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WORD COUNT 3192
TIME SUBMITTED 03-MAY-2024 09:00PM
PAPER ID 108717250

**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 92335

**Manuscript Type:** ORIGINAL ARTICLE

*Retrospective Study*

# Impact of bisphosphonate treatment on bone mineral density after kidney transplant

Bisphoshonate treatment effect in kidney transplant recipients

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**Abstract**

BACKGROUND

Mineral bone disease is associated with chronic kidney disease and persists after kidney transplantation. Immunosuppressive treatment contributes to its pathogenesis. Bisphosphonates have shown positive but not definite results.

AIM

To evaluate the effectiveness and safety of bisphosphonates in post kidney transplantation bone mineral density (BMD).

METHODS

We included kidney transplant recipients (KTRs) with BMD measurement after operation but before the initiation of treatment, and a repeat measurement at least one year later. We also evaluated the BMD in KTRs with two valid measurements after transplantation who received no treatment (control group).

RESULTS

Out of 254 KTRs, 62 (39 men) were included in the study. Bisphosphonates were initiated in 35 (20 men), 1.1±2.4 years after operation and for a period of 3.9±2.3 years while 27 (19 men) received no treatment. BMD improved significantly in those who received bisphosphonates (from -2.29±1.07 to -1.66±1.09, $p<0.0001$). Controls showed a non-significant BMD decline after 4.2±1.4 years of follow-up. Kidney function was not affected by bisphosphonates. In KTRs with established osteoporosis in comparison to those with osteopenia or normal bone mass, active treatment had a similar and significant effect.

CONCLUSION

In this retrospective study of bisphosphonate treatment in KTRs we showed that active treatment is effective in preventing bone loss irrespective of baseline BMD.

**Key Words:** mineral and bone disorders; chronic kidney disease; kidney transplant recipients

Georgopoulou GA, Papasotiriou M, Ntrinias T, Savvidaki E, Goumenos D, Papachristou E. Impact of bisphosphonate treatment on bone mineral density after kidney transplant. *World J Transplant* 2024; In press

**Core Tip:** Mineral bone disease is present in patients with CKD and shows high prevalence after kidney transplantation. In this study, kidney transplant recipients who received antiresorptive treatment with bisphosphonates showed a beneficial effect on bone mineral density irrespective of baseline values. Kidney transplant recipients who received no treatment showed a non-significant bone mineral density decline.

## INTRODUCTION

In conclusion, in this retrospective study of bisphosphonate treatment in KTRs we have shown that active treatment is effective in preventing bone loss in both male and female patients irrespective of baseline BMD.

## MATERIALS AND METHODS

In this retrospective study on the safety and efficacy of bisphosphonate treatment in KTRs we have shown that active treatment has a favorable effect on BMD in patients with established osteoporosis as well as those with mere osteopenia. Moreover, this effect was not associated with sex. Finally, we have shown that controls that received no active treatment had a minor decline in BMD overall, while the osteopenic patients who were not treated experienced a significant deterioration of their BMD.

Studies on the use of bisphosphonate treatment for the prevention of bone disease in KTRs include either parenteral preparations [9, 18] or agents administered orally on an

daily [19] or weekly basis [20]. Although parenteral administration is more copious and may discourage KTRs from persisting on treatment, it is in most cases ideal for compliance supervision. Oral treatment is more convenient for patients, especially in once weekly formulations. Nevertheless, it comes at the cost of compliance issues and a higher rate of common adverse effects, such as inflammation and erosions of the upper gastrointestinal tract. In this study, only weekly or monthly preparations of orally administered bisphosphonates were used. The dosage was 70 mg alendronate sodium (once weekly), 50 mg ibandronic acid (daily) and 75 mg risedronate sodium (for two consecutive days every month). No serious adverse effects were recorded. However, although all patients that received active treatment were asked on proper and steady use of prescribed bisphosphonate, compliance could not be otherwise confirmed.

Concerning the impact of bisphosphonates on vertebral and femoral BMD separately, there are several reports that show a positive effect, though of different magnitude. Vertebral BMD was shown to remain stable in a cohort of KTRs with osteopenia that received pamidronate for 12 months while it was reduced in controls [21]. In a randomized placebo controlled study of intravenous ibandronate, KTRs that received active treatment showed a significant increase in BMD, nevertheless this increase was not significantly different in comparison to controls [9]. In another study comprising of 35 KTRs, those that received alendronate plus elemental calcium 1000 mg daily exhibited an increase of 8.2% in vertebral BMD at 12 months after initiation of treatment [19]. In a meta-analysis of 8 studies that evaluated the impact of bisphosphonates on vertebral BMD, it was shown that treatment significantly increases vertebral BMD by 5.98% (3.77 - 8.18) [3]. As far as BMD of the femoral neck is concerned, certain studies show a significant improvement [19] that it is further enhanced after two years of follow up [22], while others show a marginal positive effect of 0.5% [23]. In a double blind placebo controlled study on the effect of zoledronic acid (4 mg) on hip geometry, active treatment appeared to enhance after six months the subperiosteal diameter, endocortical diameter, and cross-sectional moment of inertia (CSMI) at the narrow neck [24]. Overall, a meta-analysis of 5 studies has shown a significant improvement in femoral

BMD reaching 5.57% at 12 months of treatment [3]. In this study, both vertebral and femoral BMD were significantly improved with a marginally greater increase in femur. Newer therapeutic option consisting of anti-receptor activator of nuclear factor-kappaB ligand antibody (denosumab) have even shown better results in comparison to bisphosphonates in both lumbar spine and femoral BMD [25].

The favorable effect of bisphosphonates on BMD was seen in this study in all patients, irrespective of baseline T score, both in those with established osteoporosis and those with either osteopenia or even near normal BMD. Data from other studies show the same pattern of treatment effect although not thoroughly examined in different subgroups of KTRs according to baseline T score. Nevertheless, mean baseline T score in these studies is mentioned to be even in the near normal threshold over -1 SD value [9], or in the osteopenia region [21]. Active treatment in these groups of patients has shown stabilization of BMD in the short term and marginal improvement at 12 months [9, 21]. Concerning those KTRs in this study who had baseline osteopenia and received no active treatment, they showed a significant deterioration of BMD which is also shown in another study [21], although this finding is not constant as in another group of patients that received placebo, BMD was actually improved [9]. This last finding, although unexpected in some degree, is in line with our finding that KTRs with established osteoporosis did not show BMD aggravation by the absence of treatment. Nevertheless, this finding must be seen with caution as it concerned only five patients.

Concerning the safety and long term impact of bisphosphonate treatment on graft survival most studies have shown a neutral effect [7, 18]. In a study by Grotz *et al*, on the effect of ibandronate on bone loss and kidney function, it was shown that treatment correlated to fewer acute rejection episodes but graft function 12 months after transplantation was comparable to controls [23]. Overall, in a Cochrane database systematic review, it was shown that bisphosphonate treatment has no significant impact on graft survival and function, although most included studies had a short follow up period of 12 months [12]. Nevertheless, bisphosphonates were shown to reduce the risk of graft failure significantly in a nested case-control study that enrolled more

than 3800 KTRs [26]. More importantly, this study exhibited an association between increased cumulative duration of bisphosphonate administration of more than 1 year with a reduced risk of graft failure [26]. Moreover, bisphosphonate use has been associated with less acute graft rejection episodes [12]. In our study, after a mean follow up of almost 4 years, kidney function was similar between controls and those that received active treatment while no acute rejection episodes were recorded in any group.

Subgroup analysis on the effect of bisphosphonate use in KTRs depending on sex has not been thoroughly evaluated. In most studies of kidney transplant recipients, males comprise the majority [7, 9, 18, 19, 21, 23], while there is one study, where female patients predominate [27] and one with equal inclusion of men and women [2]. Moreover, there are no data on the different effect of treatment or placebo on BMD between males and females in randomized or open label trials. As most participants and actively treated KTRs are males, we can assume that favorable effects of bisphosphonates as shown in single studies are mainly affected and attributed to the action of treatment on males. In this study, we have shown that bisphosphonates have a positive effect equally in both sexes. Female KTRs showed a greater increase in BMD than males, while ΔBMD was not significantly different among males and females.

Limitations of our study include its single center and retrospective design. There was no randomization of patients and those that were treated with bisphosphonates had a significantly lower BMD value than controls. Moreover, allocation of treatment was not performed homogeneously at the early post-transplant period when the higher dose of corticosteroids is administered and the highest degree of bone mass loss occurs. Nevertheless, this feature of the study can also be interpreted in the view of favorable effects of bisphosphonates even with later initiation of treatment. Finally, no long term fracture assessment was performed and thus effectiveness of treatment in preventing fractures could not be determined. Studies on the effectiveness and long-term safety of bisphosphonates should be conducted by increasing the number of patients and determining control groups and subgroups.

## RESULTS

Overall, out of 254 KTRs, 62 (39 men) met the aforementioned criteria and were included in the study. From these patients, three had received a kidney transplant from a related living donor and all others from a deceased donor. Treatment with bisphosphonates was prescribed in 35 patietns (20 men, mean age 55.2±11 years) and 27 patients (19 men, mean age 53.4±15 years) received no such treatment. Other baseline clinical and biochemical characteristics of ~~both groups~~ patients are presented in **Table 1**. Baseline kidney function (eGFR), BMI and other clinical characteristics between the two groups showed no differences, with the exception of BMD, which was significantly lower in the treatment cohort. Initiation of treatment was 1.1±2.4 years after surgery, exept for 9 patients that received bisphosphonates in the early post-transplant period (one month after operation). Treatment was overall administered for 3.9±2.3 years.

### Bisphosphonate use

All patients received bisphosphonate oral formulations. The agents used were: alendronate sodium ($n$ = 20, 57%), risedronate sodium ($n$ = 10, 29%) and ibandronic acid ($n$ = 5, 14%). Treatment was prescribed in patients with osteopenia or established osteoporosis except for two patients that received treatment without a pathological BMD measurement.

### Impact of bisphosphonates on BMD and safety

Overall, patients that received bisphosphonates showed a significant improvement in BMD (BMD from -2.29±1.07 to -1.66±1.09, p<0.0001). The control group showed a non-significant BMD decline (BMD from -1.43±1.1 to -1.68±0.8, $P$ = 0.17) after 4.2±1.4 years of follow up (**Figure 1**). Delta BMD was also higher in treated patients (treated, 0.63±0.64 vs. -0.26±0.96 in controls, p<0.0001).

When we examined the impact of bisphosphonates on vertebral ($n$ = 13) and femoral ($n$ = 22) BMD separately, we found that vertebral BMD increased significantly from a T

score of -2.01±1.39 to -1.55±1.44 SD (ΔT score=0.46±0.5) ($P$ = 0.006) and femoral BMD from a T score of -2.46±0.82 to -1.73±0.85 SD (ΔT score=0.73±0.69) (p<0.0001) (**Figure 2**). Kidney function was not affected by bisphosphonate treatment (baseline eGFR vs. end of follow up eGFR, 61.9±15.8 vs. 62.4±16.6 mL/min/1.73 m$^2$, $P$ = 0.76, respectively) and remained unchanged in those that received no treatment as well (baseline eGFR vs. end of follow up eGFR, 59.9±14.9 vs. 59.7±17 mL/min/1.73 m$^2$, $P$ = 0.89, respectively). Moreover, tacrolimus or cyclosporine through levels were not significantly affected after the initiation of treatment and no patient stopped active treatment.

**Effect of treatment in patients with and without established osteoporosis**

When we examined the impact of bisphosphonates on BMD in patients with established osteoporosis (BMD T score < -2.5 SD) in comparison to those with osteopenia or normal bone mass, we found that active treatment had a similar and significant effect in both groups.

In controls, we noticed a significant effect of the absence of treatment mostly in those with osteopenia (BMD T score < -1 and > -2.5), as their BMD dropped significantly during follow up. In the osteoporotic patients of the control group, BMD was not affected significantly by the absence of treatment, nevertheless this group consisted only of five KTRs (**Table 2**).

**Impact of bisphosphonates according to sex**

When we examined the impact of bisphosphonates on BMD in male and female patients separately, we found that active treatment improved the T score in both sexes (**Figure 3**). This improvement was also similar as shown with Δt score (0.38±0.72 for males *vs* 0.77±0.62 for females, $P$ = 0.14). Subgroup analysis of controls according to sex, showed that T score deteriorated insignificantly during follow up in men and women equally (**Table 3**).

## DISCUSSION

**Study population**

In total, 254 successful KTRs with a functioning graft one month after surgery were performed between 1997 and 2018 at the University Hospital of Patras. In this study we examined the recipients retrospectively, in order to evaluate the impact of bisphosphonate treatment on BMD. Inclusion criteria included: age of more than 18 years at the time of surgery, availability of a BMD measurement after surgery and before the initiation of bisphosphonate treatment and of at least one BMD measurement one year or more after the initiation of treatment. Bone mineral density measurements were carried out either by hip or spine dual energy X-ray (DEXA). All available repeat measurements were performed at the same location as the original examination. All patients were prescribed supplemental calcium and vitamin D or vitamin D analogs unless contraindicated, as in those with corrected serum calcium of more than 10 mg/dL. As control group we used KTRs who had two valid BMD measurements after transplant but received no antiresorptive treatment. Bone mineral density was evaluated using the average T score at the examined site of interest. Kidney function was evaluated with eGFR using the CKD-EPI formula at the initiation of treatment and at the point of the repeat BMD measurement. Other collected data included time from surgery to the initiation of treatment, treatment duration, body mass index (BMI) and serum iPTH.

All KTRs received an IL-2 receptor blocker (basiliximab) and 500 mg of methylprednisolone intravenously, as part of immunosuppression induction treatment. Corticosteroids were gradually reduced to an oral dose of 16 mg on day 30. Standard treatment also included a calcineurin inhibitor (cyclosporine or tacrolimus) and mycophenolate mofetil (1.5-2 g/day).

Diagnostic thresholds for BMD measurements were as follows: normal, with a T score ≥-1 SD, osteopenia (low bone mass), with a T score < -1 and > -2.5 SD and osteoporosis, with a T score less than or equal to -2.5 SD [17].

The study was approved by the hospital's Ethics Committee (No. 181/14.03.2024) as a retrospective cohort study and is in accordance with the 1975 Helsinki declaration. A

written informed consent was waived due to the retrospective nature of the study which is based on already gathered historical data.

**Statistical analysis**

Continuous and qualitative variables are presented as means with standard deviations (SD) or with percentages and frequencies respectively. Normal distribution of continuous variables was examined with the Kolmogorov – Smirnov test. Differences of means between baseline and final biochemical or clinical indices of KTRs that received bisphosphonates or no treatment was examined with simple t-test (normally distributed data) or the Mann-Whitney test (skewed data). Paired t-test or Wilcoxon test (for normally distributed continuous data and skewed continuous data respectively) were used to investigate the differences among the means of baseline and repeated BMD measurements in actively treated KTRs and controls.

All tests were 2-tailed and statistical significance was set for p-values <0.05. ~~All~~ For statistical analyses we used SPSS for Windows (version 16.0 SPSS Inc. Chicago II, USA) and GraphPad Prism (version 8.0.2 for Windows, GraphPad Software, San Diego California, USA).

## CONCLUSION

Mineral bone disease is common among patients with chronic kidney disease and especially in those with end-stage kidney disease (ESKD) which often persists after kidney transplantation. Following kidney transplantation, despite improvement of kidney function, calcium and phosphate turnover and vitamin D metabolism, osteopenia or osteoporosis continue to be highly prevalent. It is estimated that the prevalence of mineral bone disease in kidney transplant recipients (KTRs) can reach up to 60% and about 0.5% have a hip fracture within the first year after operation [1,2].

The pathogenesis of bone disease after transplantation is based on several factors that include pre-procedural bone abnormalities caused by ESKD, comprising of high or low bone turnover disease or a combination of both, and in most instances it is associated

with low bone mineral density (BMD) [3,4]. Moreover, immunosuppressive drugs such as corticosteroids, reduce bone mass by inhibiting osteoblasts and stimulating osteoclast activity or by decreasing gastrointestinal calcium absorption and increasing renal calcium excretion [4]. Finally, calcineurin inhibitors (tacrolimus and cyclosporine) are a cause of bone loss as well [5]. Most of the bone loss occurs within the first 6 months after kidney transplant, mostly in trabecular bone [6] and it stabilizes or even tends to recover after 12 months [7]. This loss can reach as much as 10% during the first year after operation as shown in older cohorts [8] while bone loss is reported to be in the range of 0.1–5.7% in the lumbar spine in more recent publications of prospective trials [9]. The abovementioned data show a great difference in fracture risk rates among the years. The latter is due to several factors such as less comorbidities in KTRs, the lower preference in corticosteroids treatment, the limited follow-up time and the variety in fracture locations [10]. Independently of the degree of bone loss, KTRs show an increased risk for fractures [11]. In a cohort study from Canada, the hip fracture 10-year cumulative incidence in-KTRs was 1.7%. Moreover, KTRs had a higher 3-year cumulative incidence of non-vertebral fracture compared to the general population with no previous non-vertebral fracture [10].

Several treatment options have been tried in KTRs for the reduction of bone loss which have been thoroughly reviewed elsewhere [12]. Bisphosphonates, administered either orally or i.v., vitamin D analogues and calcitonin seem to be of benefit on BMD at the lumbar spine while bisphosphonates and vitamin D analogues can increase BMD at the femoral neck [13]. Previous guidelines recommend that treatment with bisphosphonates can be effective in postmenopausal women with osteoporosis and in glucocorticoid-induced osteoporosis [14, 15]. Nevertheless, the overall net benefit of such a therapeutic approach with bisphosphonates is still not clear in KTRs while in recent meta-analysis did not show to reduce risk for fracture [16].

Thus, the aim of this retrospective study was to evaluate the effectiveness of bisphosphonates treatment in preventing post kidney transplantation BMD loss as well as its safety.

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