# Bisphosphonates Increase Periprosthetic Bone Stock

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## INTRODUCTION

Periprosthetic particle-induced osteolysis with subsequent aseptic loosening remains the most common long-term complication associated with total joint replacements.[1-3] Wear debris including ultra-high molecular weight polyethylene (UHMWPE) particles from the articulating surfaces activate phagocytic cells at the bone-implant interface, subsequently initiating an osteolytic cascade involving peri-prosthetic granulomatous inflammation and bone resorption.[4-6] We have previously demonstrated that bisphosphonates, which inhibit osteoclastic bone resorption are effective in preventing wear debris-induced bone loss.[7] In the same model we reported that bisphosphonate treatment enhances net bone in implant porosities.[8] These observations are supported by in-vitro studies demonstrating that bisphosphonates promote osteoblastic bone formation by enhancing osteoblast recruitment from human bone marrow stromal cells,[9] stimulating osteoblast proliferation and maturation[10-11] and inhibiting their apoptosis.[12] These findings suggest that bisphosphonate treatment after joint replacements may result in a net gain of bone mass, and potentially an improved fixation of orthopaedic implants. To test if this was indeed the case, we investigated the effects of two FDA approved bisphosphonates: alendronate and zoledronate, on periprosthetic bone stock in a rabbit model of a porous coated implant. Alendronate is clinically used in treating post-menopausal osteoporosis and zoledronate is markedly effective in preventing hypercalcemia due to cancer.[13-14]

## EXPERIMENTAL MODEL

Following Institutional Animal Care and Use Committee approval, a fiber-mesh coated titanium plug (Zimmer, Warsaw, IN; 4 mm in diameter and 25 mm in length) was implanted in the intramedullary notch in both femoral condyles of 36 skeletally mature New Zealand White rabbits (3.5 – 4.0 kgs). Implants were sterilized by gamma radiation by the manufacturer before delivery. On the left femurs only, the implants were coated with submicron UHMWPE particles (about 200 x $10^6$ particles per implant) fabricated in the laboratory using a cryogenic attrition technique.[15] This UHMWPE wear debris ranging from 0.2 - 10 $\mu$m (mean 2.3 $\pm$ 0.5 $\mu$m) is clinically similar to that found around failed joint replacements,[16] and initiated osteolysis in a canine model.[7] Rabbits were randomized to three groups (control, alendronate, zoledronate). Control animals received no further treatment after surgery. Animals in the alendronate group were administered weekly subcutaneous injections of alendronate (3.0 mg/week, Fosamax, Merck, Rahway, NJ), starting intra-operatively day 0 and continued weekly thereafter until sacrifice. Animals in the zoledronate group received a single intravenous injection of zoledronate (Zometa, Novartis, East Hanover, NJ) intraoperatively at a dose of 0.015 mg/kg. Six/twelve rabbits from each group were sacrificed 6 weeks post-operative and the remaining six/twelve rabbits were sacrificed at 12 weeks.

## ANALYTICAL METHODS

### Radiographic Analysis

Bilateral contact radiographs (anteroposterior and lateral view) were performed on all rabbits after sacrifice, and evaluated qualitatively for evidence of peri-implant bone apposition and resorption. Anterioposterior radiographs were digitized and the lateral and medial cortical thickness was measured on 7 horizontal planes, spaced 2 mm apart, proximally and distally from the proximal end of the implant.

### Bone Histomorphometry

At harvest, 36 samples from 18 rabbits (3 per group) were fixed in 10% neutral buffered formalin and prepared utilizing hard tissue processing. Serial transverse sections were prepared from the proximal, middle and distal regions of the implant and stained with toluidine blue for static histomorphometry or left unstained for dynamic histomorphometry. Bone histomorphometry was performed using OsteoMeasureTM (Version 4.0) software and camera Lucida through a Nikon Eclipse E400 microscope. Bone volume density (BV/TV) and osteoid thickness (O.Th) were measured between the endosteal cortical and implant surfaces and expressed in accordance with the American Society of Bone and Mineral Research (ASBMR) nomenclature[17].

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### Statistical Analysis

Statistical analysis was performed using a one-way ANOVA and post-hoc paired, two-sided T-tests. All p-values were compared to an $\alpha$-value of 0.05 to determine significance.

## RESULTS

Radiographically, both bisphosphonate treatments resulted in more radiodense femoral condyles and a pronounced increase in periprosthetic bone apposition (Fig. 1). While the UHMWPE particle burden in group I resulted in localized scalloping and radiolucency characteristics of osteolysis, increased periprosthetic bone stock was found in both bisphosphonate treated groups with particle burden. Periprosthetic cortical thickness showed consistently higher values for groups II and III compared to group I both at 6 and 12 weeks (Fig. 2). After bisphosphonate treatment, the cortical thickness increased up to 18 % at 6 weeks ($p<0.001$) and up to 19 % at 12 weeks ($p=0.0013$).

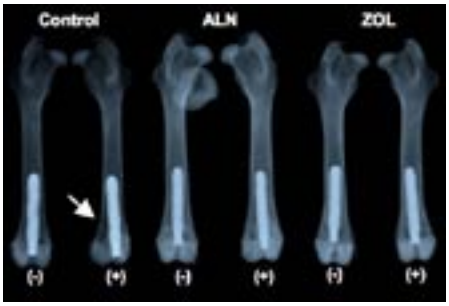


**Figure 1:** Representative A-P contact x-rays of rabbit femora with (+) and without (-) additionally introduced UHWMPE particles, 12 weeks post-op. Note particle-induced osteolysis in the control rabbits (arrow).

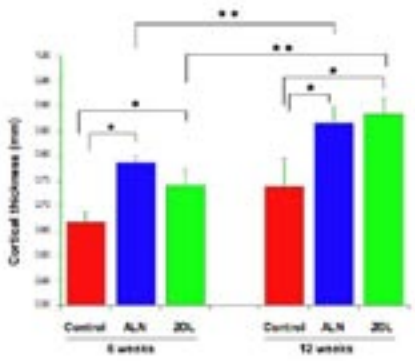


**Figure 2:** Cortical thickness for control and treatment groups at 6 and 12 weeks. [mean ± standard error; * = p< 0.05 over control; ** = p<0.05 12-week over 6-week]

Histomorphometric analyses confirmed the anabolic effects of bisphosphonates on periprosthetic bone turnover (see Table 1), particularly in the presence of UHMWPE wear particles. Following a 6-week treatment with either bisphosphonate, peri-implant bone volume density (BV/TV) doubled in femurs without added wear debris and increased more than 3-fold in the presence of wear debris. Osteoid thickness too, more than doubled after treatment with alendronate ($p=0.007$) or zoledronate ($p=0.051$). These effects were less pronounced after 12 weeks than at 6 weeks suggesting that bisphosphonates to accelerate the initial stage of periprosthetic bone healing, which would be particularly important in promoting implant osteointegration.

## DISCUSSION

In this study we provide evidence that clinically used bisphosphonates, alendronate and zoledronate have anabolic effects on periprosthetic bone turnover stock *in vivo* with and without the presence of UHMWPE wear debris. Our data suggest that bisphosphonates are capable of both inhibiting particle-induced osteoclastic bone resorption as well as stimulating osteoblastic bone formation, resulting in a net gain of peri-implant cortical and cancellous bone. One of the most striking findings of our study was a significant thickening of peri-implant cortical bone by up to 20% after 6 and 12 weeks of bisphosphonate treatment. This is particularly noteworthy since zoledronate was given as a single dose at the time of surgery. Bisphosphonate therapy induced similarly potent anabolic effects on cancellous bone turnover. Cancellous bone volume density and new bone forming activity around the implants were found to be up to 3-fold increased compared to control animals. Consistent with these findings, recent human clinical trials showed that bisphosphonates reduce periprosthetic bone loss after uncemented primary total hip and knee arthroplasty.[18-20] Our findings suggest that the effects of bisphosphonates on periprosthetic bone turnover with a net gain of cortical and cancellous bone are at least partially due to a direct stimulation of osteoblastic bone formation. Our recent in vitro studies[9,10] suggest that bisphosphonates might promote gene expression of key osteogenic transcription factors includ-

| | Bone Volume: BV/TV | | Osteoid Thickness: Os. Th [$\mu$m] | |
|---|---|---|---|---|
| GROUPS | (-) UHMWPE | (+) UHWMPE | (-) UHMWPE | (+) UHWMPE |
| Control 6 wk | 2.48 ± 0.85 | 1.82 ± 0.9 | 3.51 ± 1.4 | 3.51 ± 1.83 |
| ALN 6 wk | 4.99 ± 1.52 | 5.59 ± 1.63 | 8.15 ± 0.92 * | 8.2 ± 0.55 * |
| ZOL 6 wk | 4.31 ± 2.93 | 6.23 ± 2.69 | 5.87 ± 1.66 | 8.35 ± 0.78 * |
| Control 12 wk | 2.67 ± 0.88 | 2.92 ± 1.29 | 4.23 ± 1.47 | 4.81 ± 1.52 |
| ALN 12 wk | 3.39 ± 1.48 | 6.05 ± 1.86 | 3.82 ± 2.0 | 6.91 ± 0.76 |
| ZOL 12 wk | 1.74 ± 0.69 | 2.92 ± 1.08 | 3.15 ± 1.55 | 3.99 ± 1.65 |

**Table 1:** Histomorphometric data including periprosthetic bone volume density (BV/TV) and osteoid thickness (O.Th) [mean ± standard error; * = p< 0.05 over control] expressed in accordance with the American Society of Bone and Mineral Research (ASBMR) nomenclature[15]

ing BMP-2 and core binding factor alpha subunit 1 (cbfa-1) acting as successive differentiation triggers, which secondarily result in a pronounced recruitment, proliferation and anabolic activation of osteoblasts. Interestingly, in the present study, bisphosphonate treatment resulted in more pronounced bone formation associated with concurrent UHWMPE wear debris addition compared to conditions without added wear particles. These new findings suggest that bisphosphonate treatment may even overcompensate for the established negative effects of wear debris on osteoblastic function around implants *in vivo*.


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