

# Ibandronate and cementless total hip arthroplasty: densitometric measurement of periprosthetic bone mass and new therapeutic approach to the prevention of aseptic loosening

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## Summary

Studies of the mechanisms of periprosthetic bone loss have led to the development of pharmacologic strategies intended to enhance bone mass recovery after surgery and consequently prevent aseptic loosening and prolong the implant survival. Bisphosphonates, potent anti-resorptive drugs widely used in the treatment of osteoporosis and other disorders of bone metabolism, were shown to be particularly effective in reducing periprosthetic bone resorption in the first year after hip and knee arthroplasty, both cemented and cementless. Based on these results, we investigated the inhibitory effects of ibandronate on periprosthetic bone loss in a 2-year study of postmenopausal women that underwent cementless total hip arthroplasty. In the first 6 months both groups (A, treated with ibandronate 3 mg i.v. within five days after surgery and then with oral ibandronate 150 mg/month, plus calcium and vitamin D supplementation; and B, treated with calcium and vitamin D supplementation only) experienced bone loss, though to a lesser extent in group A. After 12 months, group A showed a remarkable BMD recovery, that was statistically significant versus baseline values (about +1, 74% of global BMD) and most evident in region R1 (+3, 81%) and R2 (+4, 12%); in group B, on the contrary, BMD values were unchanged compared with those at 6 months post-surgery. Quality of life scores also showed a greater improvement in group A, both at 6 and 12 months after surgery, likely because of the pain-reducing effects of ibandronate treatment.

**KEY WORDS:** periprosthetic bone loss; osteoporosis; ibandronate.

## Introduction

The long-term success of a prosthetic implant is the result of delicate interactions between bone and prosthesis evoked by the chan-

ged biomechanical condition. It is a well-known fact, indeed, that the introduction of a prosthesis considerably alters the physiological transmission of loads to the bones, with the consequent adaptation of the surrounding bone and the start of a remodelling process, whose expressions are alterations in the periprosthetic bone density.

The studies conducted in this field have led to the identification of the events that take place in the periprosthetic bone immediately after surgery and that may lead to the loosening of the prosthesis, thus affecting its survival. These studies also provided some insights on the chronology of these phenomena.

The first insult is the intraoperative damage, which is immediate, acute, and includes the mechanical damage, and the thermal and chemical damage. The former is the consequence of the preparation of the implant site both in cemented and direct fixation arthroplasties, while the thermal and chemical damage in cemented implants is the consequence of the polymerization reaction of methyl methacrylate, which is an exothermic reaction, and of the oxidative degradation caused by the residual chemical free radicals released by the resin, respectively (1). These are all events that imply necrotic phenomena in a more or less extensive area of the bone, which take approximately 3 months to repair (2).

Then a role is played by periprosthetic bone remodelling processes due to the subverted distribution of tensions, particularly in the proximal-medial area of the femur, where the bone, being no longer subjected to physiological loading and therefore to the mechanical stress that determines normal remodelling, slowly passes to a resorption process called 'stress shielding'. Apparently, this phenomenon is closely associated with the biomechanical characteristics of the bone-implant structure and, more specifically, with the different stiffness of the implanted material compared to the surrounding bone (3).

Conversely, new bone apposition and hypertrophy phenomena occur where the bone is stressed, which has been mainly highlighted in the distal diaphyseal region, in the proximity of the stem apex. How biomechanical signals are translated into cell signals, thus allowing for the activation of osteoclasts (resorption) or osteoblasts (bone formation), is a poorly known mechanism. The assumption is that the mechanical stimulus is translated into an electrical signal in the osteocytes and these, acting as mechanoreceptors and working as an intra-bone 'network', may subsequently activate osteoclastic or osteoblastic cell lines depending on the 'need' and characteristics of the implant (4, 5). The activation of osteoclastogenesis would be induced by the activation of the RANKL-RANK system.

One year after surgery, the periprosthetic bone loss tends to stabilize and subsequently show only a few alterations, which seem to be associated more with bone ageing than with bone remodelling (6).

Later on, five years after surgery, particle-induced osteolysis starts to occur, which is the main cause of the loosening of prosthetic components. This is due to the activation of an immune-inflammatory response caused by the detritus produced by the wear of prosthetic components due to friction. There is a recall of monocyte-macrophage cell populations, a continuous phagocytosis of wear debris, a production of cytokines and inflammatory mediators, particularly IL-1 and TNF-alpha, powerful stimulators of bone resorption by activation of the RANKL-RANK axis.

Within the framework of the monitoring of the remodelling processes that take place around the implants, the assessment of the redistribution of mineral bone density is gaining significance as it has been found to provide clinically relevant data in the early diagnosis of the processes that will lead to aseptic loosening and has a predictive value for the survival of the implant (7-9). All the bone density studies published to date have shown bone resorption in the femoral metaphyseal region, even with very high percentages (10-13).

The bone loss kinetics could be reconstructed through serial bone density measurements in different periprosthetic bone areas: at 3 months from implantation, a significant BMD reduction was observed in all the regions examined, with a subsequent slower progression, except for the calcar region, where bone loss – due to ‘stress shielding’ – progressed significantly to later stabilize in that region too after one year (14).

Furthermore, BMD alterations at 6 months were seen to have a statistically significant correlation with those observed 5 years after surgery (2), which suggests that the early periprosthetic remodelling that takes place over the first 6-12 months after surgery is also responsible for the trends that are observed in subsequent years. The assumption provided by the studies on the mechanisms that determine periprosthetic bone loss have led to the definition of pharmacological modulation strategies for that process, which have been capable of extending or facilitating bone mass recovery, supporting the efforts for a continuous innovation as regards the materials and design of the components and technologies used to prevent aseptic loosening.

A few particularly appropriate drugs for this purpose are bisphosphonates, potent antiresorptive agents used in the treatment of osteoporosis and other bone metabolism disorders.

Many *in vitro* and *in vivo* animal studies trials and human clinical trials have been conducted by using different bisphosphonate molecules which showed their effectiveness in reducing periprosthetic bone resorption over the first year of life of cemented and cementless hip and knee replacement prostheses. These agents were proved to be very promising at increasing survival rates with better and more durable results when treatment was started early, at a short distance from surgery and was continued for over 6 months (15-19).

The rationale for this lies in the capacity of these agents to block the activation of osteoclastic resorption, which is the common denominator where both early mechanical and late biological processes converge. There also seems to be a rationale in favouring osteoblastic activity (20), and consequently the integration of the prosthesis in the bone, not only due to the indirect effect of the inhibition of the enhanced osteoclastic function that re-establishes a balance between bone destruction and formation processes, allowing osteoblasts to continue their activity, but also due to a direct action. In fact, *in vivo* trials (models used to simulate the conditions of the micro-environment that is created *in vivo* when a joint prosthesis is implanted) showed the stimulation effect of the osteoblastic proliferation of some bisphosphonates, which might play an essential role in increasing periprosthetic bone ingrowth, and therefore the resistance of the implant (21). Bisphosphonates are supposed to act on the osteoblasts by up-regulating the expression of genes coding the synthesis of some morphogenetic proteins, including BMP-2 (3).

Based on the data provided by these studies, we assessed the inhibiting effects on periprosthetic osteolysis of ibandronate, a high potency aminobisphosphonate, whose peculiarity is that it can be administered either orally or intravenously, with extended dosing intervals, thanks to its high affinity for the bone mineral component and its consequent long-term persistence in the skeletal tissue, which therefore ensures excellent adherence to therapy.

This molecule had previously been studied in important controlled clinical trials on patients with osteoporosis which confirmed its capacity to significantly reduce vertebral (22-24), at first, and then femoral fracture risks (VI-BE trial) (while no similar efficacy docu-

mentation exists for proximal femoral fractures).

Although there is no data in the literature concerning human studies with the use of this molecule in the prevention of periprosthetic remodelling, the choice to use ibandronate in our patients was supported by trials that provided evidence, in terms of histomorphometric measurements, of the effects of this bisphosphonate, at doses corresponding to those used in humans for the treatment of osteoporosis, on osteoblastic activity, and consequently on the osseointegration of prostheses, and on the bone formation stimulation effect in rats that had received a cementless femoral implant (25). In another trial, the use of ibandronate determined a 50% reduction of the time required for the stabilization of bone implants (26). So, a two-year study was conducted to examine the effects of an early treatment with ibandronate on periprosthetic bone resorption in patients that had received cementless hip replacement (arthroplasty) by using two measurement methods: bone density scans for the measurement of the magnitude of periprosthetic resorption assessed as the difference between BMD shortly after surgery and follow-up BMD, and the assessment of the functional result and pain by administering the patient a quality-of-life measurement questionnaire (EQ-5D).

## Materials and methods

The study included 35 women over 60 years of age, not necessarily suffering from osteoporosis.

The study protocol required the randomization of the patients into two groups: group A, including 19 patients who received 3 mg of ibandronate i.v. (intravenously) within five days after surgery (hydroxyapatite-coated hip replacement) and then passed to oral administration with a monthly dose of 150 mg, plus calcium carbonate (1 g) and cholecalciferol (880 IU) supplementation; and a control group B, including 16 patients treated with calcium carbonate (1 g) and cholecalciferol (880 IU) supplementation.

A Hologic densitometer was used for the first DEXA scan starting, on average, from the 15th day after surgery (T0), then at 6 months (T1) and at 12 months (T2). The total BMD of the periprosthetic femur (TOT) and of the 7 Gruen sub-regions around the femur prosthesis (Figure 1), contralateral femur and rachis were measured. Statistical analysis was performed with the use of Mann-Whitney's test. The quality-of-life assessment questionnaire EQ-5D was administered at 3, 6, 9 and 12 months.

## Results

Tables 1 and 2 show the percentage differences between mean values at T1 and T2 concerning baseline BMD values at T0 in group A and B, respectively. Figures 2 and 3 provide the graphs of the values shown in Tables 1 and 2. Figures 4 and 5 show the percentage differences between means values at 6 months (T1) and 12 months (T2) versus baseline BMD values at T0 in groups A and B, respectively.

A decrease in the total periprosthetic BMD can be clearly seen in all the patients of groups A and B over the first 6 months after surgery, but in group B, whose women received only Ca and vitamin D, the decrease was of about -10.2% versus baseline values, with peaks of -11.71% in the medial metaphyseal region (R7) and -9.6% in the lateral diaphyseal region (R3). Conversely, in group A, the total BMD reduction, although not statistically significant, was of about -7.7%, a trend that was also confirmed for the other areas. At the 12th month after surgery, a reverse trend was observed in the patients treated with ibandronate (group A), with a slightly higher total BMD, in percentage terms, versus baseline (+1.74%) and even a statistically significant ( $p < 0.01$ ) bone density increase in lateral metaphyseal regions including the greater trochanter (R1 and R2), with a considerable bone mineral density recovery with dif-

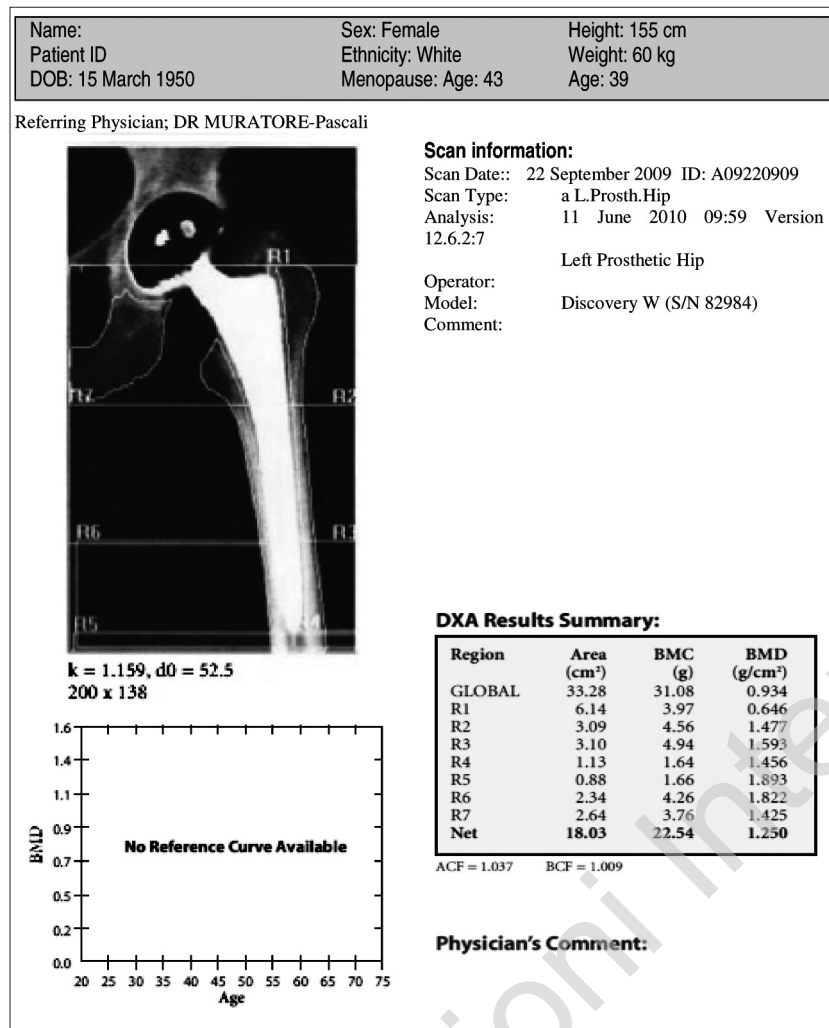


Table 1 - Percentage differences in mean values at T0, T1 and T2 versus BMD baseline values at T0 in group A.

	Total	R1	R2	R3	R4	R5	R6	R7
T0/T1	-7.70	-5.42	-2.13	-5.87	-7.85	-5.87	-6.96	-10.20
T0/T2	+1.74	+3.81	+4.12	-5.02	-5.06	-5.82	-3.09	-9.03

Table 2 - Percentage differences in mean values at T0, T1 and T2 versus BMD baseline values at T0 in group B.

	Total	R1	R2	R3	R4	R5	R6	R7
T0/T1	-10.20	-5.98	-2.53	-9.60	-8.85	-6.23	-7.50	-11.71
T0/T2	-10.20	+5.90	+2.50	-9.40	-8.80	-6.20	-7.49	-13.71

ferential values around 3% in R1 and 4% in R2.

A reduction in bone mineral density values of the global periprosthetic femur and also in the sub-regions persisted in the control group of patients treated only with calcium carbonate and cholecalciferol supplementation (group B) at the 12th month after surgery, with an important difference for region R7 where a mean decrease of 2 percentage points was observed versus values at 6 months after surgery.

Figure 7 shows a chart of quality of life trends, which seem to be improved in the two groups at both 6 and 12 months following arthroplasty implantation. However, we can see how the improvement

in the quality of life of patients treated with ibandronate (group A) is greater than the improvement obtained by group B women, which is very likely due to the greater pain reduction in group A women.

The densitometric measurement at the contralateral femur and rachis in group A, women treated with ibandronate, showed a BMD recovery, expressed in terms of percentage differences between mean values, of approximately 0.9% at 6 months and 1.4% at 12 months in the contralateral femur, 0.8% and 2.0% at the spine at 6 and 12 months, respectively. Conversely, control group B showed no BMD recovery at 6 months (-0.7% and -0.4% at the contra-

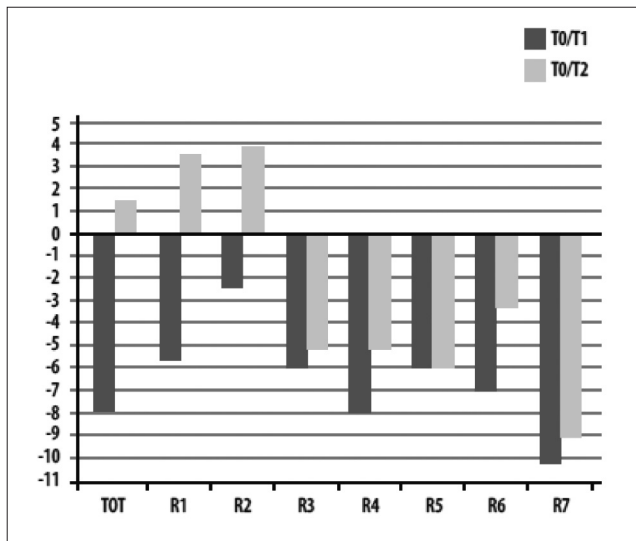


Figure 2 - Percentage differences of mean values at T0, T1 and T2 versus baseline BMD values at T0 in group A.

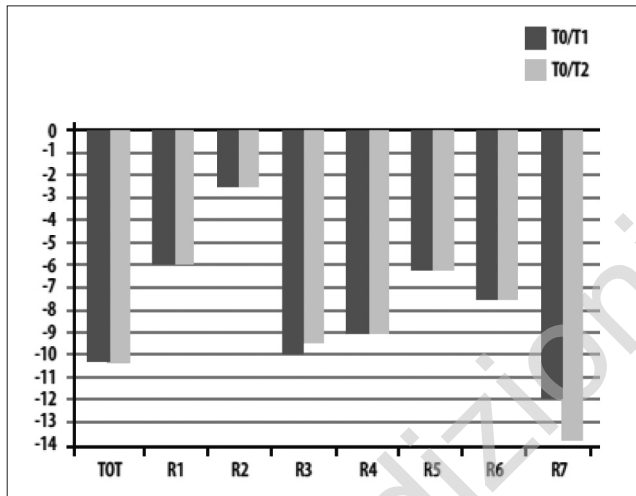


Figure 3 - Percentage differences of mean values at T0, T1 and T2 versus baseline BMD values at T0 in group B.

teral femur and spine, respectively), while the recovery at 12 months, in terms of percentage differences between mean values, was not statistically significant in both regions (0.1% and 0.5% at the contralateral femur and spine, respectively).

## Discussion

Bone remodelling in the periprosthetic femur is an inevitable process when cementless prosthesis stems are used and depends on various factors associated with both the prosthesis and the individual. While the factors associated with the prosthesis have been extensively studied and modified in connection with the bone resorption problems they created, individual 'biological' factors have not been completely identified. The underlying biochemical mechanisms of the activation of osteoblasts in periprosthetic remodelling is not totally clear. Certainly, both the mechanical and the biological actions play an essential role in the etiopathogenesis of this condition.

Based on the studies published to date, we have observed a re-

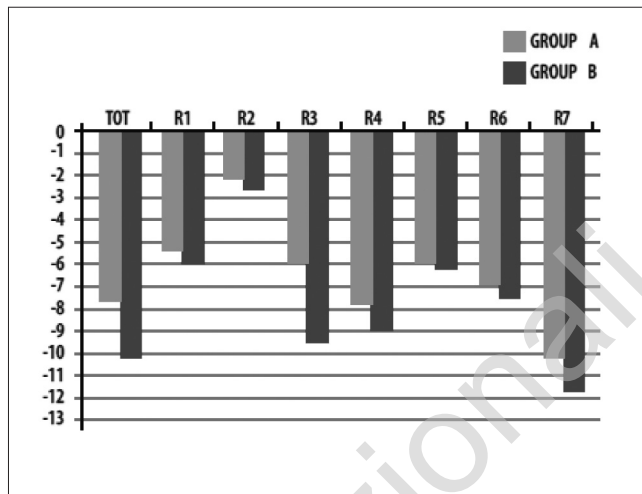


Figure 4 - Percentage differences of mean values at 6 months (T0-T1) versus baseline BMD values at T0 in groups A and B.

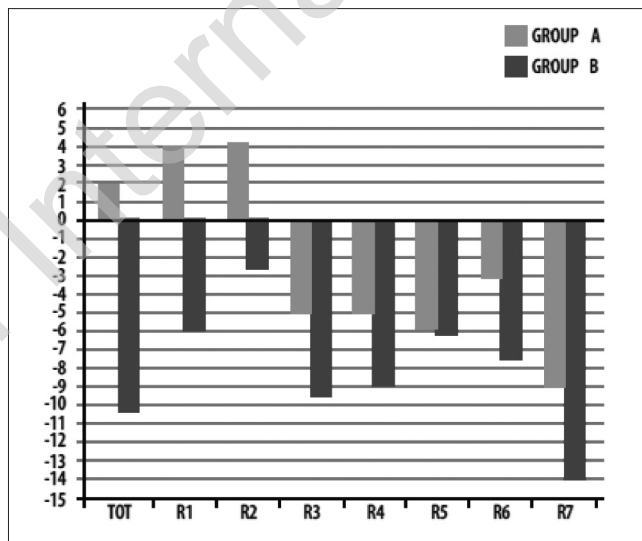


Figure 5 - Percentage differences of mean values at 12 months (T0-T2) versus baseline BMD values at T0 in groups A and B.

duction in the BMD over the first 6 months after implant in both groups, both the control group of patients treated with CA and vitamin D only (-10.2%) and the group treated with an intravenous bolus of ibandronate and subsequently with an oral ibandronate plus Ca and vitamin D therapy. However, the latter group showed a smaller global BMD reduction (-7.7%) compared to the control group (Table 1; Figures 2-4). At the 12th months, instead, a marked trend reversal is observed, with a statistically significant BMD percentage recovery compared to the baseline value at T0 of about 1.74% of the global BMD and more evident in region R1 (+3.81%) and in the lateral metaphyseal region (R2) (+4.12%). Vice versa, no global BMD recovery was observed in group B, which was virtually stabilized compared to values at 6 months (T1) (Table 2; Figures 2, 3, 5).

Comparison at 12 months, therefore, highlights a significant difference between the two groups, both for total BMD and for the BMD of the sub-regions, in favour of the ibandronate-treated group (Figure 6).

Considering that periprosthetic remodelling occurs within the first 6-12 months after surgery and is ultimately the factor that deter-

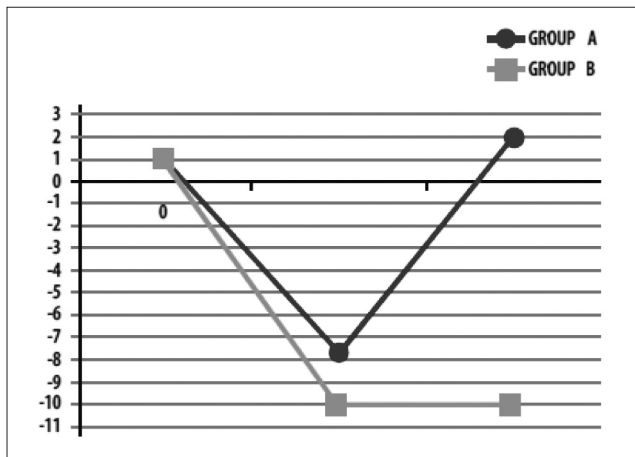


Figure 6 - Percentage differences of mean values at 12 months (T0-T2) versus baseline BMD values at T0 in groups A and B.

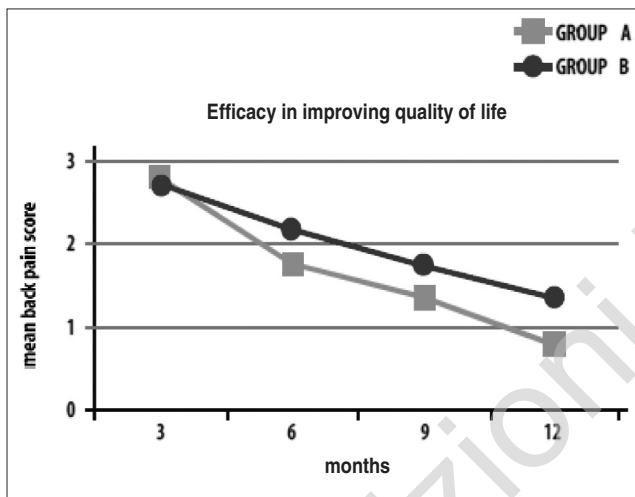


Figure 7 - Percentage differences of mean values at 12 months (T0-T2) versus baseline BMD values at T0 in groups A and B.

mines the life of the prosthesis, we can conclude that ibandronate reduces periprosthetic resorption and that said reduction is particularly evident in the medial metaphyseal region, which includes the calcar and the lesser trochanter, precisely in the points with a greater risk concerning the life of the prosthesis.

The results of this study support the usefulness of ibandronate in reducing early bone resorption.

The same quality of life determined by administering the EQ-5D questionnaire at 3, 6, 9 and 12 months was proved to be significantly improved in the group of ibandronate-treated patients versus the control group since the post-operative stage, and that difference is maintained at 3, 6, 9 and 12 months (Figure 7).

The administration of ibandronate in the post-operative stage, with an intravenous bolus and subsequently cyclic oral treatment, reduced cortical osteopenia in the calcar region of the proximal femur. This therapy could be used as a preventive measure in the prevention of post-surgery osteopenia and to oppose aseptic loosening in view of trying to increase the stability of the arthroplasty. The analgesic action of the drug may also improve pain and the quality of life already in the post-operative period, and even more at 12 months.

The antiresorptive efficacy of ibandronate was confirmed by the BMD recovery in terms of mean percentage differences at the contra-

lateral femur and rachis, both at 6 and 12 months compared to the control group, where BMD recovery was not statistically significant at 12 months.

While we are aware that the follow-up of this study is extremely short to reach a final conclusion on the possible greater survival of prostheses, in our opinion this study provides a confirmation of the anabolic effect of ibandronate, and consequently of bisphosphonates over osteoblasts. In fact, this action can increase growth within the implant porosity, thus preventing bone resorption in predisposing conditions and dramatically extending the life of arthroplasties.

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