

Comparison of Alendronate and Pamidronate on Bone Loss in Kidney Transplant Patients for the First 6 Months of Transplantation

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Introduction. Osteoporosis develops and progresses in a considerable number of kidney transplant patients. Bisphosphonates, which are used for prevention and treatment of osteoporosis, may accentuate gastrointestinal complications and lead to more nonadherence to treatment. This randomized clinical trial was conducted to compare the effect of pamidronate versus alendronate on early bone mineral density changes in kidney transplant patients.

Materials and Methods. Forty patients (27 men and 13 women), aged from 20 to 58 years, with low bone mineral density (T score < -2) in the spine, total hip, or femur neck were enrolled. Participants were randomly allocated into 2 groups to receive pamidronate or alendronate. The pamidronate group received intravenous pamidronate, 90 mg, starting from the 3rd week of transplantation for 3 months. The alendronate group started to receive oral alendronate, 70 mg per week for the same period. At baseline and 6 months, bone mineral density was measured by dual-energy x-ray absorptiometry. Gastrointestinal side effects were monitored every month.

Results. No significant difference was found in bone density changes of the lumbar area between the two groups; however, significantly less reduction in bone mineral density of the femur neck and femur occurred in the pamidronate group. Kidney function and parathyroid hormone levels were similar in the two groups before and after the study. Gastrointestinal side effects were seen in 3 patients of the alendronate group only.

Conclusions. Pamidronate was comparable to alendronate in prevention of early bone loss after kidney transplantation.

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INTRODUCTION

Recently, the number of patients suffering from end-stage renal disease is increasing, and kidney transplantation is an established solution for this.^{1,2} Even though the evolution of immunosuppressive therapy in kidney transplant recipients has led to

improved survival, it is somewhat accompanied by complications.^{3,4} One of the most important complications is drug-induced osteoporosis. Previous studies revealed that 6.8% and 8.8% of bone mineral density (BMD) can be lost by 6 and 18 months, respectively, after a successful kidney

transplantation.¹ Osteoporosis would occur at the lumbar vertebra of 17% to 49% of kidney transplant recipients, at the neck of femur of 11% to 56%, and at the distal portion of the radius of 22% to 52%, resulting in an incidence of bone fracture about 5% to 44%, which is 4-fold greater than that before transplantation.⁵⁻⁷

Osteoporotic fractures reduce quality of life, increase morbidity and mortality, and increase healthcare costs.³ Since patients' follow-up for determining fracture incidence is time consuming, assessment of bone strength could be helpful. For evaluation of bone strength, we need to assess both bone density and bone quality, the latter of which is based on bone architecture (measured by bone biopsy).⁸

Bone loss in patients with drug-induced osteoporosis has been managed in different ways. Bisphosphonates are common drugs in the treatment of osteoporosis.⁹ They decrease bone turnover mainly by inhibiting osteoclast activity and are associated with decreased fracture rates in both vertebra and nonvertebra areas in postmenopausal women.^{10,11} Alendronate is the most common bisphosphonate in the treatment of osteoporosis, especially glucocorticoid-induced bone loss. Most studies showed that alendronate among other bisphosphonates decrease fracture rate in both femur and vertebra, in addition to increasing BMD. One of the common side effects of alendronate is gastrointestinal disturbances.^{12,13}

Since transplant recipients often take a large number of drugs, adding a new medication to their regimen, such as alendronate, may be demoralizing. Pamidronate is a type of bisphosphonate administered intravenously, which is less expensive and has less significant gastrointestinal side effects. Pamidronate has been administered with different protocols in different studies.¹⁴⁻¹⁸ We compared pamidronate with alendronate in kidney transplant patients in terms of preventing bone loss and side effects.

MATERIAL AND METHODS

Participants

Forty patients included in this randomized clinical trial. Kidney transplant patients were included if they were older than 20 years old and had a T score less than -2 in the lumbar spine, femoral neck, or total hip in BMD, which was applied by dual-energy x-ray absorptiometry. Patients who had

a history of hyperthyroidism, hyperparathyroidism, hypocalcemia, hypercalcemia, fracture in the past 2 years, incapability to sit for at least 30 minutes, active gastric ulcer, achalasia, scleroderma, or any abnormalities in the esophagus which would lead to lag in esophageal emptying were excluded out from the study. Furthermore, we excluded patients with increased serum creatinine to levels higher than 3 mg/dL or a creatinine clearance (estimated using the Cockcroft-Gault formula) less than 35 mL/min during the post-transplantation period.

Interventions

Patients were randomly allocated into 2 groups to receive pamidronate or alendronate. The pamidronate group received intravenous pamidronate, 90 mg, (Pamidate, Caspian Tamin, Rasht, Iran) starting from the 3rd week of transplantation for 3 months. The alendronate group started to receive oral alendronate, 70 mg per week (Ostomod, Modava Daru, Tehran, Iran) for the same period. The research team was blind to the allocations, but not the patients. All of the patients were also receiving prednisolone, cyclosporine, mycophenolate mofetil, calcitriol and calcium carbonate after kidney transplantation.

The primary endpoint was BMD changes in the lumbar vertebrae, femur, and/or femur neck in 6 months. The secondary endpoints were changes in glomerular filtration rate and serum calcium level. Bone densitometry was performed 6 months after administration of these drugs by the same technician and instrument (Norland Bone Mineral Densitometer 433A025, Siemens, Munich, Germany). History of fracture and serum levels of creatinine, calcium, alkaline phosphates, parathyroid hormone, and cyclosporine were obtained every month.

Ethics

The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. All of the patients provided written informed consent.

Statistical analyses

Continuous data were expressed as mean \pm standard deviation values. The Fisher exact test, the chi-square test, and the Student *t* test were used to compare variables between groups. A *P* value less than .05 was considered significant.

RESULTS

All of the 40 patients completed this study. Twenty-seven were men and 13 were women, of whom 9 were in postmenopause state (Table 1). None of the patients had a history of alcohol consumption or smoking. The mean bone density and T-score at the lumbar spine, femoral neck, and total hip at baseline did not differ significantly in the pamidronate and alendronate groups. Also serum levels of creatinine, calcium, alkaline phosphates, and parathyroid hormone were comparable between the groups at baseline (Table 1).

The mean daily cumulative dosages of prednisolone, cyclosporine, calcium, and calcitriol were the same among the pamidronate and alendronate groups throughout the study. There was no incidence of fracture during study in neither of the groups. During the study, mean changes of serum creatinine, calcium, alkaline

phosphates, and parathormone levels demonstrated no significant differences between the pamidronate and alendronate groups. Also mean changes of glomerular filtration rate were comparable between the studied groups (Table 1).

At the end of study, the mean percentages of reduction of bone density in the femoral neck were 2.03% and 1.42% in the alendronate and pamidronate groups, respectively ($P = .003$). Also, the mean percentages of reduction of bone density in the femur were 1.42% and 1.40% in the alendronate and pamidronate groups, respectively ($P = .03$). The mean percentages of reduction of bone density in the lumbar vertebrae were not significantly different between the two groups (Table 2).

During the study period, 3 patients in the alendronate group experienced transient dyspepsia, while no adverse effects were reported by the patients in the pamidronate group.

Table 1. Characteristics of Kidney Transplant Recipients on Pamidronate and Alendronate

Parameter	Baseline		After 6 Months		Changes		P
	Pamidronate	Alendronate	Pamidronate	Alendronate	Pamidronate	Alendronate	
Age	38.3 (57 to 20)	37.2 (58 to 20)
Gender							
Male	13	14
Female	7	6
Body mass index, kg/cm ²	24.20 ± 3.40	24.33 ± 4.20	24.71 ± 2.90	24.34 ± 4.10	0.51 ± 1.13	0.01 ± 1.00	.15
Serum creatinine, mg/dL	1.23 ± 0.14	1.17 ± 0.11	1.27 ± 0.14	1.24 ± 0.15	0.04 ± 0.12	0.07 ± 0.14	.49
Serum calcium, mg/dL	8.62 ± 0.51	8.81 ± 0.52	8.96 ± 0.35	8.96 ± 0.50	0.33 ± 0.46	0.15 ± 0.18	.12
Serum alkaline phosphates, mg/dL	200.0 ± 47.6	217.3 ± 63.2	206.1 ± 42.3	208.4 ± 47.9	6.1 ± 33.1	8.9 ± 30.2	.14
Serum parathyroid hormone, ng/L	133.2 ± 59.7	122.3 ± 44.2	122.8 ± 44.4	120.6 ± 34.6	10.3 ± 22.3	1.7 ± 18.0	.18
Glomerular filtration rate, mL/min	77.2 ± 17.6	81.5 ± 14.8	76.6 ± 15.1	78.5 ± 15.8	0.05 ± 9.6	3.07 ± 9.5	.41

*Values are means except for gender distributions, and values in parentheses are ranges. Ellipses indicate not applicable.

Table 2. Comparison of Bone Mineral Density Between Alendronate and Pamidronate Groups*

Parameter	Baseline		After 6 Months		Changes in Bone Density, %		P
	Pamidronate	Alendronate	Pamidronate	Alendronate	Pamidronate	Alendronate	
Lumbar vertebrae							
Bone mineral density, g/cm ²	0.829 ± 0.040	0.816 ± 0.070	0.820 ± 0.040	0.802 ± 0.070	-0.50 ± 0.58	-0.64 ± 0.70	.50
T score	-1.57 ± 0.73	-1.59 ± 0.77	-1.59 ± 0.53	-1.69 ± 0.61
Femur							
Bone mineral density, g/cm ²	0.720 ± 0.070	0.734 ± 0.050	0.716 ± 0.070	0.729 ± 0.060	-1.40 ± 0.61	-1.83 ± 0.55	.03
T score	-2.35 ± 0.46	-2.23 ± 0.56	-2.41 ± 0.51	-2.31 ± 0.52
Femur neck							
Bone mineral density, g/cm ²	0.705 ± 0.070	0.711 ± 0.080	0.699 ± 0.060	0.701 ± 0.070	-1.42 ± 0.71	-2.03 ± 0.48	.003
T score	-2.46 ± 0.57	-2.37 ± 0.65	-2.48 ± 0.61	-2.46 ± 0.35

*Values are mean standard deviation. Ellipses indicate not analyzed.

DISCUSSION

Most studies have revealed that kidney transplantation is associated with rapid bone loss, mainly due to administration of steroid and calcineurine inhibitors. Corticosteroids induce bone loss through suppressive effects on osteoblast activity and enhancing effects on osteoclast activity, lowering of gastrointestinal calcium absorption, increasing renal calcium excretion, and increasing parathyroid hormone secretion, all resulting in decreased bone mass.^{19,20} Cyclosporine and tacrolimus increase bone resorption, which can lead to increased bone loss.²¹ Fractures have been reported in up to 45% of kidney transplant recipients, and they are more common among this population than patients on hemodialysis.⁸ Also, the rate of bone loss decreases with time, but the risk of fractures continues to increase.^{6,8,22}

Different kinds of medications have been used for treatment of osteoporosis in kidney transplant patients.^{9,23} Bisphosphonates have been applied in patients with osteoporosis or those who receive corticosteroid.^{16,24-27} A placebo-controlled, randomized, multicenter trial by Saag and colleagues revealed that alendronate increased bone density in the lumbar spine and the femur neck by $2.9 \pm 0.3\%$ and $1.2 \pm 0.4\%$, respectively, in patients receiving glucocorticoids.²⁸ Nayak and colleagues showed that alendronate attenuated bone loss after kidney transplantation.²⁹ In a placebo-controlled study by Fan and colleagues, kidney transplant patients who received pamidronate did not experience bone loss.¹⁶ Finally, in the study performed by Walsh and coworkers, pamidronate increased lumbar spine and the ward area BMDs by 5.7% and 0.9%, respectively, and attenuated total femur and femur neck BMDs loss in comparison with the control group.¹⁴

Previous studies showed that bisphosphonates were more effective on the lumbar vertebrae in contrast to the femoral neck to ameliorate bone density.^{14,23} Similarly, in our study, the effect of alendronate and pamidronate on the lumbar spine is more desirable compared to the femoral neck and total femur. Also, pamidronate could outreach alendronate in preservation of bone mass in the femoral neck and total femur, but not in the lumbar vertebrae. There was a significant difference between alendronate and pamidronate in preventive effects on early bone loss for total

femur and femur neck area in kidney transplant patients. The percentage of changes in bone density in our study differed from the previous trials, probably due to differences in drug type, dosage, interval of administration, duration of treatment, and patients' race.

Unwanted gastrointestinal complication occurred only in 15% of patients who received alendronate as dyspepsia. Previous studies established that dyspepsia may happen in 2% to 7% of the patients receiving alendronate. The difference may be due to low number of our patients that was not enough to extract a precise adverse effects rate. Both pamidronate and alendronate had no adverse effects on kidney function in the patients.

The present study has some limitations, and the results should be interpreted in the context of its design limitations. We followed the patients only 6 months after transplantation; thus, we do not know whether long-term effects of pamidronate on bone density is better than alendronate and also their consequences on bone fractures really differ or not. A control group was not included in this study because it has been advised to administer bisphosphonates, when BMD T score is equal to or less than -2 at the time of transplant.

CONCLUSIONS

Pamidronate seems to be comparable to alendronate in attenuating early bone loss in kidney transplant patients, and poses no additional risk of side effects.

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CONFLICT OF INTEREST

None declared.

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