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Polyetheretherketone as a Biomaterial for Spinal Applications

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Abstract
Threaded lumbar interbody spinal fusion devices (TIBFD) made from titanium have been reported to be 90% effective for single-level lumbar interbody fusion, although radiographic determination of fusion has been intensely debated in the literature. Using blinded radiographic, biomechanic, histologic, and statistical measures, we evaluated a radiolucent polyetheretherketone (PEEK)-threaded interbody fusion device packed with autograft or rhBMP-2 on an absorbable collagen sponge in 13 sheep at 6 months. Radiographic fusion, increased spinal level biomechanical stiffness, and histologic fusion were demonstrated for the PEEK cages filled with autograft or rhBMP-2 on a collagen sponge. No device degradation or wear debris was observed. Only mild chronic inflammation consisting of a few macrophages was observed in peri-implant tissues. Based on these results, the polymeric biomaterial PEEK may be a useful biomaterial for interbody fusion cages due to the polymer's increased radiolucency and decreased stiffness.

Keywords
Polyetheretherketone, Bone morphogenetic protein (BMP), PEEK, Spinal surgery, Spine fusion, Spine fusion cages

1. Introduction
Back or spine musculoskeletal impairment has been reported to represent more than half (51.7% or 15.4 million incidences) of the musculoskeletal impairments reported in the United States.[1] In the 18–84 age group, back or spine impairment is the leading cause of activity limitation and results in more lost productivity than any other medical condition.[1] It has been estimated that 4.4 million people 25–74 years of age report intervertebral disc

problems in the United States.[1] While it has been reported that 80–90% of patients with low-back pain recover by 12 weeks with non-surgical therapies such as bed rest and anti-inflammatory medications,[2] non-surgical therapies are occasionally unsuccessful for certain injuries/pathologies, including degenerative disc disease/stenosis, spondylolysis, and/or spondylolisthesis.

When conservative treatment fails, spinal fusion (arthrodesis) may be performed. In the United States, there were 279,000 operations for low-back pain in 1990 with 26 lumbar fusions performed per 100,000 persons.[2] In 1995, there were approximately 160,000 spine fusion surgeries.[1] In a literature review of 47 studies, Turner et al.[3] reported that 68% of the patients had a satisfactory outcome after lumbar fusion, but the range was between 16% and 95%. Of most concern was a 20–40% failure rate reported for lumbar spine fusion.[3]

Since the approval of spinal fusion cages by FDA in 1996, the use of these devices has become prevalent for lumbar interbody fusion (LIF).[4,5,6,7,8,9,10,11,12] Clinically, on the basis of primarily radiographic evaluation, lumbar interbody fusion with titanium spinal fusion cages has been reported to be effective for single-level LIF, with a fusion rate of 90% or higher at 1–2 years post-operatively.[5,7,8,12] Fusion rates may be between 70% and 80% in patients with multi-level fusions or with risk factors such as obesity, tobacco use, or metabolic disorders. A central question still exists with regard to the use of these radiopaque devices: “Is radiographic determination of fusion possible with titanium interbody fusion devices?” This question has been intensely debated in the recent literature.[13,14] In 2000, Cizek and Boyd[13] published an experimental study that has shown that plain radiographs and CTs of cage-instrumented cadavers showed “considerable metallic artifact.” In 2001, a prominent panel of spine surgeons and researchers were unable to develop a consensus for “successful arthrodesis” following interbody fusion with titanium interbody fusion devices.[14] Thus, the development of radiolucent spine fusion devices that are mechanically competent and biocompatible would be a great asset to the armamentarium of spine surgeons.

One non-absorbable biopolymer that has been evaluated as a biomaterial is polyetheretherketone (PEEK). PEEK has been used in a variety of industries, from aerospace and aviation to medical devices. According to InVibio®, the manufacturer of PEEK-OPTIMA® (the biomedical formulation of the PEEK material), the polymer can be processed through conventional techniques including injection molding, extrusion or machining, allowing medical device manufacturers broad design and manufacturing flexibility. PEEK has well-established mechanical and good wear characteristics, as well as excellent biocompatibility in both bulk and particulate form.[15,16,17,18,19] Rivard et al.[20] found neither necrosis nor swelling when PEEK particles were injected in tissues adjacent to the spinal cord and nerve roots of 12 New Zealand white rabbits. In 2002, Senegas[21] reported that a PEEK interspinous system of non-rigid stabilization is efficacious against low-back pain due to degenerative instability. Recently, Cho et al.[22] have evaluated PEEK cages for cervical disc disease in a group of 40 patients. They showed that the PEEK devices were able to facilitate stability and space maintenance during cervical fusions, increase cervical lordosis, and increase foraminal height.[22]

Previously published studies have shown that autograft as well as cages and other spine fusion devices, alone or packed with autograft, may not produce solid fusions.[24,25,26,27,28,29,30] Using the ovine LIF model, previous studies have shown that the augmentation strategy (augmentation of rhBMP-2) has significantly increased the fusion rate of cages compared to the same implant with autograft or alone.[10,24] The current study addresses the efficacy of autograft or rhBMP-2 loaded on a collagen sponge to achieve radiographic, biomechanic, and histologic fusion with a threaded cylindrical PEEK device.

The goals of this study were (1) to evaluate the osteocompatibility of the radiolucent PEEK polymeric device, (2) to evaluate the efficacy of the PEEK device filled with autograft or rhBMP-2 on a collagen sponge to achieve lumbar interbody spine fusion using blinded radiographic, biomechanic, and histologic measures, and (3) to evaluate the augmentation strategy of adding rhBMP-2 on a collagen sponge to stimulate bony healing in conjunction with the PEEK biomaterial.

2. Materials and methods

2.1. Animal model

The sheep lumbar spine model was specifically chosen because of the biomechanical similarities between the sheep and human lumbar spine.[31,32,34] Wilke et al.[31] characterized the biomechanical parameters (range of motion, neutral zone, and level stiffness) of sheep spines and made comparisons with data from human specimens previously published by White and Panjabi.[33] Wilke et al. found that the "ranges of motion of sheep spines for the different load directions are qualitatively similar in their craniocaudal trends to those of human specimens reported in the literature".[31] They concluded that "based on the biomechanical similarities of the sheep and human spines demonstrated in this study, it appears that the sheep spine…can serve as an alternative for the evaluation of spinal implants".[31]

2.2. Materials and study design

The PEEK interbody fusion device was evaluated in 13 skeletally mature female sheep at a 6 month survival period. Seven sheep received a PEEK cage filled with autograft. Six sheep received a PEEK cage filled with rhBMP-2 on a collagen sponge. Eight sheep levels were used for the biomechanical sham group (described below). This study was approved by the Institutional Animal Care and Use Committee. Colorado State University is in compliance with recommendations of the American College of Laboratory Animal Medicine and the PHS Guide for the Care and Use of Laboratory Animals. Animals were fasted for 24 h prior to surgery. Water was not restricted during this time. Anesthesia was induced with ketamine (4 mg/kg) and valium (7.5 mg total). After induction, sheep were maintained with isofluorane(1.5–3%) in 100% oxygen (2 L/min) during the surgical procedure. Muscle relaxants were not used. In the PEEK+autograft group, tricortical iliac crest autograft was harvested using an osteotome and mallet, and further morselized so that it could be packed into the cages. The surgical technique involved positioning the sheep in right lateral recumbency for single-level lumbar discectomy and interbody fusion at L4–L5 via a left retroperitoneal approach. Following discectomy, a 14 mm diameter×20 mm long PEEK interbody fusion device (Fig. 1a) was packed with morselized iliac crest cancellous autograft or InFuse™ bone graft substitute (Fig. 1b). The PEEK polymer implants (PEEK-Optima, Invibio, Greenville, SC) had the following mechanical properties: an elastic modulus of 3.7 GPa, a tensile strength of 100 MPa, and a ductility of 60% elongation to failure. Fabricated into the shape of the interbody fusion device as seen in Fig. 1a, the device was able to withstand a compressive load to failure of 14,100 N after sterilization. The InFuse™ bone graft substitute (Medtronic Sofamor Danek, Memphis, TN) consisted of 0.80 mL of rhBMP-2 (Wyeth Research, Cambridge, MA) at a concentration of 0.43 mg/mL applied to a Type I collagen sponge (Helistat™ collagen sponge, bovine achilles tendon, Integra Life Sciences, Andover, MA).

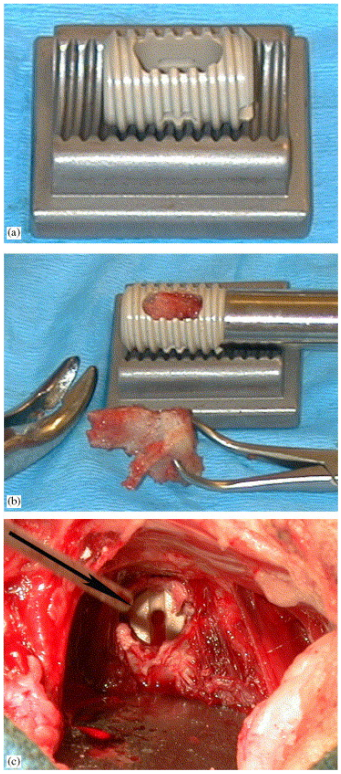

Fig. 1. (a) Appearance of the PEEK device prior to implantation. Either iliac crest autograft or rhBMP-2 on a collagen sponge was packed into the thrugrowth slot of the device. (b) Autograft being loaded into the PEEK device prior to implantation. (c) Implantation of the device (arrow) in the interbody space. The caudal direction is to the right and the cranial direction is to the left.

The animals were assigned to receive either InFuse™ or autograft at the time of surgery. Fig. 1c shows the appearance of the PEEK device in the interbody space after implantation. Pain medication after the surgical procedures included Fentanyl patches at a dose of 150 μg/h administered with a continuous percutaneous patch for 3 days. Additional pain medication included Phenylbutazone at a dose of 1 g administered orally once per day for 3 days. At the conclusion of the study, all of the sheep were euthanized with barbiturate overdose at 6 months post-operatively. The efficacy of the radiolucent device packed with either autograft or the InFuse™ bone graft substitute to effect LIF was assessed by performing radiographic, biomechanic, and histologic analyses in a blinded fashion.

2.3. Neurologic evaluations

Neurological exams were conducted daily for 7 post-operative days, at 2 months, and before euthanasia at 4 months. Neurological exams were conducted using the following scale: 0=walking without any detectable ataxia, 1=walking, slightly ataxic, 2=walking, but with noticeable weakness on one side or both sides, 3=able to stand on forelimbs but dragging rear limbs, and 4=recumbent and unable to rise.

2.4. Radiographic evaluation

Radiographs (ventrodorsal (VD) and lateral views) were taken immediately after surgery and at regular post-operative followup times. High-resolution radiographs were made after biomechanical testing (PA and lateral views) using a high-resolution radiography unit (Faxitron X-ray unit, Hewlett Packard, McMinnville, OR) and high-resolution film (Ektascan M EM-1, Eastman-Kodak, Rochester, NY). The resulting Faxitron radiographs from the treated animals and the biomechanical sham group (see Section 2.5) were read by three blinded evaluators for fusion, bone in the PEEK cages, and implant placement. The radiographs were graded in the following manner. Grade 3 was a solid fusion with no radiolucent lines surrounding the cage. Grade 2 was a probable fusion with some radiolucent lines surrounding the cage. Grade 1 was a non-fusion with significant radiolucent lines

surrounding the cage. Radiographs were also evaluated for bone present in the cage as seen from the lateral view as well as the presence of ventral (anterior) or dorsal (posterior) bony bridging.

2.5. Biomechanical testing

Ex vivo biomechanical testing was performed to quantify the stiffness of the treated motion segments by measuring load displacement behavior. The treated lumbar motion segments were dissected from the harvested lumbar spines and cleaned of extraneous soft tissues leaving the ligamentous and osseous tissues intact. Unconstrained biomechanical testing was performed in a non-destructive manner on all treated spines. Specially designed loading and base frames were secured on the caudal and cranial vertebrae, respectively. Three retroreflective markers were attached to each vertebra. Pure moments (0, 0.5, 2.5, 4.5, 6.5, and 8.5 N m) were applied in the following loading directions: flexion, extension, right and left lateral bending, and left and right axial rotation. The location of the markers was recorded at each load using three infrared video cameras (VICON cameras, Oxford Metrics, Oxford, England). The three-dimensional coordinate data were then analyzed to obtain the rotation angles and the flexibility of each motion segment. In addition to the treated animals, eight "biomechanical sham" (polymeric device implanted in normal cadaver sheep spine using the same surgical technique) motion segments were tested in the same manner. The rationale for the biomechanical sham was that it allowed for comparison of the biomechanics of the treated survival groups to the instrumented sham levels. A fused level would then have an increased stiffness and decreased flexibility compared to the instrumented sham levels. Biomechanical testing data of the biomechanical shams provide a better comparison to the non-fused survival implant than untreated normal motion segments as biomechanical shams provide an estimate of the immediate post-operative stiffness (in all six loading directions) of the stabilized spinal construct due to the implantation of the interbody device alone.[10,26]

2.6. Histologic studies

Immediately after biomechanical testing, the specimens were fixed in 10% neutral buffered formalin and bisected mid-sagittally to produce right and left halves. These halves were sequentially dehydrated in alcohols, cleared in a xylene substitute (CitriSolv, Fisher Scientific, Itasca, IL), and embedded in graded catalyzed methyl methacrylate for undecalcified histological studies. After polymerization was complete, sections were cut in the sagittal plane continuously through the explanted levels on a diamond saw (Isomet, Buehler, Lake Bluff, IL) to an approximate thickness of 150–400 μm. Approximately 10–15 sections were made in the sagittal plane through each half of the bisected level. The thickness of each section was measured with a metric micrometer. Differential staining using a trichrome stain was used to permit both histological and cytological differentiation. With this staining method, the following tissues can be differentiated on the basis of color: bone is stained blue/green, cartilage and fibrocartilage are stained dark purple, and fibrovascular tissue is stained pink. Staining of cellular and nuclear detail by the trichrome stain is similar to H&E; thus permitting cytological differentiation.

In addition to stained undecalcified sections, 4–8 undecalcified sections from each treated level were radiographed using a Faxitron radiography unit (Hewlett Packard, McMinnville, OR) and spectroscopic film (EM-1 film, Kodak, Rochester, NY). The thickness of the sections was measured with a metric micrometer (Fowler, Japan) to determine the exposure time. Sections were labeled with ultra-fine permanent markers and then exposed to the X-ray source at 20 kV and 3 mA for approximately 45 s for each 100 μm of section thickness. The samples were placed on the sheet of spectroscopic film and the film placed on a rectangular film holder. The loaded cassette assembly was inserted into the Faxitron X-ray unit and exposed to the X-radiation as described. The films were then developed, fixed, and analyzed for ossification using standard optical microscopy.

The histological slides and microradiographs were used to evaluate histologic fusion or the presence of pseudarthroses. The criterion used to assess histological fusion was a continuous bony bridge from the cranial to the caudal vertebra. A solid fusion existed if greater than 50% of the sections and corresponding microradiographs showed continuous bony bridging through the thrugrowth region of the PEEK device. A partial fusion existed if less than 50% of the sections and corresponding microradiographs showed continuous bony bridging through the thrugrowth region of the PEEK device. A non-fusion existed if none of the sections and

corresponding microradiographs showed continuous bony bridging through the thrugrowth region of the PEEK device. Analysis of the stained undecalcified sections was also used to determine the histological and cytological response to the treatments and osteocompatibility of the polymeric device. The quality of bone was evaluated both within and in contact with the PEEK implant by examining trabecular width, lamellar organization, and evidence of bone remodeling. Bone mineralization was also assessed using the trichrome stain and microradiography.

2.7. Statistical analyses

Polytomous logistic regression models were used to model the odds ratio associated with higher radiographic fusion scores among the three groups (sham, autograft, and rhBMP-2). If that test indicated that significance was found, further pair-wise comparison of the radiographic fusion scores was assessed by the logistic likelihood ratio test. Biomechanical stiffness data were non-parametric, therefore, a non-parametric statistical analysis using Kruskal–Wallis analysis of variance (ANOVA) was conducted for each loading direction. If that test indicated that significance was found, further pair-wise comparison of the biomechanical data was then made using the Mann–Whitney *U*-test. A statistical significance level of $p<0.05$ was used for all tests. The Fisher's exact test was used to compare histologic fusion rates for the two treated survival groups.

3. Results

All sheep recovered from anesthesia uneventfully and were standing and walking without signs of neurological deficits. All sheep received a score of 0 (i.e. walking without any detectable ataxia) for limb use at 7 post-operative days, at 2 months, and before euthanasia.

3.1. Radiographic results

Mean radiographic fusion scores for the biomechanical sham group and all post-operative survival time groups made by the three blinded evaluators are presented in Table 1. A lateral radiograph showing the appearance of the defect immediately after implantation of the radiolucent PEEK device filled with rhBMP-2 on a collagen sponge is seen in Fig. 2a. It can be seen from Fig. 2a that both the PEEK device and bone graft substitute are radiolucent. Biomechanical sham levels had a mean radiographic fusion score of 1.06, indicating that the three blinded radiograph evaluators were clearly able to determine non-fusions in biomechanical sham radiographs mixed in with treated survival levels. Faxitron lateral radiographs of two levels treated with the PEEK device filled with autograft at the 6 month post-operative survival time are shown in Figs. 2b and c. Both of these levels demonstrated that a solid arthrodesis has developed within the thrugrowth region of the PEEK cages. Faxitron lateral radiographs of two levels treated with the PEEK device filled with rhBMP-2 on a collagen sponge at the 6 month post-operative survival time are shown in Figs. 2d and e. Both of these levels demonstrated that a solid arthrodesis had developed within the thrugrowth region of the PEEK cages. Despite the fact that the device in Fig. 2e was rotated, a solid arthrodesis was induced by rhBMP-2 on a collagen sponge within the PEEK device. Marked radiolucencies were not observed surrounding the cages in any of the treatment groups.

Table 1. Radiographic fusion scores for the biomechanical sham group and the treated survival groups

	Evaluator 1	**Evaluator 2**	**Evaluator 3**
Sham	1	1	1
Sham	1	1	1
Sham	1	1	1
Sham	1	1	1
Sham	1	1	1
Sham	1	1	2
Average	1.00	1.00	1.17
Mean radiographic fusion score for sham group: 1.06			
PEEK+Autograft	1	1	1
PEEK+Autograft	2	2	3
PEEK+Autograft	1	1	2

	Evaluator 1	Evaluator 2	Evaluator 3
PEEK+Autograft	3	3	3
PEEK+Autograft	3	2	3
PEEK+Autograft	3	3	3
PEEK+Autograft	3	2	3
Average	2.29	2.00	2.57
Mean radiographic fusion score for PEEK+autograft group: 2.29			
PEEK+rhBMP-2	3	3	3
PEEK+rhBMP-2	3	3	3
PEEK+rhBMP-2	2	2	3
PEEK+rhBMP-2	3	3	3
PEEK+rhBMP-2	3	2	3
PEEK+rhBMP-2	3	3	3
Average	2.83	2.67	3.00
Mean radiographic fusion score for PEEK+rhBMB-2 group: 2.83			

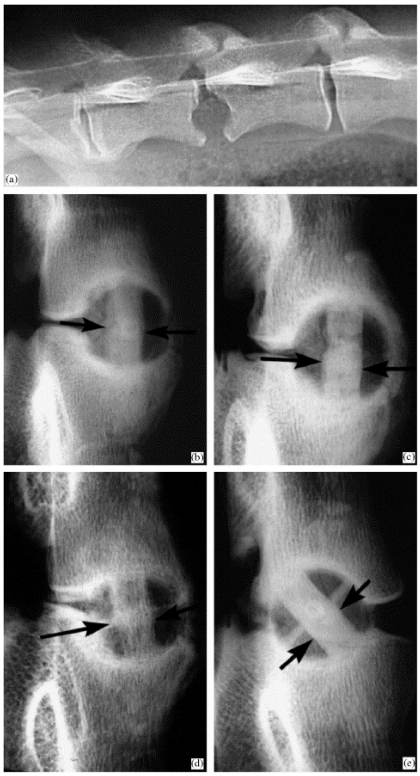

Fig. 2. Post-operative lateral radiograph (a) showing the appearance of the defect immediately after implantation of the radiolucent PEEK device filled with rhBMP-2 on a collagen sponge. Note that both the device and bone graft substitute are radiolucent. (b) and (c) Faxitron lateral radiographs of two levels treated with the PEEK device filled with autograft at the 6 month post-operative sacrifice time. A solid arthrodesis has developed within the thrugrowth region of both PEEK cages (arrows). (d) and (e) Faxitron lateral radiographs of two levels treated with the PEEK device filled with rhBMP-2 on a collagen sponge at the 6 month post-operative sacrifice time. A solid arthrodesis has developed within the thrugrowth region of both PEEK cages (arrows). Despite the fact that the device in (e) was rotated, a solid arthrodesis was induced by rhBMP-2 on a collagen sponge within the PEEK device.

Significant differences were found between treatment groups with respect to radiographic fusion scores among the three groups (sham, autograft, and rhBMP-2, polytomous logistic regression, $p<0.002$). Further pair-wise comparison showed that the PEEK+autograft group and PEEK+rhBMP-2 group tended to score higher than the sham group (logistic likelihood ratio test, $p<0.01$ for autograft, $p<0.0002$ for rhBMP-2). The difference between PEEK+autograft and PEEK+rhBMP-2 is not significant (logistic likelihood ratio test, $p<0.25$).

3.2. Ex-vivo biomechanical testing results

Biomechanical flexibility data presented as stiffness in N m/° (mean±standard deviation) for flexion and extension, right and left lateral bending, and right and left axial rotation for the intact normal spine level group (N=17), the biomechanical sham group (N=8), the PEEK filled with autograft group (N=7), and the PEEK filled with rhBMP-2 on a collagen sponge group (N=6) are presented in Fig. 3. Comparing the rhBMP-2-filled PEEK group with the PEEK+autograft group, a significant increase in stiffness was found in the loading directions of flexion and left lateral bending (Mann–Whitney *U*-test, $p<0.01$) for the rhBMP-2 group. Increases in all other loading directions were not statistically significant (Mann–Whitney *U*-test, $p>0.05$). For all six loading directions, both the PEEK+rhBMP-2 group and the PEEK+autograft group showed significantly higher stiffness than the sham group (Mann–Whitney *U*-test, $p<0.05$). Biomechanical data correlated well with radiographic and histological data for both PEEK survival groups.

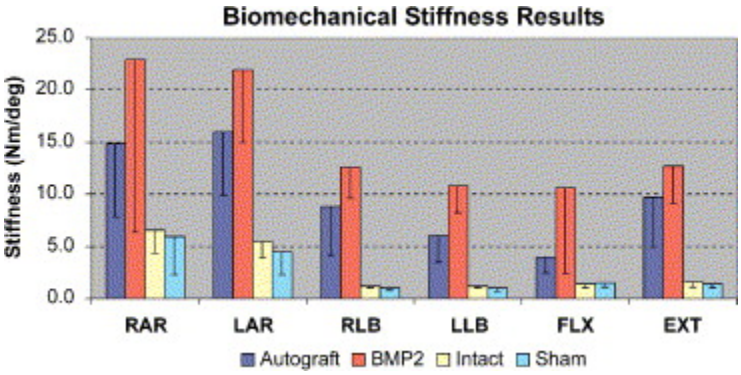

Fig. 3. Level stiffness (N m/°) for biomechanical shams and PEEK levels treated with either autograft or rhBMP-2 on a collagen sponge in right axial rotation (RAR), left axial rotation (LAR), right lateral bending (RLB), left lateral bending (RLB), flexion (FLX), and extension (EXT) in response to the applied moments. Stiffness data for unoperated normal levels (intact) are also shown as a reference.

3.3. Histological results

Histological fusion data for the three treatment groups are shown in Table 2. In the PEEK+autograft group, two levels were rated a non-fusion, one level was rated a partial fusion, and four levels were rated a histologic fusion. Representative images of the stained undecalcified sections and corresponding microradiographs from the PEEK+autograft group are seen in Fig. 4. In the PEEK+rhBMP-2 on a collagen sponge group, none of the levels was rated a non-fusion, one level was rated a partial fusion, and the remaining five levels were rated a histologic fusion. Representative images of the stained undecalcified sections and corresponding microradiographs from the PEEK+autograft group are seen in Fig. 5.

Table 2. Summary of histological fusion results for the treated survival groups

	6 months
PEEK+Autograft	5/7 (71%)
PEEK+rhBMP-2	6/6 (100%)

Fusion incidence and percent (in parenthesis) are reported.

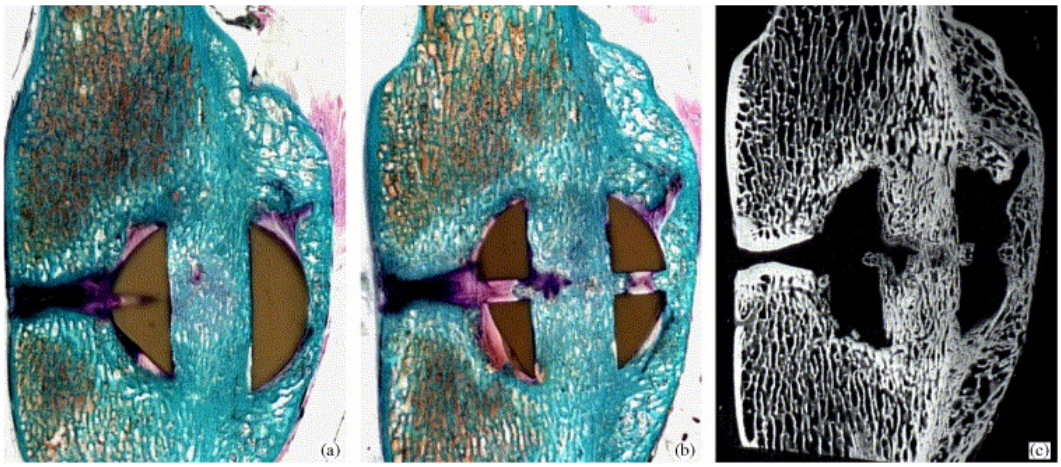

Fig. 4. Stained undecalcified sections (a) and (b) and microradiograph (c) from a spine level treated with PEEK and autograft at 6 months post-operative sacrifice time. Histologic fusion is demonstrated by continuous superior to inferior bony bridging in the thrugrowth region of the PEEK cages. Arthrodesis in the anterior margins in addition to the thrugrowth regions is also seen.

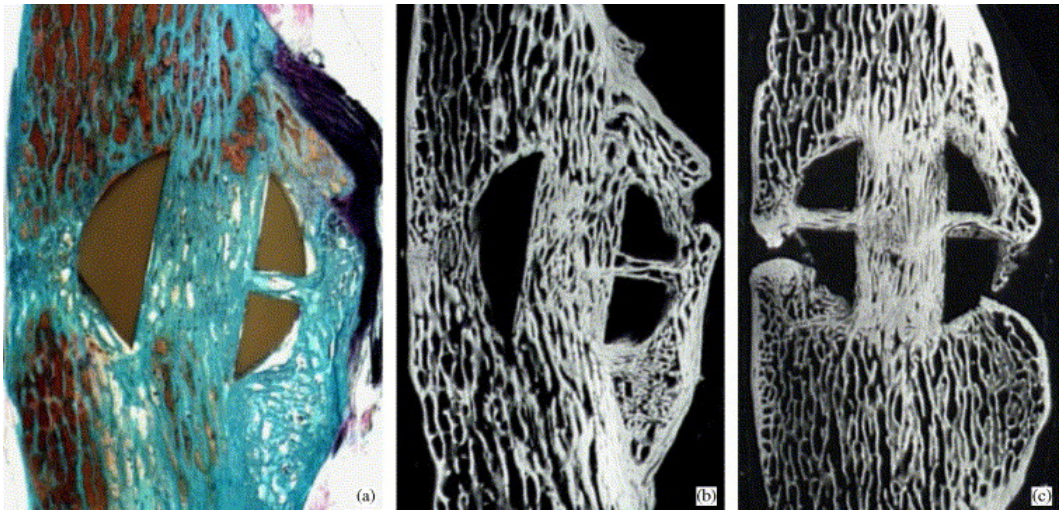

Fig. 5. Stained undecalcified section (a) and microradiographs (b and c) from two spine levels treated with PEEK and rhBMP-2 at 6 months post-operative sacrifice time. Histologic fusion is demonstrated by continuous cranial to caudal bony bridging in the thrugrowth region of the PEEK cages. (a) and (b) also show arthrodesis in the anterior and posterior margins in addition to the thrugrowth regions.

3.3.1. Fusion rates

Radiographic, biomechanic, and histologic measures for fusion were highly correlated in this study. In the PEEK+autograft group, two sheep had the PEEK devices rotated at a near 90° angle, thus obviating histologic fusion. The lack of histologic fusion resulted in significantly less stiff levels in the biomechanical analysis. While these two sheep are included in the PEEK+autograft group, the failure of these two levels to fuse is probably iatrogenic, and not related to the device or graft used. The other five sheep in the PEEK+autograft group achieved histologic fusion (4 solid and 1 partial) at 6 months. The fact that two of the cages were rotated 90° obviated histologic fusion. If these are regarded as iatrogenic failures, the histologic fusion rate would be 100%.

The implantation of the PEEK device with rhBMP-2 on a collagen sponge was successful in achieving histologic fusion. In the PEEK+rhBMP-2 group, all six sheep achieved histologic fusion (5 solid and 1 partial) at 6 months. For the most part, significant differences between radiographic, biomechanic, and histologic measures for fusion were not observed when comparing PEEK devices filled with autograft versus those filled with rhBMP-2. One

PEEK device was found to be rotated in the PEEK+rhBMP-2 group (Fig. 6a). Despite the rotation of the PEEK device, histologic fusion was demonstrated by continuous cranial to caudal bony bridging in the thrugrowth region of the PEEK cage (Fig. 6a). Figs. 6b and c show a non-fusion in a spine level treated with PEEK and autograft at 6 months. Although bone formation occurred within the thrugrowth region of the PEEK device, the rotated device obviated fusion. The histological fusion rates for the two survival groups were not significantly different (Fisher's exact test, $p>0.05$).

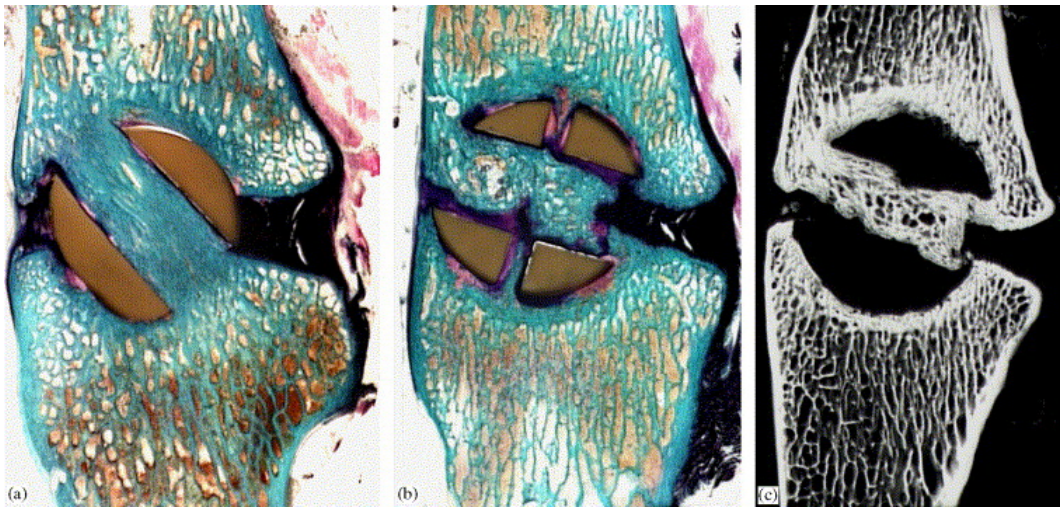

Fig. 6. Stained undecalcified section (a) from a spine level treated with PEEK and rhBMP-2 at 6 months. Despite the rotation of the PEEK device, histologic fusion is demonstrated by continuous cranial to caudal bony bridging in the thrugrowth region of the PEEK cage. Non-fusion in a spine level (b) and (c) treated with PEEK and autograft at 6 months. Although bone formation occurred within the thrugrowth region of the PEEK device, fusion was obviated by the rotated device.

3.3.2. Device interface and host response

Table 1 of the ASTM F981-99 standard was used to quantify the cytological response to the PEEK implant material in the current study. The result was a rating of 0 to 1.0 for all inflammatory cells for all implants on a scale of 0 to 3.0, indicating that no inflammation to mild chronic inflammation was observed in peri-implant tissues. The mean and standard deviation for the overall host response score was 0.54±0.14. A score of 1.0 is interpreted as a mild host response as per ASTM F981-99. There was no acute inflammatory phase present, and no neutrophils were observed in peri-implant tissues. Also, there was no evidence of a humoral or cell-mediated immune response as no plasma cells or eosinophils, and just a few lymphocytes were observed in peri-implant tissues. The predominant finding was macrophages and fibroblasts with occasional foreign body giant cells observed. Thus, only a mild chronic inflammatory response was present at 6 months. Stained undecalcified sections showed that a mixed device interface developed (Figs. 7a–c). In some regions, the PEEK device interface consisted of direct bone contact (Fig. 7a), while in other regions, there was a cartilage interface (Fig. 7b) or a fibrous interface (Fig. 7c). No evidence of implant degradation, wear debris, or osteolysis was observed in tissues adjacent to the PEEK devices. Bone mineralization adjacent to the polymeric device was found to be normal by staining (trichrome stain is similar to Masson's stain) and microradiography.

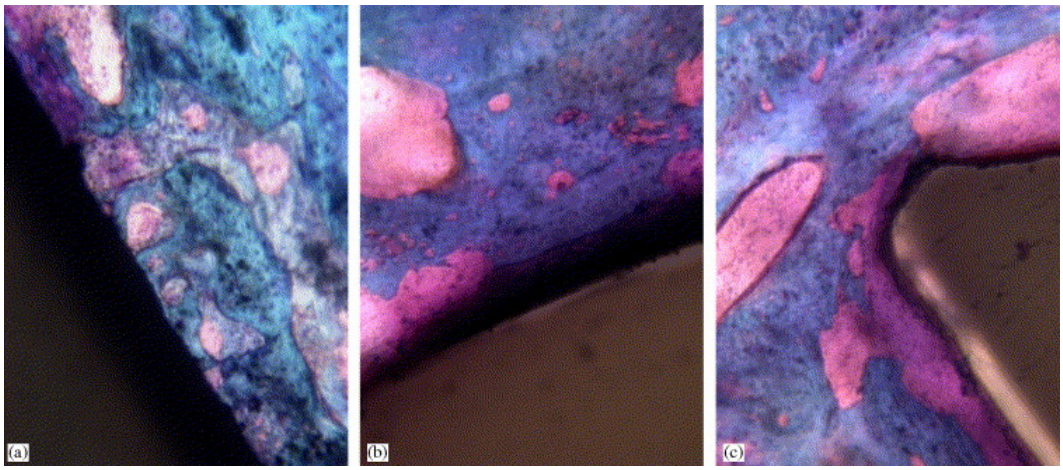

Fig. 7. Stained undecalcified sections showing the mixed device interface that developed. The PEEK device interface consisted of direct bone contact (a), cartilage interface (b), and fibrous interface (c). No evidence of implant degradation or wear debris was observed in tissues adjacent to the PEEK device. No inflammation to mild chronic inflammation was observed in peri-implant tissues.

4. Discussion

In the current study, all six sheep treated with the PEEK cage+InFuse™ achieved histologic fusion at 6 months. Five of the seven sheep (71%) treated with the PEEK cage+autograft achieved histologic fusion at 6 months. While six months provides valuable data on this device in a validated animal model, more studies and complimentary data would be needed to assess long-term performance of such a device. Nevertheless, at 6 months in the ovine LIF model, tricortical iliac crest autograft in a titanium cage (InterFix, Medtronic Sofamor Danek) produced a 37% fusion rate.[24] Also in that study, the InFuse™ bone graft substitute produced a 100% histological fusion rate at 6 months in the Interfix cage.[24] The biomechanical stability of a single cage implanted via a “lateral” retroperitoneal approach in the ovine LIF model provides a challenging healing environment. However, a better animal model does not exist at this time. Thus, fusion rates need to be viewed within the context of this animal model. Also, a mixture of tissues was observed at the device's interface. The presence of non-osseous tissues at the device's interface may obviate bone–cage–bone loading. The non-osseous tissues at the device's interface might prevent stress shielding of bone within the fusion mass.

For the radiolucent PEEK polymeric device under investigation, the three blinded radiograph evaluators were clearly able to make determinations of fusion and non-fusion that correlated with histological findings. At 6 months, the evaluators clearly saw intra-device radiolucencies associated with pseudarthrosis and continuous trabecular bridging associated with fusion. In several experimental studies reported in the literature[10,23,24,29,35] non-fusions consisted of pseudarthroses within titanium spine fusion cages, not frank pseudarthroses along the cranial or caudal device interface which would generate radiolucencies surrounding the cages. These pseudarthroses associated with titanium fusion cages are not easily detectable by current radiographic techniques. In the same model, the mean radiographic fusion score generated by three blinded radiograph evaluators for the biomechanical sham group consisting of a titanium BAK cage packed with autograft was 2.00 (indicating probable fusion).[26] In the current study, the mean radiographic fusion score for the biomechanical sham group was 1.06 (recall that grade 1 is a non-fusion). Thus, blinded evaluators could clearly evaluate radiographic non-fusion.

In the current study, PEEK devices were instrumental in stabilizing the spinal level and allowing for a fusion mass to develop in the thrugrowth region of the cage. None of the lumbar fusions in this model had any supplemental dorsal fixation for increased stability. Fusions developed regardless of whether autograft or the bone graft substitute InFuse™ was used. Tissue engineering can be thought of as an art and science by which synthetic compounds are manipulated into anatomically and/or functionally specific architectures.[27] When required,

these devices may be integrated with biologically active agents and/or living cells such that resultant properties of the whole are precisely suited to support the specific cell life prescribed for recipient tissues.[27] One concept involved in tissue engineering, which is critical in the deployment of a morphogen such as rhBMP-2, is that a biomaterial or device should provide a sheltered environment for the expression of the morphogen. This entails retention of mechanical properties after implantation and maintenance of a 3-D internal geometry as a tissue void to protect form encroachment of non-osseous tissues.[27] In the current study, the PEEK cages provided a sheltered environment for the expression of rhBMP-2 on a collagen sponge. This expression resulted in the induction of a bony fusion mass and subsequent arthrodesis of the spinal level.[27] Thus, the PEEK biomaterial does not appear to interfere with the expression of rhBMP-2.

Despite the fact that some of the PEEK devices were rotated and pseudarthroses developed, no device degradation or wear debris was observed. Thus, the PEEK device appears to be mechanically competent to withstand loads found in the spine. Even in the worst-case scenarios (development of pseudarthroses), only mild chronic inflammation consisting of a few macrophages was observed in peri-implant tissues.

5. Conclusions

Threaded titanium lumbar interbody spinal fusion devices have been reported to be 90% effective for single-level lumbar interbody fusion, although radiographic determination of fusion has been intensely debated in the literature. Using blinded radiographic, biomechanic, histologic, and statistical measures, we evaluated a radiolucent PEEK-threaded interbody fusion device packed with autograft or rhBMP-2 on a collagen sponge in 13 sheep at 6 months. Radiographic fusion, increased biomechanical stiffness, and histologic fusion were demonstrated for the PEEK cages filled with autograft or rhBMP-2 on a collagen sponge. No device degradation or wear debris was observed. Only mild chronic inflammation consisting of a few macrophages was observed in peri-implant tissues. Based on these results, the polymeric biomaterial polyetheretherketone (PEEK) may be a useful biomaterial for interbody fusion cages due to the polymer's increased radiolucency, excellent biocompatibility, and decreased stiffness.

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