

# Long-lasting effect of pamidronate on bone metabolism in osteoporosis after stopping therapy

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## Abstract

*Aim of the study:* To determine whether and when, like after estrogen withdrawal, bone loss resumes once disodium pamidronate is discontinued, even after long duration therapy. *Materials and methods:* 19 patients with osteoporosis, previously treated for  $4.3 \pm 0.5$  years (SEM) with oral cyclical intermittent pamidronate, were followed-up for  $30.3 \pm 2.2$  months after withdrawal from therapy. Lumbar spine and proximal femur BMD was measured by DXA (QDR-1000, Hologic Inc., Waltham, MA). *Results:* Lumbar spine BMD did not change significantly for the first 2 years, but decreased 1.8 % in the 3rd year ( $p < 0.001$ ). The proximal femur BMD did not change significantly for 3 years. The biological parameters of bone remodelling increased progressively with elapsing time, due to the underlying loss of pamidronate protection. *Conclusions:* after withdrawal of pamidronate therapy, a residual protecting effect was observed at the proximal femur and at the lumbar spine for 2 to 3 years. The time-interval resurgence of bone remodelling and the bone loss observed at the spine in the 3rd year suggest that there is no risk of freezing bone with pamidronate therapy, even at high doses. A long-lasting protective effect on bone mass can be expected. Periods of therapy with an active drug, interrupted by long resting periods, may produce the same protective effect as continuous therapy, owing to the levelling-off effect on bone mass observed after the first two years while on therapy. This would lead to lower expenses for a course of therapy.

**Keywords:** Pamidronate, Osteoporosis

## Introduction

In our experience, cyclical intermittent therapy with oral disodium pamidronate is able to increase bone mass, both at the lumbar spine and at midshaft forearm at least during the first two years of therapy. There appears some levelling-off effect thereafter, in patients followed up for five years on therapy<sup>1</sup>. This trend to plateauing was also observed with cyclical intravenous therapy consisting of a single infusion of 60-150 mg disodium pamidronate every three months<sup>2</sup>. All patients also received a daily oral supplement of 500 mg elemental calcium. Thus, it seems unnecessary to continue therapy beyond the third year, because no further significant effect on bone mass can be observed. Moreover, once in bone, bisphosphonates may be stored for long periods, from months up to several years (depending on the compound), normally in an apparently inactive compartment<sup>3</sup>.

However, it can be slowly released by subsequent bone remodelling and could lead to a decrease in bone loss in the long term. The aim of this study was to determine the duration of the action of disodium pamidronate on bone mass and bone remodelling after therapy withdrawal of patients suffering from involutional osteoporosis.

## Materials and Methods

Nineteen patients aged 62.5 (2.5 SEM) years suffering from involutional osteoporosis were treated either with cyclical intermittent disodium pamidronate administered orally (300 mg per day, 2 months on, 2 months off;  $n = 11$ ), or with cyclical intravenous pamidronate (60-150 mg every 2 to 3 months) for up to 4.3 (0.5 SEM) years. Bone mineral density (BMD) of the lumbar spine and of the total hip was measured, using dual energy X-ray absorptiometry (DXA) with a QDR-1000 from Hologic, Inc. (Waltham, Ma). The results were expressed in  $g/cm^2$ .

The studied biological parameters of bone remodelling consisted of total alkaline phosphatase activity (Alk. P'se: Normal Values 10-60 IU/l), fasting urinary calcium / creatinine ratio (FU Ca/creat: Normal Values  $\leq 0.150$  mg/mg)

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and fasting urinary hydroxyproline/creatinine ratio (FU Hypro/creat: Normal Values 19-37 µg/mg). The patients were followed-up for the next 30.3 (2.2) months after withdrawal from therapy.

### Results

After stopping pamidronate, lumbar-BMD did not change significantly in the first two years (mean changes: - 0.1 % the first year and + 0.7 % the second year) (Fig. 1). However, it decreased significantly (mean change: -1.8 %) in the third year. This change was statistically significant (p < 0.001) as compared to the last mean value when still on pamidronate therapy. Total hip BMD did not change significantly for the three years (mean changes: + 0.7 %, - 0.2 % and + 0.3 % during the first, second and third years, respectively). As far as the biological parameters of bone remodelling were concerned, a progressive increase in all parameters was observed from the first year of withdrawal onwards. The results are summarized in Table 1.

### Discussion

Since, when on cyclical intermittent pamidronate therapy, a plateauing effect on bone mass is observed, it may be wise to interrupt therapy after two or three years. This withdrawal of therapy can be justified in order to avoid freezing of bone remodelling. The latter risk is, however, more theoretical than real; no freezing of bone has so far been observed with pamidronate therapy<sup>4</sup>. A second justification to stop therapy is to decrease its cost, since no further gain in BMD is produced. The possibility of resuming therapy should, however, be kept in mind, if both remodelling of bone and bone loss recur. A third justification would be to decrease the potential toxicity of the medicine. No significant change in total hip BMD was observed for up to three years after

Follow-up (years)	Last year still on therapy	1st year	2nd year	3rd year after stopping APD
Alk. P'se (IU/l)	41.9 (6.0)	45.1 (3.8)*	49.7 (4.8)**	50.5 (4.3)*
FU Ca/creat (mg/mg)	0.152 (0.044)	0.140 (0.025)	0.160 (0.032)	0.182 (0.043)
FU Hypro/creat (µg/mg)	31.8 (10.9)	29.2 (7.0)	40.0 (4.4)*	41.9 (9.6)*

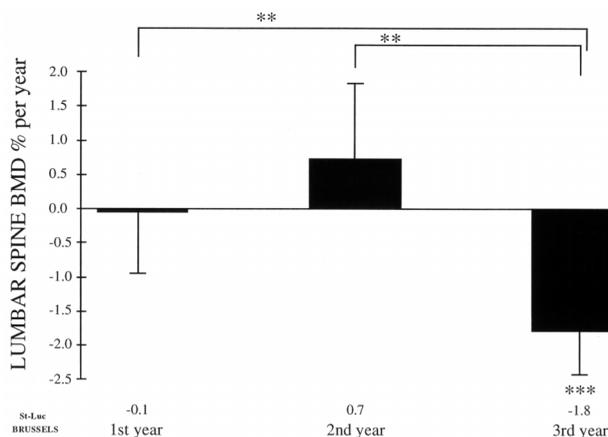
\*p < 0.05, \*\*p < 0.001, from the last year on therapy

**Table 1.** Mean values (SEM) of biological parameters of bone remodelling.

withdrawal from therapy, whereas no significant decrease in bone mass occurred at the lumbar spine for the first two years after cessation of treatment, followed by a significant bone loss during the third year.

The difference in behavior between the lumbar spine and the hip is consistent with the difference in bone composition between the two sites, the former being composed mostly of trabecular bone, a compartment more prone to rapid changes than the cortical bone which constitutes the main component of the upper extremity of the femur. The increase in bone remodelling parameters, already during the first year for some of them, is consistent with the lack of risk of freezing bone even with bisphosphonates as potent as disodium pamidronate<sup>5</sup>.

Similar results have been observed after stopping alendronate, an even more potent bisphosphonate than pamidronate<sup>6</sup>. The increase in alkaline phosphatase activity, a parameter of bone formation, as the first parameter to change is a little unexpected. An explanation could most probably be found in the better reproducibility and accuracy of this serum parameter, as compared to urine parameters like calcium and hydroxyproline, which are more prone to accidental contamination by food, if the patient does not completely comply with the technique for determining the fasting state. Whatever the explanation, there is a clear-cut trend to an increase of all parameters with elapsing time, with higher values observed when the lag-time from weaning is longer. The differences in timing between the increase in bone remodelling parameters and the recurrence of bone loss should justify the follow-up of biological parameters of bone remodelling. Their increase would help to indicate the appropriate time for resuming drug therapy, well before bone loss has started again. A longer-term cyclical therapy with pamidronate (e.g. two years on, one year off) would allow safe bone mass maintenance for years, and at a lower cost.



**Figure 1.** Bone mineral density (BMD) of the lumbar spine (% of initial value) in 19 patients suffering from involutional osteoporosis during the first, second and third year after weaning from pamidronate therapy.

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