TWO-YEAR OBSERVATION OF ARTIFICIAL INTERVERTEBRAL DISC REPLACEMENT USING SUPPLEMENTAL ULTRA HIGH STRENGTH BIORESORBABLE SPINAL STABILIZATION

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Acknowledgement: The study was supported in part by a Japanese national grant in aid of scientific research No. 08407045 and 12770775.

Running Head: Two-year study on artificial disc replacement

Abstract

Object. The two-year experimental study was conducted to investigate the efficacy of bioactive three-dimensional fabric disc (3-DF disc) for the lumbar intervertebral disc replacement. The study utilized the bioresorbable spinal fixation rod consisting of a forged composite of particulate unsintered hydroxyapatite/poly-L-lactide (u-HA/PLLA) for stability augmentation. The biomechanical and histologic alterations as well as possible device loosening were examined at two years postoperatively.

Methods. Two lumbar discs of L2/3 and L4/5 were replaced with 3-DF discs, which were augmented by two titanium screws and a spanning bioresorbable rod (HA/PLLA). The segmental biomechanics and interface bone ingrowth were investigated at six, fifteen, and twenty-four months postoperatively, when comparing with other two surgical groups of 3-DF disc alone and additional stabilization with anterior instrumentation. The replaced spinal segments with 3-DF disc augmented by bioresorbable rod procured a segmental mobility at both 15 and 24 months, however, the range of motion (ROM) in flexion and extension decreased to 49% and 40%, respectively despite statistically equivalent torsional ROM preserved. The interface histology demonstrated the excellent bony fusion between fabric surface and vertebral body. Until two-year period, no adverse tissue reaction and aseptic loosening of the device were observed.

Conclusions. The artificial disc replacement using a polymer three-dimensional fabric (3-DF disc) was viable and effective procedure with the use of bioresorbable spinal augmentation. Further refinements of device design toward a stand-alone type are necessary to obviate the need for additional spinal stabilization.

Key words: Artificial intervertebral disc, Bioresorbable spinal device, Lumbar spine, Biomechanics

Introduction

Recent treatments for spinal disorders have rapidly progressed toward the motion preservation technologies such as artificial intervertebral disc or flexible spinal stabilization. [3,4,5,7,8,10,13-21,24,37,38,41] The artificial intervertebral disc technology includes several different designs and surgical concepts. To date, some devices are undergoing multicenter clinical trials for clinical approval, [17,19] however, there has been a relatively paucity of information regarding appropriate design concepts of unconstrained or constrained, interface material and its modification, and their in vivo alterations. There have been some in vivo studies reported using several animal models, describing short-term biomechanical and histologic effects of devices.[18,20,21,24] However, when considering ultimate goals of artificial disc in preserving a disc function with mobility and stability for a long-term period, the basic studies investigating a long-term biological and biomechanical effects are essential.

The authors' artificial intervertebral disc is based on the concept of a durable, constrained, and single-component design with surface modification that enables a biologic bonding to the vertebral body. It consists of a triaxial three-dimensional polymer fabric (3-DF) woven by an ultra-high molecular weight polyethylene (UHMWPE) fiber, and spray-coated bioactive ceramics on the disc surface.[18,21,28,31] The previous studies have demonstrated that its biocompatibility, endurance, and biomechanical property were similar to those of the normal disc. [18,21,28,31] The in vivo study using a sheep model demonstrated the

excellent interface bonding and preservation of segmental spinal mobility at six months period.[21]

To further investigate long-term biological and biomechanical effects of artificial intervertebral disc replacement, the two-year study was conducted using a sheep lumbar spine model. The study also focused on the utilization of bioresorbable spinal stabilization combined with artificial disc, providing both initial spinal stabilization and late mobilization after degradation of material.

MATERIALS AND METHODS

Design and biomechanical properties of artificial intervertebral disc (3-DF disc)

The triaxial three-dimensional fabric disc was a semi-elliptically shaped near-net woven with an ultra-high molecular weight polyethylene (UHMWPE) fiber bundle, which was coated by linear low density polyethylene.[18,21,28,31] (Figure 1) The 3-DF disc consisted of a number of fibers in the x-, y-, and z-axes and their respective multilayers with some alignment ratios in three dimensions. Importantly, this prosthesis was uniform without any nucleus portion and was composed of a single material. The bioactive ceramics granules were spray-coated to the designed depth either by sintered hydroxyapatite (s-HA) or apatite-wollastonite glass ceramics granules (AW). The average diameter of ceramic granules was 2.88 and 4 micrometers, respectively.

Several human 3-DF prototypes were woven with orthogonal or off-angle fiber alignment and received cyclic tensile-compressive and torsional tests. And finally, the off-angle 45 degree model was selected based on a superior torsional property to the orthogonal and off-angle 30 degree models.[18,21,28,31] The arrangement of layer numbers and alignment ratio among three weaving axes resulted in balanced mechanical properties.

Animal model and artificial disc replacement procedure

Using thirty-six sheep, the intervertebral discs at L2/3 and L4/5 levels were totally replaced with scale-downed 3-DF discs (20x17x10 mm) through a retroperitoneal approach. After a circumferential removal of the intervertebral disc, the upper and lower endplates, and the anterior wall of spinal canal were resected. Two types of 3-DF discs coated either with s-HA or AW (3-DF HA or 3-DF AW) were randomly assigned. The animals were divided into three groups; group I: no initial fixation (N=13), group II: temporarily instrumented with Kaneda SR one-rod system (N=13) (DePuy AcroMed, Inc., Raynham, MA), group III: augmented with an ultra-high strength bioresobable rod spanning two Kaneda SR screws (N=10) (Takiron Co., LTD., Osaka, JAPAN) (Figure 2). Bioresorbable rod was made of 40% (wt%) of unsintered hydroxyapatite granules and poly-L-lactide acid (HA/PLLA). [11,12,23,29,30] Previous basic study by Furukawa et al. reported that the bending strength of the HA/PLLA composites implanted in the subcutis of rabbit was maintained at more than 200 MPa for 25 weeks.[12] At six, fifteen, and twenty-four months postoperatively, the animals were euthanized and disc-body units (DBUs) were obtained followed by the removal of spinal instrumentation.

Biomechanical and histologic analyses

The DBUs of L2-3 and L4-5 levels were mounted using a polyester resin with motion

allowed only at the disc space. The biomechanical tests were conducted with the pure moment application of 0-5 Nm to the DBUs in flexion-extension, and axial rotation with loading increments of three stages. Three-dimensional motion of the spinal segment was analyzed with the stereophotogrammetry method.[21,25,32] The possible error of this stereophotogrammetry system was 0.1 degree including the digitization procedure. Ten normal DBUs harvested from non-surgical sheep served as the control. The range of motion (ROM) and neutral zone (NZ) were calculated from torque-angle curves.[26] The neutral zone was defined as total (positive and negative) ROM at the moment of 0 Nm application.

For the histologic analysis, undecalcified sagittal sections of 40 micrometers were created and stained with Cole's hematoxylin and eosin, and Toluidine blue O. The interface histology was evaluated in terms of the surface contact between 3-DF and vertebral body and the insertion of trabeculae into the 3-DF fiber. Additionally, a University animal study review board previously approved the animal surgery, handling and housing protocols. The statistical analysis of data was performed using one-way ANOVA and a post-hoc analysis of Student-Neuman-Keuls test at a significant level of P=0.05.

RESULTS

The operative segments at six months after surgery were covered with noninfectious tight scar and incomplete bony bridging in group I. However, in group II, these changes completely disappeared and spinal mobility was preserved after removal of spinal instrumentation. There were some implant displacements without dislodgement in group I, however, all 3-DF discs were firm in place in group II. In group III, all bioresorbable rod broke due to degradation process and spinal segments procured the segmental spinal motion (Figure 3). The following biomechanical data at six months period were already reported in the first part of the study.[21] In this report, fifteen and twenty-four months data were newly presented.

The total ROM of the control group DBU at maximum moment of 5Nm showed 11.4, degrees in flexion-extension (Figure 4). The ROM decreased to 28% in group I at six months significantly. In group II, 65% of ROM was preserved when compared to control at six months. In group III, ROM significantly decreased to 49% and 40% of control values at fifteen and twenty-four months, respectively.

The total ROM of the control group DBU at maximum moment of 5Nm showed 3.53 degrees in torsion (Figure 4). The statistically equivalent ROM values of 60% and 90% were demonstrated in group I and II at six months postoperatively. In group III, 151% of ROM value was detected at fifteen months, and nearly equivalent ROM of 101% was

demonstrated at twenty-four months postoperatively.

The neutral zone of control and all surgical groups demonstrated statistically equivalent subsets both in flexion-extension and torsion (Figure 5). The data basically showed a same tendency as ROM, however, they did not reach to statistical significances due to high standard deviations.

In a histological analysis, there was no particulate debris of 3-DF fiber present in peri-implant tissues as well as no foreign body reaction such as macrophages or giant cells. The interface histology between the 3-DF disc and the vertebral body was classified into three grades with the dominant grade occupying 70% of combined upper and lower surfaces of 3-DF disc.[21] Typically, in grade 1, continuous trabeculae without soft tissue membranes inserting into the fabrics were observed (Figure 6). Grade 2 showed a gap of less than 90 microns between the 3-DF fiber and trabeculae occupied by calcified fibrocartilages. In grade 3, a soft tissue membrane occupied the interface. According to this grading system, the grades 1, 2, and 3 were 36%, 36%, and 28%, respectively in group I. However, in group II at six months, 63%, 37%, and 0% were grade 1, 2, and 3, respectively. The twenty-four month histology of group III further improved up to 80% of grade 1, and 20% of grade 2. The macroscopy and SEM clearly demonstrated that 3-DF fibers were directly surrounded by trabeculae with a direct contact.

Discussion

This serves as the first study to experimentally evaluate the mid- to long-term biomechanical and histologic changes of replaced spinal segments with artificial intervertebral disc prosthesis. Although several artificial discs were developed and experimentally evaluated in an animal model, the maximum observation periods were mostly within six months and only a few studies extended to a year.[8,20,21,24,34,38] Vuono-Hawkins, et al. evaluated their elastometric intervertebral disc spacer with a surface modification of porous hydroxyapatite plate in a canine model until twelve months.[38] The interface was occupied with dense fibrous tissues without bone ingrowth, and five of twelve spacers were migrated significantly. Urbaniak, et al. evaluated their silicone-Dacron intervertebral prosthesis in chimpanzee lumbar spines for one year.[34] Although only four animals, eight spinal levels were evaluated, 50% of animals led to spinal infections. The useful biomechanical and histologic data were not obtained. Kostuik, et al. conducted six months sheep study using their metal hinged prosthesis in the lumbar spine.[20] The six months histology showed a bony bridging between consecutive vertebral bodies with tendency of anterior device subluxation. No quantitative biomechanical data was demonstrated in this report. The largest baboon study was conducted by Cunningham, et al., evaluating anterior lumbar intervertebral replacement with AcroFlex disc prosthesis.[8] Twelve-month histology demonstrated the excellent osteointegration at the bone-metal interface, however, significant

decreases of segmental motion compared to intact spinal segments were showed in axial rotation, flexion-extension, and lateral bending. Our short-term results in a sheep model demonstrated that nearly equivalent range of motion preserved in flexion-extension and axial rotation at six months periods when using a temporary internal fixation.[21] The interface histology demonstrated an excellent osteointegration between artificial disc and vertebral disc.

In this two-year observation, we focused on any interface loosening or subsequent bony ankylosis happening in mid- to long-term period as well as the efficacy of bioresorbable internal fixation in the spine. The results showed that the bioresorbable HA/PLLA rod broke and replaced segments procured the segmental spinal mobility at fifteen and twenty-four months. Although excellent interface bony fusion was obtained at twenty-four months, the segmental spinal mobility tended to decrease with time especially in flexion and extension. This was due to significant scar and bony spur formations including fibrocartilagenous or bone tissues surrounding both end plates. However, the separate study by Takahata et al. showed the maintenance of interface strength between fifteen and twenty-four periods that highly exceeded the representative bioceramic interface with bone.[31] Importantly, this study provided further important information regarding the interface histologic and biomechanical maturation. Firstly, the bony insertion to fabric and trabeculae continuity progressed with time. Secondly, the acquisition of spinal mobility had no

deleterious effect on interface strength and histology. Until twenty-four months period, no interface bone resorption or loosening and no adverse biological reaction were observed despite the decreased segmental mobility. Limitation of the present study lies in the decreased mobility at the spinal segment, possibly eliminating the wear debris caused by friction between vertebral body and 3-DF disc. Additional non-human primate study is in progress under the preservation of physiological spinal motion to assess the long-term device loosening status.

Another focus of this study was to evaluate the bioresorbable spinal instrumentation for the artificial intervertebral disc augmentation. To date, several bioresorbable implants have been reported in the spine field.[1,2,6,9,22,27,33,35,3639,40] Those included anterior cervical plates, cervical and lumbar interbody fusion cages, resorbable film as an adhesion barrier and bone graft containment in a posterolateral fusion.[1,9,22,27,33,3539,40] The bioresorbable rods utilized in this study were fabricated from a forged composite of raw particulate hydroxyapatite/poly L-lactide (u-HA/PLLA), demonstrating a total bioresorption, osteological bioactivity, and the highest strength achieved using this kind of composite to date.[29,30] This highly distinctive and biocompatible qualities of the HA/PLLA composite are also useful for cervical and lumbar interbody fusion cages.[30] In this study, bioresorbable rods broke after six months periods and successfully procured the segmental spinal mobility. According to previous experimental data, almost five years are required until total resorption.[11]

In the present study, the replaced spinal segments with the artificial disc were separately fixed with screws and bioresorbable rods in this animal model. Ideally, the artificial disc should have a stand-alone design with the fixation mechanism to vertebral endplate, obviating the need for external augmentation. It is also practically difficult to control a degradation process and breakage period with the use of bioresorbable fixation. Therefore, we have developed several stand-alone type discs and the in vivo investigation using a baboon model is in progress.

Finally, in the recent concepts of artificial disc replacement, there are two major principles of either anterior total or posterior partial disc replacement in the lumbar spine. The former includes SB charite and Acroflex that were mainly indicated for the discogenic pain with isolated disc resorption.[7,10,14,24,41] Although the multicenter clinical study for anteriorly implanted artificial disc is underway in United States, the final clinical results are still unknown whether artificial disc replacement effectively reduces the low back pain for patients. The anterior total artificial disc has several benefits of wide surface area occupation, excellent mechanical endurance, and wide range of motion, however, surgical indications are extremely limited for degenerative disc disease and post-diskectomy status without neurological deficits.[7,10,14,24,41] The ideal surgical indications that are expected for future artificial disc replacement include lumbar degenerative disease with neurologic deficits and slight segmental instability, post-diskectomy status with instability, low-grade lumbar

spondylolisthesis, and cervical disc disease with neurologic disturbance. The posterior partial disc replacement has a future possibility of solving both disc function and neural problems by simultaneous disc replacement and neural decompression. This will effectively expand the surgical candidates for artificial disc replacement and truly exceed the spinal fusion as the spinal reconstruction method. We are still aiming at the ultimate goal of artificial disc replacement utilizing unique and flexible characteristics of 3-DF disc.

Conclusions

Two-year experimental study was performed to investigate the biomechanical and histologic changes of artificial disc replacement towards the clinical trial. Using a sheep model, two spinal segments of L2/3 and L4/5 were replaced with 3-DF discs and the segments were stabilized with two titanium screws and spanning bioresorbable rod. At 15 and 24 months postoperatively, the replaced spinal segments procured the segmental mobility with gradually decreased ROM levels, however, the excellent bony ingrowth was obtained at both time periods. The 3-DF disc has an excellent clinical potential for artificial disc despite further refinements necessary for device design and surgical strategy including different surgical approaches.

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Figure Legend

Figure 1(1A, 1B)

1A: Triaxial three-dimensional fabric disc (3-DF disc) woven by ultra-high molecular weight polyethylene (UHMWPE) fiber. The disc surface is spray-coated with bioactive ceramic granules.

1B: The fiber axis direction was arranged to 45 degrees on the lateral surface of 3-DF disc to achieve the human disc anisotropy.

Figure 2: Spinal segment reconstructed with 3-DF disc and bioresorbable rod fixation.

The 3-DF disc was anteriorly inserted through left retroperitoneal approach following a total diskectomy. The bioresorbable rod consisting of hydroxyapatite and poly-L-lactide acid (HA/PLLA) spanned two vertebral screws.

Figure 3 (3A, 3B): Lateral radiographs of reconstructed spinal segments using 3-DF disc and bioresorbable rod at 0 and 24 months postoperatively.

3A: Radiograph at postoperative 0 day. 3-DF discs were placed at L2/3 and L4/5 levels (arrows). Radiopaque bioresorbable rods were visible between two vertebral screws.

3B: Radiograph at 24 months postoperatively. No dislodgement and displacement of 3-DF

disc was demonstrated as well as scarce bridging bone formation between vertebral bodies (open arrow). The vertebral endplate at the interface showed sclerotic changes without device loosening and bone resorption. The deformation of bioresorbable rods was visible at both segments.

Figure 4: The total range of motion of disc-body unit in flexion-extension and axial rotation at maximum moment of 5 Nm.

3-DF w/o Fix (Group I): 3-DF replaced segment without initial fixation, 3-DF Fix (Group II): 3-DF replaced segment with initial fixation of Kaneda SR one-rod system at six months postoperatively. 3-DF PLLA (Group III): 3-DF replaced segment with bioresorbable stabilization system. Mean and standard errors of mean were shown. Each asterisk represents a statistical difference between control and any surgical group at p=0.01 level.

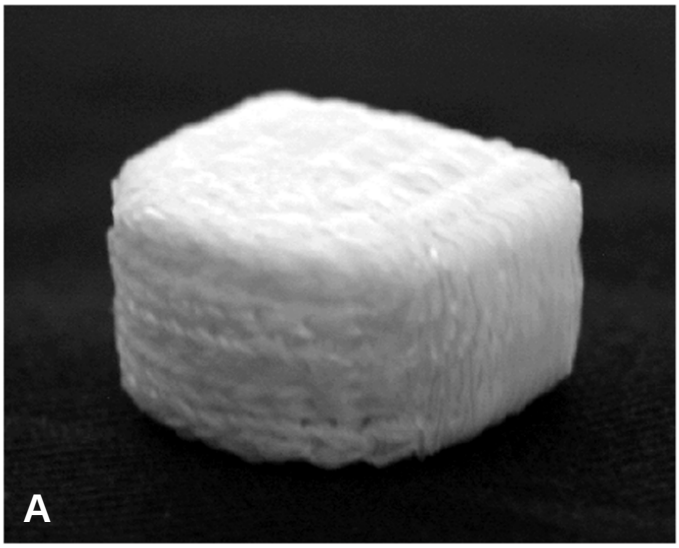
Figure 5: The total neutral zone of disc-body unit in flexion-extension and axial rotation at maximum moment of 5 Nm.

3-DF w/o Fix (Group I): 3-DF replaced segment without initial fixation, 3-DF Fix (Group II): 3-DF replaced segment with initial fixation of Kaneda SR one-rod system at six months postoperatively. 3-DF PLLA (Group III): 3-DF replaced segment with bioresorbable stabilization system. Mean and standard errors of mean were shown.

Figure 6 (6A, 6B)

6A: Sagittal histologic section of the interface between 3-DF disc (D) and vertebral body (V) demonstrating a typical grade 1 interface. There were continuous trabeculae of vertebral body on the surface of 3-DF disc without soft tissue membrane. The trabeculae inserting into the fabric inside were distributed within the coating depth of bioactive ceramics. The right side of the figure signifies the ventral side of the disc.

6B: Each 3-DF fiber (F) is directly surrounded by vertebral body trabeculae (T) without soft tissue membrane on the magnified view (magnification, x25)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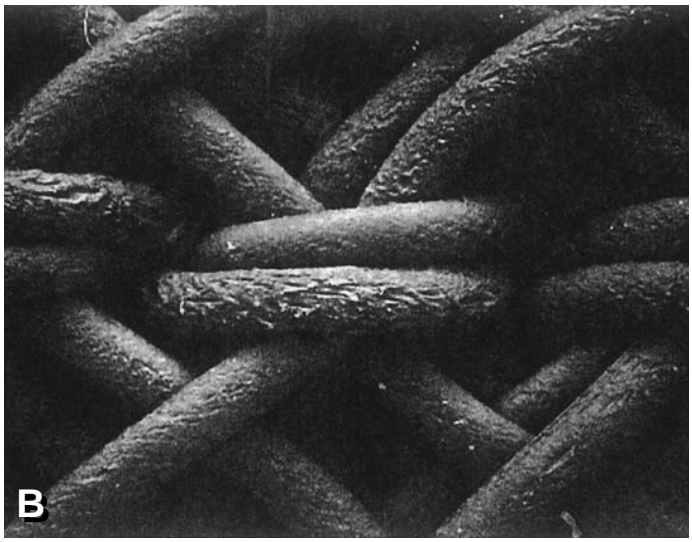
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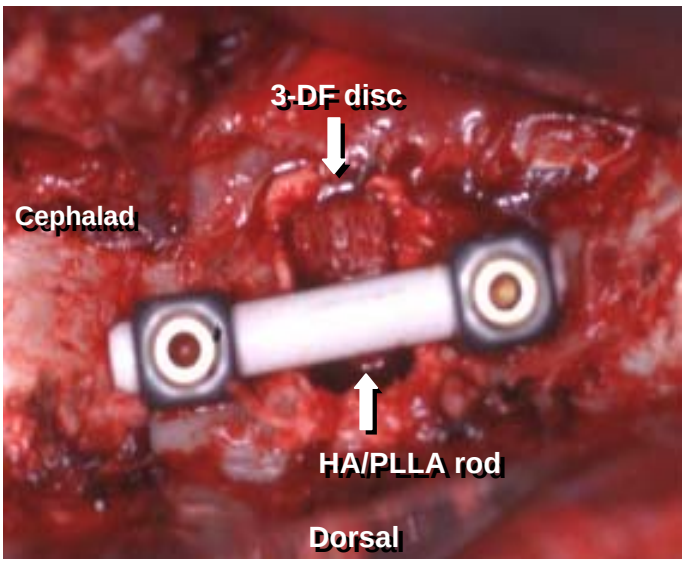
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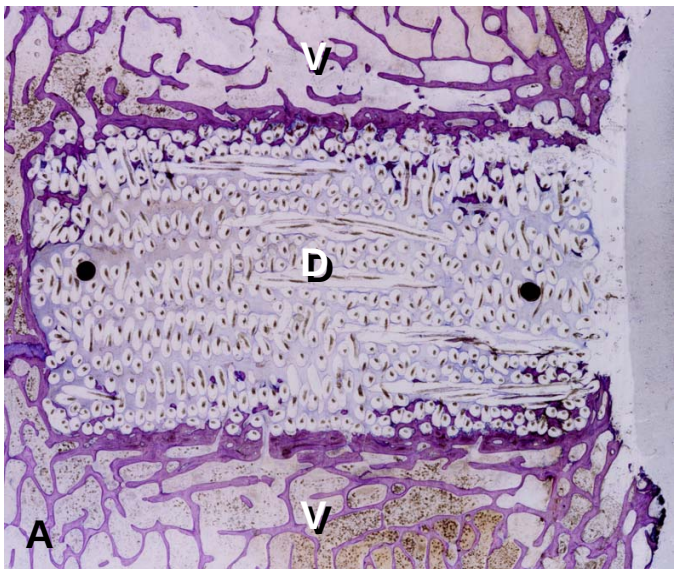
HA/PLLA rod
Dorsal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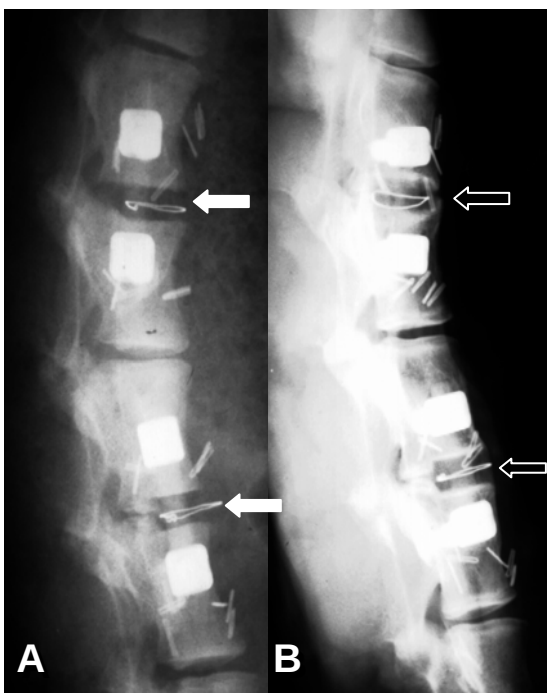
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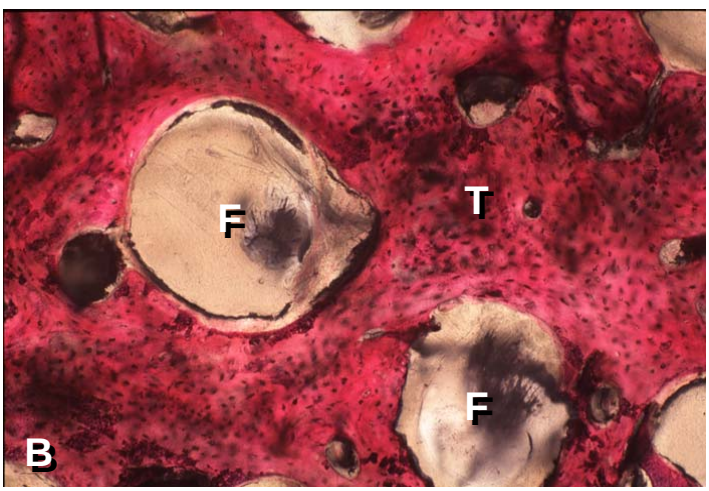
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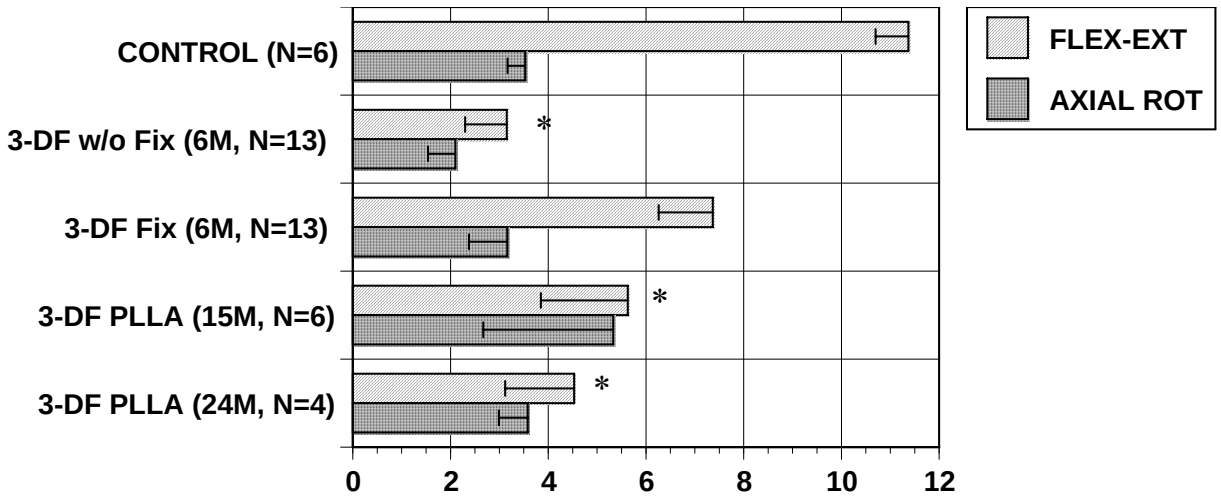
CONTROL (N=6)
3-DF w/o Fix (6M, N=13)
3-DF Fix (6M, N=13)
3-DF PLLA (15M, N=6)
3-DF PLLA (24M, N=4)
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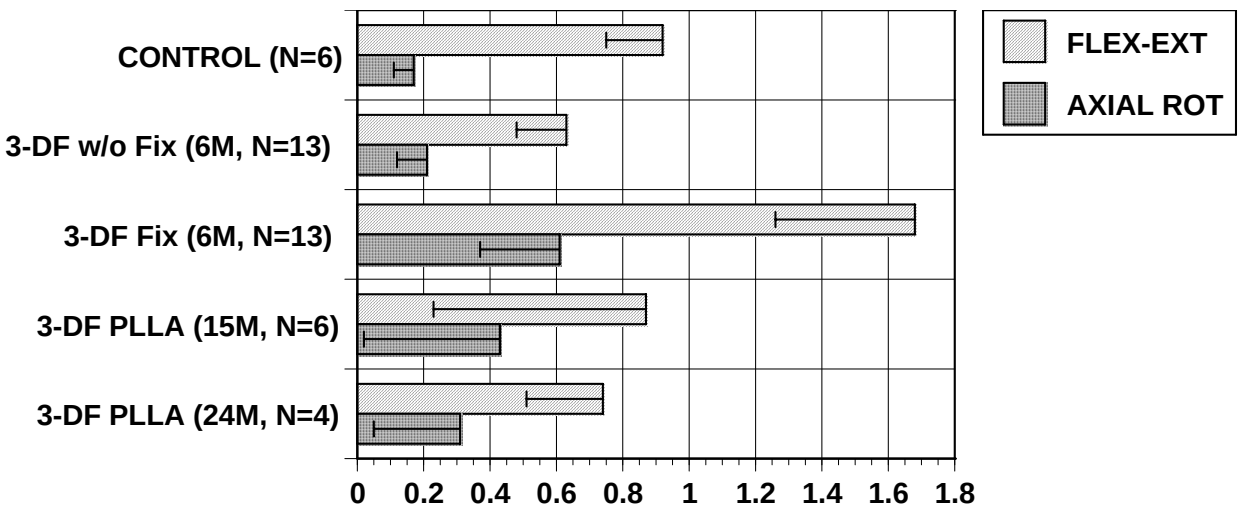
0
2
4
6
8
10
12
FLEX-EXT
AXIAL ROT


CONTROL (N=6)
3-DF w/o Fix (6M, N=13)
3-DF Fix (6M, N=13)
3-DF PLLA (15M, N=6)
3-DF PLLA (24M, N=4)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
FLEX-EXT
AXIAL ROT