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BASIC RESEARCH

Implant-delivered Alendronate Causes a Dose-dependent Response on Net Bone Formation Around Porous Titanium Implants in Canines

Jenny Ann Pura MSc, J. Dennis Bobyn PhD, Michael Tanzer MD

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Abstract

Background Bony fixation of cementless orthopaedic implants is not always achieved, particularly in challenging scenarios such as revision surgery, trauma, and tumor reconstruction. An adjunct therapy for improving porous implant fixation could improve the reliability and durability of these reconstructive procedures.

Questions/purposes In this study, we asked whether there is a positive and dose-dependent effect of the local release of the bisphosphonate alendronate from (1) alendronate/hydroxyapatite (HA) porous-coated titanium implants compared with bare metal porous controls; and (2) alendronate/HA on porous-coated titanium implants compared with HA-coated porous controls with respect to extent of bone ingrowth, bone apposition, and periimplant bone formation in a canine model?

Methods Three-dimensional printed porous-coated cylindrical implants coated with three different doses (0.02, 0.06, and 0.18 mg/cm^2) of alendronate were inserted bilaterally in the intramedullary canal of the proximal femora of 15 adult mongrel dogs (age range, 3–9 years; mean, 5 years) weighing between 36 kg and 60 kg (mean, 43 kg). In each dog, an implant coated with HA and one of three different doses of alendronate was inserted on one side while the contralateral femur had a bare metal porous control implant and an identical control implant with a coating of HA. The dose effect of locally released alendronate on the extent of bone ingrowth, bone apposition, and periimplant bone was assessed by backscattered electron microscopy of three pairs of cross-sections taken from each implant at 12 weeks after surgery. A linear mixed model was used to perform the statistical analyses to account for the correlation in the data resulting from the multiple measures performed on each dog.

Results Compared with paired bare metal controls, periimplant bone increased by 92% ($p = 0.007$), and 114% ($p < 0.001$) in the femora with the alendronate implants with a dose of 0.06 mg/cm^2, or 0.18 mg/cm^2, respectively. At a dose of 0.02 mg/cm^2, there was no difference (46% change; $p = 0.184$, with the numbers available). The comparison of the alendronate-dosed implants with their HA-coated controls showed that the intermediate dose of 0.06 mg/cm^2 alendronate had the greatest effect on net bone formation. Bone apposition was enhanced with the 0.06-mg/cm^2 alendronate femoral implants (82%; $p = 0.008$), although there was no change in bone ingrowth

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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 the McGill University Hospital Centre, Montreal, Quebec, Canada.

J. A. Pura, J. D. Bobyn, M. Tanzer
Jo Miller Orthopaedic Research Laboratory, Montreal General Hospital, Montreal, QC, Canada

J. D. Bobyn, M. Tanzer
Division of Orthopaedic Surgery, Department of Surgery, McGill University, Montreal, QC, Canada

J. A. Pura (✉)
Montreal General Hospital, 1650 Cedar Avenue, Room C9-136, Montreal, QC H3G1A4, Canada
e-mail: jennyann.pura@mail.mcgill.ca

(37% change; p = 0.902, with the numbers available). When compared with the HA-coated control implants, the greatest effect of the alendronate-dosed implants was the increased amount of periimplant bone at the intermediate dose of 0.06-mg/cm^2 (108%, p = 0.009). There was no effect of the low (0.02-mg/cm^2) and high (0.18-mg/cm^2) alendronate-dosed implants (4%, and 6%, respectively; p = 0.321, p = 0.502). Overall, all three alendronate-dosed implants revealed little to no effect on bone ingrowth compared with the HA-coated control implants.

Conclusions The local release of alendronate from a three-dimensional printed porous-coated implant from the three doses studied showed an overall improvement in bone apposition and periimplant bone at the intermediate dose compared with bare metal or with HA-coated controls, although the effect was more pronounced compared with bare metal. Long-term studies to show the effects of localized alendronate delivery and mechanical fixation would be the next step for future studies.

Clinical Relevance Local release of alendronate from a three-dimensional printed porous-coated implant may improve the reliability of cementless fixation of currently available porous-coated bare metal implants.

Introduction

The reliability of cementless implant fixation can be improved, especially in revision hip surgery or in patients whose potential for bone healing may be less than ideal [6, 21]. One approach to enhance fixation is to use bisphosphonates to modulate the bone healing response at the implant-bone interface and the surrounding region. Bisphosphonates partially suppress the resorptive phase of bone remodeling, thereby changing the balance of local bone healing toward a net increase in bone formation. As such, they have potential for use with orthopaedic devices designed for total joint replacement. Several clinical studies of large patient cohorts have shown that systemic delivery of bisphosphonates can reduce revision rates for total joint replacement implant loosening [2, 3, 7, 20], but systemic treatment exposes the entire skeleton to the drug, thereby subjecting patients to the associated risks of side effects or adverse events such as nausea, vomiting, epigastric pain, and dypsepsia [17]. This potentially can be avoided by locally releasing the bisphosphonate directly from the implant to the surrounding bone as seen in our previous radioactive studies showing insignificant levels of the drug outside the direct periimplant region exposed to the bisphosphonate [5]. Prior studies in animal models with various bisphosphonates have shown that locally administered or released bisphosphonates enhanced bone formation around implants [4, 8–11, 13, 15, 19, 24, 25, 30]. Other beneficial effects of local bisphosphonates in the short and long term include reduced periimplant bone resorption [11]; increased bone-implant contact [24, 29], increased mechanical strength of the implant-bone interface [14, 18], and increased bone ingrowth [4, 9].

Alendronate is a candidate for the clinical application of bisphosphonate-coated orthopaedic implants because it has a long history of clinical use and is widely accepted in the medical community for treatment of osteoporosis [1, 28, 30]. In a previous pilot study in dogs, using two different alendronate doses on porous implants, the efficacy of alendronate on periimplant formation was seen with the higher dose resulting in greater local bone formation 12 weeks after surgery [5]. Expanding from the pilot study, it also was necessary to determine the therapeutic dose range of contemporary implants similar to those available today.

In the current study, we asked whether there is a positive and dose-dependent effect of the local release of the bisphosphonate alendronate from: (1) alendronate/hydroxyapatite (HA) porous-coated titanium implants compared with bare metal (bare metal) porous controls; and (2) alendronate/HA on porous-coated titanium implants compared with HA-coated porous controls with respect to extent of bone ingrowth, bone apposition, and periimplant bone formation in a canine model?

Materials and Methods

Implant Structure

Cylindrical implants measuring 9 mm in diameter and either 45 mm or 90 mm in length were fabricated from titanium alloy (Ti-6Al-4V) using a direct metal laser sintering technique (ie, metal three-dimensional printing) with a build tolerance of ± 10 μm (Pipeline Biotechnology, Cedar Knolls, NJ, USA). The implants had a 6-mm solid core and a 1.5-mm thick outer porous structure consisting of a random network of struts with a mean pore size of 400 μm and a volume porosity of 65% (Fig. 1). Currently, there are no HA-coated orthopaedic implants made by direct metal laser sintering technique that are FDA-approved. All direct metal laser-sintered implants used today are bare metal. As such, one control was the bare metal porous control, which was thought to be comparable to present day implants. Bare metal control implants were left as manufactured without surface additives. The other control evaluated was an identical control implant with a coating of HA without the drug. Test implants were also plasma spray-coated with a thin (10–15 μm) layer of HA (Pipeline Biotechnology) (98% purity, 99% density, 64% crystallinity, calcium: phosphate ratio, 1.67) such that only the outermost porous structure was HA-coated, leaving the

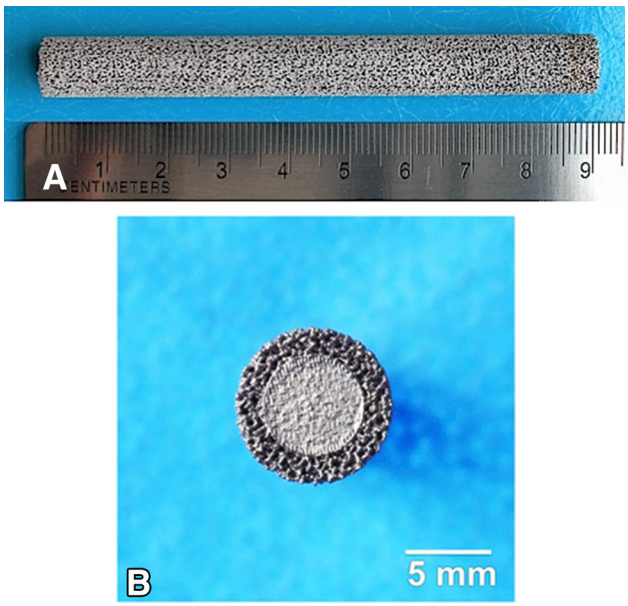

Fig. 1A–B (**A**) Longitudinal and (**B**) cross-sectional views of a hydroxyapatite-coated porous titanium femoral implant (9 mm × 90 mm) are shown.

innermost pores uncoated. The test implants subsequently were coated with commercially pure, laboratory-grade alendronate (alendronic acid trihydrate; Reddy Laboratories, Bachupally, Hyderabad, Andhra Pradesh, India) in three doses normalized to the outer implant surface area. Alendronate was dissolved in aliquots of distilled deionized water to produce doses of 0.02 mg/cm^2, 0.06 mg/cm^2, and 0.18 mg/cm^2. The 0.06 mg/cm^2 alendronate dose was chosen based on the previous successful results using a similar implant [5]. To find the lowest effective dose, a dose ⅓ this concentration was chosen (0.02 mg/cm^2). The highest dose was chosen to conform to FDA requirements of drug testing in multiples of three. Each alendronate aliquot in solution was systematically and uniformly added to an implant in a dropwise fashion along its length and around its circumference using a micropipette. As previously reported, the deposition process resulted in homogeneous saturation of the porous structure with fluid that permeated the inner pore depths through surface tension effects [16]. This technique resulted in chemical (strong) immobilization of alendronate to the outer HA coating and physical (weak) deposition of alendronate onto the innermost non-HA-coated porous structure, as described in earlier studies [4, 24]. The alendronate-dosed implants were dried overnight in an oven at 37°C and all implants were sterilized with 2.5 MRad gamma irradiation. Ancillary in vitro elution studies, following published protocols [4, 24], confirmed an initial alendronate burst release of 40% ± 10% within the first hour of soaking in distilled deionized water (owing to hydration and diffusion of bisphosphonate from the innermost, non-HA-coated pores) followed by a longer-term, slower release from the outermost HA coating (where the bisphosphonate initially was immobilized).

A power analysis was performed to estimate the sample size required for detecting a difference in the bone formation parameters with and without alendronate coating. Increases of 60% combined with SDs of 40% were conservatively estimated based on prior canine studies using the same implant model [4, 24]. Setting the α error level to 0.05 and β level error of 50%, the estimated sample size for each alendronate dose was four.

Surgical Procedure

Fourteen healthy, skeletally mature mongrel dogs (eight males, six females) weighing between 35 kg and 45 kg were used for this study. The institution's ethical review committee in accordance with the Canadian Council on Animal Care approved the animal study protocols. There were five dogs in each of the three dose cohorts (0.02 mg/cm^2, 0.06 mg/cm^2, 0.18 mg/cm^2 alendronate). In each dog, using an open intramedullary nailing type of surgical procedure, the implants were placed in the intramedullary canal of the proximal femora. Implant placement was done carefully so that the implant on each side was in the same segment of the femur as the contralateral implant. A non-weightbearing implant model was chosen to eliminate the variable of loading and the clinical problems that can occur after joint replacement (eg, dislocation, implant loosening). For each dog in a dose cohort, bilateral femoral surgery initially was performed using a 90-mm long alendronate-dosed implant on one side and two 45-mm control implants stacked one on the other on the contralateral side. The bare metal control was placed superiorly in the metaphysis and the HA-coated control was placed just inferiorly in the femoral diaphysis.

Approval was obtained from the Institutional Animal Care Review Committee. All dogs were prepared for surgery using an identical anesthesia protocol and all dogs received the same drugs throughout the experiment. Approximately 30 minutes before surgery, a subcutaneous injection of 0.3 mg/mL buprenorphine was given. Fifteen minutes before induction, the dog received a 10 mg/mL butorphanol, 25 mg/mL acepromazine, and 0.5 mg/mL atropine injection. A 100-µg fentanyl patch was placed for postoperative analgesia. For induction, sodium pentobarbital (Somnotol; Ceva Santé Animale, Libourne, France) 54.7 mg/mL was given. Antibiotic prophylaxis was administered with 500 mg/5 mL of Cefazolin (Apotex Inc, Quebec, Canada) intravenous push before the start of surgery and repeated after skin closure. Anesthesia was

maintained with 1.5% to 2% isoflurane and 2 L oxygen. After surgery, the dogs were given 0.3 mg/mL buprenorphine as a subcutaneous injection. This dose of 0.01 to 0.02 mg/kg was given every 6 to 8 hours until 12 to 18 hours once the effects from the fentanyl patch began. Postoperatively, 25 to 50 mg/kg/day of cephalexin (500 mg/tablet) was given orally twice a day for 10 days.

All 15 dogs tolerated the surgery well and were ambulatory and active within 2 to 3 days after surgery.

After the initial surgery at 12 weeks, an anesthetic overdose of pentobarbital, 120 mg/kg (240 mg/mL) was given. The femora were harvested to yield 12-week femoral specimens. There were no infections or other postoperative complications. However, postmortem radiographs showed that the alendronate-dosed implant of one dog in the 12-week 0.06-mg/cm^2 cohort was surgically malpositioned and perforated the femoral intramedullary canal. Because this prevented the possibility of paired data comparison, this dog was excluded from the data analysis and the dose-response study included five dogs in the 0.02-mg/cm^2 and 0.18-mg/cm^2 cohorts and four dogs in the 0.06-mg/cm^2 cohort.

Sample Preparation

The bones were processed for undecalcified thin-section histologic analysis [4, 24]. Each bone-implant construct was sectioned transversely with a low-speed diamond cutoff apparatus (Buehler, Lake Bluff, IL, USA) at 2-mm intervals and the sections were contact-radiographed with a Faxitron® Model 43855A system (Faxitron® X-Ray Corp, Lincolnshire, IL, USA). All implants appeared stable based on visual inspection of contact radiographs of the femora. No radiographs were taken before sacrifice. Three paired sections from the alendronate-dosed and control implants were matched based on anatomic position from the top, middle, and bottom ⅓ of each sectioned implant and imaged with backscattered scanning electron microscopy (Hitachi S-3000N; Hitachi High Technologies America, Inc, San Jose, CA, USA) at ×20 magnification. Backscattered imaging was conducted to better differentiate between calcified bone and noncalcified bone. Computerized image analysis based on gray-level discrimination was performed (white was identified as the implant, black as void space, and grey as calcified bone) using ImageJ software Version 1.6.0–12 (National Institutes of Health, Bethesda, MD, USA) and a validated program to measure three bone formation parameters: bone apposition, bone ingrowth, and periimplant bone. Bone apposition was defined as the percentage of the implant perimeter that was in direct contact with bone. This was calculated by quantifying the total length of each bone segment that is completely at the interface of the implant and then dividing that value by the circumference of the implant. Bone ingrowth was defined as the percentage to which the bone has occupied the accessible space in the porous coating of the implant. The defined region of interest was identified as the total area that the implant (seen as white) covered. The implant's area was subtracted from the total region of interest to generate the remaining area as void space. In this available space, the percentage of grey was identified as bone. This value resulted in the percent bone ingrowth based on the total area minus the implant. Periimplant bone was defined as the area surrounding the implant. A radius of 2.5 mm from the implant was specified based on a previous study that showed that bone formation that resulted from local bisphosphonate elution was localized to the periimplant region [5]. Periimplant bone was calculated by taking the percentage of bone found in the area of the 2.5 mm radius and dividing this by the total area defined by this medullary space, not including the area of the implant. To account for implants in contact with cortical bone or in the designated periimplant space, the area occupied by the cortical bone was excluded.

Statistical Analysis

The paired data from each dose group of three section pairs were combined into mean values for analysis to determine the mean differences between each alendronate dose and the respective controls. Each data point measured the drug effect (alendronate versus control) on an outcome (bone ingrowth, bone apposition, or periimplant bone) while accounting for the section on which the measure was taken. To account for the correlation in the data resulting from the multiple measures performed on each dog, linear mixed models were used to perform the statistical analyses. A p-value less than 0.05 was used to test for significant differences between groups.

Results

From contact radiographs, there was no noticeable difference in the amount of periimplant bone for any of the alendronate doses compared with the bare metal control (Fig. 2). The high-resolution contact radiographs of the transverse histologic sections indicated all alendronate-dosed and control implants were surrounded by normal-appearing bone with no evidence of radiographic loosening. More periimplant bone was typically apparent around alendronate-dosed implants compared with controls. This finding was more clearly evident on visual inspection of the

backscattered scanning electron micrographs of the alendronate doses 0.02 mg/cm^2 (Fig. 3), 0.06 mg/cm^2 (Fig. 4), and 0.18 mg/cm^2 (Fig. 5). The overall quantitative bone formation data showed considerable interanimal variability in absolute values for the 12-week response data comparison between alendronate-dosed implants and bare metal control implants (Table 1). This is helpful to evaluate mean relative differences in each alendronate-dose cohort in addition to the mean absolute differences (Fig. 6). The lowest dose, 0.02 mg/cm^2 alendronate, showed no difference in periimplant bone formation (+46%; p = 0.184), bone ingrowth (+7%; p = 0.433), or bone apposition (+44%; p = 0.053) compared with their bare metal controls. The intermediate 0.06-mg/cm^2 alendronate dose showed increases for the alendronate-dosed implants compared with the paired bare metal control implants for bone apposition (+82%; p = 0.008) and periimplant bone (+92%; p = 0.007). The highest 0.18-mg/cm^2 alendronate dose showed a reduction in bone ingrowth (−35%; p = 0.003), but a substantial increase (+114%; p < 0.001) in periimplant bone.

From contact radiographs, there was no noticeable difference in the amount of periimplant bone for any of the alendronate doses compared with the HA controls (Fig. 2). The high-resolution contact radiographs of the transverse histologic sections indicated all alendronate-dosed and HA control implants were surrounded by normal-appearing bone with no evidence of radiographic loosening. More periimplant bone typically was apparent around alendronate-dosed implants compared with HA controls. This finding was more clearly evident on visual inspection of the backscattered scanning electron micrographs of the alendronate doses 0.02 mg/cm^2 (Fig. 3), 0.06 mg/cm^2 (Fig. 4), and 0.18 mg/cm^2 (Fig. 5). The quantitative comparison of the alendronate-dosed implants with their HA-coated controls showed that the intermediate dose of 0.06 mg/cm^2

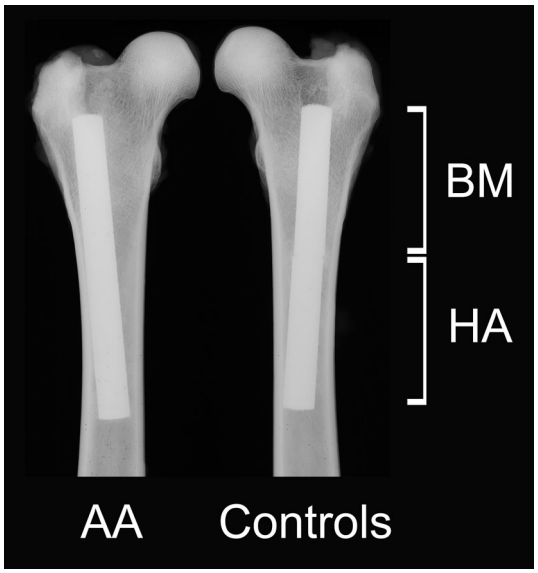

Fig. 2 A contact radiograph of bilateral femurs obtained after sacrifice, shows placement of the 90-mm long alendronate (AA)-dosed femoral implant and the two stacked 45-mm control femoral implants; the implants were stacked to minimize the gap between the bare metal (BM) and hydroxyapatite (HA) control implants.

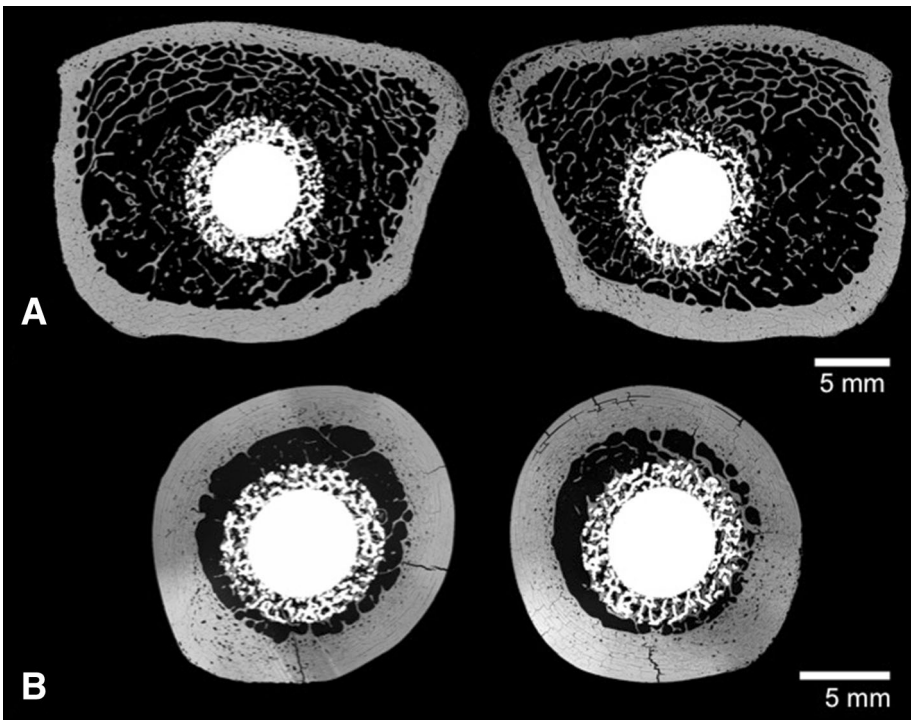

Fig. 3A–B Paired 12-week femoral cross-sections of the 0.02-mg/cm^2 alendronate dose cohort with (**A**) bare metal and (**B**) hydroxyapatite control are shown in these backscattered electron microscopy images. There is increased periimplant bone formation around the alendronate-dosed implants compared with the contralateral controls.

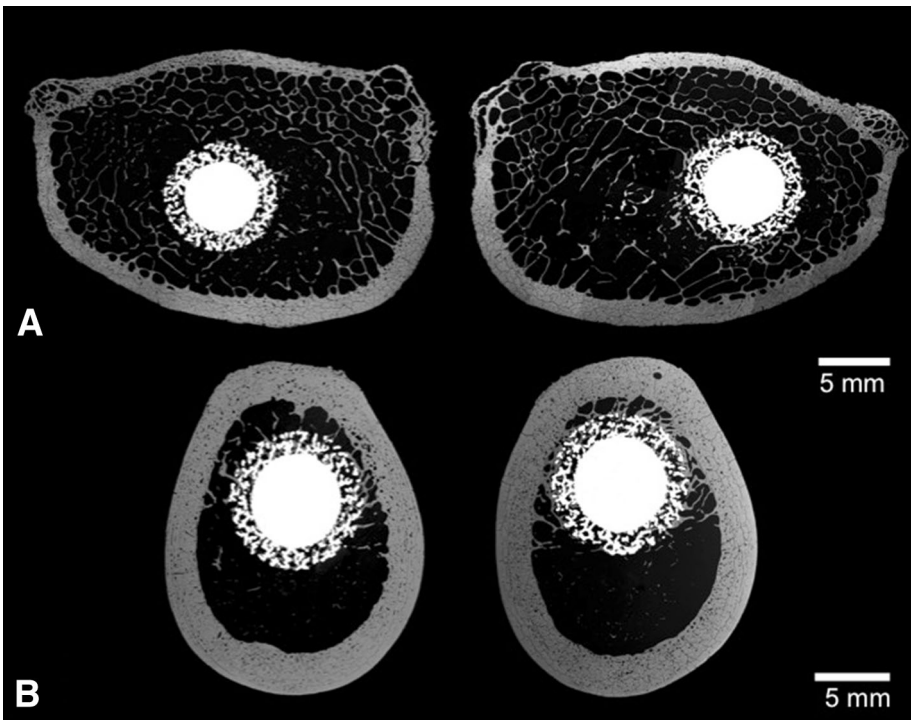

Fig. 4A–B Backscattered electron microscopy images of paired 12-week femoral cross-sections of the 0.06-mg/cm^2 alendronate dose cohort with (**A**) bare metal and (**B**) hydroxyapatite controls show increased periimplant bone formation around the alendronate-dosed implants compared with the controls.

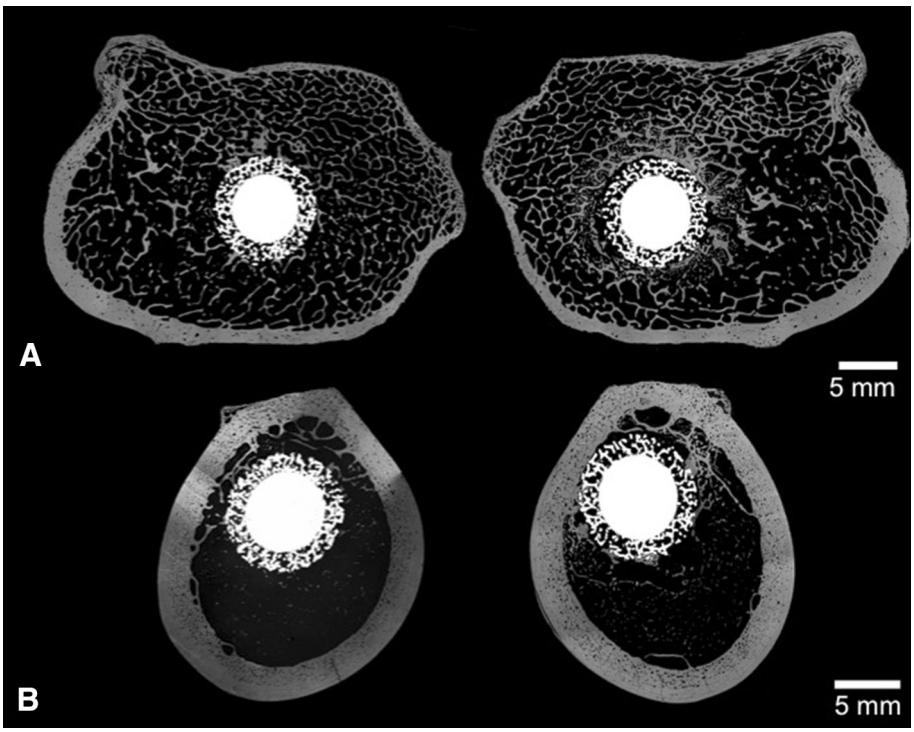

Fig. 5A–B Backscattered electronic microscopy images of paired 12-week femoral cross-sections of the 0.18-mg/cm^2 alendronate dose cohort with (**A**) bare metal and (**B**) hydroxyapatite controls show increased periimplant bone formation around the alendronate-dosed implants compared with the controls.

alendronate had the greatest effect on net bone formation (Table 2). Of the three doses, the 0.06-mg/cm^2 alendronate dose showed the greatest improvement in periimplant bone formation (+108%; p = 0.009) (Fig. 7). Neither the 0.06 mg/cm^2 nor the 0.18 mg/cm^2 alendronate-dosed cohorts with HA-coated control implants, which were located in the canal of the primarily fatty femoral diaphysis, positively enhanced bone ingrowth or bone apposition. On balance, the 0.06-mg/cm^2 alendronate dose was the most consistent for overall improvement of at least one or two of the three bone formation parameters in bare metal (Table 1) and HA (Table 2) control comparisons.

Table 1. Twelve-week response data comparison between alendronate-dosed implants and bare metal control implants

Dose	Bone ingrowth in BM control	Bone ingrowth in alendronate	Bone ingrowth mean relative difference	Bone apposition in BM control	Bone apposition in alendronate	Bone apposition mean relative difference	Periimplant bone BM control	Periimplant bone alendronate	Periimplant bone mean relative difference
0.02 mg/cm^2	22 ± 8	25 ± 10	+7%	18 ± 6	24 ± 7	+44%	12 ± 7	14 ± 7	+46%
			p = 0.433			p = 0.053			p = 0.184
0.06 mg/cm^2	22 ± 16	22 ± 5	+37%	16 ± 4	24 ± 7	+82%	9 ± 1	14 ± 3	+92%
			p = 0.902			p = 0.008			p = 0.007
0.18 mg/cm^2	16 ± 5	9 ± 4	−35%	17 ± 2	21 ± 8	+17%	11 ± 3	23 ± 6	+114%
			p = 0.003			p = 0.081			p < 0.001

Absolute values listed as mean ± SD; relative differences listed as percentage difference; five animals for all cohorts except four for 12-week 0.06-mg/cm^2 cohort; BM = bare metal.

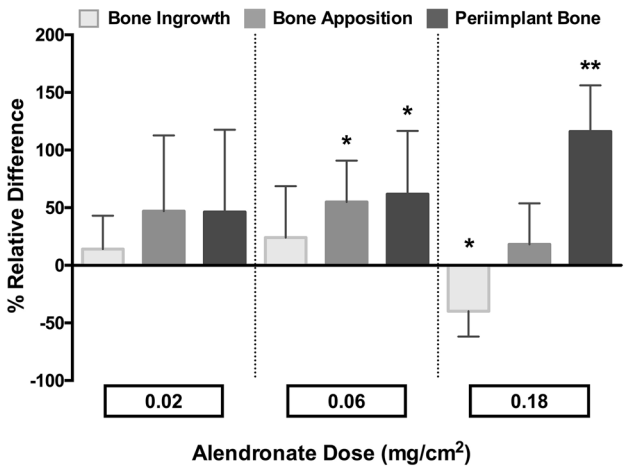

Fig. 6 The 12-week femoral relative differences (mean and SD) with 0.02 mg/cm^2 alendronate, 0.06 mg/cm^2 alendronate, and 0.18 mg/cm^2 alendronate doses compared with their bare metal control are shown. *p < 0.05; **p < 0.001.

Discussion

The biologic fixation of porous implants used in reconstructive procedures is not always reliable, especially in circumstances in which native bone stock and/or healing capacity is suboptimum [1, 6, 21, 28]. Using the implant to deliver a bisphosphonate compound to surrounding bone has been shown in animal studies to enhance local bone formation [4, 5, 8, 24], but questions regarding the optimum dose remain. Our study was designed to assess an appropriate dose for potential clinical use. The primary findings were that overall, of the three dose levels we examined, the 0.06 mg/cm^2 alendronate dose provided the best overall improvement for enhancing bone apposition and periimplant bone formation parameters for bare metal and HA coated three-dimensional printed porous implants.

There were several limitations to this study. First, the intramedullary implant model does not represent a fully functioning joint replacement with attendant physiologic loading. As such, the bone-implant interface did not experience the forces that can influence bone remodeling. However, the nonweightbearing implant model was chosen to eliminate the variable of loading and the clinical problems that can occur after joint replacement (eg, dislocation, implant loosening). Another limitation was that the paired section control data were obtained in different parts of the femurs. Stacking of the two controls was done to minimize the number of animals needed to do the study. The density of cancellous bone differs between the proximal and distal femoral regions, being more abundant in the proximal femora. This is why the data were paired and each anatomic site was not compared with the other. Related to this was the inevitable surgical challenge in positioning

Table 2. Twelve-week response data comparison between alendronate-dosed implants and HA control implants

Dose	Bone ingrowth in HA control	Bone ingrowth in alendronate	Bone ingrowth mean relative difference	Bone apposition in HA control	Bone apposition in alendronate	Bone apposition mean relative difference	Periimplant bone HA control	Periimplant bone alendronate	Periimplant bone mean relative difference
0.02 mg/cm^2	27 ± 7	27 ± 14	−6%	19 ± 7	27 ± 11	+45%	8 ± 4	6 ± 3	+4%
			p = 0.926			p = 0.012			p = 0.321
0.06 mg/cm^2	26 ± 11	22 ± 13	−3%	14 ± 6	22 ± 8	+85%	5 ± 1	9 ± 2	+108%
			p = 0.355			p = 0.132			p = 0.009
0.18 mg/cm^2	22 ± 7	15 ± 19	−7%	20 ± 4	24 ± 25	+5%	9 ± 2	14 ± 9	+6%
			p < 0.001			p = 0.221			p = 0.502

Absolute values listed as mean ± SD; relative differences listed as percentage difference; five animals for all cohorts except four for 12-week 0.06-mg/cm^2 cohort; HA = hydroxyapatite.

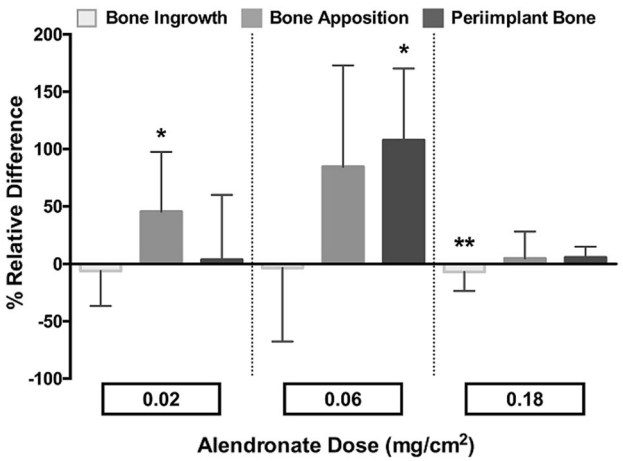

Fig. 7 The 12-week femoral relative differences (mean and SD) with 0.02 mg/cm^2 alendronate, 0.06 mg/cm^2 alendronate, and 0.18 mg/cm^2 alendronate doses compared with hydroxyapatite are shown. *p < 0.05; **p < 0.001.

implants in left and right bones in exactly the same anatomic location and alignment, sometimes causing differences in periimplant bone density along the implant lengths. This was addressed in the dose-response studies by anatomically matching the left and right bone sections or segments (proximal sections and distal sections) under analysis. We do not believe that there were any meaningful effects on the control side from systemic distribution of alendronate from the doped implants, based on a previous study of radioactivity showing insignificant levels of drug outside the direct periimplant region exposed to the bisphosphonate [16]. Another limitation was that the use of mongrel dogs precluded controlling for age, sex, size, and breed. In this regard it may have been preferable to use purebred animals of one sex in a relatively narrow age range to better eliminate variables that might influence the bone healing response in the presence of bisphosphonate. Furthermore, it is not clear from this study if the sex of the dog affects the activity of alendronate on bone ingrowth, or periimplant bone formation. The sample was too small to be able to know.

Although in vivo studies have shown HA can improve bone formation and allow gap healing, its effectiveness in clinical use has been conflicting [22, 23, 26, 27]. Implants with relatively smooth porous coatings or surfaces will have a greater benefit from HA coatings than implants that have inherently rougher surface microtexture [12]. In the current study, the three alendronate-dosed cohorts with HA-coated implants showed no positive effect on bone ingrowth or bone apposition. Whether this is related solely to HA or influenced by the extent of cancellous bone surrounding the implant in these two different regions of the femur is unclear. The primary effect of alendronate on the

HA control implants in the current study was a net increase in periimplant bone formation (Table 2), as initially reported by Bobyn et al. [5], This degree of periimplant bone formation is even more impressive than that seen in the proximal femur because of the paucity of cancellous bone surrounding the implant in the canine diaphysis.

There was generally a periimplant osteogenic response to all three alendronate doses (Table 1). However, the implants with the highest 0.18-mg/cm^2 alendronate dose had less bone ingrowth at 12 weeks and no improvement in bone apposition, thereby excluding it as a clinically appropriate dose. The smallest 0.02-mg/cm^2 alendronate dose resulted in less absolute periimplant bone relative to the intermediate 0.06-mg/cm^2 alendronate dose. At 12 weeks, it showed no increases in any of the bone formation parameters. The intermediate 0.06-mg/cm^2 alendronate dose provided a net gain in all three bone formation parameters (although the change in bone ingrowth was not significant, with the numbers available) and therefore this dose appears to be the most appropriate target for subsequent studies. Our study did not address the bone outside our defined region of interest. However, we assumed, based on a previous study, that the effect of the bisphosphonate is highly localized and did not have any significant accumulation outside the periimplant bone we analyzed in this study [16].

Clinical studies of large patient cohorts have shown that chronic systemic bisphosphonate therapy can offer benefits to patients undergoing total joint arthroplasty, including reduction of periprosthetic bone loss [2, 3], reduction of implant migration [7], and reduction in revision rate [20]. However, these benefits need to be balanced against the risk of adverse events related to chronic bisphosphonate therapy [17], including atypical femur fracture. The rationale for local alendronate delivery is very distinct from systemic dosing, in that local delivery uses a single, relatively low dose of a relatively mild bisphosphonate, thus potentially avoiding the exposure to systemic dosing and its attendant risks; however, this needs to be verified. Based on previous studies [4, 5, 24] and the pharmacokinetics of bisphosphonates, we theorize that once the initial net gain in local bone formation occurs (hopefully improving the rate and extent of biologic implant fixation), the local bisphosphonate presence may decrease with time while the bone-implant interface remodels as required in response to physiologic loading.

Based on this in vivo canine study and a pilot study [5], it appears that an alendronate dose in the range of 0.06 mg/cm^2 may be a reasonable level to further study for enhancing periimplant bone around bare metal and HA coated three-dimensional printed porous-coated implants. Additional studies in humans are required to clarify its potential in enhancing fixation of porous cementless implants, with and without compromised bone stock.

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