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Local Bisphosphonate Treatment Increases Fixation of Hydroxyapatite-Coated Implants Inserted with Bone Compaction

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Abstract

It has been shown that fixation of primary cementless joint replacement can independently be enhanced by either: (1) use of hydroxyapatite (HA) coated implants, (2) compaction of the peri-implant bone, or (3) local application of bisphosphonate. We investigated whether the combined effect of HA coating and bone compaction can be further enhanced with the use of local bisphosphonate treatment. HA-coated implants were bilaterally inserted into the proximal tibiae of 10 dogs. On one side local bisphosphonate was applied prior to bone compaction. Saline was used as control on the contralateral side. Implants were evaluated with histomorphometry and biomechanical pushout test. We found that bisphosphonate increased the peri-implant bone volume fraction (1.3-fold), maximum shear strength (2.1-fold), and maximum shear stiffness (2.7-fold). No significant difference was found in bone-to-implant contact or total energy absorption. This study indicates that local alendronate treatment can further improve the fixation of porous-coated implants that have also undergone HA-surface coating and peri-implant bone compaction.

Keywords

bisphosphonate; implant fixation; bone compaction; canines

Long-term survival of uncemented total joint replacements relies upon initial mechanical stability and sustained osseointegration in order to prevent migration and implant loosening.^{1–4}

Initial mechanical stability depends in part on press-fit implantation of components.⁵ We have previously shown that bone compaction, a bone preparation technique, can enhance initial and early mechanical stability.^{6, 7} The bone compaction technique creates a zone of in situ autograft by sequentially expanding an undersized cavity before implant insertion. The implant is placed in tight press-fit.⁸ Local alendronate treatment can preserve the zone of autograft thus increasing the biomechanical fixation of porous coated Ti-alloy implants. Alendronate is a second-generation bisphosphonate with the ability to inhibit bone resorption.⁹ Several studies have investigated the effect of bisphosphonate on various types of implant fixation.^{10–13} The general findings are increased osseointegration or reduced implant migration.

The fixation of an implant is not only dependent on the quality of the peri-prosthetic bone, but also depends on the surgical technique, and surface coating.¹⁴ Several experimental and clinical studies have shown that implants coated with surface coating of hydroxyapatite (HA) increase implant fixation and osseointegration.^{15–17} Given the good performance of the HA-coating on the bone/implant interface and also with the surgical technique of bone compaction on the peri-implant bone, we found it interesting to investigate whether implant fixation can be further improved by local application of alendronate.

We tested the hypothesis that local alendronate treatment would increase the biomechanical fixation, peri-implant bone volume fraction, and bone-to-implant contact of HA-coated implants inserted with bone compaction after 12 weeks in a canine model.

MATERIALS AND METHODS

Study Design

We used 10 purpose-breed female hound dogs with a mean weight of 23 kg (20–25 kg). Skeletal maturity of all dogs was confirmed by radiographs of the distal femur and proximal tibia, which showed closure of the respective epiphyseal plates. This study was approved by our institution's Animal Care and Use Committee. Institutional guidelines for the treatment and care of experimental animals were followed.

Using the compaction technique (Fig. 1), one plasma-sprayed HA-coated titanium implant was inserted into the proximal part of each tibia. Alendronate was administered locally in one of the knees. Saline was used as a control in the contralateral knee. The alendronate and control implants were systematically alternated between the left and right knee with random start. The observation period was 12 weeks.

Implants

We used 20 custom-made titanium alloy (Ti-6Al-4V) implants with a plasma-sprayed porous-coated Ti-6Al-4V surface with an additional 50- μ m layer of plasma-sprayed HA. The implants were cylindrical with a height of 10 mm and diameter of 8.0 mm. The surface coatings were applied by Biomet Inc. (Warsaw, IN) in the manner used to prepare clinical human implants. The used surface coating technique results in a roughness (R_a) of 41 μ m and a pore size of 200–1000 μ m at the substrate and the surface of the coating, respectively.⁴ X-ray diffraction analysis performed by manufacture demonstrated a crystallinity of 60% and that 45–70% of the coating consisted of HA.

Surgery

All surgery was done using sterile conditions and with the dogs under general anesthesia. The proximal anteromedial surface of the tibia was exposed using a medial incision. Then a 2.5-mm K-wire was inserted perpendicular into the surface of the proximal part of tibia. The K-wire was inserted 20 mm distal to the tibia plateau. Over the K-wire, a cannulated step drill with a diameter of 5.0 mm the first distal 10 and 8 mm proximally was used to drill a 12.0-mm deep hole. All drilling was at low speed with two revolutions per second to avoid thermal trauma to the bone. Prior to surgery, 120 mg alendronate (Merck Sharp & Dohme, West Point, PA) was dissolved in 60 mL saline. This alendronate solution was kept sterile at 5°C and used for all 10 surgeries. In one knee, 5mL of the alendronate solution (2 mg alendronate per 1 mL saline) was injected with a syringe into the hole for 60 s. The same amount of saline was used as control in the contra lateral knee. After soaking the bone for 60 s, excess bisphosphonate or saline solution together with blood coming from the marrow cavity was sucked away. The bone cavity was not irrigated. Next, the diameter of the 10.0 mm deep part of the hole was gradually expanded from 5.0 to 8.0 mm using custom-

designed compaction tools (Fig. 1). This resulted in a 12.0-mm deep hole with a diameter of 8.0 mm, where the diameter at the 10.0-mm depth was in part obtained by compaction and the diameter at the 2.0-mm superficial part was obtained by drilling. Immediately after compaction, the implant was inserted into the 10.0-mm deep part of the cavity. This ensured that the implant was surrounded by compacted cancellous bone. Post-operative radiographs were taken to confirm correct placement of the implant in cancellous bone. Antibiotics (Rocephin, Sandoz GmbH, Kundl, Austria) were administered immediately before surgery and 3 days postoperatively. Analgesics (Buprenox, Hospira Inc., Lake Forest, IL) were used for the first 3 postoperative days. The dogs were allowed unrestricted weightbearing postoperatively. All dogs were euthanized 12 weeks postoperatively, and the bones were collected for preparation and analyses.

Specimen Preparation

Two specimens containing the implant and surrounding bone were cut from each tibia perpendicular to the long axis of the implant using a water-cooled band saw (Exact Apparatebau, Nordenstedt, Germany) (Fig. 2). The first and most superficial specimen with a thickness of 3.5 mm was stored at -20°C and used for later biomechanical testing. The second specimen with a thickness of 6.5 mm was fixed in 70% ethanol and used for later histomorphometrical analysis. Preparation of specimens and subsequent evaluation were performed blinded.

Biomechanical Testing

Implants were tested to failure by axial push-out test on an MTS Bionics Test Machine (MTS, Eden Prairie, MN). The specimens were placed on a metal support jig with a 9.4-mm diameter central opening. Centering the implant over the opening assured a 0.7-mm distance between the implant and support jig as recommended.¹⁸ Implants were pushed from the peripheral side toward the inside of the bone. A preload of 3 N defined the start of the test. We used a displacement rate of 5 mm/min, and continuous load versus displacement data were recorded. Ultimate shear strength (MPa) was determined from the maximum force applied until failure of the bone-implant interface. Maximum shear stiffness (MPa/mm) was obtained from the slope of the linear section of the load versus displacement curve. Total energy absorption (kJ/m^2) was calculated as the area under the load displacement curve until failure. All push-out parameters were normalized by the cylindrical surface area of the transverse implant section tested.

Histomorphometry

Specimens were dehydrated gradually in ethanol (70–100%) containing basic fuchsin, and embedded in methylmethacrylate. Four vertical uniform random sections were cut with a hard tissue microtome (KDG-95, MeProTech, Heerhugowaard, The Netherlands) around the central part of each implant as described by Overgaard et al.¹⁹ Before making the sections, the implant was randomly rotated around its long axis. The sections were cut parallel to this axis. The 25 μm -thick sections were cut with a distance of 400 μm , and counterstained with 2% light-green (BDH Laboratory Supplies, Poole, England).²⁰ With this protocol, bone was stained green and nonmineralized tissue red.

Blinded histomorphometrical analysis was done using a stereological software program (CAST grid, Olympus Denmark A/S, Ballerup, Denmark). Bone-to-implant contact was defined as the implant surface covered with woven or lamellar bone and estimated using sine-weighted lines, whereas bone volume fraction was estimated by point counting in a 0–1000 μm around the implants. Discrimination between woven and lamellar bone was done based on morphological characteristics: woven bone had random orientation of osteocytes, large osteocytes, and random orientation of collagen fibers, whereas lamellar bone was

arranged in parallel lamellae. In addition, polarized microscopy applied to reveal the parallel lamellar structure of lamellar when difficulties in discrimination between woven and lamellar bone were encountered. The specimen preparation and stereological software made it possible to obtain unbiased estimates even though anisotropy of cancellous bone exists.¹⁹

Statistical Analysis

We used Intercooled Stata 9.0 (Stata Inc., College Station, TX) for statistical analysis. All variables were normally distributed both before and after log transformation. Statistical analyses were done on ratios between paired data, which were not normally distributed. All variables were therefore log-transformed and Student's paired *t*-test was performed on absolute differences between normally distributed log-transformed paired data. Two tailed *p*-values below 0.05 were considered statistically significant. Results are presented as medians of relative differences between the paired data. The 95% confidence intervals were obtained by back transformation of log-transformed data unless otherwise stated.

Correlation analyses were done between relative paired increases in biomechanical and histomorphometrical parameters. All assumptions for correlation analysis were met.

RESULTS

Surgery

All dogs completed the 12-week observation period. No clinical signs of infection were present at time of euthanization.

Biomechanical Testing

We found an approximately 2.5-fold increase in maximum shear strength and maximum shear stiffness for the alendronate group compared to their respective controls. No significant increase was found in total energy absorption (Table 1).

Histomorphometrical Analysis and Histology

The local alendronate treatment caused a 129% median increase (95% CI: 60–236%, *p*=0.0008) in peri-implant bone volume fraction. The increase was due to a 179% median increase (95% CI: 99–292%, *p* = 0.0001) in woven bone volume fraction and a 127% median increase (95% CI: 43–262%, *p* = 0.0031) in lamellar bone volume fraction (Fig. 3).

We found no difference in the amount of woven or lamellar bone in contact with the implant surface between the two groups (Fig. 4).

The most striking histological difference between the two groups was a 1 mm zone with relative dense cancellous bone around the implants from the alendronate group. Further away from the implant surface no histological difference in bone density was seen. The bone in the proximity of the implant from the alendronate consisted of lamellar bone chips and trabeculae covered with woven bone. The cancellous bone around the control implants seemed to be more remodeled, because fewer lamellar bone chips were seen. No delaminating of the HA-coating was seen (Fig. 5).

The paired increases in the biomechanical implant fixation can be partly explained by the paired increases in lamellar bone fractions (Table 2).

DISCUSSION

The purpose of this study was to investigate whether local application of alendronate could increase early fixation of HA-coated implants inserted by bone compaction technique. We found that alendronate treatment increased biomechanical fixation, and the amount of both woven and lamellar bone around the implant. The alendronate treatment did not affect the amount of bone in contact with the HA-coated implant surface.

Our model is designed to imitate the portion of a cementless joint replacement surrounded by cancellous bone. The canine was chosen as test animal since its cancellous bone structure closely resembles human bone.²¹ The paired design of this study allowed us to eliminate the effect of biological differences between animals. Our implant model is not weight bearing and thereby limited because the effects of direct load transfer are not addressed. Furthermore, only 10 animals were included in this study. Given the relative statistically power, any statistically nonsignificant difference should be interpreted with caution.

When bisphosphonate is topically added to cancellous bone most of it will adsorb to the bone surface while a small amount will stay unbound in solution between the trabeculae. A too high concentration of the unbound bisphosphonate may not only inhibit the osteoclasts but also the osteoblasts, and thus new bone formation.²² It is important that the concentration of unbound free bisphosphonate is below the toxic level. The omission of not irrigating a bone cavity after soaking it in bisphosphonate could therefore be potential deleterious. In this study we soaked the bone cavity with 5 mL saline containing 10mg alendronate and observed an increased biomechanical fixation and implant osseointegration. However, in another study investigating bone grafting and not compaction, soaking allograft in the same dose of alendronate decreased biomechanical fixation and implant osseointegration.²³ This difference could be due to reduction of unbound alendronate by the bleeding from the drill hole or by the suction applied after the soaking period in this study. An efficient and safe way to remove unbound potential toxic bisphosphonate could be with irrigation of the drill hole after soaking the bone in bisphosphonate.

In this study, alendronate treatment was able to increase two out of three biomechanical parameters for HA-coated implants inserted with the use of bone compaction. A likely explanation for the increased biomechanical fixation is the increased preservation of lamellar bone by the locally applied alendronate. This is supported by our correlation analyses, which show a significant correlation between the amount of lamellar bone and biomechanical implant fixation. We have previously shown a correlation between the amount of bone and biomechanical fixation.²⁴

The bone compaction technique creates a dense zone of lamellar bone around the implant.⁷ Alendronate is a potent inhibitor of bone resorption.⁹ A preservation of the zone of compacted bone is a possible explanation for the increased amount of lamellar bone around the implants in the alendronate group. Furthermore, a preservation of the compacted bone would result in a larger surface increasing new bone formation through the process of osteoconduction. This could explain the consistent increase in the amount of woven bone around the implants in the alendronate group. Another explanation for the increased amount of new bone could be that the antiresorptive effect of alendronate prolongs the remodeling of woven bone. This is in accordance with others studies.^{25, 26}

We did not find any difference in the amount of bone in contact with the HA-coated implant surface between the two groups. Other studies have shown a positive effect of bisphosphonate on bone in contact with a HA-coated implant.^{27, 28} A threshold could exist, beyond which the bone-to-implant contact is extremely difficult to enhance. The implants in

this study are placed in extreme press-fit due to the spring-back effect of the compacted bone, and thereby in contact with a relative high amount of bone at time zero.²⁹ Furthermore, the HA-coating on the implants in this study is known to have osteoconductive properties.³⁰ It could be that the combined effect of the bone compaction technique and HA coating leaves little room for improvement by alendronate in this model.

In conclusion, the results from this study are promising. We found the local alendronate treatment could increase the fixation of HA-coated implants inserted with bone compaction. As initial implant stability is important for long-term implant survival, the combined effect of local bisphosphonate treatment and bone compaction might be beneficial for HA-coated joint replacements. However, the results should be extrapolated with caution since only one alendronate concentration and one time period was investigated.

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Figure 1.
Schematic diagram showing the steps in the bone compaction technique.

Figure 2. Schematic diagram showing the specimen preparation. Each bone-implant specimen is cut into two pieces: 6.5 mm for histomorphometrical analysis, and 3.5 mm for biomechanical push-out test.

Bone surface fraction

Figure 3.
Bone volume fractions in a 0–1000- μ m zone around implants. Paired data are connected by line.

Bone surface fraction

Figure 4.
Bone-to-implant contact. Paired data connected by line.

Figure 5. Representative photomicrographs of samples from the same animal. The samples were stained with basic fuchsin and counterstained with 2% light green. Implant appears as black, marrow as red, and bone as green. Note the increased amount of bone around the alendronate implant. Bar = 1.0 mm.

Table 1**Biomechanical Results**

	Max Shear Strength, MPa	Max Shear Stiffness, MPa/mm	Total Energy Absorption, kJ/m²
Control	1.59 (0.98;2.19)	10.0 (6.21;15.6)	0.3 (0.2;0.4)
Alendronate	2.91 (2.20;3.62)	25.2 (19.7;30.7)	0.5 (0.3;0.7)
Alendronate/Control	2.1 (1.4;3.0) [*]	2.7 (1.7;4.5) ^{**}	1.6 (0.9;2.9) ^{***}

Data are presented as mean for each treatment group (control or alendronate) or median for the relative paired increases (alendronate/ control). 95% CI in parentheses.

^{*}
 $p=0.0014$.

^{**}
 $p=0.0013$.

^{***}
 $p=0.095$.

Table 2

Correlations between Relative Paired Increases in Histomorphometrical and Biomechanical Results

	Max Shear Strength	Max Shear Stiffness	Total Energy Absorption
Bone surface fraction			
Woven bone	0.11 ($p = 0.36$)	0.01 ($p = 0.75$)	0.16 ($p = 0.26$)
Lamellar bone	0.57 ($p = 0.012$)	0.44 ($p = 0.035$)	0.45 ($p = 0.033$)
Bone volume fraction			
Woven bone	0.01 ($p = 0.76$)	0.01 ($p = 0.82$)	0.004 ($p = 0.87$)
Lamellar bone	0.53 ($p = 0.016$)	0.57 ($p = 0.011$)	0.26 ($p = 0.14$)

Data are presented as R -squared with p -values in parentheses.