Effect of alendronate on bone ingrowth into porous tantalum and carbon fiber interbody devices

An experimental study on spinal fusion in pigs

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ABSTRACT **Recent studies have reported that bisphosphonates reduce the resorption of grafted bone and inhibit bone resorption at a bone-implant interface. However, it is not known whether bisphosphonates affect bone ingrowth into porous biomaterial or spine fusion interbody devices with an autograft. In this study, 18 pigs (9 in each group) underwent anterior intervertebral lumbar arthrodeses at L2–3, L4–5 and L6–7. Each level was randomly allocated to one of the 3 implants: a solid piece of porous tantalum (Hedrocel), a porous tantalum ring or a carbon fiber cage both packed with an autograft. Alendronate was given orally to one of the groups. The radiographic and histological findings in the two groups 3 months after operation were similar in these devices. Histological examination showed that the original graft was entirely replaced by new trabecular bone in both groups. On histomorphometric analysis, the bone volume fraction, both inside the central hole of porous tantalum ring and in the porous tantalum, was larger in the pigs given alendronate than in the controls, but the fraction inside and around the central hole of the carbon fiber cage was not affected by this treatment. Short-term alendronate treatment, in a relatively low dose, does not impair the formation of new bone, but increases bone ingrowth into the central hole of the porous tantalum ring and the pores of the porous tantalum in this porcine model. This may be an effective way to enhance early biologic fixation of porous intervertebral implants.**

Spinal fusion is commonly performed, but the rate of failure in obtaining a solid bone fusion may be as high as 45% (Steinmann and Herkowitz 1992, Zdeblick 1993). Although autogenous bone graft is the gold standard for spinal fusion, there is a limit to its mass, and complications are associated with bone harvest (Younger and Chapman 1989, Banwart et al. 1995). The advances in material engineering have led to renewed interest in osteoconductive materials and yielded materials that may function not only as traditional bone graft expanders, but also as a scaffold for bone ingrowth. Preliminary studies in animals, with transcortical porous tantalum implants have shown that the material can support rapid and extensive bone ingrowth (Bobyn et al. 1999a). The tissue response to porous tantalum acetabular cups indicates that the porous tantalum material is effective for biologic fixation in a canine model (Bobyn et al. 1999b). The biomechanical property of porous tantalum biomaterial is sufficient to withstand a physiological load, under specific conditions, such as an acetabular cup (Poggie et al. 1998).

Bisphosphonates are widely used clinically to treat bone diseases characterized by excessive bone resorption (Fleisch 1993). Treatment with alendronate specifically inhibits bone resorption and thereby reduces the rate of bone turnover (Garnero et al. 1994). Daily treatment with alendronate increases the bone mass and reduces the incidence of fractures in postmenopausal women with osteo-

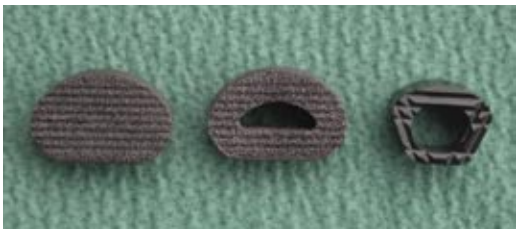

Figure 1. Three types of implants: a solid piece of porous tantalum (left), a porous tantalum ring with a central hole and a peripheral rim (middle), and a carbon fiber cage with a central large opening and a peripheral narrow rim (right).

porosis (Liberman et al. 1995). A randomized double-blind clinical study has confirmed that clodronate prevents prosthetic migration by inhibiting bone resorption (Hilding et al. 2000). However, no data have been reported as to whether bisphosphonates affect bone ingrowth into porous biomaterial and ALIF devices in humans or experimental animals. We have developed a porcine anterior lumbar interbody fusion (ALIF) model with a carbon fiber cage packed with autogenous bone graft (Li et al. 2002). Using this model, we evaluated the effect of alendronate on autogenous free bone grafting and spinal fusion interbody devices.

Animals and methods

Study design

We used 18 12-week-old female Danish Landrace pigs from different litters, weighing about 50 kg. They were randomly assigned to 1 of 2 groups of 9 pigs: an experimental group given alendronate (ALN) and a control group (control) given no alendronate. Each pig underwent anterior intervertebral lumbar arthrodeses at L2–3, L4–5 and L6–7 (Li et al. 2002). Each level was randomly allocated to undergo 1 of 3 procedures: (1) implantation of a solid piece of a porous tantalum; (2) implantation of a porous tantalum ring with an autogenous iliac crest bone graft; (3) implantation of a carbon fiber cage with an autogenous iliac crest bone graft. Each implant was secured with two staples (22 × 16 mm, Howmedica GmbH, Schönkirchen, Germany). The pigs were observed for 3 months before they were killed. They had been bred for scientific purposes and were handled according to the Danish law on animal experiments.

Implants. We used 3 types of interbody devices (Figure 1). The first was a solid piece of porous tantalum (PT-Solid). The second was a porous tantalum ring (PT-Ring), which had a central hole machined into a face, leaving a 5 mm-wide peripheral rim in contact with the endplate for axial load support (23 × 15 × 9 mm). The porous tantalum implants (trade name Hedrocel) are commercially available for spinal fusion in humans and were manufactured and kindly supplied by Implex Corp., Allendale, NJ, USA. The third, the Brantigan Cervical I/F carbon fiber cage (CF-Cage), which is commercially available for cervical fusion in humans, has a central large opening and peripheral narrow rim (8 mm standard, Acromed Corp., Cleveland, OH, USA).

Alendronate administration. The ALN animals received alendronate orally (Fosamax, MSD b.v., Denmark) in a daily dose of 10 mg from the second day after the operation until completion of the study. The tablet was given to them between two meals. The initial dosage was 0.17 (SD 0.014) mg/kg body weight.

Surgery

Anesthesia. The animals were premedicated with 25 mg midazolam and 200 mg azaperon intramuscularly. Orotracheal intubation was started after they were given an intravenous injection of 20 mg etomidate. Anesthesia was maintained by inhalation of isoflurane (1.5%) and an intravenous injection of ketamine (10 mL/hour).

Surgical procedure. Under aseptic conditions, an autogenous bone graft was taken from the left iliac crest with the pig placed in a right recumbent position. It was then placed in a supine position with the legs tied to the table. The abdomen was prepared and draped, and a paramedian abdominal incision made. The rectus abdominis muscle and its sheath were incised and retracted. The inner-most layer, the fascia of the m. transversus abdominis, was dissected with care, to avoid damaging the peritoneum lying immediately underneath it.

After separating and retracting the peritoneum and its contents, the quadratus lumborum and psoas major muscles came into view. The anterior lumbar spine was easily identified because of its thick and shining anterior longitudinal ligament. After ligating and cutting the segmental vessels,

the L2–3, L4–5 and L6–7 intervertebral discs were excised together with the cranial and caudal endplates and part of the anterior longitudinal ligament. The bone graft was morselized and put into the central hole of the implants (Table 3). After insertion, each implant was secured with 2 staples. The abdominal muscle and the sheath of the rectus abdominis were carefully sutured, and the skin closed by running sutures. Prophylactic ampicillin and analgesic buprenorphine were given before and immediately after surgery, and twice a day during the following 3 days.

Housing, fluorochome labeling, and sacrifice. All pigs were kept in single boxes at the Danish Institute of Agricultural Sciences, Research Center Foulum, and fed a normal diet containing 1.4% calcium and 0.7% phosphorus (percentage of food weight). The controls were kept for mean of 94 (91–96) days, and the ALN animals were kept for 93 (90–96) days. 3 days before they were killed, fluorochrome was given with tetracycline (20 mg/kg) intravenously. They were killed under general anesthesia after 3 months by an intravenous injection of pentobarbital (0.4 mg/kg).

Radiography

After killing, the spinal column from L1 to L7 with the sacrum was removed en bloc, stripped of soft tissue, and transported to the laboratory and stored at –20 ºC, pending examination. Plain posteroanterior and lateral radiographs and conventional tomographs of the lumbosacral spine were taken. We saw radiolucent lines at the vertebrae-implant interface in some specimens when plain radiographs and conventional tomographs were taken. We divided the radiolucent lines into 3 grades in a blinded manner. Grade 0 was no radiolucent line. Grade 1 was 1 radiolucent line located on vertebrae-implant interface. Grade 2 was 2 radiolucent lines located at a vertebrae-implant interface.

Histology and histomorphometry

Specimen preparation. Implant specimens at L2–3, L4–5, and L6–7 were harvested together with adjacent vertebral bone. The specimens were machined with a water-cooled diamond blade. Each vertebrae-implant specimen was cut into halves longitudinally through the center of the implants in the sagittal plane. One half was randomly chosen for histomorphometric processing, and the other used for the fluorochrome study. Specimens for histomorphometric examination were dehydrated in graded ethanol (70–99%) containing 0.4% basic fuchsin and embedded in methyl methacrylate. 50 μm-thick sections were cut at 500 μm-intervals between each section. Each was cut to a thickness of 50 μm, using the sawing microtome KDG 95 (Meprotech, Galileistraat 24, NL-17045E, Heerhugowaard, The Netherlands). The surface was counterstained with 2% light green for 2 minutes. 4 sections were made from each vertebrae-implant specimen.

Histology. In the qualitative histological analysis, all sections were evaluated in a blinded manner, and the types of bone tissue, bone marrow and fibrous tissue were identified under the light microscope. Yellow fluorochrome labeling was used to identify lamellar bone under polarized light. We divided the pattern of tissue ingrowth into porous tantalum and tissue ongrowth onto the carbon fiber cage into 3 grades. Grade 2 was bone in/ongrowth into the implant material from both vertebral sides with or without an inner side having a central hole, and little, if any, partly fibrous tissue surrounding the implant. Grade 1 referred to bone in/ongrowth into the implant material from one vertebral side and/or the inner side of a central hole in the ring/cage, and partly fibrous tissue surrounding the implant. Grade 0 was no bone in/ongrowth into the implant material, and fibrous tissue surrounding the entire implant.

Histomorphometry. We used a stereological software program (CAST-Grid, Olympus Denmark A/S, Albertslund, Denmark) for histomorphometry. This is based on a user-specified grid applied to microscopic fields captured on the monitor (attached to a light microscope, objective ×4, ocular ×10).

Ingrowth was defined as the central hole of the ring/cage and the pore of porous tantalum filled by bone, bone marrow or fibrous tissue (as a percentage). It was estimated by using the point-counting technique. About 1200 points on 4 sections per implant were counted in each region of interest.

Implant-in-bone healing at the vertebrae-implant interface was defined as the region from the implant surface to 2 mm from the surface of the bone, bone marrow or fibrous tissue (as a percentage). It was

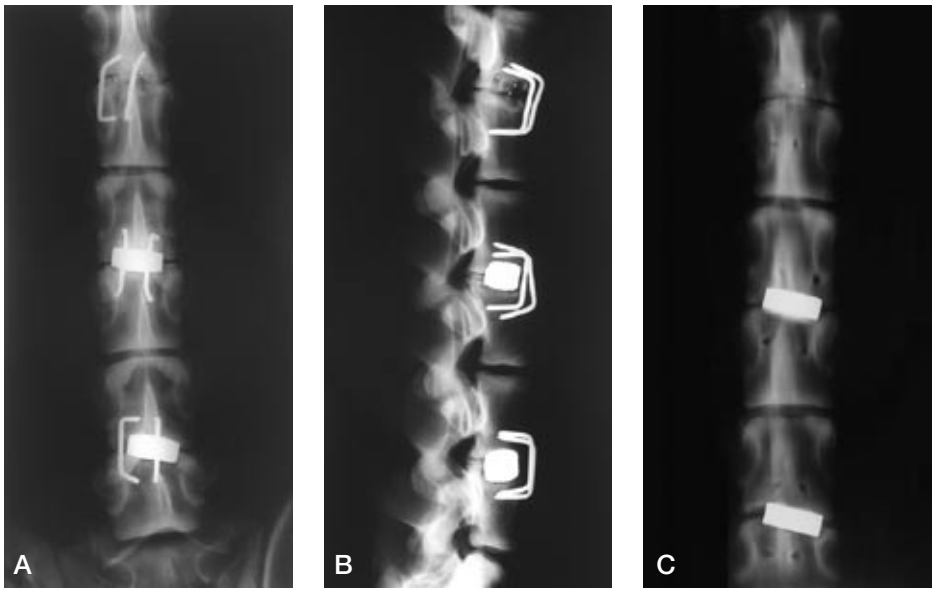

Figure 2. Plain posteroanterior (A) and lateral (B) radiographs and conventional tomograph (C).

estimated by using the point-counting technique. About 500–1200 points on 4 sections per implant were counted in each region of interest.

Graft-in-bone healing at the vertebrae-graft interface was defined as the region from the implant surface to 2 mm from the surface of bone, bone marrow or fibrous tissue (as a percentage) and was estimated by using the point-counting technique. About 600–1200 points on 4 sections per implant were counted in each region of interest.

To evaluate the accuracy of the method, we calculated an interobserver error of 6.9% and an intraobserver error of 7.4% after double-counting of 60 sections from 15 implants by two blinded observers.

Statistics

The chi-square test was used for nonparametric values. The statistical analyses of parametric data included two-way analyses of variance (ANOVA) for repeated measures of the tissue volume fraction. The group (ALN vs. control) was used as the between-subjects factor and implants (PT-Solid, PT-Ring, and CF-Cage) as the within-subjects factor. When significant main effects or an interaction between the main effects was found, specific comparisons were made with the student's t-tests and paired t-tests. In all cases, exact p values were given and we considered $p < 0.05$ to represent significant effects. The statistical analysis was done with SPSS version 10.0 statistical software (SPSS, Chicago, IL, USA).

Table 1. Radiolucent lines at vertebrae-implant interfaces

Implants	n	ALN group (grades)			Control group (grades)			P-values
		0	1	2	0	1	2	
PT-solid	18	1	6	2	0	6	3	1.0
PT-ring	18	3	6	0	2	6	1	1.0
CF-cage	18	7	2	0	6	1	2	0.6

Results

Radiographic evaluation (Figure 2)

Posteroanterior and lateral views and conventional tomographs of the spine were taken. The tantalum implants were opaque on plain radiographs and conventional tomographs. Because of the radiopaque nature of porous tantalum, it was not easy to see from the radiograph whether bone ingrowth into the implants had occurred. We saw some radiolucent lines at the vertebrae-implant interface. The findings in the devices were similar in the alendronate-treated pigs and the controls (Table 1).

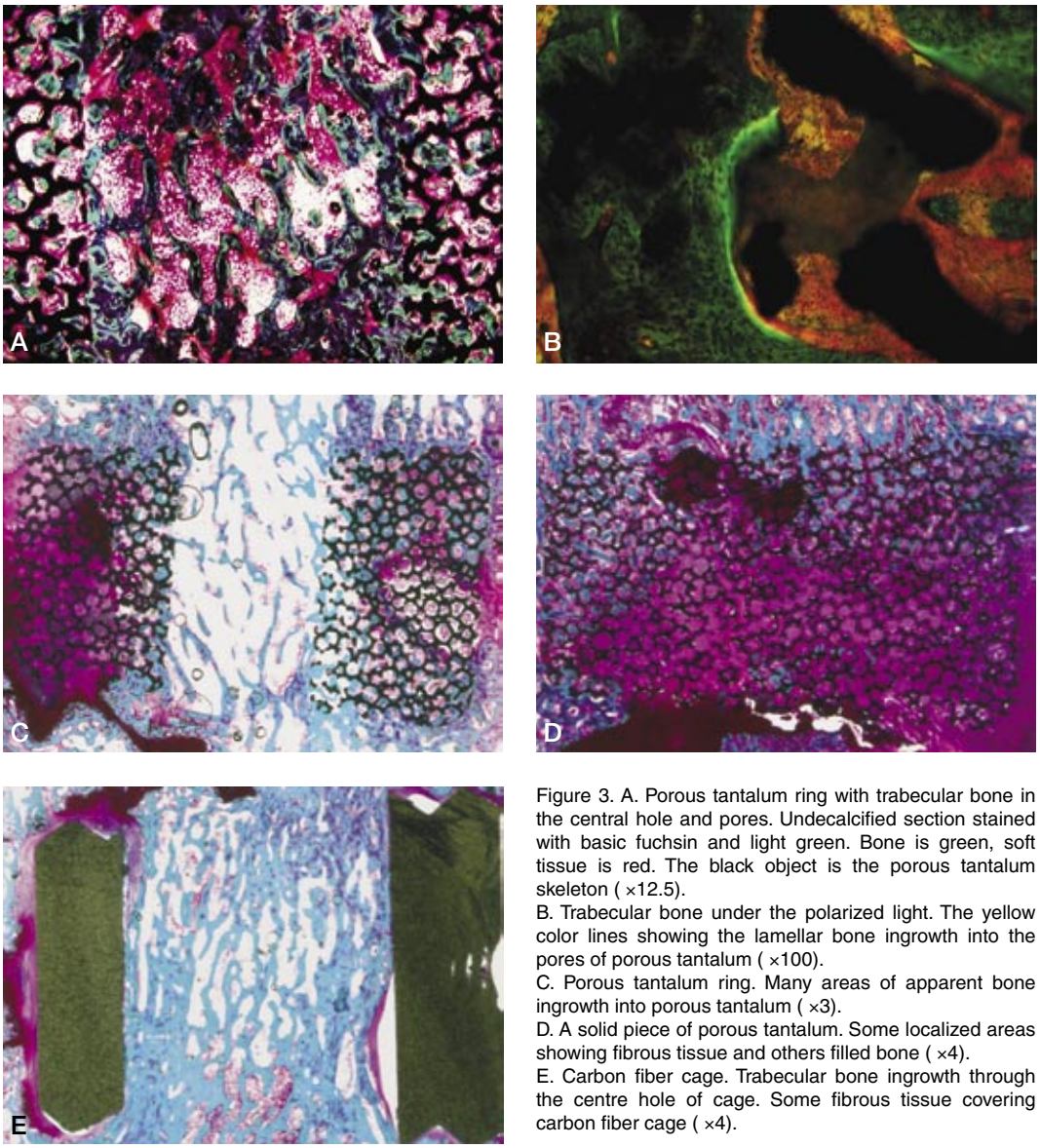

Figure 3. A. Porous tantalum ring with trabecular bone in the central hole and pores. Undecalcified section stained with basic fuchsin and light green. Bone is green, soft tissue is red. The black object is the porous tantalum skeleton (×12.5).
B. Trabecular bone under the polarized light. The yellow color lines showing the lamellar bone ingrowth into the pores of porous tantalum (×100).
C. Porous tantalum ring. Many areas of apparent bone ingrowth into porous tantalum (×3).
D. A solid piece of porous tantalum. Some localized areas showing fibrous tissue and others filled bone (×4).
E. Carbon fiber cage. Trabecular bone ingrowth through the centre hole of cage. Some fibrous tissue covering carbon fiber cage (×4).

Histological examination (Figure 3)

Examination with under the light microscope and polarized light microscope showed that the original graft had been totally replaced by new trabecular bone in both groups. The vertebrae-implant interface showed many areas of apparent bone ingrowth into biomaterial, but also some localized areas of fibrous tissue. In some specimens, fibrous tissue completely surrounded the implants. The pattern of tissue ingrowth into the porous tantalum implants and of tissue ongrowth onto the carbon fiber cage were similar in each device in the alendronate-treated pigs and the controls (Table 2).

Table 2. Bone in/ongrowth into three implants

Implants	n	ALN group (grades)			Control group (grades)			P-values
		0	1	2	0	1	2	
PT-solid	18	1	6	2	0	7	2	1.0
PT-ring	18	3	5	1	3	5	1	1.0
CF-cage	18	1	7	1	0	5	4	0.3

Table 3. Preoperative amount of bone graft and bone ingrowth after 3 months. The mean values (SD) are shown for the amount of bone graft and the volume fraction of bone in the various implants in the ALN and control groups

Groups	Amount of graft (g) PT-ring	CF-cage	Volume fraction (%) PT-ring	CF-cage	Volume fraction (%) PT-solid	PT-ring
ALN	0.78 (0.08)	0.99 (0.05)	60 (7)	61 (10)	17 (11)	21 (15)
Control	0.68 (0.08)	1.00 (0.11)	41 (10)	56 (11)	9 (10)	12 (10)

Table 4. Implant-in-bone healing and graft-in-bone healing at vertebrae-implant interface. The mean values (SD) are shown for bone and fibrous tissue in the various implants in the ALN and control groups

	ALN group			Control group		
	PT-solid	PT-ring	CF-cage	PT-solid	PT-ring	CF-cage
Implant-in-bone healing (%)						
Bone	47 (7)	46 (5)	45 (8)	41 (6)	37 (7)	44 (7)
Fibrous tissue	25 (11)	20 (5)	31 (8)	34 (9)	29 (12)	26 (9)
Graft-in-bone healing (%)						
Bone		51 (7)	52 (12)		41 (12)	53 (5)
Fibrous tissue		18 (4)	17 (4)		21 (6)	15 (1)

Histomorphometry

Bone ingrowth. The bone ingrowth into the central hole was greater in the alendronate-treated group than in the controls ($p = 0.009$, as regards the group effect in the analysis of variance). In the comparison of the group effect, although the mean value in alendronate-treated pigs was greater than in the controls, the difference between the group effect was significant in the central hole of the porous tantalum ring ($p < 0.001$, as regards the student's t-test with the variances not assumed to be equal), but did not reach significance in the central hole of the carbon fiber cage (Table 3). The bone ingrowth into the pores of the porous tantalum was also greater in the alendronate-treated group than in the control group ($p = 0.008$, as regards the group effect in the analysis of variance). In the comparison of the 2 groups, the difference between the group effect in a solid piece of porous tantalum and in the porous tantalum ring was not significant (Table 3).

Implant-in-bone healing. The volume fraction of bone at the vertebrae-implant interface was greater in the alendronate-treated group than in the control group ($p = 0.003$, concerning the group effect in the analysis of variance). Although the difference between these was significant, the difference between the group effect was significant in the porous tantalum ring ($p = 0.007$, using the student's t-test with the variances not assumed to be equal), but it was not significant in the solid piece of porous tantalum or in the carbon fiber cage (Table 4).

The analysis of variance for the volume fraction of fibrous tissue at the vertebrae-implant interface indicated that neither the group nor the interaction between the implants and group was significant (Table 4).

Graft-in-bone healing. We found no change in the volume fraction of bone in the regions of the vertebrae-graft interface in the alendronate-treated group, as compared to the control group, and no significant interaction between the implants and the group.

The analysis of variance for the volume fraction of fibrous tissue in the regions of the vertebrae-graft interface indicated that neither the group nor the interaction between the implants and group was significant (Table 4).

Discussion

Bisphosphonates are potent inhibitors of bone resorption (Fleisch et al. 1969) and animal studies have shown that alendronate inhibits bone resorption at the bone-implant interface (Shanbhag et al. 1997, Åstrand and Aspenberg 1999). No data are available on the effects of chronic administration of bisphosphonates on spinal fusion with ALIF devices in humans or experimental animals.

The present study shows that chronic administration of alendronate, in an oral dose of 10 mg daily for 3 months, increased new bone formation inside the central hole of a porous tantalum ALIF device with an autogenous bone graft and bone ingrowth into the pores of the porous tantalum. Histological examination showed that the original graft was totally replaced by new trabecular bone in both groups. Theoretically, greater bone ingrowth into porous tantalum should increase the interface mechanical strength, and improve biologic fixation in spinal fusion.

Porous tantalum is a new biomaterial that has many interconnecting pores, average 400–500 μm, and a high volume porosity in all implants ranging from 75–80% (Bobyn et al. 1999a). We selected the observation period on the basis of our previous experience with the porcine ALIF model, using carbon fiber cages with an autogenous bone graft (Li et al. 2002).

The oral dose of alendronate, which was well tolerated, was equivalent to that given to humans.

The increase in bone volume fractions in the central hole of porous tantalum ring, the pores of porous tantalum and the region adjacent to the porous tantalum ring suggest that alendronate may stimulate the formation of bone and have a beneficial effect on bone formation, but the mechanisms whereby alendronate produces such effects are not completely understood. Recently, bisphosphonates have been shown to have a direct affect by reducing osteoclastic resorption of grafted bone by up-regulating the osteoclast inhibitory factor (OCIF) mRNA expression, while inducing osteoblastic activation by up-regulating osteocalcin and alkaline phosphatase mRNA expression in graft tissue (Myoung et al. 2001). A previous study (Giuliani et al. 1998) showed that alendronate, in lower concentrations—i.e, 10^{-9} to 10^{-11} mol/L—stimulated the formation of early osteoblast precursors. These lower concentrations resemble the dose used in the present study, and suggest that osteoblastic activation is involved. Bisphosphonates inhibit bone resorption secondary to the regional accelerated phenomenon (RAP) after surgical procedures in rats (Yaffe et al. 1995) and canines (Shanbhag et al. 1997, Åstrand and Aspenberg 1999, 2002). In our study, RAP was probably inhibited, but our study design did not permit an independent evaluation of the effect of RAP because of the 3-month follow-up.

Despite a significant increase in bone volume of the tissue adjacent to the porous tantalum rings when the pigs were treated with alendronate, the radiographic and gross histological results showed no significant difference between the 2 groups. This suggests that neither of these methods is sufficiently sensitive to detect changes in tissue composition.

The histomorphometric analyses of the volume fraction of fibrous tissue at the vertebrae-implant interface and vertebrae-graft interface indicated that alendronate had no significant effect. These findings indicate that alendronate did not inhibit the formation of fibrous tissue. This might be caused by relative motion between bone tissue and the implants (Pilliar et al. 1981). A rat model with initial interface shear motion showed that alendronate did not prevent instability-induced bone resorption (Åstrand and Aspenberg 1999). The effects of alendronate on prosthetic loosening have been evaluated on radiographs or histological examinations of soft tissue in canine total hip replacements. The continuous administration of alendronate effectively inhibited bone lysis for the 24-week duration of the study (Shanbhag et al. 1997). A randomized double-blind clinical study indicated that clodronate prevented prosthetic migration by early inhibition of bone resorption (Hilding et al. 2000). It seems essential to maintain the initial stability with fixation of the interface between bone and the implant. In our model, some segments may have relative micromotion, which forms fibrous tissue and prevents bone ingrowth into the porous tantalum implant at the vertebrae-implant interface.

In conclusion, the short-term bisphosphonate alendronate treatment, with a comparatively low

dose, increased bone ingrowth into the central hole of a porous tantalum ring and into the pores of a porous tantalum in a porcine ALIF model. So far as we know, this is the first time that alendronate has been shown to stimulate bone ingrowth into any ALIF device. This may be an effective method for early biologic fixation in spinal fusion in pigs. Our data support the need for more research on the long-term effects of alendronate before clinical trials.

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No competing interests declared.

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