Transient Local Bone Remodeling Effects of rhBMP-2 in an Ovine Interbody Spine Fusion Model

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Abstract

Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is a powerful osteoinductive morphogen capable of stimulating the migration of mesenchymal stem cells (MSCs) to the site of implantation and inducing the proliferation and differentiation of these MSCs into osteoblasts. Vertebral end-plate and vertebral body resorption has been reported after interbody fusion with high doses of rhBMP-2. In this study, we investigated the effects of 2 rhBMP-2 doses on peri-implant bone resorption and bone remodeling at 7 time points in an end-plate-sparing ovine interbody fusion model.

Methods: Twenty-one female sheep underwent an end-plate-sparing discectomy followed by interbody fusion at L2-L3 and L4-L5 using a custom polyetheretherketone (PEEK) interbody fusion device. The PEEK interbody device was filled with 1 of 2 different doses of rhBMP-2 on an absorbable collagen sponge (ACS): 0.13 mg (1·) or 0.90 mg (7·). Bone remodeling and interbody fusion were assessed via high-resolution radiography and histological analyses at 1, 2, 3, 4, 8, 12, and 20 weeks postoperatively.

Results: Peri-implant bone resorption peaked between 3 and 8 weeks in both the 1· and the 7· rhBMP-2/ACS-dose group. Osteoclastic activity and corresponding peri-implant bone resorption was dose-dependent, with moderate-tomarked resorption at the 7·-dose level and less resorption at the 1·-dose level. Both dose ($p < 0.0007$) and time ($p <0.0025$) affected bone resorption significantly. Transient bone-resorption areas were fully healed by 12 weeks. Osseous bridging was seen at all but 1 spinal level at 12 and at 20 weeks.

Conclusions: In the ovine end-plate-sparing interbody fusion model, rhBMP-2 dose-dependent osteoclastic resorption is a transient phenomenon that peaks at 4 weeks postoperatively.

Clinical Relevance: Using the U.S. Food and Drug Administration (FDA)-approved rhBMP-2 concentration and matching the volume of rhBMP-2/ACS with the volume of desired bone formation within the interbody construct may limit the occurrence of transient bone resorption.

Previous literature has demonstrated the osteoinductive capabilities of recombinant human bone morphogenetic protein-2 (rhBMP-2) and its ability to effect bone healing in osseous defects, long-bone defects, and spine fusions [1-10]. Through chemotaxis, rhBMP-2 draws mesenchymal stem cells (MSCs) to the site of implantation while inducing the proliferation and differentiation of these MSCs into osteoblasts [1]. The current carrier for rhBMP-2 is an absorbable collagen sponge (ACS) made of cross-linked type-I bovine collagen [11-13].

In 2002, following extensive preclinical work and U.S. Food and Drug Administration (FDA)-approved clinical studies, the combination of 1.5 mg/mL of rhBMP-2 on the ACS carrier (INFUSE Bone Graft;Medtronic Sofamor Danek) was approved as an autograft replacement in certain anterior lumbar interbody fusions. Since then, it has been used successfully to induce spine fusion. [14-32] However, with increasing clinical use, vertebral end-plate or vertebral body resorption has been observed after interbody fusion with various BMP doses, surgical techniques, and interbody constructs. [21,22,25,28,33,34] This resorptive phenomenon can be difficult to visualize on radiographs but appears as decreased mineral density on computed tomography (CT) scans approximately 3 to 6 months after surgery. [21,22,25,28,33,34] The resorptive zones are usually transient with progressive bone formation and fusion occurring overtime. [21,22,25,28] A previous ovine study demonstrated that overfilling cancellous osseous defects with rhBMP-2/ACS and/or hyperconcentrating rhBMP-2 resulted in dose-dependent transient osteoclastic activity and peri-implant resorption. [35]

The cause and histological composition of these resorption zones have not been examined in a clinically relevant experimental interbody fusion model. The goal of this study was to investigate the effects of 2 rhBMP-2 doses on periimplant bone resorption and bone remodeling at 7 time points in a novel end-plate-sparing ovine interbody fusion model. We hypothesize that transient osteoclastic resorption of peri-implant bone would occur in a dose-dependent fashion at early time points.

Materials and Methods

Animal Model

The previously validated interbody fusion procedure with a retroperitoneal transpsoas approach in sheep was used as the experimental model. [6,9,10,36] The study was approved by the Institutional Animal

Care and Use Committee. A novel end-plate-sparing technique was utilized to mimic more current clinical surgical techniques with impacted interbody constructs.

Materials and Study Design

Twenty-one skeletally mature (2 to 3-year-old) nongravid female sheep underwent an end-plate-sparing discectomy and interbody fusion at L2-L3 and L4-L5 using an ovine-customized polyetheretherketone (PEEK) interbody interbody fusion device measuring 16 ·12 · 4.5 mm with an internal volume of approximately 0.3 cm3. The PEEK interbody devices were filled with 1 of 2 different doses (1· or 7·) of rhBMP-2 on an ACS carrier (Table I). The 1·dose consisted of 0.3 mL of 0.43 mg/mL of rhBMP-2, for a total of 0.13 mg. This concentration was previously found to be effective for interbody fusion in the ovine model.[6,9,10] The 7· dose consisted of 0.6 mL of 1.50 mg/mL of rhBMP-2 for a total of 0.90 mg. Fentanyl patches were used for the management of postoperative pain.

Osteoclastic activity, bone remodeling, and the development of interbody fusion within the PEEK cages were studied radiographically and histologically by evaluating 3 spinal levels at 1, 2, 3, 4, 8, 12, and 20 weeks after treatment with each of the 2 doses. At sacrifice, CT scans, high-resolution radiography, and histological analysis were performed.

Radiographic Evaluation

Axial CT scans with a slice thickness of 1.5 mm and sagittal and coronal reconstructions were performed on all 21 explanted spines (L1-L6). A highresolution radiography unit (Faxitron; Hewlett Packard) and film (EKTASCAN B/RA Film 4153; Kodak) were used to produce a high-resolution posteroanterior radiograph of the explants. Additionally, 4 sagittal slabs (6 to 7mmthick) through each disc space were produced and scanned using high-resolution radiography.

Histological Studies

Approximately 20 undecalcified histological sections were produced per level. The histological criterion used to assess fusion was a continuous osseous bridge from the cranial to the caudal vertebra. A vertebral level was considered to have solid fusion if ‡50% of the sections and corresponding microradiographs showed continuous osseous bridging through the thrugrowth region of the PEEK device, a partial fusion if <50% of the sections and corresponding microradiographs showed continuous osseous bridging, and no fusion if none of the sections and corresponding microradiographs showed continuous osseous bridging.

Quantitative Radiography

Faxitron high-resolution no-magnification radiographs of all 4 slabs from each of the treated ovine lumbar levels were scanned using a video camera (model DFC 280; Leica Microsystems). A millimeter scale was placed in the field, and the macroscopic magnification was kept constant during imaging. Image analysis software (Image-Pro Plus, version 5.1; Media Cybernetics) was used for each of the spatially calibrated radiographic images to measure peri-implant resorption areas. The investigators were blinded to the implant assignments.

Statistical Analysis

A regression analysis using a least squares model was performed to determine the effects of the dose and post-implantation time point on the quantitative radiography results for peri-implant bone resorption. A Student t test was used to examine differences between 2 time points.

TABLE I Treatment Groups and Post-Implantation Time Points Evaluated

rhBMP-2/ACS Volume*	rhBMP-2 Solution Concentration†	Effective rhBMP-2 Dose/Concentration	Postoperative Time Points Evaluated (wk)
1x	1x	1	1, 2, 3, 4, 8, 12, 20
2x	3.5x	7x	1, 2, 3, 4, 8, 12, 20

*A volume of 0.3 mL appropriately filled the interbody construct. †The effective concentration for sheep interbody fusion has been reported to be 0.43 mg/mL.[6,9,10]

Results

Quantitative Radiography Showing Peri-Implant Bone Resorption Peaking Between 3 and 8 Weeks

Mean quantitative radiography measurements of periimplant bone resorption in the 1· and 7·-dose groups at all time periods are shown in Figure 1. Peri-implant bone resorption peaked between 3 and 8 weeks in both groups. Both dose ($p < 0.0007$) and time ($p < 0.0025$) affected total bone resorption significantly. Bone resorption was significantly greater at the 3 and 4-week time points than at the earliest (2-week) time point and the 2 latest (12 and 20-week) time points (a = 0.05, power =0.95).

Radiographic and Histological Results

At 1 Week Post-Implantation

Radiography showed minimal-to-no remodeling of the superior or inferior cortical end plates at the 6 spinal levels analyzed at 1 week after treatment. Neither osteoclastic resorption nor new bone formation was observed within the disc spaces of any of the 6 treated levels. No osseous exostoses were seen. At all of the treated levels, the ACS implant was observed within the thrugrowth region of the PEEK interbody construct.

At 2 Weeks Post-Implantation

CT scans demonstrated minimal-to-no end-plate remodeling at 2 weeks post-implantation. In the 1·-dose group, histological images and microradiographs demonstrated intact cortical end plates with a very small amount of bone remodeling consisting of both osteoclastic resorption and intramembranous ossification (Fig. 2-A). However, in the 7·-dose group, histological analysis and microradiography showed resorption of the cortical end plates that ranged from a subtle rarified appearance (Fig. 2-B) to focal resorption of the cortical end plates. Histological analysis showed osteoclastic resorption extending into osseous trabeculae of the vertebral bodies at all 3 spinal levels in the 7·-dose group and at 1 level in the 1·-dose group. Evidence of osteoid (pink) and intramembranous ossification on mineralized de novo osseous spicules (green) was observed within the PEEK interbody construct at a 1·-dose spinal level (Fig. 2-C), and focal osteoclastic resorption of the cortical end plates was observed adjacent to the PEEK interbody construct at another 1·-dose spinal level (Fig. 2-D). The ACS implant was observed within the PEEK interbody construct at all levels treated 2 weeks before analysis (Figs. 2-A and 2-B).

At 3 Weeks Post-Implantation

Radiographically, all levels treated with the 7· dose demonstrated moderate-to-marked peri-implant resorption. One of the 3 levels treated with the 1· dose demonstrated minimal-to-moderate resorption on radiography. On histological analysis, all of the 7·-dose spinal levels and 1 of the 3 levels treated with the 1· dose showed a rarified appearance of the cortical end plates that correlated with increased focal osteoclastic resorption of the cortical osseous end plates extending well into osseous trabeculae of the adjacent vertebral bodies (Figs. 3-A, 3-B, and 3-C). Some unmineralized osteoid formed via intramembranous ossification was observed at the periphery of the resorption zones (Fig. 3-D). Loose granulation tissues were found within the PEEK implant and within peri-implant resorption zones. The other 2 levels treated with the 1· dose showed less bone resorption (Figs. 4-A and 4-B). The ACS implant was observed within the PEEK interbody construct at all treated levels.
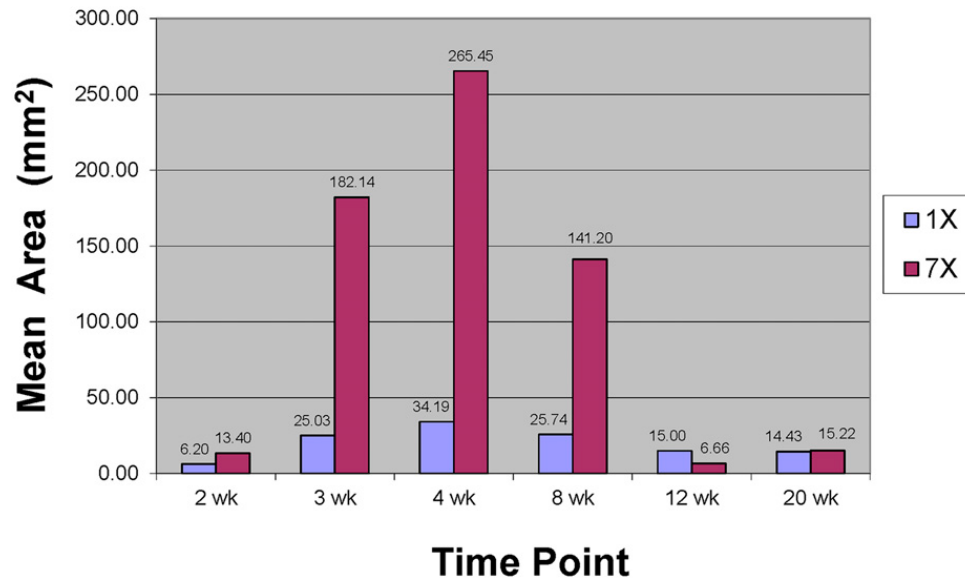

Fig. 1 Mean quantitative radiography measurements of peri-implant resorption areas at all time periods following application of 1· and 7· doses of rhBMP-2.

Peri-implant bone resorption peaked between 3 and 8 weeks in both dosing groups.
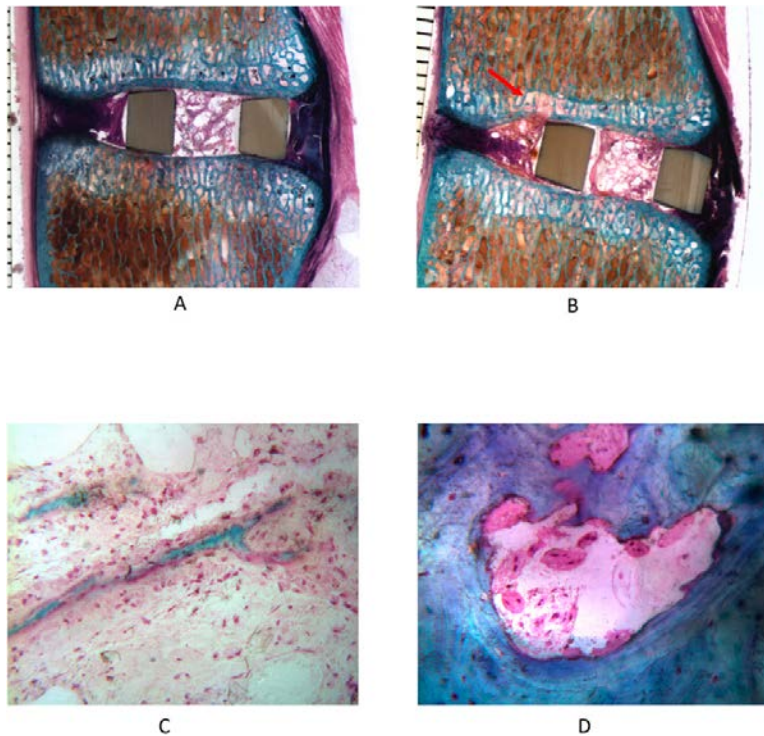
Fig. 2 Figs. 2-A and 2-B Stained undecalcified sections from spinal levels 2 weeks after treatment with a 1· dose (Fig. 2-A) or 7· dose (Fig. 2-B) of rhBMP-2. Both histological images demonstrate substantial preservation of the cortical end plates. No remodeling of the superior or inferior cortical end plates was observed adjacent to the PEEK interbody construct in the 1·-dose group at 2 weeks, but subtle remodeling changes were observed in the 7·-dose group (arrow). The ACS implant is seen within the thrugrowth region of the PEEK interbody constructs. Fig. 2-C Evidence of osteoid (pink) and intramembranous ossification on mineralized de novo osseous spicules (green) were observed within the PEEK interbody construct in a 1·-dose spinal level at the 2-week time point (trichrome stain, original magnification = 200·). Fig. 2-D Focal osteoclastic resorption of the cortical end plates was observed adjacent to the PEEK interbody construct at a 1·-dose spinal level at the 2-week time point (trichrome stain, original magnification = 200·).

At 4 Weeks Post-Implantation

All 7·-dose spinal levels demonstrated moderate-to-marked peri-implant bone resorption on radiographs, with histological analysis showing substantial end-plate changes and bone resorption extending well into osseous trabeculae of the adjacent vertebral bodies. Histological analysis showed the greatest amount of bone resorption at 4 weeks post-implantation (Fig. 5-A). Unmineralized osteoid formed via intramembranous ossification was frequently observed at the periphery and within the resorption zones. Early stages of de novo bone formation resulting in early histologically evident fusion were found at 1 of the 3 levels in the 7·-dose group (Fig. 5-B). One of the 3 levels in the 1·-dose group demonstrated moderate resorption radiographically and histologically, whereas the other 2 levels in the 1·-dose group showed less peri-implant resorption (Fig. 5-C). Granulation tissues were found within the PEEK implant and within peri-implant resorption zones. In 4 of the 6 treated levels, the ACS implant was observed within the PEEK interbody construct.

At 8 Weeks Post-Implantation

At 8 weeks, CTscans showed minimal end-plate changes at the 1·-dose spinal levels and moderate-to-marked end-plate and vertebral body resorption at 1 level that had received the 7· dose. This was confirmed by histological analysis as osseous resorption with osteoclasts present on the

surfaces of osteopenic trabeculae. Histological analysis of the 7·-dose spinal levels showed substantial end-plate changes and boneremodeling areas. Although end-plate changes and bone resorption extended well into osseous trabeculae of the vertebral bodies, osseous healing with hypodense mineralized trabeculae could be observed within these resorption zones and in the thrugrowth region of the disc space on the microradiograph (Fig. 6-A). Numerous foci of intramembranous ossification are seen on the surfaces of the developing osseous fusion mass within the thrugrowth region of the PEEK device at a 7·-dose level (Fig. 6-B). At higher magnification, hypertrophied osteoblasts in intramembranous ossification on osseous trabeculae of the developing fusion mass were observed within the PEEK interbody fusion device (Fig. 6-C). All 3 of the 7·-dose levels showed evidence of exostoses, which in some cases bridged the disc spaces. Intramembranous and endochondral ossification within the thrugrowth region of the PEEK interbody fusion device was a routine histological finding in both treatment groups. Osteoclastic activity on rarified trabeculae was observed in bone of the adjacent vertebral body, some distance away from the PEEK implant, and within the thrugrowth region of the PEEK device (Fig. 6-D). ACS was not observed at any treated levels at 8 weeks on histological analysis. An incidental histological finding was intracellular PEEK particulate debris and an attendant focal mild chronic inflammatory host response consisting primarily of macrophages with some foreign-body giant cells at a majority of the treated levels (Fig. 6-E). One unusual histological finding was a fluid-filled lined cyst adjacent to the PEEK device in the 1·-dose group (Fig. 6-F).
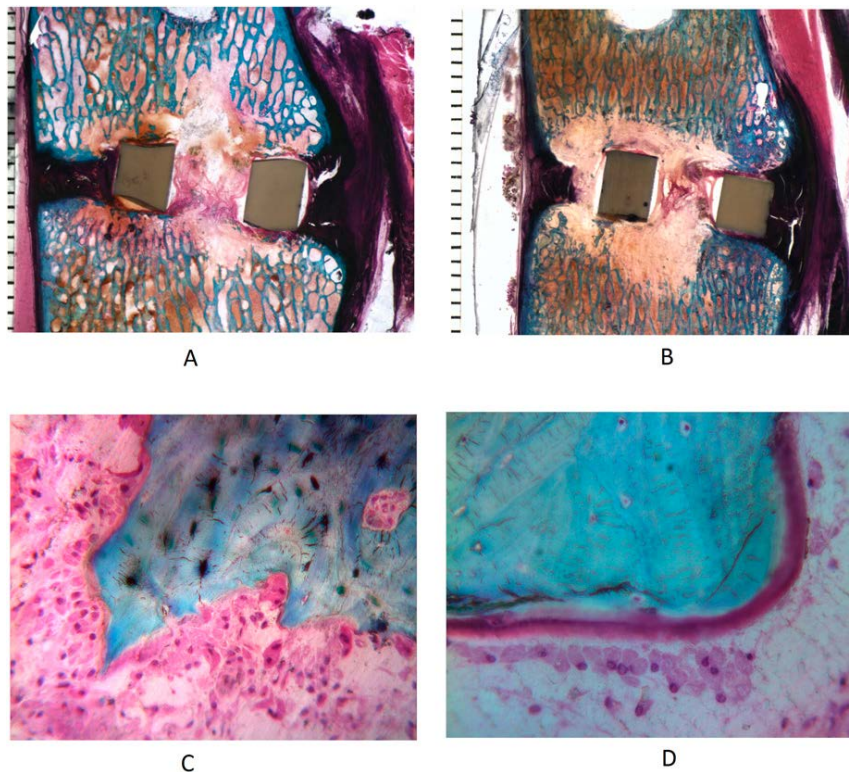

A

B

C

D

Fig. 3 Figs. 3-A and 3-B Stained undecalcified sections from spinal levels 3 weeks after treatment with a 7· dose of rhBMP-2. Fig. 3-C Histological analysis showed substantial end-plate changes as well as osteoclastic resorption extending well into osseous trabeculae of the superior and/or inferior vertebral bodies at all 3 spinal levels in the 7·-dose group at 3 weeks (trichrome stain, original magnification = 200·). Fig. 3-D Some unmineralized osteoid formed via intramembranous ossification was observed at the periphery of the resorption zones (trichrome stain, original magnification = 313·).
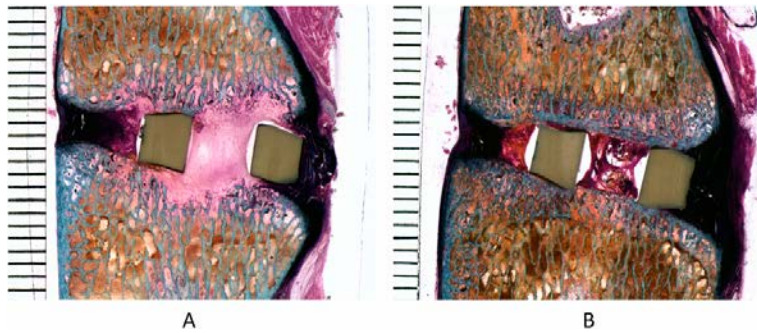
Fig. 4 Stained undecalcified sections from spinal levels 3 week after treatment with a 1· dose of rhBMP-2. One of the 3 levels treated with the 1· dose demonstrated moderate resorption of the end plates on histological analysis (Fig. 4-A), whereas the other 2 levels treated with the 1· dose showed less bone resorption (Fig. 4-B) and substantial preservation of the cortical end plates.
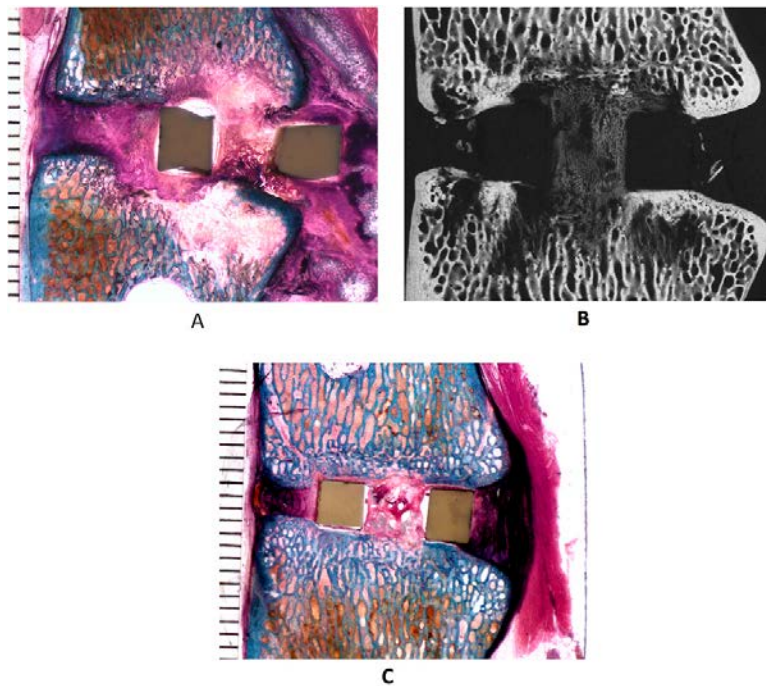

Fig. 5 Figs. 5-A and 5-B Stained undecalcified section (Fig. 5-A) from, and microradiograph (Fig. 5-B) of, spinal levels 4 weeks after treatment with a 7· dose of rhBMP-2. Histological analysis showed substantial end-plate changes as well as bone resorption extending well into osseous trabeculae of the superior and/or inferior vertebral bodies at all 3 levels in the 7·-dose group at 4 weeks. Unmineralized osteoid formed via intramembranous ossification can be observed at the periphery of the resorption zones. The microradiograph shows hypodense osteopenic de novo bone in previous resorption zones and in the thrugrowth region of the disc space, indicative of the early stages of histologically evident fusion at 4 weeks. Fig. 5-C A stained undecalcified section from a spinal level 4 weeks after treatment with the 1· dose, showing less bone resorption and substantial preservation of the cortical end plates.

At 12 Weeks Post-Implantation

At 12 weeks, CT scans showed limited evidence of end-plate remodeling and demonstrated bone formation through the thrugrowth region of the PEEK interbody devices. Except for 1 of the 1·-

dose spinal levels, all treated levels demonstrated complete bridging bone on CT. The CT findings correlated well with the findings of the histological analysis, which showed 1 fusion, 1 partial fusion, and 1 non-fusion at the 1·-dose levels and 2 fusions and 1 partial fusion at the 7·-dose levels. In both groups, the bone was isodense with respect to native trabeculae on microradiography (Fig. 7). With the exception of some pitting of the end plates at 1 of the 1·-dose levels, end-plate changes were not observed. Microradiography showed that previous bone-remodeling areas that had extended well into the vertebral bodies were now fully healed, with isodense-to-slightly hypodense trabeculae. Bridging and non-bridging exostoses were a frequent finding in both groups. All 6 treated levels had intracellular PEEK particulate debris and an attendant focal mild chronic inflammatory host response consisting primarily of macrophages with some foreign-body giant cells. One unusual histological finding was a small subclinical infection with numerous segmented neutrophils limited to tissue adjacent to the PEEK implant at the 1·-dose spinal level at which histological analysis showed non-fusion.

At 20 Weeks Post-Implantation

At 20 weeks, all treated levels showed osseous fusion across the disc space on CTscans. Except for 1 of the 1·-dose levels, all treated levels had either a partial or complete fusion seen on histological analysis. One level in the 7·-dose group demonstrated solid fusion outside the PEEK device and fusion progression within the device. In both treatment groups, the incorporated bone of the fusion mass was isodense with respect to native trabeculae onmicroradiography (Fig. 8). PEEK particulate debris was not observed.
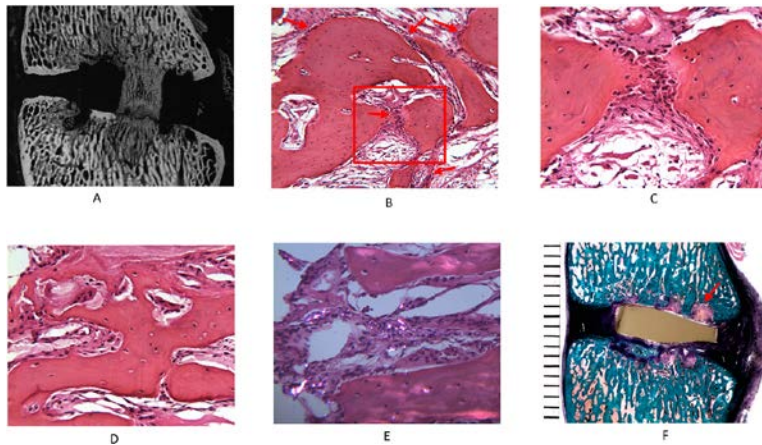

Fig. 6 Fig. 6-A Microradiograph of a spinal level 8 weeks after treatment with a 1· dose of rhBMP-2, showing end-plate changes and bone resorption extending well into osseous trabeculae of the superior and inferior vertebral bodies. Osseous healing with hypodensemineralized trabeculae can be observed within these resorption zones and in the thrugrowth region of the disc space. Fig. 6-B Numerous foci of intramembranous ossification (arrows) are seen on the surfaces of the developing osseous fusion mass within the thrugrowth region of the PEEK device in this 7·-dose spinal level at 8 weeks (hematoxylin and eosin, original magnification = 79·). Fig. 6-C Higher-magnification micrograph of the boxed region in Fig. 6-B, showing hypertrophied osteoblasts in intramembranous ossification on osseous trabeculae of the developing fusion mass within the PEEK interbody fusion device (hematoxylin and eosin, original magnification= 200·). Fig. 6-DOsteoclastic resorption of bonewas still observed8weeks post-implantation in a 7·-dose spinal level at8weeks (hematoxylin and eosin, original magnification = 200·). Fig. 6-E An incidental finding of the 8-week histological analysis was intracellular PEEK particulate debris (birefringentmaterial) and an attendant focalmild chronic inflammatory host response (hematoxylin and eosin, partially polarized light,

originalmagnification = 200·). Fig. 6-F One unusual histological finding in the 1·-dose group was a fluid-filled lined cyst (arrow) adjacent to the PEEK device.
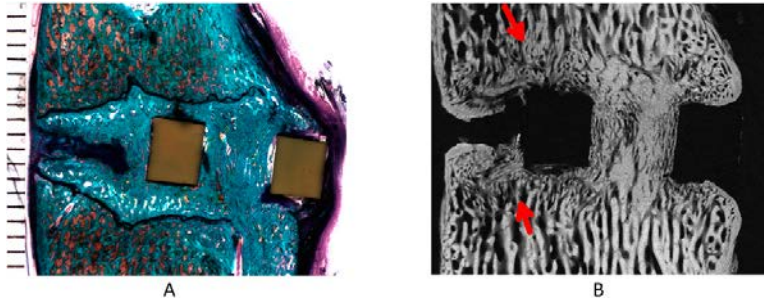

Fig. 7 Fig. 7-A Stained undecalcified section from a spinal level showing solid fusion 12 weeks after treatment with a 7· dose of rhBMP-2. Fig. 7-B Microradiograph of a spinal level 12 weeks after treatment with a 7· dose demonstrates bridging bone from the cranial to caudal vertebral bodies that is isodense with respect to the native trabeculae. Previous bone-remodeling areas (arrows) that had extended well into the vertebral bodies are now fully healed with isodense-to-slightly hypodense osteopenic trabeculae. Note the difference in trabecular thickness between these areas (arrows) and native trabeculae of the vertebral bodies.
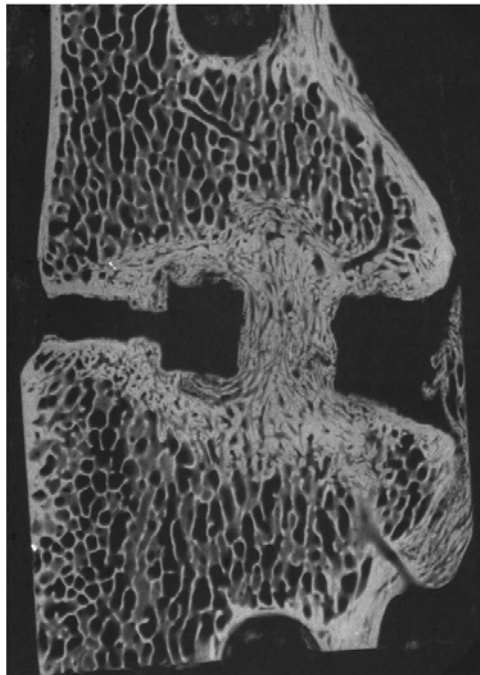
Fig. 8 Microradiograph of a spinal level showing histological evidence of solid fusion with dense mineralized trabeculae in the thrugrowth region of the disc space 20 weeks after treatment with a 7· dose of rhBMP-2.

Discussion

In this end-plate-sparing sheep model, osteoclastic activity and corresponding peri-implant bone resorption was dosedependent, with the 7·-dose spinal levels demonstrating moderate-to-marked resorption and the 1·-dose levels demonstrated minimal-to-no resorption. By 20 weeks, transient bone-resorption effects were not observed and bridging bone was seen regardless of the rhBMP-2 dose. The time to healing was not altered by increasing the dose. Findings similar to those in the current study

were previously reported by Toth et al.35, whose chronologic study demonstrated bone resorption with subsequent osseous healing in association with application of rhBMP-2 in a corticocancellous sheep distal femoral model. With immediate access to cancellous bone in that distal femoral model, a 7· dose of rhBMP-2 caused increased osteoclastic activity and peri-implant bone resorptionwith marked resorption by 1 week35. Inall of their treatment groups, the osteoclastic response was transient with no osteoclastic activity and substantial new bone formation by 4 weeks35. Immediate cancellous access caused osteoclastic resorption to peak at 1week in that study, whereas the delayed cancellous access associated with the cortical end-plate-sparing model in our study resulted in osteoclastic resorption peaking at 3 to 4 weeks.

As can happen in any animal model, inter-animal variability with respect to bone remodeling was observed in the current study. Transient bone-resorption areas varied in both size and location, with the greatest variability in size occurring in the 7·-dose group. The location of the transient bone-resorption areas varied from cranial to caudal in relation to the thrugrowth region of the PEEK implant and was also seen posterior to the implant, particularly at the 3-week time point in the 7·-dose group. While settling of the PEEK interbody fusion device into the cortical end plate was observed in both groups, dose-dependent subsidence was not observed. A lateral 2-screw and single-rod construct was used to provide some postoperative stability and may have limited the potential for substantial subsidence to occur.

The literature suggests that BMPs can affect osteoclastic activity, with a stimulatory effect on the formation of osteoclasts or their bone resorptive capacity, or both.[37-44]

Although a number of FDA-approved clinical investigations have been conducted with rhBMP-2/ACS,[15-22,24] to our knowledge transient bone resorption has been reported in only 1. Burkus and colleagues[21,22] reported that 14 (18%) of 79 patients developed remodeling zones between 3 and 12 months after treatment with 8.4 to 12 mg of rhBMP-2/ACS combined with 2 threaded allograft dowels. By 24 months, all remodeling zones had resolved and a 99% fusion rate had been achieved.

Other clinical studies have demonstrated transient bone resorption following implantation of rhBMP-2/ACS. Meisel and colleagues[28] reported bone resorption following posterior lumbar interbody fusion with application of 12 mg of rhBMP-2/ACS within PEEK interbody spacers. At 3 months postoperatively, 17 patients were noted to have reduced mineral density on CTscans. However, these resorption zones were transient, resolving by 6 months. Pradhan et al.[34] reported resorption of the graft and end plates following the use of rhBMP-2/ACS with ring allografts. Finally, Hansen and Sasso[25] reported on a single patient who had a transient resorptive response following the use of rhBMP-2/ACS in anterior lumbar interbody fusion with an allograft ring.

One limitation of the current study is the fact that the variables of increasing rhBMP-2/ACS fill of the interbody fusion device and hyperconcentration of the rhBMP-2 were not examined individually as potential drivers of heightened osteoclastic resorption. However, it is important to recall that the 1· and 7· doses that we selected had been examined previously in an ovine corticocancellous distal femoral model[35]. As discussed above, these doses demonstrated the largest difference in transient osteoclastic activity and peri-implant bone resorption. The 7· dose represents a worst-case scenario in which the user underdilutes the rhBMP-2 to increase the solution concentration while overfilling the thrugrowth

region of the interbody fusion device. While this is unlikely to occur in clinical practice, it is possible and was therefore included as a worst-case dosing scenario. Importantly, in the previous ovine distal femoral corticocancellous model[35], overfilling with (2·) and hyperconcentration of (3.5·) the rhBMP-2 were examined as standalone variables and both resulted in heightened osteoclastic activity and peri-implant bone resorption compared with what was seen in the 1· group. As 1· and 7· doses performed similarly regardless of whether the distal femoral or cortical end-plate-sparing interbody fusionmodel was used, it can be assumed that both bone-forming environments are susceptible to rhBMP-2 dose-dependent transient osteoclastic activity and peri-implant bone resorption.

In conclusion, osteoclastic activity and corresponding peri-implant bone resorption were rhBMP-2-dose-dependent in an end-plate-sparing ovine interbody fusion model in which a custom-designed PEEK interbody construct had been implanted via a transpsoas retroperitoneal approach; 7·-dose levels resulted in moderate-to-marked resorption while 1·-dose levels resulted in minimal-to-no resorption. By 20 weeks, transient bone-resorption effects were not observed and bridging bone was seen by the blinded assessors regardless of the dose. Increasing the dose had no effect on the time to healing. Using the FDA-approved rhBMP-2 concentration and matching the volume of rhBMP-2/ACS with the volume of the desired bone formation may limit the occurrence of transient bone resorption.

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