has improved, pamidronate may offer no additional benefit to calcium and vitamin D in improvement of metabolic condition of these patients.

Regarding BMD changes, patients had no significant bone loss during the study, but no difference was observed between the two groups, and pamidronate showed no superiority to calcium and vitamin D in prevention of bone loss. In untreated patients, the mean bone mineral density of the lumbar vertebrae decreased by 8.8 ± 7.0% during the 18 months after transplantation, with most of the loss occurring within the first 6 months.[18] In another study on untreated kidney transplant patients, marked and progressive bone loss was found in women at the lumbar spine and significant decrease in BMD was reported in men at femoral neck, 6 months after transplantation.[25] In our study, there was no loss of BMD in the treatment or control group. Both groups in the trial were treated with calcium and vitamin D. It seems that for detecting the effect of bisphosphonates in preventing bone loss, continuing follow-up and measurement of BMD 12 months and later would be needed. It is concluded that in short term (6 months), treatment with calcium and vitamin D has a sufficient effect to prevent early bone loss after kidney transplantation.

Omidvar and colleagues compared oral alendronate, 70 mg/w, with intravenous pamidronate, 90 mg for 3 months, from the 3rd week of transplantation. They followed their patients for 6 months. Pamidronate was comparable to alendronate in prevention of posttransplant early bone loss.[20] In a study by Fan and associates, low-dose pamidronate, 30 mg, preoperatively and 1 month after transplantation prevented early bone loss at 3 months and 1 year after transplantation. Nonetheless, in these two studies, patients had not received calcium and vitamin D after transplantation.[11] In another study by Walsh and colleagues, pamidronate was considered an effective

agent in increasing BMD.[26] Pamidronate dose was higher in their study than ours (1 mg/kg) and was administered in 1, 4, 8 and 12 months after transplant. In this study, BMD changes at 3 and 6 months after transplantation was not significantly different, but after 12 months, BMD changes were significant between the two groups.[4] The dose of pamidronate in our study was lower (30 mg) and the drug was administered 2 days and 3 months after transplantation. Another major difference between our study and Walsh and colleagues' study was the time of BMD measurement after transplantation. In our study BMD was measured 6 months after transplantation.

Similar to Walsh and colleagues' study, Torregrosa and coworkers suggest that adding pamidronate to calcium and vitamin D could be helpful in bone loss prevention. The latter two studies followed patients for a longer period of time (12 months). This longer follow-up may detect further BMD changes, which are not evident in the first 6 months of transplantation and treatment. Therefore, different follow-up durations may be a reason for different results. In addition, as Mitterbauer and coworkers emphasize in their meta-analysis, the optimal duration and dose of pamidronate therapy have yet to be determined.[22]

CONCLUSIONS

Our study suggests that administration of calcium and vitamin D following kidney transplantation may be beneficial to counterbalance the substantial bone loss occurring within 6 months after transplantation, and addition of low-dose pamidronate has no beneficial effect on BMD in this short interval after kidney transplantation.

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CONFLICT OF INTEREST

None declared.

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