Bisphosphonate Remains Highly Localized After Elution From Porous Implants

Kimberly McKenzie MEng, J. Dennis Bobyn PhD,
Jacinta Roberts MEng, Dorota Karabasz BSc,
Michael Tanzer MD

Published online: 31 August 2010
© The Association of Bone and Joint Surgeons® 2010

Abstract

Background Local elution of zoledronic acid from a porous implant reportedly enhances periimplant bone formation and implant fixation. However, there is no information in the literature on the extent to which eluted bisphosphonate remains localized around the implant or becomes systemically distributed.

Questions/purposes We ascertained to what extent eluted zoledronic acid remains local and whether there is systemic exposure after local elution from porous implants.

Methods A hydroxyapatite-coated porous tantalum implant dosed with 100 µg ¹⁴C-labeled zoledronic acid was implanted into the left femoral intramedullary canal of six dogs. Bone samples near to and distant from the implant were harvested from three dogs at 6 weeks and three dogs at 52 weeks. The concentration of radiolabeled bisphosphonate in each sample was quantified using liquid

scintillation spectrophotometry and its distribution in periimplant bone was revealed by exposing histologic sections to autoradiography film.

Results In all six dogs, the concentration of zoledronic acid in immediate periimplant bone was two orders of magnitude higher than in any other sampled tissue, averaging 732.6 ng/g at 6 weeks and 377.2 ng/g at 52 weeks. Minute amounts of zoledronic acid (≤ 7.2 ng/g) were detected throughout the skeleton, indicating some escape into the circulation after local elution. Autoradiographs revealed the greatest concentration of zoledronic acid on and within the implant, with rapid decrease short distances away and no uptake within the femoral cortex.

Conclusions Zoledronic acid eluted from an implant remains mainly localized with minimal systemic distribution.

Clinical Relevance Local bisphosphonate elution reduces the risk of systemic side effects and skeletal bisphosphonate exposure.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research. This work was performed at Montreal General Hospital, McGill University.

K. McKenzie, J. Dennis Bobyn (✉), J. Roberts, D. Karabasz, M. Tanzer
Jo Miller Orthopaedic Research Laboratory, Montreal General Hospital, Montreal, Canada
e-mail: john.bobyn@mcgill.ca

J. Dennis Bobyn
Division of Orthopaedics, McGill University,
1650 Cedar Avenue, Rm LS1-409, Montreal, QC H3G1A4,
Canada

Introduction

Although achieving adequate fixation of porous coated hip and knee implants is generally predictable, it is often more difficult to achieve reliably in scenarios in which host bone is mechanically weak or otherwise compromised [23, 24]. One approach to address fixation challenges is to increase local bone formation by the direct elution of a bisphosphonate compound from the implant. Once released from the implant and bound to the mineral phase of bone, the bisphosphonate interferes with osteoclast metabolism and suppresses resorption, thereby tipping the balance of bone turnover in favor of a net gain in bone formation [6, 22]. This has been reproducibly demonstrated in studies using

alendronate [3, 8, 12], clodronate [11], ibandronate [10], and zoledronic acid [5, 7, 20, 21, 25–27], the most potent and long-lasting bisphosphonate and one of several third-generation compounds being used clinically to mitigate the effects of osteoporosis [4, 16]. The effect of local zoledronic acid elution on net local bone formation around animal implants can be quite striking, with increases in bone ingrowth, bone apposition, and periimplant bone ranging from 60% to 130% within 12 weeks of surgery and persisting out to 1 year postoperatively [5, 27].

Two questions surrounding bisphosphonate therapy of any type are what systemic side effects the drug may have and what long-term effects on skeletal remodeling may develop [1, 2, 9, 13, 15, 17–19]. It seems likely these questions would be less important with direct bisphosphonate elution from an implant because less drug is utilized than with systemic administration and the drug is delivered locally. There are, however, no data to support this presumption.

We therefore ascertained to what extent eluted zoledronic acid remains local and whether there is systemic exposure after elution from porous implants.

Materials and Methods

Six mongrel dogs between 2 and 5 years of age and weighing between 25 and 30 kg were used for the experiment. Porous implants doped with 100 μg ^{14}C -labeled zoledronic acid were inserted into one femur of each animal. Quantitative and qualitative measurements of zoledronic acid concentration were made according to the dependent variables of skeletal location (near to and distant from the implant) and time (6 weeks and 52 weeks).

The cylindrical implants (50 mm long, 5 mm in diameter) were manufactured from a porous tantalum biomaterial (Trabecular MetalTM; Zimmer, Inc, Warsaw, IN). The material was previously characterized to have an average pore size of 430 μm and a volume porosity of approximately 75%. The implants were plasma spray coated by a commercial vendor (Orchid Bio-coat, Southfield, MI) with a 10- to 15- μm layer of hydroxyapatite (98% purity, 99% density, 64% crystallinity, calcium:phosphate ratio of 1.67) to serve as a partial immobilizer of zoledronic acid. A solution of 500 μL distilled deionized water containing 100 μg ^{14}C -labeled zoledronic acid (Novartis Pharma, Basel, Switzerland) (specific activity, 6.51 Mbq/mg) was evenly distributed over each implant using a micropipette, after which the implant was dried at 50°C for 24 hours and then sterilized with ethylene oxide and packaged until the time of implantation. The use of radiolabeled zoledronic acid enabled accurate detection of the bisphosphonate in tissue using liquid scintillation

spectrophotometry. The 100 μg dose was at the uppermost level utilized in prior studies using similar porous tantalum ulnar and femoral intramedullary implants [5, 27]; the heating and sterilization procedures were identical to those used in earlier studies and confirmed by the drug manufacturer, together with radiolabeling, to have no deleterious effect on activity of the compound. Although the exact in vivo elution characteristics are unknown, the in vitro zoledronic acid elution characteristics of the implant were previously described to consist of an initial burst release of unbound compound within the first few hours followed by a much slower continuous release over several weeks [27].

Anesthesia was induced using sodium pentobarbital and maintained with 3% isoflurane and oxygen. Intravenous cefazolin was administered in two 0.5 g doses in sterile water, once before and once after surgery. The left hindleg was shaved and prepped in standard fashion. After a small incision over the proximal end of the femur and splitting of the gluteus medius, a 5 mm diameter hole was drilled into the intramedullary canal of the femur through the piriformis fossa, a procedure much like a blind intramedullary rodding. An implant was tapped into the hole and seated at a level about 15 to 20 mm distal to the level of the femoral neck, without irrigation prior to insertion. Bleeding from the hole in the piriformis fossa was minimal after implant insertion but the hole was sealed with bone wax as a precaution against bleeding into the joint space. The incision was closed using Vicryl sutures. Analgesia consisted of a 100 mg Fentanyl patch placed before surgery and intramuscular buprenorphine (0.02 mg/kg) immediately after surgery and twice over the following 16 hours. All dogs returned to normal weightbearing activities 1 to 2 days after surgery. Postoperative management included environmental enrichment and free daily exercise for one hour.

Three animals were each sacrificed at 6 weeks and 52 weeks; euthanasia was induced with an overdose of intravenous pentobarbital (120 mg/kg). At both 6 and 52 weeks, the left and right femora, tibiae, radii, and humeri were harvested. Additionally, at 52 weeks, small pieces of liver, kidney, heart, spleen, lung, vastus lateralis, iliac crest, patella, clavicle, acetabulum, talus, scaphoid, metatarsal, and metacarpal were also harvested. Soft tissue surrounding bony samples was stripped and all tissue samples were frozen at -60°C until required, at which time they were thawed to room temperature for subsequent processing.

The six left femora with the implant were imaged by contact radiography (Fig. 1) in a Faxitron[®] MX-20 apparatus (Hewlett-Packard, Lincolnshire, IL) before being serially sectioned using a band saw with a blade thickness of 0.6 mm. The left femora were entirely sectioned at approximately 1-cm intervals, including the region with the implant. Each implant-containing bone segment was

Fig. 1 A contact radiograph illustrates the implant position and division into six segments approximately 1 cm in length. In two femora at 52 weeks the proximal and distal segments included

approximately 5 mm of implant and were embedded in acrylic for examination with radiography and autoradiography.

divided in half using a handheld high-speed sectioning wheel (Dremel, Racine, WI) and the implant was mechanically separated from the cortical halves. Bone that adhered to the implant surface was manually scraped off with a scalpel to the edge of the implant and the bone shavings were added to the cortical halves for eventual analysis using liquid scintillation. In two of the three 52-week femora with implants, two bone segments from each femur were reserved for autoradiography, one from the proximal end of the implant and one from the distal end, each containing an implant segment about 5 mm long (Fig. 1).

The right femora together with the tibiae, radii, and humeri were also entirely sectioned at 1-cm intervals using a band saw. The other bone and soft tissue samples were sufficiently small that they did not require any further sectioning before processing. The bone segments and other tissue samples were defatted in a 1:1 solution of ether-acetone for 24 hours, dehydrated in 100% ethyl alcohol 24 hours, and dried overnight in an oven at 42°C. Each dried sample was transferred into a preweighed plastic vial and weighed to determine its dry mass. The tissue was dissolved in 6 N HCl using a ratio of approximately 25 mL acid per 1 g dry tissue, with the total amount of acid in the vial recorded for each sample. Complete tissue dissolution occurred over a 1-week period, with the samples left in an oven at 42°C and mixed occasionally using a Barnstead Type 16700 mixer (Barnstead Thermolyne Corp, Waltham, MA).

For each dissolved tissue sample, 600 μ L HCl solution was added to a clean vial for analysis using liquid scintillation spectrophotometry. This aliquot was diluted to 2 N HCl by adding 1.2 mL distilled, deionized water to the vial. Liquid scintillation cocktail (Ultima Gold™ AB; Perkin Elmer USA, Waltham, MA) was added to the vial in a ratio of 10:1 cocktail to HCl solution. After mixing, 14 C levels were determined using a Packard Tri-Carb® 2100TR liquid scintillator spectrometer (Packard Instrument, Co, Meriden, CT). Measurements were recorded in counts per minute (CPM). Once background counts were subtracted, the mass of zoledronic acid in each vial was ascertained

using a 12-point calibration curve based on known masses of zoledronic acid in liquid scintillation cocktail. Using the known starting masses of tissue and volumes of acid combined to form solutions for analysis, the liquid scintillation measurements were used to determine the concentration of zoledronic acid per gram of dry tissue for each sample.

At 6 weeks and 52 weeks, mean zoledronic acid concentration values and standard deviations were calculated for all the collective segments of each long bone apart from the implant-containing femora, the collective segments of all long bones apart from the implant-containing femora, the collective segments of bone immediately adjacent to each implant in the left femur, and the collective proximal and distal segments of the left femur distant from the implant. The various means were compared using multiple unpaired two-tailed Student's *t* tests and multiple hierarchical models. The 52-week zoledronic acid concentration values for each bone segment, proximal to distal within the 3 right femora and the 6 radii, tibiae, and humeri were averaged and plotted to demonstrate the variation in concentration between metaphyseal and diaphyseal values. The relationship was estimated by a linear model which included linear and quadratic terms after adjusting for bone location.

The proximal and distal bone-implant segments from the two 52-week femora were processed for undecalcified thin sectioning. After dehydration in graded ethanol solutions of 70% and 95%, the segments were placed in a 1:1 solution of ether-acetone for defatting, followed by final dehydration in 100% ethanol. They were immersed in partially polymerized methylmethacrylate monomer (Sigma-Aldrich Corp, St Louis, MO) activated with 0.05% benzoyl peroxide (Anachemia Science, Lachine, Quebec, Canada) and vacuum infiltrated for 4 to 5 hours in a dessicator jar followed by room temperature curing for a week. The embedded segments were sectioned using a diamond blade saw (Buehler Isomet® 1000; Buehler, Markham, Ontario, Canada) into multiple transverse serial sections about 0.5 mm in thickness. The sections were aligned and radiographed, placed onto autoradiography film (BioFlex

MSI film; Clonex, Markham, Ontario, Canada) in a dark room and sealed in a light-tight cassette for 2 weeks, after which the film was developed to reveal the presence and location of ^{14}C -labeled zoledronic acid within each bone-implant section.

Results

The mean zoledronic acid concentration in the cortical bone adjacent to the implant (periimplant bone) was $732.6 \text{ ng/g} \pm 358.8 \text{ ng/g}$ bone at 6 weeks (Table 1). At 52 weeks the zoledronic concentration in periimplant bone was $377.2 \text{ ng/g} \pm 66.1 \text{ ng/g}$ (Table 1, Fig. 2), less variable and lower by approximately half ($p = 0.06$, hierarchical model). The zoledronic acid concentration was not evenly distributed within the bone immediately adjacent to the implant at either time period, there being a distinctly bell-shaped distribution with the peak lying proximal to the center of the implant (Fig. 3). The zoledronic acid concentration was highly localized near the implant, dropping as much as an order of magnitude just 1 cm to 2 cm proximal or distal to the implant, at both 6 weeks and 52 weeks. The measured mean concentrations in the most proximal and distal left femoral bone segments were each two orders of magnitude lower than the mean concentration adjacent to the implant ($p = 0.04$, Student's *t* tests).

The mean zoledronic acid concentration in the various individual osseous tissue samples from near and remote skeletal sites (excluding periimplant bone) ranged from 5.8 ng/g to 7.0 ng/g at 6 weeks (Table 1), and from 1.9 ng/g to 7.1 ng/g at 52 weeks (Table 1, Fig. 2). The mean concentration in the collective remote skeletal sites diminished

from $7.0 \text{ ng/g} \pm 3.0 \text{ ng/g}$ at 6 weeks to $5.1 \text{ ng/g} \pm 0.7 \text{ ng/g}$ at 52 weeks ($p = 0.01$, hierarchical model). Compared with the much greater mean concentrations in periimplant bone, all mean concentrations in bones other than the left femur were associated with $p = .02$ at 6 weeks (Student's *t*-tests) and $p = .0006$ at 52 weeks (Student's *t*-tests). In each of the long bones without an implant, there was a parabolic shape of zoledronic acid concentration at both time periods (Fig. 4). Both the linear and quadratic terms of the linear model were associated with a greater

Fig. 2 A diagram shows the skeletal distribution of zoledronic acid at 52 weeks, illustrating mean drug concentrations (ng/g dry bone) in sites additional to those sampled at 6 weeks. The mean zoledronic acid concentration in periimplant bone was 377.2 ng/g , greater than in any of the remote bone sites ($p = .0006$, Student's *t* tests). (The canine schematic is reproduced under license from www.fotolia.com.)

Table 1. Mean zoledronic acid concentration in the common bone sites sampled in the three dogs at 6 weeks and 3 dogs at 52 weeks

Bone	Average mass zoledronic acid (ng/g bone)	
	6 weeks	52 weeks
Right radius	6.1 ± 3.9	4.6 ± 0.4
Left radius	5.8 ± 4.6	6.2 ± 2.4
Right tibia	6.9 ± 5.3	3.3 ± 2.6
Left tibia	5.9 ± 3.3	3.0 ± 2.1
Right humerus	6.2 ± 2.6	5.2 ± 1.1
Left humerus	5.6 ± 2.7	5.3 ± 0.8
Right femur	7.0 ± 3.0	5.2 ± 1.0
Overall (all 7 bones above)	6.2 ± 3.4	4.7 ± 0.7
Left femora (periimplant bone)	$\dagger 732.6 \pm 358.8$	$\ddagger 377.2 \pm 66.1$

$\dagger$ Compared with means in other long bones at 6 weeks, $p = 0.02$.

$\ddagger$ Compared with means in other long bones at 52 weeks, $p = .0006$.

Fig. 3 A graph illustrates the zoledronic acid concentration at 52 weeks as a function of centimeter intervals along the three femora with implants. The straight lines under the curves indicate the position of each implant in the femur relative to the zoledronic acid concentration. In the most proximal and distal ends of the femora the concentration of zoledronic acid was comparable to that found at other skeletal sites (two orders of magnitude less than in periimplant bone).

Fig. 4 A graph illustrates the average zoledronic acid concentration in the 3 dogs at 52 weeks as a function of location along the length of long bones. The data were combined for the 3 right femora, the 6 tibiae, the 6 humeri and the 6 radii. The parabolic distribution of drug concentration with greater values in the metaphyses than in the diaphyses was associated with $p < 2e-16$ (linear model).

zoledronic acid concentration in the metaphyses compared with the diaphyses, both terms with $p < 2e-16$.

The radiographs of the 52-week histologic sections revealed abundant periimplant bone, less so for the proximal sections (Fig. 5) than for the distal sections (Fig. 6). The amount of bone within the intramedullary canal of these sections (Fig. 6) decreased noticeably with distal location, adjacent sections being approximately 1 mm apart. The autoradiography films revealed the presence and location of zoledronic acid within the transverse sections as dark grey or black images. In all sections, the strongest presence of zoledronic acid coincided with the location of the implant, indicative of residual drug on the implant struts or within the bone that had formed within the implant pores of the proximal (Fig. 5) and distal (Fig. 6) sections. Zoledronic acid was also present, but to a lesser extent, within the cancellous intramedullary bone surrounding the implant, as it also was lining the endosteal border. With increasing distance from the implant, the presence of zoledronic acid noticeably diminished, being strongest near the center of the intramedullary canal and less so toward

Fig. 5A–B Proximal serial transverse sections of implant and surrounding bone from a 52-week femur are shown in a contact radiograph (A) and the corresponding autoradiograph (B). The implant is present in the bottom three sections. The autoradiography reveals zoledronic acid is strongly concentrated in and around the implant, with diminished content proximal to the implant and in surrounding bone.

◀**Fig. 6A–B** Distal serial sections of implant and surrounding bone from a different 52-week femur are shown in a contact radiograph (**A**) and a corresponding autoradiograph (**B**). The implant is present in the top three sections. The autoradiography revealed zoledronic acid was strongly concentrated in and around the implant, with diminished content distal to the implant and in surrounding bone. The presence of zoledronic acid around the outer edge of the cortex is indicated by arrows.

the cortex. In sections proximal or distal to the implant in both dogs, the drug was also faintly visible lining the endosteal border. In one of the two dogs, zoledronic acid was also very faintly visible outlining the periosteal border of the sections, those with and without the implant (Fig. 6). No appreciable zoledronic acid was evident within the cortex itself.

Discussion

Several studies have demonstrated the utility of locally applied or delivered bisphosphonates for enhancing periimplant bone formation and implant fixation although none have shown to what extent the drug becomes skeletally distributed. It would be preferable for the bisphosphonate to remain localized to the implant site to minimize potential systemic side effects and unnecessary skeletal bone remodeling. This study aimed to quantify to what extent eluted zoledronic acid from porous implants was localized and whether there was systemic exposure after local elution.

There are several limitations to this study. First, the distribution of zoledronic acid was not measured along the length of the implants and it therefore cannot be stated with absolute certainty that an asymmetric dosing was not responsible for the bell-shaped distribution that was measured in periimplant bone. However, as described in prior publications, the zoledronic acid was mixed in an aqueous solution and applied evenly along the implant length and circumference during application; the likelihood was therefore for more even distribution than not. Second, a better estimate of the remaining systemic burden of zoledronic acid could have been made had excreted bisphosphonate in the urine been measured. This was not done due to the practical difficulty in animal handling. Third, no control implants without zoledronic acid were included in the study, thus negating the opportunity to make direct comparisons with the local net bone formation around drug-eluting implants. However, this was not the purpose of the study and such comparisons have been made previously, with clear demonstration of the net bone enhancement caused by local zoledronic acid elution. Fourth, only a single dose of zoledronic acid was studied; it is possible that higher or lower doses would be differently

distributed locally and systemically, although the 100 µg dose was at the upper end of what has previously been shown as effective for enhancing net bone formation around and within porous implants. Smaller bisphosphonate doses would be expected to result in lower concentrations in local and remote bone. Of most importance was the relative zoledronic acid concentration that was measured locally compared with systemically. Fifth, studying more implants at each time period might have provided a stronger statistical indication of whether the zoledronic acid concentration in periimplant bone decreased with time, although this was clearly evident in remote bone sites. The data from each of the 3 implants at each period of 6 weeks and 52 weeks were however sufficient to uniformly indicate significantly elevated zoledronic acid concentrations locally compared with systemically. We do not believe any of these limitations substantially influence the data or the study conclusions.

The question about whether eluted bisphosphonate remained primarily localized around the implant was answered in the affirmative using two different experimental techniques. The first technique, liquid scintillation counting of radiolabeled zoledronic acid, revealed drug concentrations immediately adjacent to the implant that were one order of magnitude greater than in bone slightly proximal and distal to the implant and two orders of magnitude greater than in the metaphyseal bone of the implanted femur and in bone at remote sites in the skeleton. The data indicated the zoledronic acid concentration in periimplant bone diminished between 6 weeks and 52 weeks, a statistically stronger result for remote bone sites than periimplant bone because of higher sample size. This suggests that drug diffusion into the circulation and excretion continued beyond 6 weeks, possibly boosted by osteoclastic bone remodeling progressively releasing compound. At both time periods, the zoledronic acid distribution in the bone segments immediately adjacent to the implants was consistently bell-shaped instead of uniform along the implant length, with the peak slightly skewed toward the proximal end of the implant. The proximal skewing might have been due to mechanical removal of surface compound as it was inserted with a press fit within the reamed intramedullary hole, with accumulation more proximally. It might also have been due to proximal pooling of blood with eluted compound. The precise reason for the bell-shaped distribution is uncertain, but ancillary studies describing the net bone-enhancing effect of local zoledronic acid elution have not reported a similar distribution of periimplant bone. Autoradiography was the second technique for demonstrating a strong concentration of drug on and/or within the implant, with marked attenuation millimeters away from the implant, either proximally, distally or radially, and only faint presence

within endosteal and periosteal bone. There was a subtle difference in zoledronic acid distribution between the sections studied by autoradiography at 52 weeks in that one dog showed faint evidence of drug at the periosteal border of the cortex while the other did not. In neither dog was drug apparent within the cortex itself; this suggests zoledronic acid may have reached the periosteal region via the circulation as opposed to diffusion through cortical bone. Amanat et al. [2] also showed with autoradiography the presence of radiolabeled zoledronic acid within rat bone that had been exposed to the drug but since the model did not involve local elution from an implant the drug distribution at and near the implant was not studied.

The presence of very low concentrations of zoledronic acid in the remote skeleton at both time periods answered the question about whether local elution would result in systemic distribution. Presumably this occurred through diffusion of the compound at the implant site into the local circulation. Much of the drug that entered the circulation would have been excreted quite rapidly; up to 50% of systemically injected zoledronic acid is cleared in the urine within 24 hours [14], with additional clearance thereafter. As would be expected, the drug concentration was somewhat greater in the metaphyses of the long bones where there is more cancellous bone and hence greater surface area than in the diaphysis. There are no other data in the literature that compare exactly with the findings of the present study, however two previous studies using locally applied radiolabeled bisphosphonates described systemic drug distribution. In a rat study of mucoperiosteal flap surgery Yaffe et al. [28] applied 22 µg of ¹⁴C-labeled alendronate directly to alveolar bone via a soaked gelatin sponge. The mean total amount of drug measured in the left tibia after 60 minutes was 3.2% of the applied dose (0.7 µg). In a 6 week rat study in which ¹⁴C-labeled zoledronic acid was locally injected as a bolus to closed femur fractures, Amanat et al. [2] measured drug levels in the contralateral femur averaging approximately 0.7 µg/g bone tissue, about half the concentration measured at the fracture site. Very much lower levels of systemic distribution were measured in the present study involving canines (slower metabolic rate), a surgical model with less direct and acute exposure to the circulation, longer study period(s), lower zoledronic acid dose (by body weight), a different method of drug delivery (slower rate by elution), and more comprehensive sampling of skeletal sites.

Ascertaining that eluted zoledronic acid remained highly localized near the implant site, with minute systemic or skeletal exposure, was important for two reasons. First, the findings suggest that local drug elution would be unlikely to cause adverse effects as are sometimes reported clinically with intravenous administration to patients with osteoporosis. This is further supported by the fact that the

initial zoledronic acid dose on the implant was very low compared with amounts used clinically. Second, the very low concentration of zoledronic acid found in remote skeletal sites suggests adverse bone remodeling of the skeleton would be minimal or absent after local drug elution. There is some concern that bone exposed to bisphosphonate therapy in the long term may be prone to adverse changes in strength, fracture toughness, or modulus owing to incomplete remodeling and repair [1, 9, 13, 15]. In the present study, the concentration of zoledronic acid in remote skeletal sites was 50-fold to 200-fold less than the concentration found in periimplant bone, so substantial remodeling effects would not be expected. It should be added that ancillary studies of zoledronic acid-eluting implants have found increases in net periimplant bone formation are very much confined to the immediate space around the implant border [5, 21, 22, 25, 27]. This is consistent with the findings of this study and suggests the relatively low concentrations of zoledronic acid measured one or more cm away from the implant, and therefore even more so at remote skeletal sites, are probably subtherapeutic from a bone-remodeling standpoint.

Acknowledgments We thank the Canadian Institutes of Health Research for funding of the study, Zimmer Inc for provision of the implants, Novartis Pharma for provision of the ^{14}C -labeled zoledronic acid, and Dr. Lawrence Joseph for professional statistical advice.

References

- Allen MR, Iwata K, Phipps R, Burr DB. Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. *Bone*. 2006;39:872–879.
- Amanat N, McDonald M, Godfrey C, Bilston L, Little D. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res*. 2007;22:867–876.
- Åstrand J, Aspenberg P. Topical, single dose bisphosphonate treatment reduced bone resorption in a rat model for prosthetic loosening. *J Orthop Res*. 2004;22:244–249.
- Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356:1809–1822.
- Bobyn JD, McKenzie K, Karabasz D, Krygier JJ, Tanzer M. Locally delivered bisphosphonate for enhancement of bone formation and implant fixation. *J Bone Joint Surg Am*. 2009;91:23–31.
- Drake MT, Clarke BT, Khosla S. Bisphosphonates: mechanisms of action and role in clinical Practice. *Mayo Clin Proc*. 2008;83:1032–1045.
- Gao Y, Zou S, Liu X, Bao C, Hu J. The effect of surface immobilized bisphosphonates on the fixation of hydroxyapatite-coated titanium implants in ovariectomized rats. *Biomaterials*. 2009;30:1790–1796.
- Garbuz DS, Hu Y, Kim WY, Duan K, Masri BA, Oxland TR, Burt H, Wang R, Duncan CP. Enhanced gap filling and osteoconduction associated with alendronate-calcium phosphate-coated porous tantalum. *J Bone Joint Surg Am*. 2008;90:1090–1100.
- Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, Howe TS. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. *J Bone Joint Surg Br*. 2007;89:349–353.
- Hilding M, Aspenberg P. Local peroperative treatment with a bisphosphonate improves the fixation of total knee prostheses. A randomized, double-blind radiostereometric study of 50 patients. *Acta Orthop*. 2007;78:795–799.
- Hilding M, Ryd L, Toksvig-Larsen S, Aspenberg P. Clodronate prevents prosthetic migration: a randomized radiostereometric study of 50 total knee patients. *Acta Orthop Scand*. 2000;71:553–557.
- Jakobsen T, Baas J, Kold S, Bechtold JE, Elmengaard B, Soballe K. Local bisphosphonate treatment increases fixation of hydroxyapatite-coated implants inserted with bone compaction. *J Orthop Res*. 2009;27:189–194.
- Kwek EB, Koh JS, Howe TS. More on atypical fractures of the femoral diaphysis [Letter]. *N Engl J Med*. 2008;359:316–318.
- Legay F, Gauron S, Deckert F, Gosset G, Pfaar U, Ravera C, Wiegand H, Schran H. Development and validation of a highly sensitive RIA for zoledronic acid, a new potent heterocyclic bisphosphonate in human serum, plasma and urine. *J Pharm Biomed Anal*. 2002;30:897–911.
- Lenart BA, Lorch DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med*. 2008;358:1304–1306.
- Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357:1799–1809.
- Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res*. 2000;15:613–620.
- Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone*. 2001;28:524–531.
- Papapetrou PD. Bisphosphonate-associated adverse events. *Hormones*. 2009;8:96–110.
- Peter B, Gauthier O, Laib S, Bujoli B, Guicheux J, Janvier P, van Lenthe GH, Müller R, Zambelli PY, Boulter JM, Pioletti DP. Local delivery of bisphosphonate from coated orthopedic implants increases implants mechanical stability in osteoporotic rats. *J Biomed Mat Res Part A*. 2006;76:133–143.
- Peter B, Pioletti DP, Laib S, Bujoli B, Pilet P, Janvier P, Guicheux J, Zambelli PY, Boulter JM, Gauthier O. Calcium phosphate drug delivery system: influence of local zoledronate release on bone implant osteointegration. *Bone*. 2005;36:52–60.
- Russell RG, Xia Z, Dunford JE, Oppermann U, Kwaasi A, Hulley PA, Kavanagh KL, Triffitt JT, Lundy MW, Phipps RJ, Barnett BL, Coxon FP, Rogers MJ, Watts NB, Ebtino FH. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann NY Acad Sci*. 2007;1117:209–257.
- Saleh KJ, Mulhall KJ, Hofmann AA, Bolognesi MP, Laskin RS. Primary total knee arthroplasty outcomes. In: Barrack RL, Booth RE Jr, Lonner JH, McCarthy JC, Mont MA, Rubash HE, eds.

- Orthopaedic Knowledge Update 3 - Hip and Knee Reconstruction*. Rosemont, IL: Amer Acad Orthop Surg; 2006:93–110.
24. Sporer S, Paprosky WG, Berry DJ. Hip revision. In: Barrack RL, Booth RE Jr, Lonner JH, McCarthy JC, Mont MA, Rubash HE, eds. *Orthopaedic Knowledge Update 3 - Hip and Knee Reconstruction*. Rosemont, IL: Amer Acad Orthop Surg; 2006:457–474.
25. Stadelmann VA, Gauthier O, Terrier A, Bouler JM, Pioletti DP. Implants delivering bisphosphonate locally increase periprosthetic bone density in an osteoporotic sheep model: a pilot study. *Eur Cell Mater*. 2008;16:10–16.
26. Suratwala SJ, Cho SK, van Raalte JJ, Park SH, Seo SW, Chang SS, Gardner TR, Lee FY. Enhancement of periprosthetic bone quality with topical hydroxyapatite-bisphosphonate composite. *J Bone Joint Surg Am*. 2008;90:2189–2196.
27. Tanzer M, Karabasz D, Krygier JJ, Cohen R, Bobyn JD. Bone augmentation around and within porous implants by local bisphosphonate elution. *Clin Orthop Relat Res*. 2005;441:30–39.
28. Yaffe A, Binderman I, Breuer E, Pinto T, Golomb G. Disposition of alendronate following local delivery in a rat jaw. *J Periodontol*. 1999;70:893–895.