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ORIGINAL ARTICLE - SPINE

Endplate changes after lumbar discectomy with and without implantation of an annular closure device

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Abstract

Background The implantation of a bone-anchored annular closure device (ACD) might be associated with the developed new endplate changes (EPC) after surgery.

Methods A post hoc analysis has been done in patients from a prospective randomized multicenter study. All patients underwent limited lumbar discectomy with intraoperative randomization into the groups limited lumbar discectomy alone or additional ACD implantation. Low-dose lumbar computed tomography (CT) and clinical investigations were performed preoperatively and 12 months after the operation.

Results A total of 554 patients were randomized. After exclusion of dropouts, the per-protocol population included 493 patients (251 in the control group and 242 in the ACD group); the follow-up rate was ≥ 90%. The number of patients showing EPC at baseline was similar in both groups. The number of patients showing EPC and the total EPC lesion area significantly increased in both groups over time, but significantly increased more in the EPC group for the superior and inferior endplate (all $P < 0.0001$). There was no association of pre-existing number and size of EPC with sex, age, or smoking habits. Correlation of clinical variables showed no relation with number, size, and increase of EPC area after surgery.

Conclusions Patients with primary lumbar disc herniation show EPC in the corresponding segments. There is a significant increase of lesion number and size within 12 months after discectomy. This increase is significantly more pronounced in the ACD group. Presence and growth of EPC is not correlated with low-back pain or ODI.

Keywords Annular closure device · Lumbar discectomy · Outcome

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Introduction

Preliminary data have shown that the addition of a bone-anchored annular closure device (ACD) to limited discectomy may reduce the risk of reherniation in patients at high risk for reherniation [3]. However, using magnetic resonance imaging (MRI), it has been demonstrated that over 50% of patients undergoing limited discectomy with ACD placement developed new endplate changes (EPC) after surgery compared to 10% in a historical control group [2]. Those EPC consisted of any structural defect such as chipping, scalloping, or forming of erosions that were not due to the overall shape of the endplate. In addition, another study using similar definitions of EPC has shown that the number of changes significantly increased from preoperatively to 1 year after the operation in patients undergoing lumbar discectomy [15]. However, both studies have considerable limitations with respect to imaging modality, study design, and statistical power, which prevents

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conclusions on true prevalence of EPC and their clinical significance in a lumbar segment after disc surgery. In addition, lumbar EPC have only infrequently been described in the literature, with different imaging modalities and without clinical correlation.

The aim of the present study was therefore to characterize the prevalence and development of EPC and their clinical significance in patients with primary lumbar disc herniation that undergo limited discectomy with and without additional implantation of an ACD. For that purpose, a post hoc analysis has been performed on data from a prospective, randomized multicenter study. The study protocol has been published elsewhere [5]. Part of the study protocol involved extensive clinical and radiological assessments including low-dose lumbar computed tomography (CT) preoperatively and annually 12 months after the operation in order to investigate any bony reactions associated with the bone-anchored ACD.

Materials and methods

Patient selection and management

This post hoc analysis is based on patient data from a prospective, multicenter, and randomized study of patients with lumbar disc herniation with or without implantation of an ACD. The trial has been registered at the United States National Institutes of Health Clinical Trials Registry (NCT01283438) and has been approved by the ethics committee (EC) of each participating site; all study subjects signed an EC-approved informed consent. Detailed information on inclusion and exclusion criteria and patient management are provided in the published study protocol [5]. In short, inclusion criteria included (1) age between 21 to 75 years; (2) MRI-confirmed one-level disc herniation between L1 and S1 (presence of neural compression); (3) insufficient success of conservative treatment > 6 weeks; (4) posterior disc height of ≥ 5 mm at index level; (5) presence of leg pain with a score of ≥ 40/100 in the visual analog pain intensity scale (VAS); (6) positive straight leg raise or femoral stretch test; (7) the Oswestry Disability Index (ODI) score of at least 40/100 at baseline; and (8) psychosocially, mentally, and physically able to fully comply with the clinical protocol and willing to adhere to follow-up schedule and requirements.

Clinical assessment included multiple exams such as motor muscle strength and sensory neurological evaluation among others. For the present investigation, however, only the following clinical items were used preoperatively and 12 months after the operation: leg and back pain intensity using the VAS score and ODI. For VAS leg, the VAS pain score of the affected leg has been used. With regard to imaging, only multiplanar computed tomography (CT) at the index level were used preoperatively and 12 months after the operation.

After consenting for the study, patients underwent surgery for disc herniation. Following removal of extruded disc material, the defect size was measured using sizing paddles. Patients with a vertical defect size below 4 or above 6 mm or a horizontal size below 6 or above 10 mm were excluded from the study. The remaining patients were intraoperatively randomized (1:1) with the use of a Web-based system that enabled computer-generated random treatment assignment. The study arms were limited posterior discectomy alone (control group) or limited posterior discectomy plus implantation of an annular closure device (ACD group). After that point, the operation was finished for the control group. The ACD group received the implantation of the closure device under fluoroscopic control with the anchor positioned optionally in the superior or inferior vertebral body. The total discal tissue removed during surgery was stored dry; the volume was measured using an appropriate sterile syringe.

All the trial surgeons were experienced in performing the two trial interventions. Figure 1 shows images of the implant (Barricaid®, Intrinsic Therapeutics, Inc., Woburn, USA).

Assessment of CT

For the present investigation, the preoperative and 12-month postoperative CT data of both groups were assessed for the presence and size of EPC by an independent institution (Intrinsic Imaging LLC, Bolton, Massachusetts, USA). An EPC has been defined as a localized osseous defect that did not match the physiological shape of the endplate, recognizing that this shape may vary among subjects [10]. This included structures such as fracture or chipping and reactions including scalloping, erosions, cysts, or other irregularities. The investigating radiologists had no access to clinical outcome data and were blinded to any subject confidential information and site assessments. Every image at each time point was reviewed by two independent radiologists. Results were kept consistent with the use of an adjudicator.

Using CT axial images and sagittal reconstructions, the independent lab recorded the number of EPC in the inferior (1) and superior (2) vertebral body and approximated the size of each change (3) by measuring the major and minor dimensions of the EPC in the sagittal, coronal, and axial plane. The major dimension was defined as the largest dimension of the lesion in the given plane. The minor dimension was defined as the largest lesion dimension that was perpendicular to the axis defined by the major dimension.

Using these raw data, the authors approximated each lesion to be elliptical and calculated the area (mm^2) according the standard formula ($\pi \times A \times B$) with A being the half of the major and B being the half of the minor dimension. Areas were calculated for each plane (sagittal, coronal, and axial) and summed for each EPC. The total areas of superior, inferior, and all EPC were calculated. From those values, the difference

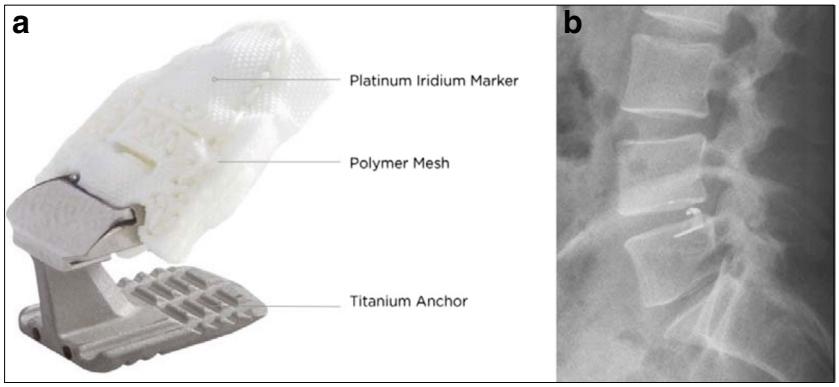

Fig. 1 **a** The annular closure device (ACD) consists of a flexible woven polyester mesh (Dacron®) that includes an iridium marker. The mesh is attached to a titanium bone anchor. **b** Lateral radiograph of an implanted ACD. Typically, as shown here, the anchor is implanted in the lower vertebra and the mesh inside the disc space. Alternatively, the anchor can be implanted in the upper vertebra (not shown)

was calculated between the 12-month and the preoperative follow-up.

Using these pre- and postoperative radiological findings, various associations and correlations with clinical symptoms and factors such as sex, age, smoking habits, and body mass index were performed. In addition, number and size of EPC were correlated with the total volume of removed discal tissue.

Statistical analysis

For analysis, clinical and radiological raw data were available. Differences between the two treatment groups were analyzed with the use of Student's *t* test, Fisher's exact test, the Wilcoxon two-sample test, or the Cochran-Armitage trend test. In order to compare the two samples "pre" and "post" regarding numbers of EPC or areas, the Wilcoxon tests for two paired samples have been used. Correlations were calculated using the Pearson or Spearman correlation coefficients. All statistical analyses were done by CW using the statistical software SAS (SAS 9.3, SAS Inc., Cary, NC 27513–2414, USA). Differences were considered significant when P was < 0.05. Radiological variables are given as mean values ± standard deviation (SD); clinical scores are presented as median/minimum/maximum.

Results

In total, 554 patients were randomized, 278 for the control group and 276 for the ACD group. All patients of the control group received the planned treatment. Of the ACD group, nine patients did not receive an implant due to the following reasons: in four patients, the individual nerve root anatomy prevented implantation. In further five patients, implantation was unsuccessful and was abandoned. In four of these cases, the mesh did not fully enter the disc. In one case, inadequate visualization and retraction led to nerve root damage and implantation was also

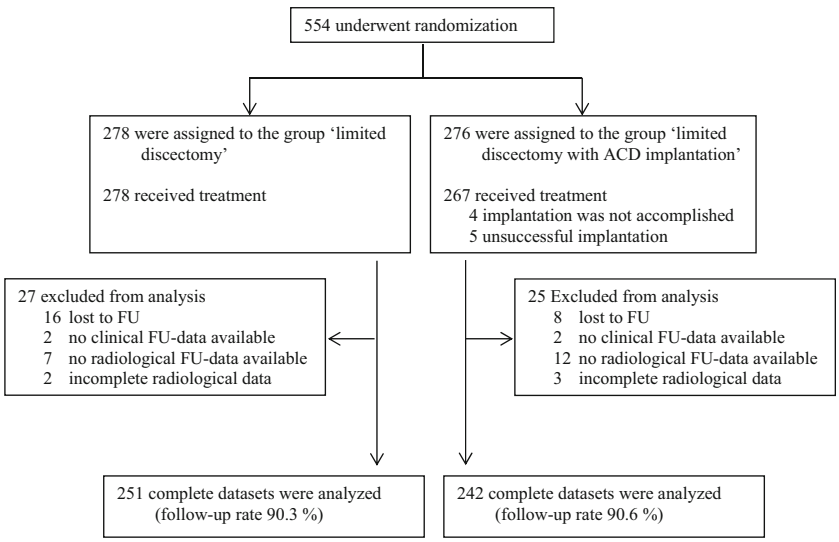

Fig. 2 Randomization, treatment, and 1-year follow-up. Follow-up (FU), annular closure device (ACD)

not performed. Per study protocol, reimplantation was not allowed in these five subjects.

Data of 27 additional patients in the control group could not be analyzed, as 16 were lost to follow-up (FU) and in two, no clinical and in seven, no radiological data were available. In two more patients, the radiological dataset was not complete. Data of 25 additional patients in the ACD group were excluded, as eight were lost to follow-up (FU) and in two, no clinical and in 12, no radiological data were available. In three more patients, the radiological dataset was not complete. Therefore, the per-protocol analysis included 493 patients (251 in the control group and 242 in the ACD group) with a follow-up rate at 1 year after operation of ≥ 90% (Fig. 2).

Baseline characteristics

None of the preoperative baseline characteristics including smoking habits showed significant differences between groups (Table 1). Due to the additional implantation of the ACD, the duration of surgery in this group was 69.7 ± 31.5 min, which was significantly longer compared to control (51.4 ± 25.2; $P < 0.0001$). The preoperative clinical variables such as VAS back, VAS of the affected leg, and ODI showed no significant differences at baseline. Detailed values are shown in Table 2.

The number of patients showing EPC at baseline was similar in both groups (Table 3). For the superior endplate, in 26 out of 226 control and in 37 out of 205 ACD patients, one or more EPC were present ($P = 0.088$). In the inferior endplate, 15 out of 237 control and 17 out of 225 ACD patients showed one or more EPC ($P = 0.632$). Table 4 shows the preoperative lesion areas, which were 20.0 and 20.9 mm^2 in the superior endplates of the control and ACD group ($P = 0.123$) and 11.4 and 7.4 mm^2 in the inferior endplates of the control and ACD group ($P = 0.821$).

Table 2 Clinical variables

Variable	Control group ($N = 251$)	ACD group ($N = 242$)	P value
VAS back			
Preoperative	64 (0/100)	66 (0/100)	0.945
12 months	12 (0/94)	9 (0/90)	0.105
P value	< 0.0001	< 0.0001	
VAS leg			
Preoperative	83 (41/100)	85 (42/100)	0.645
12 months	3 (0/93)	2 (0/83)	0.033
P value	< 0.0001	< 0.0001	
ODI			
Preoperative	56 (40/100)	58 (40/90)	0.225
12 months	9 (0/78)	8 (0/70)	0.642
P value	< 0.0001	< 0.0001	

Given values are median (minimum/maximum)

VAS visual analog scale, ranging from 0 to 100 with 0 absence of pain and 100 the worst imaginable pain for back and leg, *ODI* the Oswestry Disability Index, *ACD* annular closure device

Follow-up

As expected, clinical variables significantly improved from preoperatively to 1 year after the operation (Table 2), which was independent of the treatment group. However, VAS leg in

Table 1 Baseline characteristics

Variable	Control group ($N = 251$)	ACD group ($N = 242$)	P value
Age	44.0 (10.5)	42.9 (10.7)	0.279
BMI	26.3 (4.1)	26.2 (4.0)	0.764
Female:male	97:154	100:142	0.581
Current smoker	107	105	0.928
Ever smoked	156	150	1.000
Pack-years	17.6 (13.8)	17.3 (22.1)	0.801
Volume of nucleus removed (cm^3)	1.3 (0.8)	1.3 (0.9)	0.843
Operated level			
L 2/3	1	2	
L 3/4	5	8	0.129
L 4/5	91	107	
L 5/S1	154	125	
OP time (min)	51.4 (25.2)	69.7 (31.5)	< 0.0001
Follow-up time (months)	12.1 (1.9)	12.1 (1.0)	0.702

Given values are N or mean (SD) when appropriate

BMI body mass index, *ACD* annular closure device

Table 3 Number of patients with endplate changes

		Control group		ACD group		*P* value†
		Yes	No	Yes	No	
Superior endplate	Pre OP	26	225	37	205	0.088
	Post OP	60	191	141	101	< 0.0001
	P value*	$P < 0.0001$		$P < 0.0001$		
Inferior endplate	Pre OP	15	236	17	225	0.632
	Post OP	25	226	87	155	< 0.0001
	P value*	$P = 0.088$		$P < 0.0001$		

Given values represent the number of patients with or without endplate changes separate for the superior and inferior endplate

*The Wilcoxon tests for two paired samples

†The Wilcoxon two-sample test

the ACD group was significantly better 12 months after the operation compared to control.

With regard to radiological changes, the number of patients showing EPC increased in both groups 1 year after the operation except for the lower endplate in the control group (all $P < 0.0001$, Table 3). However, the difference between study groups was highly significant with 60 out of 191 control and 101 out of 141 ACD patients having one or more EPC in the superior endplate ($P < 0.00001$), and with 25 out of 226 control and 87 out of 155 ACD patients showing one or more EPC in the inferior endplate after surgery ($P < 0.0001$).

The total lesion area of postoperative EPC significantly increased in both groups over time (Table 4). However, the postoperative lesion area after surgery was 44.6 and 130.7 mm^2 in the superior endplates of the control and ACD group, respectively ($P < 0.0001$), and 19.3 and 47.0 mm^2 in the inferior endplates of the control and ACD group, respectively ($P < 0.0001$). The difference between the mean postoperative and preoperative lesion areas was also highly significant with 24.6 and 109.8 mm^2 in the superior endplates of the control and ACD group, respectively ($P < 0.0001$), and 7.9 and 39.6 mm^2 in the inferior endplates of the control and ACD group, respectively ($P < 0.0001$).

Figure 3 shows representative examples of the morphological appearance of small, medium, and large EPC for both groups.

Associations and correlations

The association of pre-existing number and size of EPC with several factors such as sex, age, or smoking habits failed to establish a significant relationship (Table 5).

The correlation of the intensity of postoperative VAS back and ODI scores with the number, size, and increase of EPC area revealed no significant relation at 12 months after surgery (Table 6). In addition, the volume of removed discal tissue had no influence on the increase of the total lesion area from preoperative to 12 months after the operation ($N = 493$; $r = -0.224$; $P = 0.618$; the Pearson correlation coefficient).

Discussion

The present investigation shows that EPC may be present in 10–15% of patients with lumbar disc herniation within the affected segment and that these EPC increase in number and size within 12 months after lumbar discectomy. The insertion of an ACD was associated with a significantly greater increase of the number and size of these EPC. The increase of lesion size was independent of the discal volume that had been removed during surgery. Structural changes are not associated with clinical deterioration.

Comparison of the present results to historical reports is difficult since lumbar EPC in general have only infrequently been described in the literature. In addition, most authors conducted epidemiological projects or studies on cadavers with

Table 4 Lesion areas

		Control group $N = 251$	ACD group $N = 242$	*P* value†
Superior endplate	Pre OP	20.0 (0/972.9)	20.9 (0/763.5)	0.1224
	Post OP	44.6 (0/852.3)	130.7 (0/984.8)	< 0.0001
	P value*	$P < 0.0001$	$P < 0.0001$	
	Post-pre	24.6 (− 155.0/473.0)	109.8 (− 263.5/984.8)	< 0.0001
Inferior endplate	Pre OP	11.4 (0/546.4)	7.4 (0/231.3)	0.8210
	Post OP	19.3 (0/916.6)	47.0 (0/498.9)	< 0.0001
	P value*	$P = 0.0071$	$P < 0.0001$	
	Post-pre	7.9 (− 210.3/443.2)	39.6 (− 101.3/468.7)	< 0.0001

Given values represent the mean values together with extreme values (min/max) of the added areas (mm^2) from each plane (sagittal, coronal, and axial)

*The Wilcoxon tests for two paired samples

†The Wilcoxon two-sample test

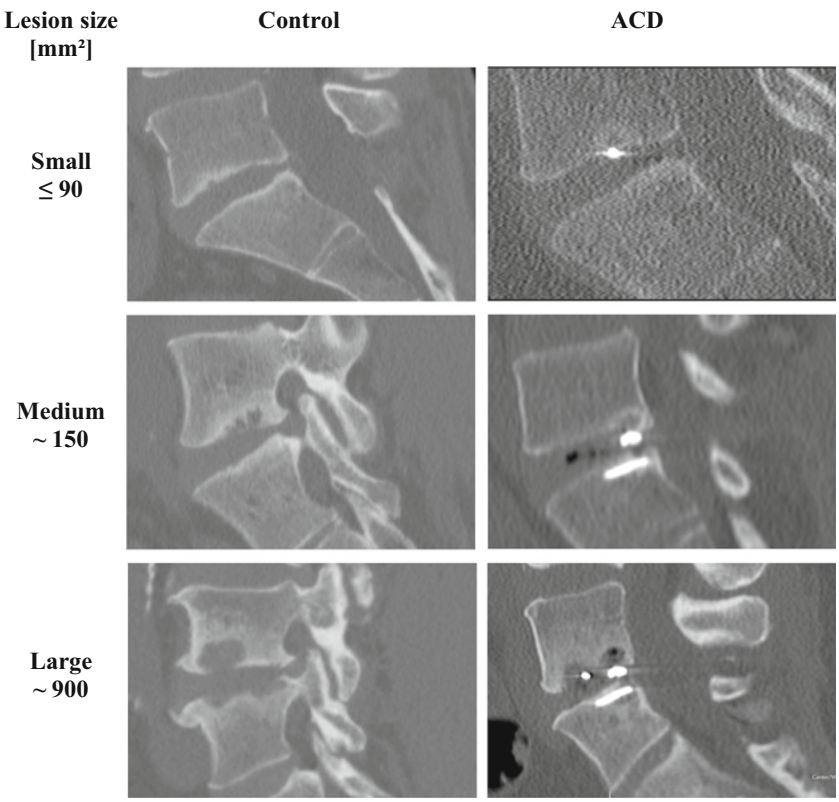

Fig. 3 Sagittal reconstructions from CT-scans 1 year after surgery. Three classes of lesion sizes are exemplary shown: small lesions of about 90 mm^2, medium-sized lesions with about 150 mm^2, and large lesions with about 900 mm^2 total lesion area. Left column shows control patients, right column ACD patients

patients that received spinal imaging for reasons other than disc herniation [4, 9, 11, 13, 14]. As such, different imaging modalities were used, which results in a wide variety of prevalence values for EPC in the literature.

It appears that the terminology for EPC is heterogeneous, since some investigators use this term synonymous to Schmorl's nodes (SN) [8]. However, SN seem to represent a different entity, as shown below. The anatomy-based study of Wang et al. categorized lumbar endplate lesions into SN, fracture lesions, erosion lesions, or calcification lesions [13]. The most common endplate lesion type was represented by small SN with a frequency of 22%, followed by larger lesions, termed "erosions" (14.1%) [13]. Frequency of both lesion types correlated with increasing age and might therefore also correlate with increasing spinal degeneration. Our study proved that lumbar EPC are generally a common finding

Table 5 Associations and correlations—pre OP data

		Pre OP lesion size (mm^2)*	Pre OP number of lesions
Sex	Female ($N = 197$)	28.5 (0–934.84)	0.22 (0–4)
	Male ($N = 296$)	30.8 (0–1104.34)	0.21 (0–3)
		$P = 0.932$	$P = 0.979$
Current smoker	Yes ($N = 212$)	28.6 (0–1104.3)	0.21 (0–4)
	No ($N = 281$)	30.9 (0–898.5)	0.22 (0–3)
		$P = 0.999$	$P = 0.927$
Smoke history	Ever ($N = 306$)	23.0 (0–1104.3)	0.18 (0–3)
	Never ($N = 187$)	41.2 (0–898.5)	0.28 (0–4)
		$P = 0.069$	$P = 0.084$
		Correlation coefficients according to the Pearson	Correlation coefficients according to the Spearman
Pack-years	$N = 493$	$r = -0.014$; $P = 0.763$	$r = -0.088$; $P = 0.852$
Age	$N = 493$	$r = 0.001$; $P = 0.981$	$r = 0.007$; $P = 0.882$
BMI	$N = 493$	$r = 0.025$; $P = 0.577$	r = 0.007; $P = 0.885$

*Given values represent the mean values together with extreme values (min/max) of the added areas from each plane

Table 6 Associations and correlations—post OP data

		Post OP VAS back	ODI
Lesions present	No ($N = 255$)	8 (0/94)	8 (0/70)
	Yes ($N = 238$)	12 (0/91)	10 (0/78)
		$P = 0.076$	$P = 0.119$
		Correlation coefficients according to the Spearman	Correlation coefficients according to the Spearman
Number of lesions	$N = 493$	$r = 0.079$; $P = 0.080$	$r = 0.071$; $P = 0.115$
Area of lesions	$N = 493$	$r = 0.087$; $P = 0.053$	$r = -0.047$; $P = 0.301$
Increase of lesion area	$N = 493$	$r = 0.082$; $P = 0.068$	$r = -0.046$; $P = 0.313$

Given values in the upper part represent the postoperative median values (min/max). In the lower part, *r* represents correlation coefficient and *P* the corresponding *P* value

VAS visual analog scale, ranging from 0 to 100 with 0 absence of pain and 100 the worst imaginable pain, *ODI* the Oswestry Disability Index

and mostly affect both endplates. Interestingly, the present investigation shows a similar prevalence of EPC with 79 patients (15.9%) showing one or more EPC prior to surgery. Thus, EPC described in the present investigation are rather attributable to "erosions." However, the present investigation is not representative in the description of the general prevalence of lumbar "erosions," since this was not an epidemiological study and only one segment of patients with lumbar disc herniations was included.

In the 12 months FU, there was an increasing number of EPC detectable in both groups, which might be explained with progressing segmental degeneration. In addition, all patients had surgery with partial removal of intradiscal tissue. This could represent an additional trauma that is inevitably applied to the affected segments. It therefore seems consequential to assume a higher frequency of EPC 1 year after surgery. However, the ACD group suffered a significant increase of both number and size of EPC. It is therefore conceivable to assume a relation of increasing number and size with the implant. By analyzing the location of EPC, it is striking that the lesion size increased in particular in the upper endplates. A possible explanation could be that the ACD titanium anchor has been implanted into the lower endplate in the majority of cases. As the mesh of the ACD is designed to flip upwards, some pressure will be applied onto the upper endplate. This could be an additional mechanical stress for the upper endplate and might be the reason for a significant increase in total lesion size.

One of the most striking results of the present study certainly represents the lack of correlation of the observed EPC with clinical outcome variables, in particular low-back pain. It has been hypothesized that damage to the endplate and the underlying trabecular bone might be associated with low-back pain [12]. In a femur mouse model, bone marrow is innervated remarkably rich and heterogeneous with sensory and sympathetic fibers [7]. And also in human vertebral bodies, nerve bundles have been found within areas of osteoporotic spinal fractures [1]. Thus, damaged endplate regions are thought to be the source of pain caused by an adverse combination of endplate nerve proliferation plus chemical sensitization and mechanical stimulation [6].

However, although EPC in the present investigation increased in size and number and also extended into the vertebral bone marrow, no correlation could be found with low-back pain or ODI in the present cohort. Possibly, other sources of EPC formation, such as acute trauma or osteoporotic fractures, play a more relevant role in the generation of skeletal pain.

Another interesting finding is the fact that correlation of the preoperative number and size of EPC with several clinical variables revealed no meaningful association. In particular, age, gender, BMI, and smoking habits did not influence presence, number, or size of EPC. In contrast, previous studies showed a significant association with age, male gender, height, and body weight [8]. However, different patient populations were investigated and different imaging modalities were used, which may account for diverging results.

The main strength of the present study is its prospective randomized design with inclusion of over 500 patients and excellent follow-up rates.

However, the multicenter design might also represent a limitation as the operative techniques may vary between centers. It is furthermore unknown if individual surgical details have an impact on the development of EPC. The absence of a purely non-operative group circumvents the characterization of the natural course of EPC. In addition, EPC were only investigated in the operated levels. It would have been interesting to follow additional EPC in untreated segments of the same patients serving as an internal control. However, resource limitations did not allow for additional assessments. Due to a number of inclusion/exclusion criteria, the population that has been included is not representative for all patients undergoing discectomy. The observations need to be interpreted with respect to the limitations of the study.

Conclusion

Patients with primary lumbar disc herniation show EPC in the corresponding segments. There is a significant increase of lesion number and size within 12 months after discectomy. This increase is significantly more pronounced in the ACD group. Presence and growth of EPC is not correlated with low-back pain or ODI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the corresponding institutional research committees (multicenter study) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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