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Morphology and Clinical Relevance of Vertebral Endplate Changes Following Limited Lumbar Discectomy With or Without Bone-anchored Annular Closure

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The device that is the subject of this manuscript is being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) as an adjunct to a limited lumbar discectomy procedure to replace missing or damaged section of the annulus identified at the time of surgery.
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ABSTRACT

Study Design. Post hoc analysis of a randomized controlled trial.

Objective. To characterize the morphology and clinical relevance of vertebral endplate changes (VEPC) following limited lumbar discectomy with or without implantation of a bone-anchored annular closure device (ACD).

Summary of Background Data. Implantation of an ACD following limited lumbar discectomy has shown promise in reducing the risk of recurrent herniation in patients with large annular defects. However, the interaction between the ACD and the lumbar endplate over time is not well understood.

Methods. Patients undergoing limited lumbar discectomy with large post-surgical annular defects were randomized intraoperatively to receive additional ACD implantation or limited lumbar discectomy only (Controls). VEPC morphology, area, and volume were assessed with low-dose CT preoperatively and at 1 and 2 years follow-up.

Results. Of 554 randomized patients, the as-treated population consisted of 550 patients (267 ACD, 283 Controls). VEPC were preoperatively identified in 18% of patients in the ACD group and in 15% of Controls. At 2 years, VEPC frequency increased to 85% with ACD and 33% in Controls. Device- or procedure-related serious adverse event (8% vs. 17%, $P = 0.001$) and secondary surgical intervention (5% vs. 13%, $P < 0.001$) favored the ACD group over Controls. In the ACD group, clinical outcomes were comparable in patients with and without VEPC at 2 years follow-up. In the Control group, patients with VEPC at 2 years had higher risk of symptomatic reherniation vs. patients without VEPC (35% vs. 19%, $P < 0.01$)

Conclusions. In patients with large annular defects following limited lumbar discectomy, additional implantation with a bone-anchored ACD reduces risk of postoperative complications despite a greater frequency of VEPC. VEPC were associated with higher risk of symptomatic reherniation in patients treated with limited lumbar discectomy, but not in those who received additional ACD implantation.

Key words: Annular closure, Discectomy, Disc herniation, Endplate change, Vertebral endplate change, Lumbar, Sciatica, Spine surgery

Level of Evidence: 2

INTRODUCTION

The vertebral endplate serves as the interface between the intervertebral disc and the adjacent vertebral body. The lumbar vertebral endplates consist of cartilaginous and osseous components that provide structural support during loading and serve as a nutrition pathway from vertebral capillaries to the intervertebral disc nucleus.[2] Structural changes in the intervertebral disc may induce vertebral endplate remodeling due to altered loading transmission patterns.[3] Concomitant with the higher prevalence of disc degeneration with increasing age is a higher frequency of vertebral endplate changes (VEPC).

VEPC are disruptions in endplate integrity that may be characterized as Schmorl's nodes, fracture, erosion, or calcification.[4] VEPC are a common imaging finding in older asymptomatic adults and in those with low back pain. In cadaveric spines of middle-aged men, VEPC were identified in approximately 50% of lumbar levels.[4] In patients with symptomatic lumbar disc herniation, VEPC are identifiable in 58% to 97% of patients.[5,6] VEPC are also commonly found following lumbar discectomy with incidences ranging from 34% to 78%. In these same studies, the relationship of VEPC frequency and morphology with clinical outcomes following lumbar discectomy was weak or nonexistent.[7-9] Overall, the origin, nature, and clinical relevance of VEPC remain unclear.

Patients with large annular defects following lumbar discectomy have high rates of recurrent disc herniation.[10] Implantation of a bone-anchored annular closure device (ACD) following lumbar discectomy is a promising procedure that reduces the risk of recurrent herniation in this patient population.[11-13] However, the interaction between the ACD and the lumbar endplate over time is not well understood. The only known study to examine this relationship was a retrospective comparison of 40 patients treated with sequestrectomy and 45

patients who additionally underwent ACD implantation.[14] While the incidence of VEPC over approximately 2 years follow-up was higher in the ACD group (52% vs. 10%), the reherniation rate on imaging irrespective of symptoms was lower with ACD implantation (5% vs. 50%). Small sample size and potential for treatment bias confound interpretation of these findings. The purpose of this post hoc analysis from a randomized controlled trial was to characterize the frequency and morphology of VEPC following limited lumbar discectomy in patients with large annular defects, to determine the influence of additional ACD implantation on VEPC frequency and morphology, and to describe the relationship of VEPC with clinical outcomes.

MATERIALS AND METHODS

Study Design

We report a post hoc analysis from a multicenter randomized controlled trial in patients with large annular defects allocated to receive a bone-anchored ACD following limited lumbar discectomy vs. patients treated with limited lumbar discectomy alone. The primary aim of the study was to determine if additional ACD implantation in patients with large annular defects following limited lumbar discectomy would lower the risk of reherniation compared to limited lumbar discectomy alone. The purpose of this post hoc analysis was to characterize VEPC in these patients and to determine their relationship with clinical outcomes. The clinical trial was approved by local ethics committees and informed consent was obtained from all individual participants included in the study. The trial was prospectively registered at ClinicalTrials.gov (NCT 01283438).

Participants

Eligible patients were 21 to 75 years of age, with single-level disc herniation between L1 and S1 confirmed on magnetic resonance imaging, with disc height at least 5 mm, and unresolved symptoms following at least 6 weeks of nonsurgical treatment. Main exclusion criteria included spondylolisthesis with >25% slip, prior index level surgery, and severe vertebral body degeneration. Magnetic resonance imaging (MRI) with T1- and T2-weighted axial and sagittal images, low-dose, multiplanar computed tomography (CT), and flexion/extension x-rays were performed. A complete list of inclusion and exclusion criteria was reported elsewhere.[15]

Study Interventions

Magnification-assisted limited discectomy was performed via an interlaminar transflaval approach.[16] After completion of the discectomy, the final eligibility criterion was applied intraoperatively which required an annular defect of 4 to 6 mm tall and 6 to 10 mm wide. Patients meeting this requirement were then randomly allocated intraoperatively to receive limited lumbar discectomy only (Controls) or additional ACD implantation. Following randomization, no additional disc material was removed in either group. Patients allocated to ACD received a bone-anchored implant (Barricaid, Intrinsic Therapeutics, Woburn, MA, USA) comprised of a flexible polymer occlusion component to close the annular defect and a titanium anchor to secure the occlusion component to an adjacent vertebral body. In Control patients, the procedure was completed by standard incision closure.

Follow-up

Patients returned for clinical follow-up at 6 weeks, 3 months, 6 months, 1 year, and 2 years. Low-dose CT, MRI, and flexion-extension x-rays were performed at 1 and 2 years. Owing to better visualization of osseous structures, assessment of VEPC was performed by multiplanar CT scans of the index level with two-dimensional reconstruction. The CT scan was obtained using a low-dose protocol with 1.5 mm slice thickness, field of view ≤10 cm, and 120 kVp, resulting in an estimated effective dose less than 0.38 mSv per scan, or 10% that of a typical lumbar CT scan.[17] CT images were read by two board-certified radiologists at an independent imaging core laboratory (Intrinsic Imaging, LLC, Bolton, MA, USA) who were blinded to patient outcomes. Disagreement between raters was resolved with adjudication by a third radiologist.

Outcome Measures

VEPC was defined as any osseous disruption of the superior or inferior vertebral endplate on CT that could not be explained by the overall shape of the endplate, recognizing the variation in morphology among vertebral endplates.[18] VEPC area was approximated by measuring the major and minor change area in the sagittal, coronal, and axial planes. Assuming an elliptical shape, VEPC area in each plane was calculated as $(AB)(\pi/4)$, where A represented the major dimension and B represented the minor dimension. The location of individual VEPC was mapped at the slice with maximal change area. Total VEPC volume was derived from the sum of VEPC areas using a linear regression model ($y = 0.0063x$, $r = 0.83$) developed by a separate imaging core laboratory (Medical Metrics, Inc., Houston, TX, USA). Average disc height was taken from lateral x-rays.

Clinical outcomes included device- or procedure-related serious adverse events (SAE), symptomatic reherniation, reoperation for reherniation, and changes in pain severity of the most affected leg, back pain severity, and Oswestry Disability Index (ODI) scores. Seriousness and relatedness of adverse events was determined by an independent data safety monitoring board comprised of physicians who did not otherwise participate in the study. Symptomatic reherniation was defined as a herniation at the index level identified during follow-up that was reported as an adverse event, surgically verified during reoperation, or identified by the imaging core laboratory in a patient with at least moderate back-related disability (≥40/100 on ODI), radicular symptoms, or neurologic deterioration. Clinically meaningful improvements in patient reported outcomes were defined as ≥20-point decrease in leg pain severity on a 0 to 100 visual analogue scale (VAS), ≥20-point decrease in back pain severity on a 0 to 100 VAS, and ≥15-point decrease in ODI on a 0 to 100 scale.

Statistical Analysis

All analyses were performed on an as-treated population where patients who did not receive an ACD were included in the Control group for analysis purposes. Baseline patient characteristics were presented as means and standard deviations for continuous variables and counts and percentages for categorical variables. Group comparisons were performed with Student's t-test for continuous data or Fisher's exact test for categorical data. Logistic regression using a forward-backward stepwise elimination variable selection process was performed to determine the association of covariates with risk of VEPC at 2 years.[19] Logistic regression results were reported as odds ratio (OR) and 95% confidence interval. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Recruitment and Follow-up

Between December 2010 and October 2014, 554 patients from 21 European hospitals were randomly allocated to limited lumbar discectomy with additional ACD implantation (n=276) or limited lumbar discectomy only (Control; n=278). A list of participating centers and investigators is provided in **Supplement Table 1**. Implantation of the ACD was unsuccessful in five patients, including one case of nerve root injury during attempted implantation. The as-treated population forms the basis for this report and consisted of 267 patients in the ACD group and 283 Controls. At 2 years, compliance with clinical and imaging follow-up was 93% in the ACD group and 90% in Controls (**Fig. 1**).

Baseline Patient Characteristics

Baseline patient characteristics were well-matched between treatment groups (**Table 1**). Mean patient age was 44 years and 60% were male. Patients typically presented with severe radiculopathy and moderate-to-severe back-related disability. VEPC were preoperatively identified in 18% of patients in the ACD group and in 15% of Controls. When comparing patients with or without VEPC at baseline irrespective of treatment allocation, VEPC were identified most commonly at L4-L5 and in patients with greater volume of nucleus removal. No other baseline characteristic was different when comparing patients with or without VEPC at baseline (**Table 2**).

Postoperative Course of Vertebral Endplate Changes

Over 2 years, the percentage of patients with VEPC significantly increased in each group, with VEPC more common in patients treated with ACD. VEPC was observed in 15%, 29%, and 33% of Controls at baseline, 1 year, and 2 years, respectively. Corresponding frequencies in the ACD group were 19%, 72%, and 85% (**Fig. 2**). In the ACD group, the frequency of VEPC in the superior and inferior endplate at 2 years was 75% and 66% at L4-L5 and 75% and 43% at L5-S1. In Controls, same frequencies were 32% and 23% at L4-L5 and 28% and 12% at L5-S1. Through 2 years, 31% of VEPC in the ACD group were located proximate to the occlusion component of the device.

VEPC volume significantly increased in both groups over 2 years follow-up, with greater volume increases in the ACD group ($P = 0.001$). In each treatment group, VEPC volume appeared to be self-limiting. That is, in patients with VEPC at 1 year, subsequent VEPC growth followed an exponential distribution where larger VEPC grew at a slower rate compared to smaller VEPC (**Fig. 3**). The typical VEPC comprised <1% of vertebral body volume, with the largest observed VEPC occupying <8% of vertebral body volume. Representative VEPC evolution over 2 years in a patient in the ACD group is shown in **Fig. 4**.

In univariate logistic regression, ACD group (OR=11.0, $P < 0.001$), VEPC at baseline (OR=7.5, $P = 0.001$), change in disc height (OR=1.1 per 1 mm decrease, $P = 0.01$), and index level between L2-L3 and L4-L5 (OR=1.6, $P = 0.01$) were associated with VEPC at 2 years. In multivariate analysis, VEPC at baseline (OR=24.0, $P = 0.001$), ACD group (OR=15.2, $P < 0.001$), and disc height change at 2 years (OR=1.2 per 1 mm decrease, $P < 0.01$) were independently associated with VEPC at 2 years (**Table 3**).

Relationship of Vertebral Endplate Changes to Clinical Outcomes

Despite the higher frequency and greater volume of VEPC in the ACD group, main outcomes at 2 years favored the ACD group over Controls including symptomatic reherniation at index level (11% vs. 24%, $P < 0.001$), secondary surgical intervention (5% vs. 13%, $P < 0.001$), and device- or procedure-related SAE (8% vs. 17%, $P = 0.001$). The frequency of wound-related SAEs was comparable with ACD vs. Controls (1% vs. 2%), including 1 patient in each group with dural tear and 1 patients in each group with wound infection. No differences between ACD and Controls were noted in the percentage of patients achieving clinically important improvements in leg pain severity (94% vs. 93%, $P = 0.86$), back pain severity (67% vs. 65%, $P = 0.64$), or ODI (92% vs. 94%, $P = 0.60$) at 2 years.

In the ACD group, symptomatic reherniation and associated reoperation rates were comparable in those with vs. without VEPC at 2 years. Further, risk of SAE was lower in patients with vs. without VEPC at 2 years (5% vs. 21%, $P < 0.01$). This was mainly attributable to lower risk of reherniation (3% vs. 11%) and device deficiency (e.g. device migration, mesh detachment [1% vs. 11%]) in ACD patients with vs. without EPC. Subsidence of the occlusion component into the adjacent vertebral endplate was identified in 36% of ACD patients at 2 years. Neither the presence of occlusion component subsidence nor the presence of VEPC in the proximity of the ACD occlusion component influenced any clinical outcome. In contrast, Control patients with VEPC at 2 years had greater risk of symptomatic reherniation (34% vs. 19%, $P = 0.01$) and device- or procedure-related SAE (24% vs. 14%, $P < 0.05$) vs. those without VEPC (**Table 4**). Reoperation for reasons other than reherniation was performed with comparable frequency during follow-up in ACD vs. Controls (12 vs. 9 procedures). In the ACD

group, larger VEPC at 2 years did not influence clinical outcomes whereas the risk of complications in the Control group increased with increasing VEPC volume (**Fig. 5**).

DISCUSSION

In this post hoc analysis of a randomized controlled trial, we identified several important findings related to occurrence of VEPC in patients with large annular defects following limited lumbar discectomy. First, VEPC were common preoperative imaging findings in patients with symptomatic lumbar disc herniation. Second, VEPC were identified more frequently over 2 years follow-up in patients treated by limited lumbar discectomy with additional ACD implantation vs. limited lumbar discectomy alone. Third, VEPC growth rate over 2 years was dependent on VEPC volume, with larger VEPC growing at an exponentially slower rate, which appears to translate into a self-limiting course. Fourth, additional implantation of an ACD resulted in lower risk of SAE, recurrent disc herniation, and reoperation, independent of VEPC. Finally, VEPC were associated with higher risk of symptomatic reherniation in patients treated with limited lumbar discectomy, but not in those who received additional ACD implantation.

We found no evidence that VEPC frequency, location, or volume negatively influenced clinical outcomes in the ACD group through 2 years follow-up. That clinical outcomes were superior with ACD despite the significantly higher frequency of VEPC compared to Controls suggests that VEPC development may have originated via different mechanisms. The etiology of new VEPC development following ACD implantation remains speculative, but appears to be mechanical in nature with disruptions occurring due to the initial herniation, surgical treatment, and/or placement of mechanical implants. While VEPC were frequently identified proximate to the ACD, VEPC in the Control group were typically identified within the same regions of the

vertebral endplate. We were unable to adequately evaluate VEPC etiology since the first postoperative CT scan was taken at 1 year follow-up and more frequent scanning cannot be justified due to radiation concerns. Results of the multivariate logistic regression analysis identified pre-existing VEPC as the primary risk factor for VEPC at 2 years post-surgery, with ACD treatment group and disc height loss also associated with VEPC development. Regardless of cause, it appears that VEPC development in ACD patients does not influence clinical outcomes. Further, larger VEPC observed in the ACD group had slowing growth rates between 1 and 2 years. Imaging studies in the perioperative period as well as beyond 2 years could be helpful to clarify etiology and long-term course of VEPC.

In contrast to the benign nature of VEPC in the ACD group, presence of VEPC was associated with greater risk of symptomatic reherniation and SAE vs. those without VEPC in Controls. While VEPC are a common finding after lumbar discectomy,[7-9] the relationship between VEPC and clinical outcomes following lumbar discectomy is inconsistent. This inconsistency could be attributable to differences in how VEPC are described in the literature, which may include Schmorl's nodes, fracture, erosion, or calcification.[4] While erosions are the principal type of VEPC observed in the lumbar vertebrae,[14] VEPC type was not assessed in this study. Further, assessment of VEPC using CT instead of MRI may have influenced these relationships.

This study had several strengths including randomized study design, large sample size, and independent evaluation of CT images. There were also several limitations. First, since CT was performed preoperatively and at annual follow-up visits, we were unable to precisely determine the date of VEPC origin in most cases. Second, VEPC were evaluated at the index level, but not at adjacent lumbar levels. Third, these results may not be generalizable to all

patients undergoing limited lumbar discectomy since a large post-surgical annular defect was a criterion for study enrollment. Finally, longer patient follow-up is required to draw more definite conclusions regarding ACD efficacy, and the nature and clinical relationship of VEPC following limited lumbar discectomy.

CONCLUSION

In patients with large annular defects following limited lumbar discectomy, additional implantation of a bone-anchored ACD reduces risk of postoperative complications despite a greater frequency of VEPC. VEPC were associated with higher risk of symptomatic reherniation in patients treated with limited lumbar discectomy, but not in those who received additional ACD implantation.

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FIGURE LEGENDS

Fig. 1. CONSORT flow diagram in as-treated population.

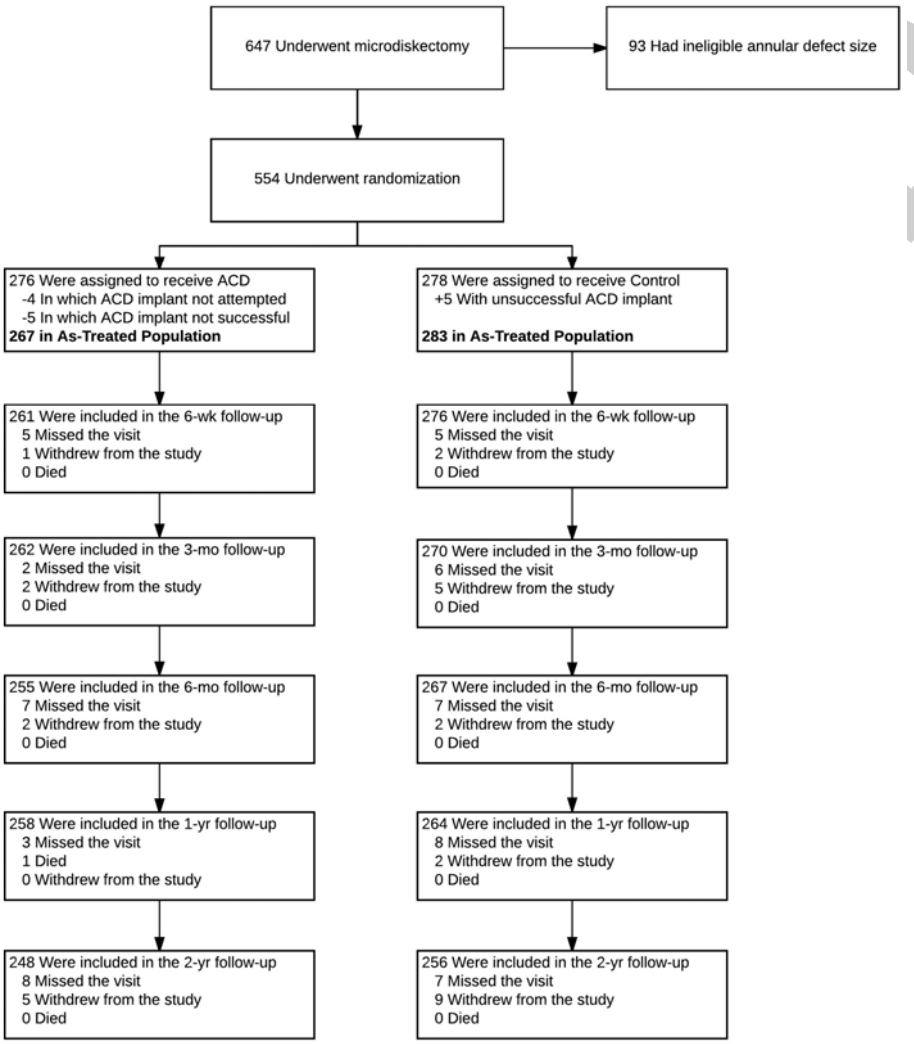


Fig. 2. Proportion of patients with same-level vertebral endplate change (VEPC) confirmed by low-dose computed tomography at each follow-up interval. ACD=annular closure device.

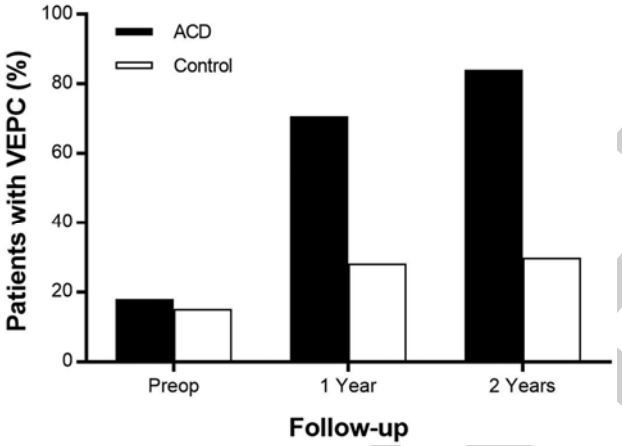


Fig. 3. Relationship of vertebral endplate change (VEPC) volume at 1 year with subsequent VEPC volume change during subsequent year. In patients treated with limited lumbar discectomy, with or without annular closure device (ACD) implantation, larger VEPC at 1 year grew at a slower rate compared to smaller VEPC.

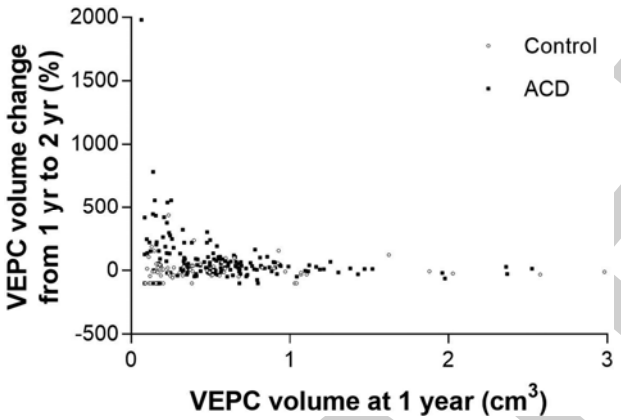


Fig. 4. Representative evolution of a vertebral endplate change (VEPC) at L4-L5 in a patient treated with limited lumbar discectomy and additional annular closure device (ACD). No VEPC was identified preoperatively on low-dose computed tomography. Postoperatively, a VEPC developed proximate to the occlusion component of the ACD, as indicated by the radiopaque marker within the mesh shown in the 2 year sagittal image. Sclerotic margin noticeable at 2 years suggests VEPC healing.

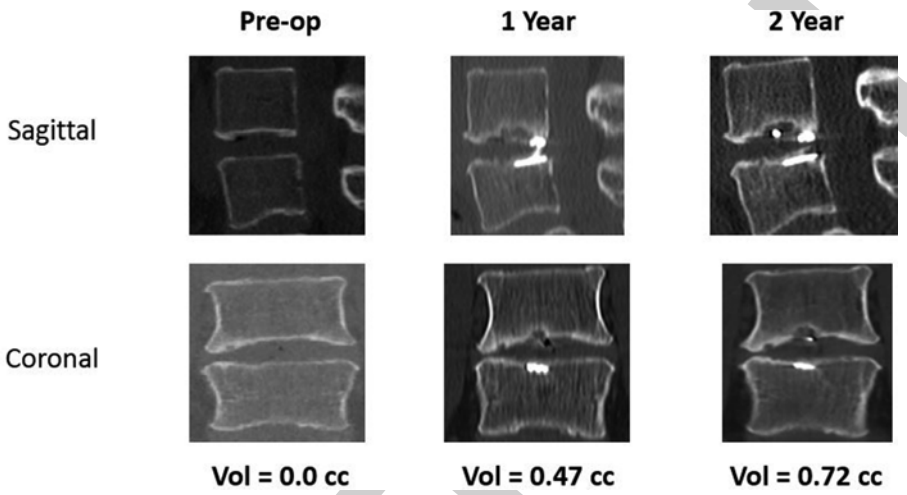
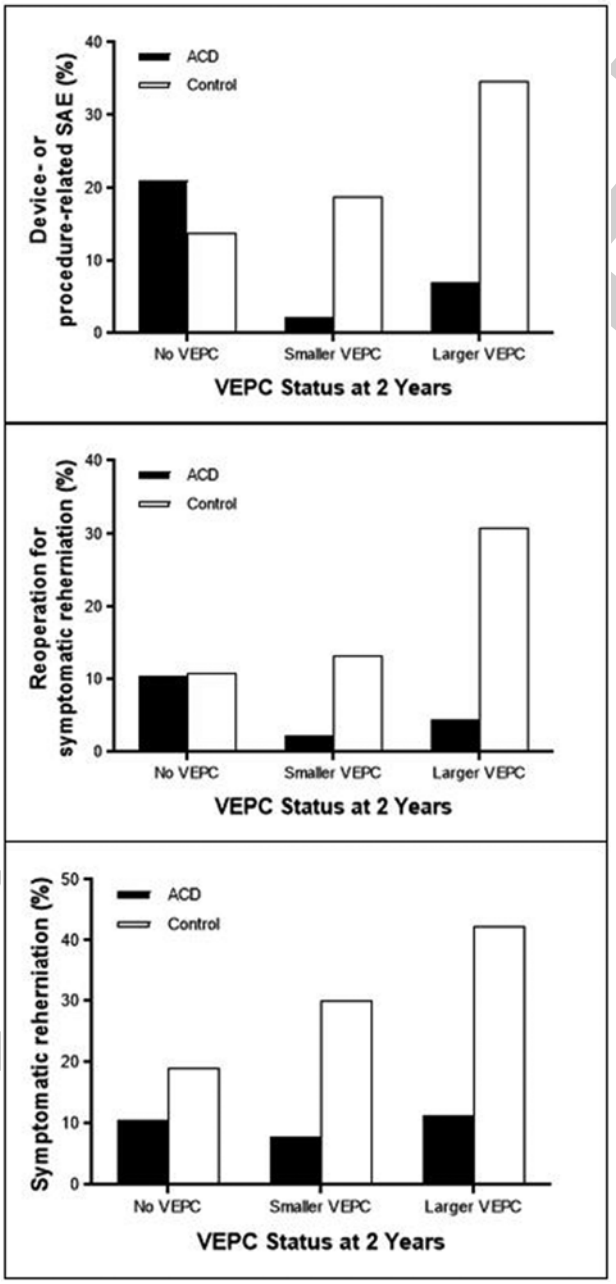


Fig. 5. Relationship of vertebral endplate change (VEPC) volume at 2 years with clinical outcomes at 2 years. Smaller VEPC defined as > 0 to < 0.48 cm^3 (median); larger VEPC defined as ≥ 0.48 (median) to 3.53 cm^3 (maximum). ACD=annular closure device.



TABLES

TABLE 1. Baseline patient characteristics by treatment group.*

Characteristic	ACD	Control
Age, yr	43±11	44±10
Male sex, % (n/N)	58% (155/267)	61% (172/283)
Body mass index, kg/m^2	26±4	26±4
Smoking history, % (n/N)	63% (169/267)	63% (179/283)
Visual-analogue scale for leg pain	81±15	81±15
Visual-analogue scale for back pain	57±30	56±31
Oswestry Disability Index score	59±12	58±14
Disc height, mm	8.9±2.1	8.8±2.1
Volume of nucleus removed, ml	1.3±1.0	1.3±0.8
Index level, % (n/N)		
L2-L3	1% (2/267)	<1% (1/283)
L3-L4	3% (8/267)	2% (5/283)
L4-L5	45% (121/267)	36% (103/283)
L5-S1	51% (136/267)	62% (174/283)
VEPC volume, % (n/N) †		
0 cm^3	82% (214/261)	85% (237/279)
> 0 to < 0.23 cm^3 (median)	10% (26/261)	7% (19/279)
≥ 0.23 (median) to 2.32 cm^3 (maximum)	8% (21/261)	8% (23/279)

ACD=annular closure device; VEPC=vertebral endplate change.

* Values are mean±SD or percentage (n/N).

† VEPC volume calculated as the total volume of VEPC identified in superior and inferior vertebral body. In 1 patient per group, VEPC was identified but total volume was not calculable.

TABLE 2. Patient characteristics by presence of vertebral endplate changes at baseline.*

Characteristic	VEPC	No VEPC	*P* value
Age, yr	44±10	43±11	0.71
Male sex, % (n/N)	58% (53/91)	60% (269/451)	0.82
Body mass index, kg/m^2	27±4	26±4	0.44
Smoking history, % (n/N)	54% (49/91)	65% (292/451)	0.06
Visual analogue scale for leg pain	80±15	81±15	0.60
Visual analogue scale for back pain	57±31	56±31	0.63
Oswestry Disability Index score	58±12	59±13	0.59
Disc height, mm	8.5±2.1	8.9±2.1	0.11
Volume of nucleus removed, ml	1.4±1.1	1.2±0.9	0.04
Index level, % (n/N)			0.04
L2-L3	1% (1/91)	<1% (2/451)	
L3-L4	2% (2/91)	2% (11/451)	
L4-L5	52% (47/91)	38% (171/451)	
L5-S1	45% (41/91)	59% (267/451)	

VEPC=vertebral endplate change.

* Values are mean±SD or percentage (n/N).

TABLE 3. Logistic regression analysis of predictors of vertebral endplate change at 2 years.

Characteristic	Unit of measure	OR	95% CI	*P* value
Univariate analysis				
Treatment group	ACD vs. Control	11.0	7.1, 17.0	<0.001
VEPC at baseline	Yes vs. no	7.5	3.7, 15.4	<0.001
Disc height change at 2 years	Per 1 mm decrease	1.1	1.0, 1.3	0.01
Index level at L5-S1	No vs. yes	1.6	1.1, 2.3	0.01
Disc height at baseline	Per 1 mm increase	1.1	1.0, 1.2	0.17
VAS for back pain at baseline	Per 10 point increase	1.0	1.0, 1.1	0.32
Disc height at 2 years	Per 1 mm increase	1.0	0.9, 1.0	0.36
Sex	Male vs. female	1.2	0.8, 1.7	0.37
Body mass index	Per 5 kg/m^2 increase	1.1	0.9, 1.3	0.59
Smoking history	Yes vs. no	1.1	0.7, 1.5	0.72
Age	Per 10 year increase	1.0	0.9, 1.2	0.81
VAS for leg pain at baseline	Per 10 point increase	1.0	0.9, 1.1	0.92
Volume of nucleus removed	Per 1 ml increase	1.0	0.8, 1.2	0.92
ODI score at baseline	Per 10 point increase	1.0	0.9, 1.1	>0.99
Multivariate analysis				
VEPC at baseline	Yes vs. no	24.0	8.1, 70.9	<0.001
Treatment group	ACD vs. Control	15.2	9.2, 25.2	<0.001
Disc height change at 2 years	Per 1 mm decrease	1.2	1.1, 1.4	<0.01

ACD=annular closure device; CI=confidence interval; ODI=Oswestry Disability Index; OR=odds ratio; VAS=visual analogue scale; VEPC=vertebral endplate change.

TABLE 4. Clinical outcomes by treatment group and presence of vertebral endplate change at 2 years.

Outcome	ACD			Control		
	VEPC (n=205)	No VEPC (n=37)	*P* value	VEPC (n=82)	No VEPC (n=167)	*P* value
Complications						
SAE	5%	21%	<0.01	24%	14%	<0.05
Symptomatic reherniation	10%	11%	>0.99	35%	19%	0.01
Reoperation for reherniation	4%	11%	0.10	20%	11%	0.08
Patient-reported outcomes						
Leg pain decrease ≥20 points	94%	92%	0.71	94%	93%	>0.99
Back pain decrease ≥20 points	68%	60%	0.34	70%	63%	0.33
ODI decrease ≥15 points	92%	92%	>0.99	94%	95%	0.78

ACD=annular closure device; ODI=Oswestry Disability Index; SAE=device- or procedure-related serious adverse event; VEPC=vertebral endplate change.