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ORIGINAL ARTICLE

Nucleus replacement could get a new chance with annulus closure

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Abstract

Purpose Disc herniations are usually treated by decompression of the spinal nerves via a partial nucleotomy. As a consequence of reduced disc height (DH), reduced intradiscal pressure (IDP) and increased range of motion (ROM), accelerated degeneration may occur. Nucleus replacement implants are intended to restore those values, but are associated with the risk of extrusion.

Methods In six fresh frozen lumbar spinal segments (L2-3/L3-4/L4-5/L5-S1, age median 64.5 years (57–72), Pfirrmann grade 2–3), a prolapse was provoked through a box defect (6 × 10 mm) in the annulus. The herniated nucleus material was removed and replaced by a novel collagen-based nucleus implant. An annulus closure device sealed the defect. ROM, neutral zone (NZ) and IDP were measured in the (1) intact and (2) defect state, (3) postoperatively and (4) after cyclic loading (n = 100,000 cycles) applying pure moments (± 7.5 Nm) in flexion–extension, lateral bending and axial rotation. Additionally, the change in DH was determined. Extrusion of implants or nucleus material was evaluated macroscopically.

Results In all specimens, a prolapse could be provoked which decreased DH. Subsequent nucleotomy changed ROM/NZ and IDP considerably. Initial values could be restored by the implantation. Macroscopically, none of the implants nor nucleus material did migrate after cyclic loading.

Conclusions In this study, a prolapse followed by a nucleotomy resulted in a biomechanical destabilisation. Implantation of the nucleus replacement combined with an annulus closure restored the intact condition without showing signs of extrusion nor migration after cyclic loading. Hence, nucleus replacements could have a new chance in combination with annulus closure devices.

Keywords Lumbar disc herniation · Nucleotomy · Nucleus replacement · Annulus repair · In vitro study

Introduction

Acute low back pain is often associated with lumbar disc herniation. However, its exact causes are still not completely investigated. The surgical standard for treating disc herniations with acute low back pain with associated signs of nerve impingement is usually the decompression of the spinal nerves by performing a partial nucleotomy without the subsequent reconstruction of the defect in the annular wall [1, 2].

Various studies report symptomatic reherniations after lumbar discectomy up to 17% [3–9]. Repeated surgical treatments that are necessary to manage these reherniations are associated with lower success rates compared to the treatments of the initial herniations [2, 10, 11]. Biomechanically, this partial nucleotomy might lead to a reduction in disc height (DH) and intradiscal pressure (IDP) with an increase in range of motion (ROM) [12, 13]. This might result in an

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accelerated degeneration [14, 15] due to the inappropriate compressive load on the annulus [12, 14, 15] which manifests radiographically as disc bulging [16, 17]. Furthermore, the loss of disc height could lead to overstressing of the facet joints [18]. On one hand, this might cause degeneration of the facet joints, as well. On the other hand, painful compression of the nerve roots could be the consequence of the accompanied narrowing of the intervertebral foramina [18].

In order to prevent the disc from reherniation as well as from accelerated degeneration processes due to the nucleotomy, other treatments for disc herniations have focused on preserving more nucleus volume. Beside the sequestrectomy treatment which reduced the rate of reherniations from 10 to 5% [19], nucleus replacement implants have been developed with the intention of restoring DH, ROM and IDP. In principle, the restoration of those properties was successful [13, 20], but the problem of extrusion could not be solved yet [13, 21]. Hence, the idea was to combine a nucleus replacement implant with an annulus sealing device in order to prevent extrusion while restoring the biomechanical properties of the intact disc.

Different sealing methods as adhesive bonding or different suture materials for annulus repair exist and have been investigated [22–24]. Often, those techniques failed and thus resulted in nucleus extrusion, again [25–27]. The use of mechanical annulus repair devices with anchoring in the bony endplate or vertebra adjacent to the treated disc seemed to be more promising [9, 28].

The aim of this study is to evaluate whether a collagen-based nucleus replacement implant similar to the one described by Wilke and Heuer [13, 29] in combination with a biomechanically and clinically evaluated annulus closure device [9, 28, 30] is generally capable of adequately restoring the biomechanical properties of an intact disc. Apart from that, it should be verified by a long-term test whether the implants stayed intact, in place and hence, sufficiently reduced the risk of reherniations.

Methods

Specimens

Eight monosegmental lumbar segments were obtained from four fresh frozen human cadaver spines (L2-S1, age median 64.5 years (57–72 years), BMD median 100.1 mgCaHA/cm^3 (78.3–163.5 mgCaHA/cm^3), 2 m:2f) (Table 1). All soft tissue was removed preserving all bony structures, the intervertebral discs, ligaments and facet capsules. Prior to preparation, MRI and CT were performed. BMD was assessed through a QCT measurement. Criteria for general exclusion were fractures, tumors, a low disc height (≤ 6.5 mm), patients with osteoporosis (overall BMD ≤ 80.0 mgCaHA/

Table 1 Detailed information about tested segments used for the investigation of a novel nucleus replacement implant in combination with an annulus closure device

Specimen #	Segment	Sex	Age in years	BMD in mgCaHA/cm^3	DH in mm	Pfirrmann grade	Defect side	Actual defect size (hxw) in mm	Removed nucleus weight in g	Removed nucleus volume in cm^3	Implant volume in cm^3
1a	L3-4	m	68	164.0	10.4	2	Right	6×9	0.17	0.15	0.24
1b	L5-S1				8.5	3	Left	6×10	0.21	0.17	0.24
2a	L2-3	f	61	99.1	7.6	2	Right	7×10	0.31	0.28	0.37
2b	L4-5				7.2	3	Left	5×9	0.26	0.24	0.30
3	L3-4	m	57	78.3	8.5	2	Left	6×10	0.33	0.30	0.37
4	L5-S1	f	72	101.0	7.4	3	Left	6×10	0.26	0.24	0.36
Median (range)			64.5 (57.0–72.0)	100.1 (78.3–164.0)	8.05 (7.2–10.4)	2.5 (2–3)		6×10 (5×9–7×10)	0.26 (0.17–0.33)	0.24 (0.15–0.30)	0.33 (0.24–0.37)

cm^3), severe degeneration or other diseases that might have influenced the biomechanical properties of the specimens. Six specimens with a degeneration grade 2 or 3 (according to Pfirrmann [31]) and a posterior disc height of 8.1 mm (7.2–10.4 mm) have been included into the trial. Six to eight screws (Spax 3 × 20) were inserted into the cranial endplate of the upper and the caudal endplate of the lower vertebrae before embedding in polymethylmethacrylate (PMMA, Technovit 3040, Heraeus Kulzer, Wehrheim, Germany). Flanges were mounted on the PMMA embedment for proper mounting into the testing machines. Until testing, specimens were stored in triple sealed polyethylene bags at −20 °C. Prior to testing, the specimens have been carefully thawed overnight at +4 °C.

Test protocol

ROM, IDP and change in DH were measured in the intact state, after creating a defect, postoperatively and after dynamic loading (n = 100,000 cycles). ROM and neutral zone (NZ) were assessed during a quasistatic flexibility test in a universal spine tester [32] by simultaneous optical motion tracking with the Vicon MX13 system (Vicon Motion Systems Ltd., Oxford, UK). Pure moments of ±7.5 Nm were applied in flexion–extension (FE; +: flexion, −: extension), lateral bending (LB; +: left LB, −: right LB) and axial rotation (AR; +: left AR, −: right AR). A special pressure sensor for measurements up to 50 bars (Mammendorfer Institut für Physik und Medizin GmbH, Mammendorf, Germany) was implanted from lateral to measure hydrostatic pressure directly in the centre of the nucleus pulposus during the flexibility test (Fig. 1). After each flexibility test, the change in DH was measured in an Instron materials testing machine (Instron 8871, Norwood, MA, USA) by applying an axial load of 100 N resulting in different travel paths of the testing cylinder (resolution 10 µm) (Fig. 2a). For a worst-case scenario, a box-cut defect was cut into the posterolateral part of the annulus using a box-cutting tool with the size of 6 mm x 7 mm. The part that was cut out from the annulus was removed, and the actual size of the created defect was measured. The specimens were then subjected to a dynamic cyclic loading test protocol with 5,000 cycles that has already been used in a previous study [28] to provoke a prolapse through the defect in the annulus. In this so-called hula hoop test, a sinusoidal axial load ranging from 100 to 600 N was applied at 5 Hz, eccentrically with a lever arm of 30 mm from the longitudinal axis of the specimen [28]. The specimens were caudally flanged onto a rotation base with a rotation speed of 360°/min, so that the created moment acted circumferentially (Fig. 2). In case a clear prolapse (Fig. 3) could be observed after completing 5,000 cycles of the hula hoop test, only the nucleus material that completely extruded and the nucleus material within the annulus were removed. Volume and weight were measured and recorded. It was replaced by a nucleus implant which is a native highly compressed collagen-type-I matrix (RESTORE, 3D Spine Matrix Biotechnologie GmbH, Krems, Austria). Additionally, a CE-marked and recently FDA-approved annulus closure device (Barricaid®, size 10, Intrinsic Therapeutics Inc., Woburn, MA, USA) sealed the defect.

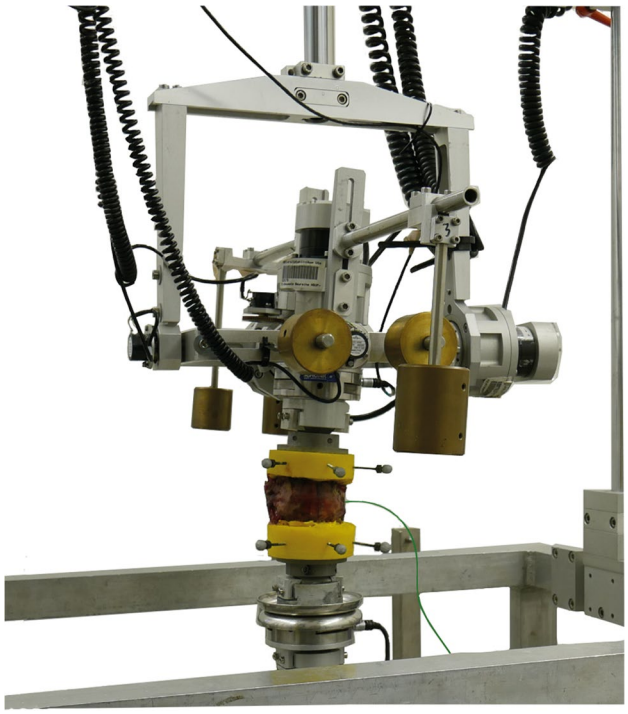

Fig. 1 Universal spine tester [32] where the flexibility test was performed to measure ROM and IDP. The IDP pressure sensor was implanted from lateral (green cable) to measure hydrostatic pressure directly in the centre of the nucleus pulposus

After implantation, the specimens were subjected to a long-term dynamic cyclic loading protocol (hula hoop) for 100,000 cycles. Possible extrusion of either the implants or nucleus material was evaluated macroscopically. X-ray images were compared to detect signs of subsidence. After the test, all specimens have been cut in the transverse plane. Material migrations into the surrounding nucleus and annulus tissue of the disc could be detected by manipulation.

Statistical analysis

Statistical analysis was performed with SPSS (IBM® SPSS® Statistics version 24; IBM Corp., Armonk, NY) for the change in DH, the ROM and IDP measurements of the tested lumbar segments in every testing condition. Normal distribution could not be proven by Shapiro–Wilk test with a p value of 0.05. Therefore, median and ranges are provided for all data and nonparametric tests for distribution-free data were performed.

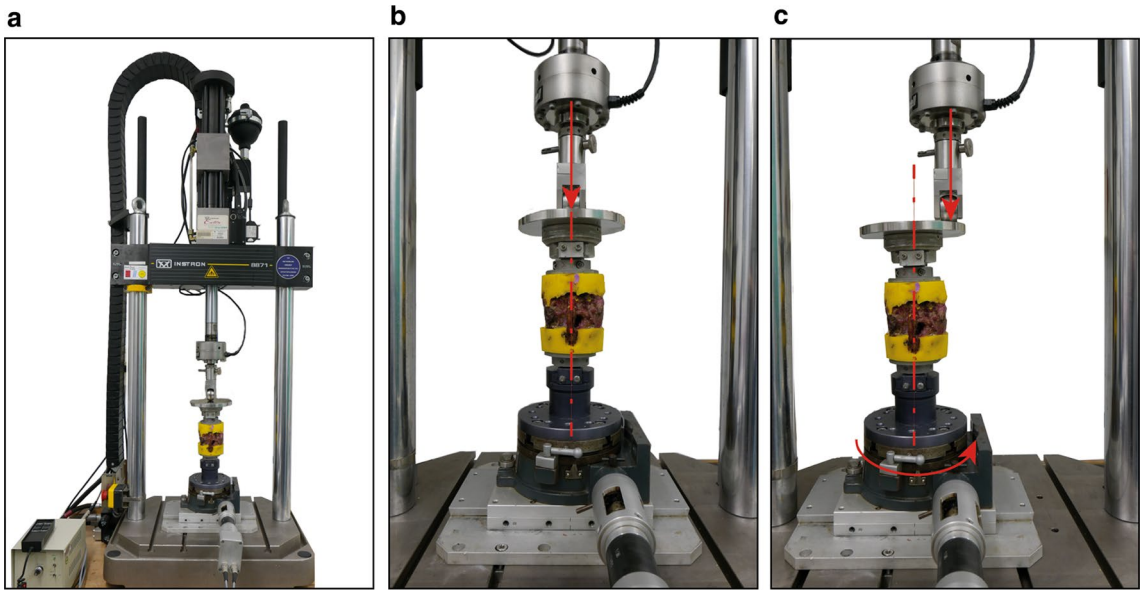

Fig. 2 **a** Instron servo-hydraulic materials testing machine with rotational base and piston for axial load application. **b** DH measurement with application of an axial load of 100 N. **c** Hula hoop test: Dynamic cyclic loading with sinusoidal load application from 100–600 N at a lever arm of 30 mm

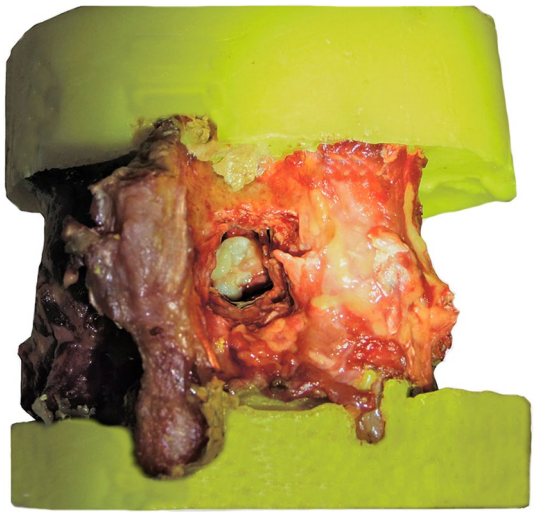

Fig. 3 Herniated disc with laminotomy to enable observation of the prolapse of the disc that was provoked during the cyclic loading with 5000 cycles

Significant differences were assessed using the Friedman test with a significance level set to $\alpha = 0.05$. A Bonferroni post hoc test was used to correct error rates within the single groups.

Results

In all specimens, a clear prolapse with extruded nucleus material could be provoked successfully (Fig. 3). The prolapse was provoked through a box-cut defect by applying 5,000 cycles of dynamic cyclic loading (hula hoop test). After the removal of the nucleus material, the implantation of the nucleus replacement and the annulus closure device could be performed appropriately. After the long-term dynamic cyclic loading for 100,000 cycles, neither macroscopic migration, subsidence nor extrusion of the implants, the nucleus or other disc material could be observed (Fig. 4).

The disc height did not considerably decrease due to the box-cut defect in the posterolateral part of the annulus. The defect actually measured in average 6 mm x 10 mm (Table 1). Subsequently to the dynamic cyclic loading of 5,000 cycles, the nucleus material that extruded through these defects and the nucleus material within the annulus were removed. The average volume of the removed material was 0.24 cm^3 (0.15–0.30 cm^3), and the average weight was 0.33 g (0.17–0.33 g) (Table 1). This led to a clear decrease in DH, 0.5 mm in average (0.3–0.7 mm) (Fig. 5). The DH could be almost restored to the initial value by the implantation of the nucleus implant (volume of 0.33 cm^3 (range 0.24–0.37 cm^3), Table 1) in combination with the annulus closure device (Fig. 5). DH significantly decreased 0.8 mm in average (0.3–1.2 mm) after the long-term cyclic loading (100,000 cycles) with $p = 0{,}035$.

Accordingly, the flexibility test did not show any clear differences of the median intact ROM and NZ values

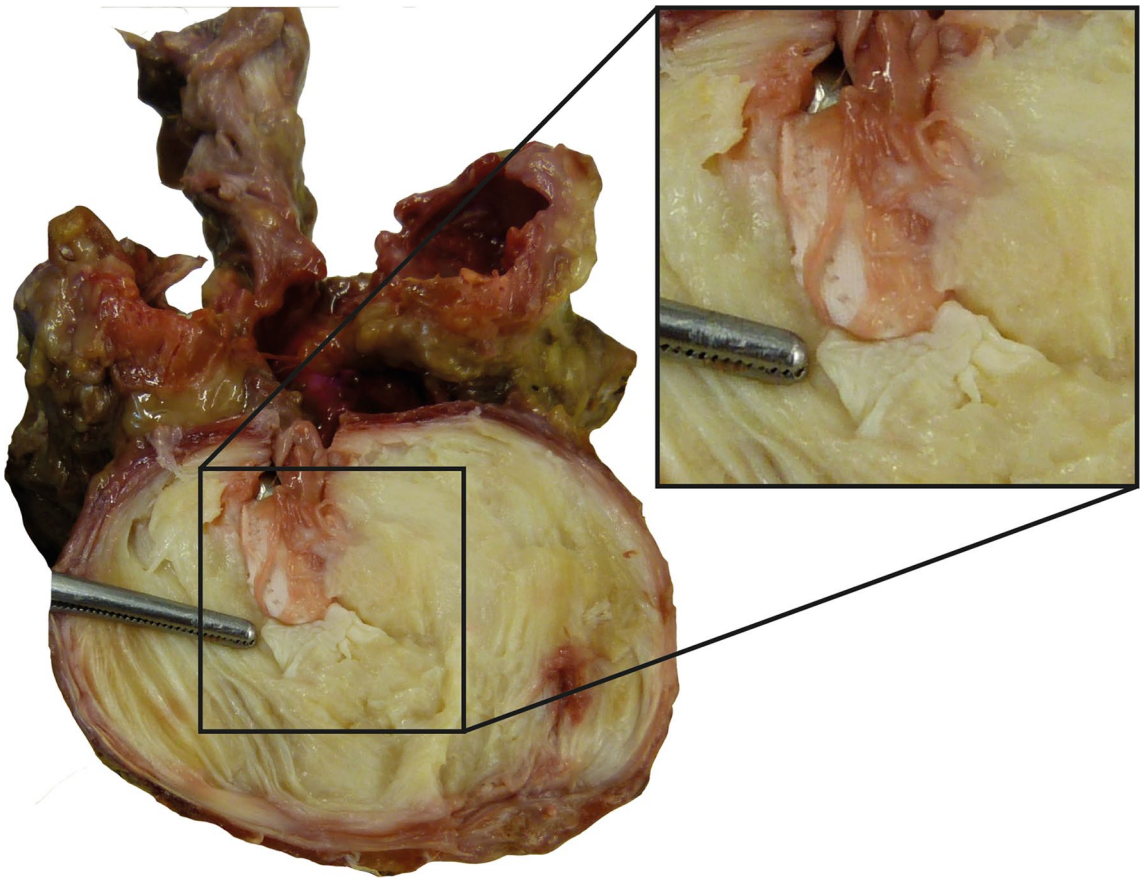

Fig. 4 Transverse section through a disc following 100,000 cycles of loading. Both the nucleus replacement (tweezer tip) and the annulus repair device (posterior to the nucleus replacement) are still contained within the disc periphery on the posterolateral aspect of the annulus

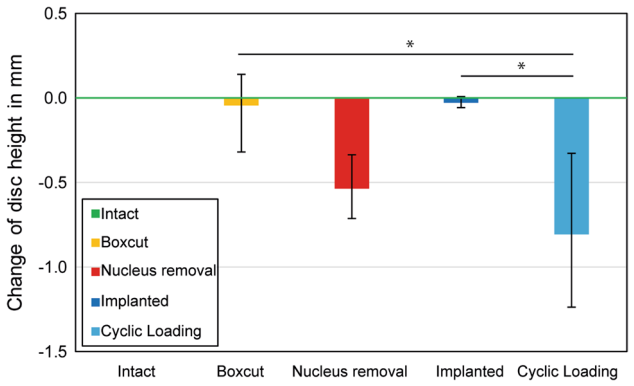

Fig. 5 Median and ranges for the change of DH in mm after loading with 100 N in all testing conditions, $*p < 0.05$

after creating the box-cut defect. ROM and NZ slightly increased except in flexion. The provocation of the prolapse and removal of nucleus material led to an increase in ROM and NZ in all tested motion directions, even significantly for the median ROM values in right LB to −5.1°, compared to intact −4.5° ($p = 0.035$) and right AR to −2.6°, compared to intact −2.1° ($p = 0.014$) (Fig. 6). Due to the implantation of the nucleus replacement and annulus closure implants, the ROM and NZ values of the intact specimens could be attained completely, whereas after cyclic loading, those values increased again and significantly for flexion ($p = 0.019$), extension ($p = 0{,}035$) and left LB ($p = 0.035$) (Fig. 6).

The IDP measurements during the flexibility tests showed a similar tendency (Fig. 7). Although the box-cut defect did not generally lead to a decrease in the IDP, the range in LB was remarkably larger (Fig. 7). After the prolapse and removal of the nucleus material, IDP decreased in all motion directions and significantly in right LB to 0.5 MPa, compared to intact 0.8 MPa ($p = 0.035$) (Fig. 7), accordingly to the findings in ROM and DH. The implantation of the native collagen-type-I nucleus implant and annulus closure device increased IDP again, so that the initial values of the intact specimens have been reached in all motion directions, except in extension. After the long-term cyclic loading with 100,000 load cycles, IDP did change, but not following the same pattern for different loading planes as it could be observed for the ROM (Figs 6, 7).

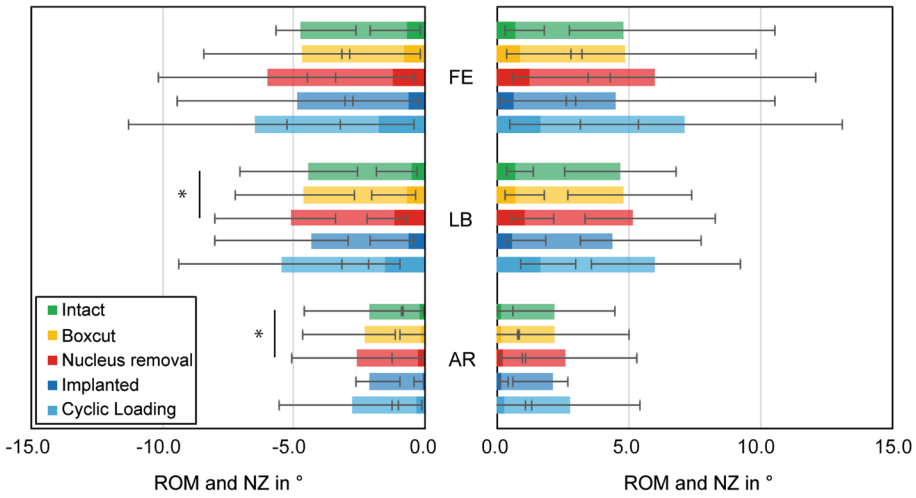

Fig. 6 Median and ranges for ROM (brighter bars) and NZ (more intense bars) in all motion planes FE (+: flexion, −: extension), LB (+: left lateral bending, −: right lateral bending) and AR (+: left axial rotation, −: right axial rotation) for pure moments of ± 7.5 Nm assessed with the spine tester, $*p < 0.05$

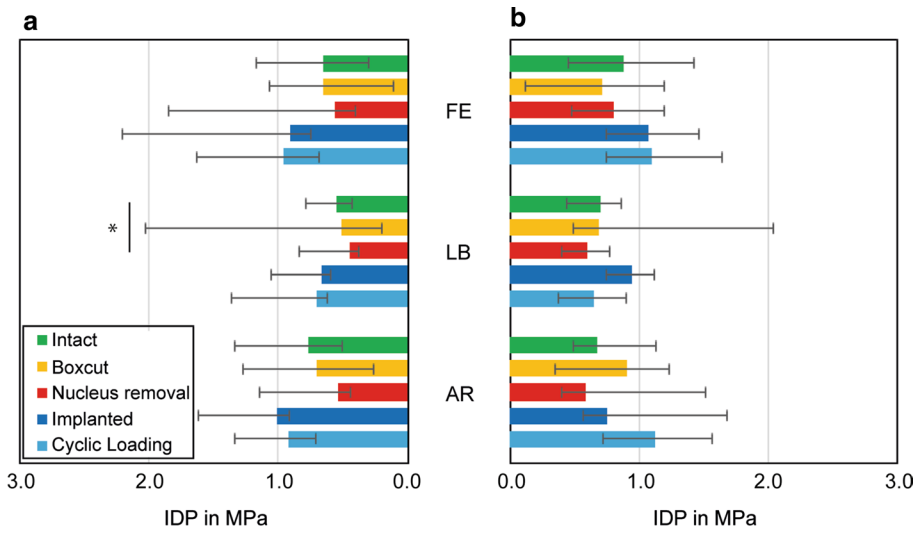

Fig. 7 Median and ranges for IDP in all motion planes FE, LB and AR for pure moments of ± 7.5 Nm assessed with the spine tester, $*p < 0.05$; **a** extension, right LB, right AR and **b** flexion, left LB, left AR

Discussion

With the present study, we showed that a nucleus replacement implant (native highly-compressed collagen-type-I matrix) could prevent further disc herniation following discectomy treatment while restoring the biomechanical properties of an intact disc again if it is combined with an annulus closure device. Macroscopically, no signs of migration, subsidence or extrusion of the implants or disc material could be detected after a long-term cyclic loading test for 100,000 cycles. With the combination of both types of implants, it was possible to restore the biomechanical properties (based on DH, ROM, NZ and IDP measurements) of an intact segment in a normal, physiological state.

As the prevention from reherniations seems to be successful combining the nucleus replacement implant with the annulus closure device, it could be concluded that the annulus closure device was the part of the combination that inhibited extrusions in human lumbar discs. This assumption complies with results from a previous biomechanical study with the annulus closure device stand-alone performed by Wilke et al. [28] and with clinical experiences with this annulus closure device from Parker et al. and Thomé et al. [9, 30].

Primary restoration of the biomechanical properties was not possible with the annulus closure device alone [28] but potentially with a previous version of the nucleus replacement implant used in this study stand-alone [13, 29] and with a prosthetic disc nucleus [20]. Unfortunately, the restored biomechanical values could not be maintained during long-term testing, in general [28] or because of extrusion [29]. In the present study, restoring the biomechanical values for DH, ROM, NZ and IDP was possible by the implantation of the nucleus replacement implant combined with the

annulus closure device. It could be assumed that the nucleus replacement implant was the part of the implant combination that was responsible for the general restoration of the biomechanical properties.

However, during long-term cyclic loading for 100,000 cycles the biomechanical properties of the tested specimens deteriorated. Especially, this became obvious in the decrease in DH, and the higher flexibility (ROM and NZ) in flexion, extension and left LB. This could be explained by dehydration of the disc over time and starting decomposition of the human specimens due to the long testing time period. Because of the long-term cyclic loading test with a duration of 8 h, the total testing protocol including specimen dissection and preparation could not be realised within 20 h of testing which was recommended by Wilke et al. [33]. Changes in the material properties of the nucleus implant due to that dehydration could not be investigated within this biomechanical in vitro study, but the effect should be comparable to the previous stand-alone testing [13]. The focus of the long-term cyclic loading test lied on the evaluation of possible migration or extrusion of either one of the implants or disc or nucleus material, respectively. Therefore, the results of the biomechanical parameters gained after this long-term test should not be over-interpreted.

In order to investigate the implant combination in a worst-case scenario, a box-cut defect of 6 mm x 10 mm was cut out of the posterolateral part of the annulus. During preliminary testing, the enlargement of the defect could be observed, so that a cutting tool of 6 mm x 7 mm was used to create a standardised defect of the desired size. It could be assumed that because of the high initial IDP of the specimens, the annulus fibres have been subjected to high tensile loads, but relaxed after the defect which resulted in a bigger defect. One limitation of the established box-cut defect is that it is not physiologic and that, hence, the prolapse is not provoked physiologically. To the best of our knowledge, in vitro, a prolapse in an intact disc has not been provoked by simulation of physiologic activities without any defect so far. Only with superphysiological loading conditions, such as hyperflexion [34] compressive loads [35, 36] or under complex loading conditions [37–40], the provocation of a prolapse has been already reported as well as through a bigger defect [28]. As the worst-case scenario for the annulus closure device used in this study was already established in its previous biomechanical investigation by Wilke et al. [28], the findings of both studies are more comparable. Furthermore, this former biomechanical investigation reported a decreasing likelihood of herniations with increasing degree of degeneration [28, 41]. In this study, limitations result from the small but generally accepted specimen number [33] specimen number with a higher median age of 64.5 years than patients usually treated and with a mild to moderate degeneration of grade 2 to 3, according to Pfirrmann [31] (Table 1). Hence, the successful provocation of a prolapse seemed to be more likely through the box-cut defect. Finally, in all segments, a prolapse through the box cut could be provoked successfully. Another limitation might be the small amount of removed and replaced nucleus material (Table 1). Considering latest findings for the treatment of disc herniations, as much nucleus material as possible, should be preserved in order to prevent reherniations [19].

Interestingly, the box cut itself did not change the biomechanical properties of the disc measurably till the prolapse occurred and nucleus material was removed. It could be assumed that the matrix of the nucleus pulposus itself or fibres in the transition zone sufficiently prevent nucleus material from extrusion. The slight decrease in IDP in flexion resulting from the box cut and again the increase in IDP after removal of the herniated material as well as the IDP increase in left AR could be a sign of migrations of the nucleus material towards the defect. This could be explained by changes in the pressure and stress distribution [42] that was generated during the flexibility test by the unilaterally impaired disc.

Based on the results after implantation, it can be concluded that the combination of the novel nucleus replacement and the annulus closure device was able to restore the biomechanical properties of the intact disc. Subsequently after the implantation, ROM and IDP were higher than in the intact disc. A larger volume of nucleus replacement that was implanted compared to the removed material could explain this. With respect to a possible remaining compressibility of the synthesised nucleus replacement material within the disc right after implantation, the primarily higher values for ROM and IDP could have been compensated during the long-term testing, again.

This study aimed to biomechanically investigate the use of a novel nucleus replacement in combination with an annulus closure device for the treatment of lumbar herniations in order to prevent reherniations and to inhibit accelerated degeneration of the herniated segment. In general, restoring disc height and stability of the segment should be possible with nucleus replacement implants [13]. However to the best of our knowledge, none of the many existing concepts for nucleus replacement developed so far was able to assert themselves due to the high risk of extrusion [29].

In this biomechanical in vitro study, it was verified for the first time that the closure of a large defect in the annulus and, simultaneously, restoration of the biomechanical properties of an intact motion segment could be possible. Furthermore, the combination of the nucleus replacement implant and annulus closure device did not show any signs of implant extrusion or reherniation after long-term dynamic testing. Appropriate distribution of compressive loads of the annulus in different movements could be regained which might inhibit accelerated degeneration [12, 14, 15]. Considering

the findings of this biomechanical in vitro study, nucleus replacement implants could get a new chance if they are combined with annulus closure devices.

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Compliance with ethical standards

Conflict of interest The study was financed by 3D Spine Matrix Biotechnologie GmbH, Krems, Austria. The annulus closure devices and surgical support were provided by Intrinsic Therapeutics Inc., Woburn, USA. None of the authors has any contribution to one of the companies.

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