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Original article

# Use of pamidronate for osteoporosis treatment in public health care in Brazil

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ABSTRACT

*Purpose:* The use of bisphosphonates for osteoporosis is effective in reducing the risk of fractures. However, oral formulations are sometimes not well tolerated or are contraindicated. Due to its availability in Brazilian public health system, pamidronate is frequently prescribed for osteoporosis, despite the lack of studies demonstrating its anti-fracture efficacy and the absence of FDA or EMEA approval for this purpose. The aim of this study was to evaluate the bone mineral density (BMD) response to pamidronate in a group of women with osteoporosis in a tertiary care hospital.

*Patients and methods:* The medical records of women with osteoporosis who received pamidronate for up to two years of treatment were reviewed. Patients were stratified at high or intermediate risk of fracture.

*Results:* A total of 70 women were in treatment with pamidronate. Among them, 74% were at high risk of fracture. A significant gain in spine BMD after 24 months of treatment was observed ($p = 0.012$). There was no difference between the groups of high and not high risk of fracture. At the femur, no significant increase in BMD was present, though, a strong negative correlation with high PTH levels ($r = -0.61$; $p = 0.003$) was seen. In the multivariate analysis BMI at 12 months had impact in the response to the treatment.

*Conclusion:* The intravenous pamidronate in a group of postmenopausal women with predominant high risk of fracture promoted an isolated gain in the spine BMD, even though, clinical randomized trials are needed to confirm its anti-fracture efficacy.



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## Uso de pamidronato para o tratamento da osteoporose no sistema público de saúde no Brasil

*Palavras-chave:*
Pamidronato
Densidade mineral óssea
Osteoporose

RESUMO

*Justificativa:* O uso de bisfosfonatos para a osteoporose é eficaz na redução do risco de fraturas. No entanto, as formulações orais às vezes não são bem toleradas ou são contraindicadas. Em razão da sua disponibilidade no sistema público de saúde brasileiro, o pamidronato é frequentemente prescrito para a osteoporose, apesar da falta de estudos que demonstrem a sua eficácia antifratura e da ausência de aprovação da *Food and Drug Administration* (FDA) ou da *European Medicine Agency* (Emea) para essa finalidade. O objetivo deste estudo foi avaliar a resposta da densidade mineral óssea (DMO) ao pamidronato em um grupo de mulheres com osteoporose em um hospital terciário.

*Pacientes e métodos:* Revisaram-se os prontuários médicos de mulheres com osteoporose que receberam pamidronato por até dois anos de tratamento. As pacientes foram estratificadas em risco alto ou intermediário de fratura.

*Resultados:* Estavam em tratamento com pamidronato 70 mulheres. Entre elas, 74% tinham alto risco de fratura. Observou-se um ganho significativo na DMO da coluna vertebral após 24 meses de tratamento (p = 0,012). Não houve diferença entre os grupos de risco de fratura alto e não alto. No fêmur, não foi encontrado aumento significativo na massa óssea; contudo, observou-se uma forte correlação negativa com altos níveis de PTH (r = -0,61; p = 0,003). Na análise multivariada, o IMC aos 12 meses teve impacto na resposta ao tratamento.

*Conclusão:* O pamidronato intravenoso em um grupo de mulheres na pós-menopausa predominantemente com alto risco de fratura promoveu um ganho isolado na DMO da coluna vertebral, embora sejam necessários ensaios clínicos randomizados para confirmar sua eficácia antifratura.



## Introduction

Bisphosphonates represent the major drugs in the therapeutic arsenal of osteoporosis. They are powerful anti-resorptive agents, deposited in mineral bone, and their diversity in action and anti-fracture efficacy may be clinically warranted depending on the strength of connection and detachment to the bone tissue.[1] Among the four bisphosphonates approved for osteoporosis treatment, based on double-blind randomized controlled trials, zoledronate has the greatest affinity for bone, followed respectively by alendronate, ibandronate, and risedronate.[2]

Pamidronate is a nitrogen-containing bisphosphonate with an intermediary potency to inhibit bone reabsorption, and it was initially indicated for preventing bone metastasis growth in different types of cancer.[1,3] The efficacy of pamidronate has been demonstrated in the treatment of lytic bone metastasis; to control hypercalcemia of malignancy in multiple myeloma; in the prevention of osteoporosis induced by glucocorticoids or secondary to chemotherapy or immunosuppressive drugs after solid organ and stem cell transplantation.[4–13]

The pamidronate has been extensibly used since 1991 and became standardized by the public health agency for osteoporosis treatment. It started to be widely used due to its availability in the public health care system and the lack of other formally approved parenteral anti-resorptive drugs for osteoporosis treatment at that time. It is important to note that this is the only non-oral medication for osteoporosis treatment available in our public health care system. However, pamidronate has never been approved for osteoporosis treatment and, despite its frequent use in daily practice for many patients with intolerance to oral bisphosphonates, prospective studies are lacking in evidence to support pamidronate's anti-fracture efficacy.

## Objectives

### *Primary*

The aim of this study is to evaluate the therapeutic response to pamidronate in the BMD gain of spine and total femur, in a group of postmenopausal women with osteoporosis, followed in an osteoporosis outpatient clinic for a treatment period of up to 36 months.

### *Secondary*

To evaluate the influence of clinical aspects such as age, fracture risk, and dose of pamidronate administered per year on the response to the treatment.

## Methods

### *Study design and patients*

In 2006, due to the availability of intravenous pamidronate in the Hospital de Clinicas da UFPR, the Bone Metabolism Unit started its application in patients with osteoporosis.

A retrospective study was conducted with patients on treatment for osteoporosis with intravenous pamidronate. The study was approved by the Ethics Committee on Human Research of the HC–UFPR.

### Patients

All patients treated with pamidronate from October 2006 to October 2010 were initially included. The vast majority of patients had been diagnosed with postmenopausal osteoporosis, followed by glucocorticoid-induced osteoporosis. Patients with secondary osteoporosis due to malabsorptive syndromes, gastrointestinal surgery, prolonged immobilization, and intolerance to oral bisphosphonates were also included. The exclusion criteria were males and patients with any disease that could interfere with bone or calcium or vitamin D metabolism, as well as those with malignancies.

In Brazil, any algorithm is available to classify osteoporosis patients by the severity of risk factors for fracture. Patients were classified as having high and intermediate fracture risk based on known clinical data, to date, the value of BMD T score, own or family history of a past fragility fracture, and risk factors for osteoporosis such as menopause or premature ovarian failure, smoking, rheumatoid arthritis, chronic use of glucocorticoids or immunosuppressive drugs, low weight, malabsorptive syndromes, prolonged immobilization, and family history of osteoporosis.[14]

Considering that Frax algorithm is not recommended for patients previously treated,[15] we characterized patients taking into account traditional risk factors. High risk patients were: older than 75 years; own or family history of vertebral or femoral fracture; older than 65 years with three or more risk factors for osteoporosis or with a *T* score <−3.0 SD.

In the intermediate risk group were those patients younger than 75 years with two risk factors and no major osteoporotic fracture, or with a *T* score <−3.0 SD and less than two risk factors; those younger than 65 years without risk factors with oral intolerance to bisphosphonates, whereas the *T* score was >−3.0 SD or with osteopenia and one risk factor.

### Protocol

As a retrospective study, the authors did not interfere with the decision to use the medication and were not responsible for the care of patients. Patients received intravenous pamidronate infusion, at a total dose of 90 mg diluted in 500 ml of saline or 5% dextrose solution, for a period of four hours, every six months, according to the routine protocol of the Bone Metabolism Unit. All patients were vitamin D3 sufficient at the time of the first infusion and were supplemented with vitamin D and with calcium if their intake was below the daily needs.

### BMD assessment

BMD at the lumbar spine (L1–L4) and total femur was measured at 0, 12, 24, and 36 months of treatment by DXA, GE Lunar Prodigy Advance PA +302284 (GE Medical Systems, Madison, WI) with a coefficient of variability of 0.010 g/cm$^2$ for lumbar spine and 0.012 g/cm$^2$ for proximal femur and by Hologic QDR – 1000W (Hologic, Inc., Waltham, MA), with a coefficient of variability of 0.046 g/cm$^2$ for lumbar spine and 0.052 g/cm$^2$ for proximal femur. The evaluation of each patient was performed, considering only the results of the same equipment.

### Medical records evaluation

The medical records were reviewed in search of information regarding gender; own or family history of a past fragility fracture and risk factors for osteoporosis, such as menopause or premature ovarian failure, smoking, rheumatoid arthritis, chronic use of glucocorticoids or immunosuppressive drugs, low weight, malabsorptive syndromes, or prolonged immobilization. The results of creatinine (Picrato Alcaline method, reference 0.57–1.11 mg/dL), parathyroid hormone – PTH (Quimioluminescence method, reference 12–68 pg/ml) and calcium (Arsenazzo III method, reference 8.5–10.5 mg/dL), both using ARCHITECT ci8200®, Abbott; 25(OH) vitamin D3 (Quimioluminescence method – LIAISON®, DiaSorin, reference 30–100 ng/mL) of the first time of infusion and of the subsequent visits, when available, were captured.

### Statistical analysis

A descriptive analysis was performed and the results were described as mean, median, minimum, maximum values, and standard deviations. Student's *t test* was used to evaluate the gain in BMD between two particular moments for paired samples. To compare the two different groups (high and intermediate) between two particular time points, the Student's *t* test was performed for independent samples.

In order to quantify the association between two variables–gain in BMD between two particular moments and the determinant conditions of this variation, we estimated the *Pearson* correlation coefficient, having investigated the following variables: total pamidronate dose per year, age, BMI, and PTH. The Fisher exact test assessed the association between two dichotomous qualitative variables.

To predict the value of multiple variables to the response in BMD gain, an analysis of Multiple Linear Regression was done. We applied the logistic regression model to assess the association between the explanatory variables and likelihood of treatment response (characterized as gain or stability of BMD at the time). The Wald test was used to evaluate the hypothesis of interest on the explanatory variables. The results were expressed as mean or median for parametric or nonparametric data respectively and $p\ value < 0.05$ was considered statistically significant. Data were analyzed with the Statistica v.8.0 software.

## Results

Of the initial 127 patients, 39 were excluded, 14 men and 25 female patients with the following diagnosis: primary hyperparathyroidism, hyperthyroidism, tumor-induced osteomalacia, hypophosphatemic rickets, osteogenesis imperfecta, fibrous bone dysplasia, and malignancies. Four patients died of other causes during treatment and two had pamidronate

intolerance; the data of these six patients were not included in the analysis. The total number of patients who showed no exclusion criteria and who completed the study was 74. Of this total, 49 patients had BMD evaluation in the first year of treatment, 21 in the second year, and only 18 in the third year of treatment. The data of 70 patients who had BMD in the first two years of treatment were analyzed.

During the treatment, a significant loss of tracking of the patients as well as a greater interval between the doses of medication was observed. The mean dose decreased from 213 mg per year in the first 12 months to 167 mg per year over the next 24 months and to 150 mg per year after 36 months of follow-up.

### *Clinical, laboratory, and demographic data*

A total of 70 women with a mean age of 68 years old, most of whom (93%) were Caucasian and 49 (70%) at high risk of fracture, were evaluated. The mean BMI was 25.9 kg/m$^2$, the mean serum PTH was 50.78 (18–102) pg/mL, and the serum calcium was 9.4 (8.4–10.4) mg/dL, within the normal range. Among the group with high risk of fracture, 40 (80%) had a fracture in the past, while in the intermediate risk group only 6 (30%) had a past history of fracture. There were two femoral fractures during the treatment, considered a treatment failure, and pamidronate was substituted by teriparatide at the 12- and 24-month time period, respectively. The clinical characteristics are summarized in Table 1. Renal function, assessed by Glomerular Filtration Rate (MDRD study equation) between the periods of pamidronate application were normal. Due to logistic reasons, renal function was not assessed routinely immediately after infusion of pamidronate, but before the next infusion.

**Table 1 – Demographic and clinical characteristics of patients.**

| | |
|---|---|
| Total number | 70 |
| *Age (years) Mean* | 68.9 (50–89) |
| *BMI (kg/m$^2$) Mean* | 25.9 (15–42) |
| *Ethnicity* | |
| White | 65 (92.85%) |
| Black | 1 (1.40%) |
| Mulatto | 4 (5.75%) |
| *Risk* | |
| High | 49 (70%) |
| Non-high | 21 (30%) |
| *Fracture* | |
| Vertebral | 13 (18.57%) |
| Femur | 12 (17.14%) |
| Non-vertebral | 21 (30%) |
| *PTH Mean* | 50.78 (18–102) |
| *Calcium (mg/dL) Mean* | 9.42 (8.4–10.4) |
| *GRF Mean* | 77.82 (35.1–168.8) |
| *25OH D Mean* | 33.88 (12.8–76.8) |

Calcium, (reference 8.5–10.5); PTH, Parathyroid hormone pg/mL (reference 12–68); GRF, Glomerular Filtration Rate mg/dL (MDRD study equation); 25OHD, 25(OH) Vitamin D3 (reference 30–100 ng/mL); BMI, body mass index.

### *Evaluation of the effect of the treatment on BMD increment*

The analysis of BMD at the spine at 0, 12, and 24 months, by Student's *t* test, showed a significant gain: an average of 0.024 g/cm$^2$ ($p = 0.012$) after 24 months of treatment and a tendency ($p = 0.051$) in the first 12 months. No significant change in BMD at the femur was observed at the different time points (Fig. 1).

### *The influence of age, PTH, fracture risk, and annual dose of pamidronate on the BMD change*

In the spine, the linear association analysis did not show any correlation between the BMD gain with age, PTH, past use of bisphosphonates and the subgroups of fracture risk in any time point of evaluation, however, the BMI had a weak positive association with the BMD gain at 12 months ($p = 0.046$ and $r = 0.29$).

The BMD gain in femur showed a negative association with PTH values at 24 months ($p = 0.003$ and $r = -0.61$) (Fig. 2) and with BMI at 36 months ($p = 0.002$ and $r = -0.78$).

The multivariate analysis of the BMD gain in spine and femur in each time point, as a dependent variable, and age, PTH, fracture risk, and the annual dose of pamidronate (considering the reduction of the dose per year according to the time of treatment) as independent variables, revealed that there was no evidence of association between the explanatory variables and the BMD gain in spine or femur in the first 12 months of treatment. Nevertheless, at 24 months, a negative association was found between the gain in femoral BMD and the three variables: age, dose of pamidronate and PTH ($p = 0.002$). When controlling either for PTH and dose of pamidronate or for age and PTH, no significance was found ($p = 0.220$ and $p = 0.788$, respectively). However, controlling for age and dose of pamidronate, a negative correlation was observed between the PTH levels and femoral BMD changes ($p = 0.005$). Thus, it was estimated that for every increase of 1 pg/ml in PTH levels, there was a decrease of 0.0015 g/cm$^2$ in

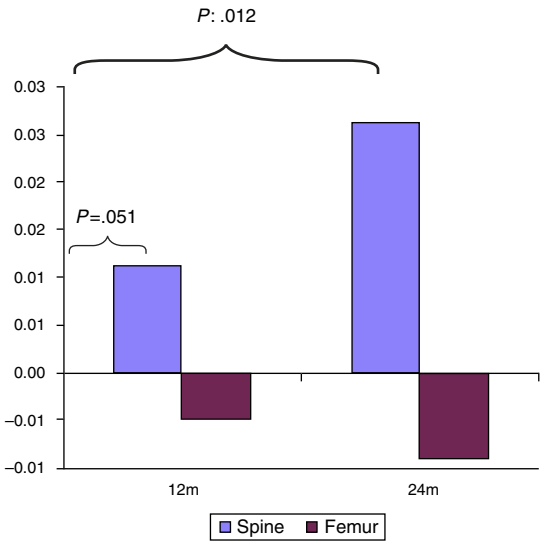


**Fig. 1 – Change in BMD (mean g/cm$^2$) at spine and total femur in time.**

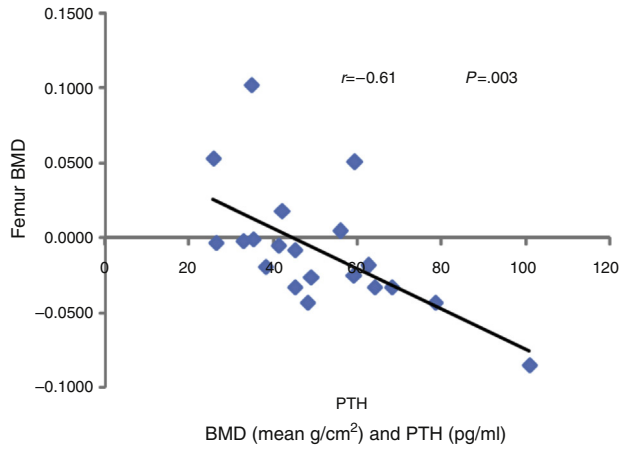


**Fig. 2 – Correlation of the change in PTH levels and femur BMD after 24 months of treatment by Pearson correlation coefficient.**

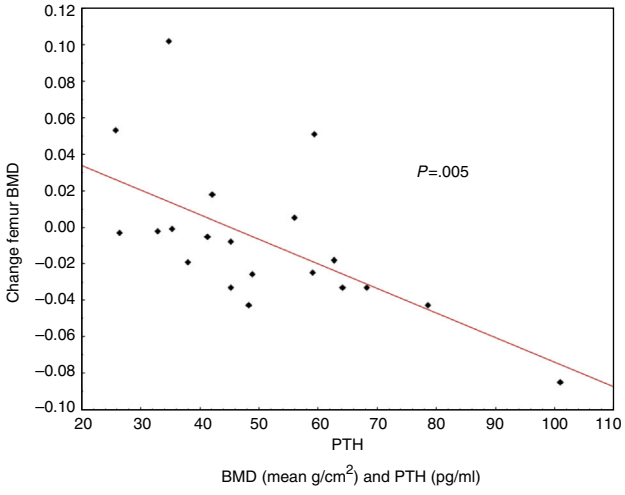


**Fig. 3 – PTH levels and femur BMD change after 24 months of treatment by Multiple Linear Regression (Controlled for age and dose of pamidronate).**

the BMD of femur; 33.1% of the femoral BMD gain at 24 months were explained by age, PTH and dose of pamidronate (Fig. 3).

The multivariable analysis of the positive treatment response (defined as gain or stability of BMD in time), controlled for age, PTH, fracture risk, BMI and dose of pamidronate, demonstrated an association of BMI with a positive response in femur ($p = 0.043$). It was estimated that for each increase in one unit of BMI (kg/m$^2$) the patient was 1.25 times more likely to respond to treatment – OR:1.25 (1.0–1.55) (Table 2). In the spine BMD, controlling for the same variables, only a trend of association was observed between the positive response to treatment and the highest administered dose of pamidronate per year ($p = 0.052$).

**Table 2 – Multivariable analysis of treatment response in femur controlled for the main variables at 12 months.**

| Variable | *p* Value | Odds ratio | 95% C.I. |
|---|---|---|---|
| Age | 0.36 | 1.05 | 0.94–1.17 |
| PTH | 0.625 | 1.01 | 0.97–1.05 |
| Risk estratification | 0.065 | 0.15 | 0.02–1.20 |
| BMI (kg/m$^2$) | 0.043 | 1.25 | 1.00–1.55 |
| Pamidronate dose (mg/12 months) | 0.279 | 1.01 | 0.99–1.02 |

Pamidronate dose was considered the reduction of the dose per year according to the time of treatment.
CI, confidence interval; Treatment response, BMD gain/stability versus BMD loss; BMI, body mass index.

## Discussion

This retrospective study evaluating the BMD response to intravenous pamidronate in a group of postmenopausal women showed an increase in spine BMD only after 24 months of treatment, unlike other studies showing a positive response after 12 months of treatment.[16–19] In addition, there was no change in femoral BMD, explained by the heterogeneity of etiology of the osteoporosis in this group, short (24 months) follow-up, and lower BMD speed gain at this site, which could not be considered a treatment failure.[20–22] But we must emphasize that when we stratified the women according to two subgroups of treatment response (responders and non-responders), the main determinant for the femoral BMD gain was the BMI.

Despite the lack of studies demonstrating the efficacy of pamidronate in reducing the risk of vertebral or non-vertebral fractures, this medication has been long used for the treatment of diseases with increased bone turnover.[5–13]

Regardless the exclusion of patients with the diagnosis of primary hyperparathyroidism, the previous treatment of vitamin D deficiency before pamidronate infusion and the recommended supplementation of cholecalciferol and calcium according to the local protocol, we still observed an elevated PTH level in a subgroup of patients. Vitamin D deficiency during the two years of treatment could not be excluded. This reality reflects the majority of patients treated in our institution, with low socioeconomic status, low capacity to understand the treatment, and low attendance at medical visits. Other possibilities are the low compliance of vitamin D use, not available for free in a healthy public system, or the use of pharmaceutical formulations without reliable quality.

As shown in this study, by statistical models of univariate and multivariate analysis, PTH levels were correlated with lower gain in femoral BMD, rich in cortical bone, an observation already seen in either primary or secondary hyperparathyroidism.[23–26]

The time of treatment expected for maximum anti-fracture efficacy and BMD gain is well established for alendronate, but little is known about pamidronate.[20–22] In this study we observed a benefit in spine BMD after 24 months. Unfortunately, this study did not allow an analysis of the fracture risk reduction.

We observed great difficulty in maintaining the proposed therapeutic regimen, demonstrated by the tendency to reduce the pamidronate dose per year, even though an alternative scheme of treatment was used (90 mg pamidronate every six months). This irregular use of pamidronate (in time and dosage) can interfere with the observed results. This circumstances must be taken into account when treating the public

health system patients. The demonstrated effectiveness of the medications by studies under optimal conditions, does not translate to the real life of our patients. The long-term difficulty in maintaining treatment, as well as the required treatment adherence, could impair the results of this therapeutic regimen.

Numerous limitations were observed, since this was a real life, cross-sectional study and not a double-blind randomized controlled trial. The group that received pamidronate was not homogeneous, had a high risk of fracture, lost infusions, and possibly had a concomitant vitamin D deficiency. However, the importance of this study was not lost, because it reflects the reality seen in patients with poor socioeconomic status and low attendance at medical visits. Rather, it exposes a critical view that under these treatment conditions (either the patient or the infrastructure available) we will not get a favorable result as presented in other studies.[16–19] Moreover, as the pamidronate is not yet an approved medication for osteoporosis treatment and has great adherence concerns, our health care system should review its standardization for this purpose.

## Conclusion

Our study demonstrated that the use of intravenous pamidronate increased spine BMD after 24 months of treatment. No response was observed in femoral BMD. This population reflects the majority of patients treated in our service, and maybe in other tertiary care hospitals in our country. Pamidronate is not an approved medication for osteoporosis treatment; however, it is the only non-oral option available in our public health system for patients who have osteoporosis and contraindications to oral bisphosphonates.

## Conflicts of interest

The authors declare no conflicts of interest.

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