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# Influence of lumbar intervertebral disc degeneration on the outcome of total lumbar disc replacement: a prospective clinical, histological, X-ray and MRI investigation

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## Abstract

*Introduction* The role of fusion of lumbar motion segments for the treatment of axial low back pain (LBP) from lumbar degenerative disc disease (DDD) without any true deformities or instabilities remains controversially debated. In an attempt to avoid previously published and fusion-related negative side effects, motion preserving technologies such as total lumbar disc replacement (TDR) have been introduced. The adequate extent of preoperative DDD for TDR remains unknown, the number of previously published studies is scarce and the limited data available reveal contradictory results. The goal of this current analysis was to perform a prospective histological, X-ray and MRI investigation of the index-segment's degree of DDD and to correlate these data with each patient's pre- and postoperative clinical outcome parameters from an ongoing prospective clinical trial with ProDisc II (Synthes, Paoli, USA).

*Materials and methods* Nucleus pulposus (NP) and annulus fibrosus (AF) changes were evaluated according to a previously validated quantitative histological degeneration score (HDS). X-ray evaluation included assessment of the mean, anterior and posterior disc space height (DSH). MRI investigation of DDD was performed on a 5-scale grading system. The prospective clinical outcome assessment included Visual Analogue Scale (VAS), Oswestry Disability Index (ODI) scores as well as the patient's subjective satisfaction rates.

*Results* Data from 51 patients with an average follow-up of 50.5 months (range 6.1–91.9 months) were included in the study. Postoperative VAS and ODI scores improved significantly in comparison to preoperative levels ($p < 0.002$). A significant correlation and interdependence was established between various parameters of DDD preoperatively ($p < 0.05$). Degenerative changes of NP tissue samples were significantly more pronounced in comparison to those of AF material ($p < 0.001$) with no significant correlation between each other ($p > 0.05$). Preoperatively, the extent of DDD was not significantly correlated with the patient's symptomatology ($p > 0.05$). No negative influence was associated with increasing stages of DDD on the postoperative clinical outcome parameters following TDR ($p > 0.05$). Increasing stages of DDD in terms of lower DSH scores were not associated with inferior clinical results as outlined by postoperative VAS or ODI scores or the patient's subjective outcome evaluation at the last FU examination ($p > 0.05$). Conversely, some potential positive effects on the postoperative outcome were observed in patients with advanced stages of preoperative DDD. Patients with more severe preoperative HDS scores of NP samples demonstrated significantly lower VAS scores during the early postoperative course ($p = 0.02$).

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*Conclusion* Increasing stages of DDD did not negatively impact on the outcome following TDR in a highly selected patient population. In particular, no preoperative DDD threshold value was identified from which an inferior postoperative outcome could have been deduced. Conversely, some positive effects on the postoperative outcome were detected in patients with advanced stages of DDD. Combined advantageous effects of progressive morphological structural rigidity of the index segment and restabilizing effects from larger distraction in degenerated segments may compensate for increasing axial rotational instability, one of TDR's perceived disadvantages. Our data reveal a "therapeutic window" for TDR in a cohort of patients with various stages of DDD as long as preoperative facet joint complaints or degenerative facet arthropathies can be excluded and stringent preoperative decision making criteria are adhered to. Previously published absolute DSH values as contraindication against TDR should be reconsidered.

**Keywords**  Total disc replacement · Disc arthroplasty · Disc degeneration · Degenerative disc disease · Histological degeneration

## Introduction

Fusion of lumbar motion segments has previously been claimed to be the "gold standard" for the treatment of true deformities and instabilities of the lumbar spine that had proved unresponsive to conservative treatment. However, its role in the treatment of axial low back pain (LBP) from lumbar degenerative disc disease (DDD) remains controversially debated. A variety of early and late complications such as adjacent segment pathologies have been reported in a considerable number of patients following the surgical intervention [1–12].

In an attempt to avoid these fusion-related negative side effects, motion preserving technologies such as total lumbar disc replacement (TDR) procedures have been introduced. Their clinical efficacy has been demonstrated by a variety of class I to class IV studies worldwide [13–26].

However, the adequate extent of preoperative DDD for TDR remains controversially debated, the number of previously published studies is scarce and the limited data available reveal contradictory results. Moore et al. [27] were able to show delayed but significant changes of the facet joints at the index and adjacent levels during the progressive stages of DDD in a standardized animal model of disc degeneration. Significant preoperative facet joint degeneration remains to be one commonly agreed upon contraindication against TDR [28–31]. Thus, well-justified concern arises from possible degenerative changes in the

facet joints with increasing stages of DDD with a potential detrimental effect on TDR outcome. Based on these concerns, different study groups have independently defined various contraindications against TDR. Zeh et al. and Lemaire et al. reported that a reduction in DSH of >50 % was considered a contraindication against TDR [20, 32] whilst other authors defined varying absolute DSH values as inclusion/exclusion criteria [30, 31, 33, 34]. Since their introduction, however, these previously defined contraindications have not been evaluated or confirmed with evidence based data.

The goal of this current analysis was to perform a prospective histological, X-ray and MRI investigation of the index-segment's degree of DDD and to correlate these data with each patient's pre- and postoperative clinical outcome parameters from an ongoing prospective clinical trial with ProDisc II (Synthes, Paoli, USA).

## Materials and methods

### Preoperative diagnosis and patient selection

All patients included in this study are part of an ongoing prospective clinical trial with ProDisc II (Synthes, Paoli, USA). Disc replacement was performed for the treatment of patients with predominant (≥80 %) axial low back pain originating from lumbar degenerative disc disease. Indications and contraindications for this procedure have been thoroughly outlined previously [13, 24, 26, 28–31]. A summary of exclusion criteria from this study is listed in Table 1.

All patients were non-responders to an intensive inpatient and outpatient conservative treatment program conducted over a minimum 6-month period.

**Table 1** Exclusion criteria/contraindications

| |
|---|
| Central or lateral spinal stenosis |
| Predominant radiculopathy |
| Facet joint arthrosis/symptomatic facet joint complaints |
| Spondylolysis/spondylolisthesis |
| Spinal instability (iatrogenic/altered posterior elements, e.g. following laminectomy) |
| Major deformity/curvature deviations (e.g. scoliosis) |
| Metabolic bone disease (e.g. manifest osteoporosis/osteopenia) |
| Previous operation with severe scarring and radiculopathy |
| Compromised vertebral body (irregular endplate shape) |
| Previous/latent infection |
| Metal allergy |
| Spinal tumour |
| Post-traumatic segments |

The preoperative diagnosis was made on the basis of lumbar X-rays taken in ap and lateral view, functional flexion/extension images and preoperative MRI of the lumbar spine.

Preoperatively, all patients underwent fluoroscopically guided spine infiltrations to rule out non-discogenic pain sources. Patients who demonstrated a significant and reproducible pain relief (≥50 %) following infiltrations of the facet or the sacroiliac joints were not considered candidates for TDR.

The role of discography in identifying discogenic pain remains debatable. Previous studies showed a high rate of false positive and negative results equally [35], failure of the patient to distinguish between concordant and non-concordant pain [36], 100 % 'memory pain' in patients with abnormal psychometric testing [36] as well as 0.5 % infection rate [36, 37]. Furthermore, recent studies have shown that the degenerative process within a disc can be initiated with a mere needle puncture, i.e. performed during lumbar discography [27, 38–46]. Therefore, discography was not employed as a diagnostic tool in the present study.

Disc spaces were approached through a mini-open laparotomy and a retroperitoneal approach as described previously [47, 48]. Insertion of the ProDisc implant was performed according to the manufacturers guidelines [49].

## Study documentation

All data were recorded within the framework of an ongoing prospective clinical trial. Patients were examined preoperatively, followed by routine clinical and radiological examinations at 3, 6 and 12 months postoperatively, annually from then onwards. Study documentation was standardized and included the Visual Analogue Scale (VAS), Oswestry Disability Index [50], as well as numerous clinical and radiological parameters. The patient's subjective outcome evaluation was based on a 3-scale grading system, namely 'highly satisfied', 'satisfied' and 'not satisfied'.

At all pre- and postoperative FU examinations, radiological images were obtained which included standard ap, lateral and functional images taken between maximum flexion and extension movements.

## Study cohort definition and inclusion criteria

In order to create a homogenous study population, the following additional inclusion and exclusion criteria were defined:

- Only monosegmental TDRs were included.
- Histological sample of nucleus pulposus (NP) and/or annulus fibrosus (AF) available in all patients, preoperative MRI and X-rays where available.

- Exclusion of patients with combined fusion and disc replacement procedures or TDR for the treatment of adjacent segment instability.
- No history of postoperative revision surgery.
- Exclusion of spondylophyte formations at the index segment

## Radiological evaluation

The hard copies of the patient's preoperative radiographic X-ray films were scanned using a high-resolution scanner and a standard image-capture software program. The images were then transferred to a computer station for further analysis. All measurements were performed with the aid of a custom-made medical image analysis software (Medimage V 5.0, VEPRO AG, Pfungstadt, Germany). With the aid of computer guidance, all images were corrected for radiographic magnification error. Standard implant reference points and implant dimensions (Fig. 1) were used to determine the percentage of magnification error [51]. Well-defined vertebral body geometries were measured on largely magnified postoperative digital X-ray images and were calibrated for length according to precisely defined implant geometries such as the top fin of the upper implant endplate which remains constant at 17.1 mm for various implant sizes (Fig. 1). These distances were used to calibrate distances on preoperative images. All following distance measurements were automatically corrected accordingly.

The anterior and posterior disc space height (DSH) was determined preoperatively from standard lateral standing radiographs. DSH was measured by using the shortest
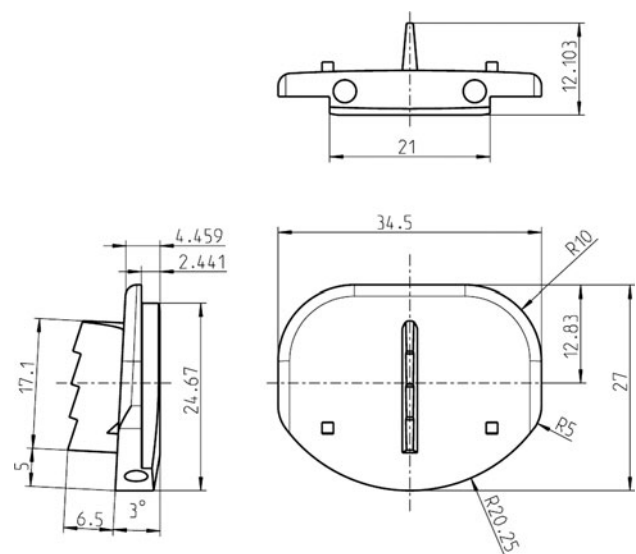


**Fig. 1** Endplate geometries of the Prodisc-L implant, superior endplate size medium (M), with 6° of lordosis. The length of the fin remains constant with 17.1 mm for various ProDisc-L endplate geometries
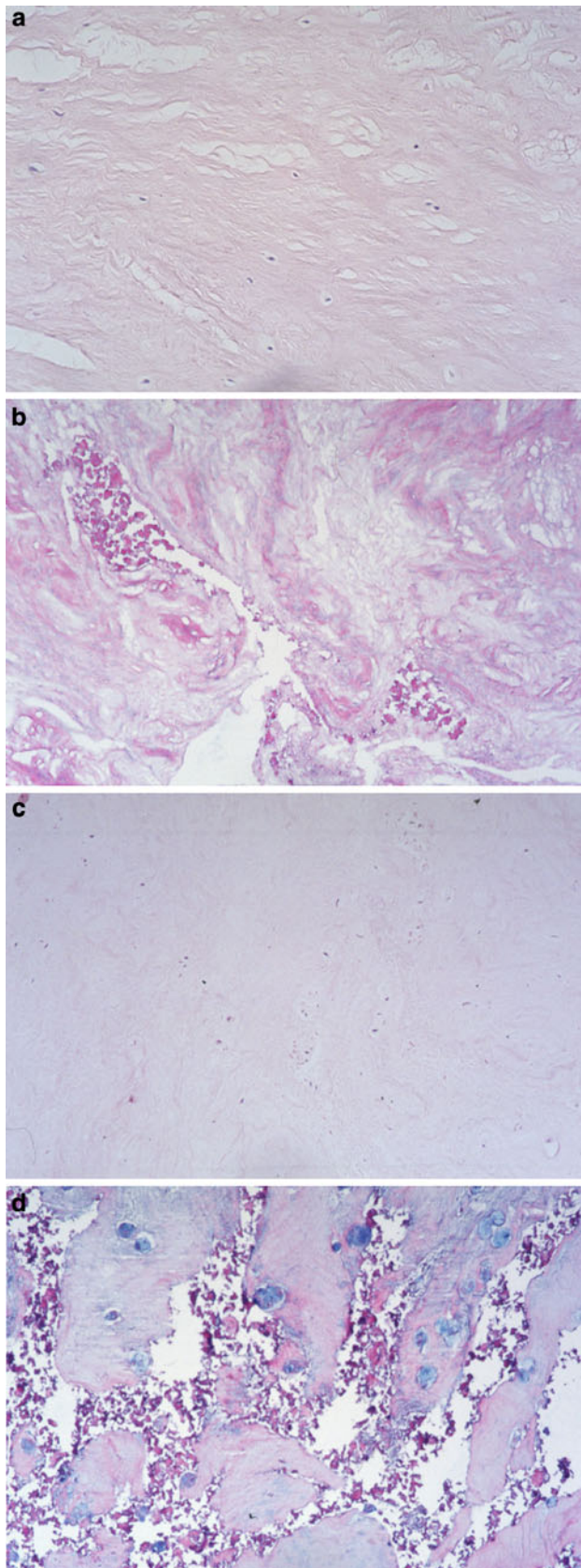
◀ **Fig. 2** Histomorphological features of normal and pathological disc tissue specimens [Haematoxylin and Eosin (H&E), ×300]. **a** Sample from the (inner) annulus fibrosus with fairly parallel arranged collagen fibres and few unremarkable cells (HDS score 0). **b** Annulus fibrosus tissue area with clefting and extensive granular matrix alteration (HDS score 6). **c** Nucleus pulposus section with fibrocartilaginous matrix and very slightly enhanced, single layered nuclear chondrocytes (HDS score 1). **d** Nucleus pulposus section with extensive clefting, granular matrix changes and focal clonal chondrocyte proliferation (HDS score 10)

distance between the anterior and posterior edges of the vertebral endplates as reference points. As described previously, the mean distance between the anterior and posterior DSH was considered to represent the mean disc height [39, 45, 52–55].

The measurements were performed by two independent observers (F.H., E.H.). The observers were blinded to the clinical results. The means of all measurements were calculated and incorporated into the final statistical analysis.

MRI investigation

All MRI images were evaluated by two skeletal radiologists who are specialized in the evaluation of spinal pathologies (US, A.S.). Both radiologists were blinded to the clinical results and were not included in the process of pre- or postoperative decision making.

The condition of the intervertebral disc at the index level was evaluated on all MRI images. The degree of disc degeneration was classified on a 5-scale grading system as described by previously Pfirrmann et al. [56].

Histological evaluation

All tissue samples from this current study were obtained intraoperatively from the index-segment's disc space. The tissue samples were immediately fixed in 4–6 % buffered formaldehyde, pH 7.4, for a duration of approx. 12–16 h. In cases with residual bone material or calcifications, the samples were carefully decalcified in 0.1 M EDTA, pH 7.4. The paraffin-embedded specimens were cut into slices (2–4 μm) and routine stainings were performed (Haematoxylin and Eosin (H&E), Masson-Goldner or Elastica van Gieson's connective tissue stain, Alcian blue-PAS). The histomorphological distinction between annular and nuclear disc tissue was performed by light microscopic criteria, particularly under polarized light, allowing the evaluation of the organization of the collagen network (Fig. 2a–d) [57].

The following histological parameters were taken into account: extent of cellularity, structural changes of granular and/or mucoid alteration and the formation of clefts and

**Table 2** Parameters collected for the histologic assessment of disc degeneration and scoring

| Criteria | Grading |
|---|---|
| Cell density (chondrocyte proliferation): multiple chondrocytes growing in small rounded groups or clusters sharply demarcated by a rim of territorial matrix | 0 = no proliferation |
| | 1 = increased cell density |
| | 2 = connection of two chondrocytes |
| | 3 = small size clones (several chondrocytes grouped together, 3–7 cells) |
| | 4 = moderate size clones (8–15 cells) |
| | 5 = huge clones (>15 cells) |
| Structural alterations (tears and clefts): concentric tears following the collagen fibre bundles orientation in the annulus fibrosus or radiating defects extending from the nucleus pulposus to the outer annulus lamellae parallel or oblique to the end-plate (clefts) | 0 = absent |
| | 1 = rarely present |
| | 2 = present in intermediate amounts between 1 and 3 |
| | 3 = abundantly present |
| | 4 = scar tissue |
| Granular changes: eosinophilic-staining amorphous granules within the fibrocartilage matrix | 0 = absent |
| | 1 = rarely present |
| | 2 = present in intermediate amounts between 1 and 3 |
| | 3 = abundantly present |
| Mucous degeneration: cystic, oval or irregular areas with an intense deposition of acid mucopolysaccharides (i.e. sulfated glycosaminoglycans) staining dark blue with Alc-PAS | 0 = absent |
| | 1 = rarely present |
| | 2 = present in intermediate amounts between 1 and 3, |
| | 3 = abundantly present |
| Histologic Degeneration Score (HDS) | 0–15 points |

tears. All data were obtained as a summary score from 0 to 15 which was recorded for each patient for both annulus and nucleus structures, with 0 delineating none and 15 the most advanced degenerative changes (Table 2).

In a previously conducted histological investigation, one of the senior authors of this study (A.N.) was involved in the development and evaluation of this quantitative classification system for both histological annulus fibrosus (AF) and nucleus pulposus (NP) changes of intervertebral discs (Histological Degeneration Score, HDS) [57]. All tissue samples from this study were quantitatively rated and evaluated accordingly as outlined in Table 2.

The classification system has been thoroughly evaluated with regard to validity, practicability and reliability. The interrater reliability, as demonstrated by means of Kappa statistics, has previously been reported to range between moderate to excellent ($\kappa$ values 0.49–0.98) [57–59].

In the first part of this study, all parameters representative of lumbar DDD were evaluated separately and correlated with each other in a horizontal analysis to establish any possible interaction. In the second part of this study, a longitudinal analysis was performed to establish the influence of preoperative DDD on the patient's symptomatology preoperatively as well as on the postoperative clinical outcome parameters.

### Statistical analysis

All data were statistically evaluated by an external, independent statistician not involved in the process of pre- or postoperative decision making (W.H.). Pearson's and Spearman's correlation coefficients with corresponding statistical tests were computed. One factorial ANOVAs with unpaired and two-sided Student's $t$ tests as post hoc tests were applied to test for significant differences among means. Two-sided and paired Student $t$ tests were used to compare dependent samples. Statistical significance was established with $p < 5\%$. All computations and illustrations were done with Statistica 6.1 (StatSoft, Tulsa, OK, USA) [60].

### Results

Fifty-one patients were included in the final statistical analysis. A description of the preoperative histological and radiological parameters of DDD is delineated in Table 3; the overall pre- and postoperative clinical results are outlined in Table 4.

The average follow-up was 50.5 months (range 6.1–91.9 months), with 92.2 % of all patients ($n = 47/51$)

**Table 3** Overall results of preoperative parameters of disc degeneration

| Histological evaluation (Histological Degeneration Score, HDS) [57, 58] | |
|---|---|
| Nucleus pulposus ($n = 44$) | 11.4 |
| | Range 7–14 |
| | SD ± 2.0 |
| Annulus fibrosus ($n = 45$) | 7.6 |
| | Range 4–12 |
| | SD ± 2.2 |
| X-ray investigation ($n = 35$) | |
| Disc space height$_{anterior}$ | 8.6 mm |
| | Range 5.9–13.1 mm |
| | SD ± 2.1 |
| Disc space height$_{posterior}$ | 5.0 mm |
| | Range 2.3–7.4 mm |
| | SD ± 1.2 |
| Disc space height$_{mean}$ | 6.8 mm |
| | Range 4.1–9.7 mm |
| | SD ± 1.5 |
| MRI investigation ($n = 30$) | |
| Disc degeneration (Pfirrmann classification) [56] | 0 to <3rd degree DDD |
| | $n = 0/30$ (0 %) |
| | 3rd degree DDD |
| | $n = 2/30$ (6.7 %) |
| | 4th degree DDD |
| | $n = 9/30$ (30.0 %) |
| | 4th–5th degree |
| | $n = 3/30$ (10.0 %) |
| | 5th degree DDD |
| | $n = 16/30$ (53.3 %) |

completing a min. 12-month FU. A FU of >2 years was available in $n = 40$ patients (78.4 %), >4 years in $n = 26$ patients (51.0 %), and >6 years in $n = 16$ patients (31.4 %), respectively.

Study population

$n = 32$ patients were male (62.7 %), $n = 19$ were female (37.3 %) with an average age of 42.4 years (range 29.8–62.1 years). All TDR's were performed monosegmentally at the levels L5/S1 ($n = 38$, 74.5 %), L4/5 ($n = 9$, 17.6 %), L3/4 ($n = 2$, 3.9 %), L4/S1 ($n = 1$, 2.0 %) or L5/6 ($n = 1$, 2.0 %), respectively.

TDR was performed for the treatment of DDD with ($n = 21$; 41.2 %) and without Modic changes ($n = 9$; 17.6 %). In $n = 14$ patients (27.5 %), TDR was performed following a previous discectomy. In $n = 7$ patients (13.7 %), TDR was performed for the treatment of DDD

with an accompanying central disc bulge and clinically predominant axial LBP (≥80 %).

Clinical outcome

The clinical results for the entire study cohort are outlined in Table 4. For both parameters VAS and ODI we observed a highly significant postoperative improvement in comparison to preoperative levels ($p < 0.002$). At the last FU examination, 75.6 % of all patients ($n = 34/45$) were 'highly satisfied', 17.8 % ($n = 8/45$) reported a 'satisfactory' outcome, whilst 6.7 % ($n = 3/45$) were 'not satisfied' with their subjective outcome of the operation.

Parameters of disc degeneration

The overall results for all parameters of disc degeneration which were assessed in the current study are outlined in Table 3.

*X-ray evaluation*

*Disc space height* The mean preoperative disc space height (DSH) was 6.8 mm (range 4.1–9.7 mm) as established from the measurement of both independent observers. It was 8.6 mm for the anterior DSH (range 5.9–13.1 mm) and 5.0 mm (range 2.3–7.4 mm) for the posterior DSH, respectively.

*MRI investigation*

The degree of preoperative disc degeneration is outlined in Table 3. The majority of all patients showed advanced stages of disc degeneration on preoperative MRI images, classified as 4th degree ($n = 9/30$; 30.0 %), 4–5th degree ($n = 3/30$; 10.0 %) or 5th degree ($n = 16/30$; 53.3 %). Only $n = 2$ patients (6.7 %) were classified as 3rd degree DDD according to the Pfirrmann classification system [56].

*Histological evaluation*

*Histo Degeneration Score (HDS) of annulus and nucleus tissue samples* HDS scores of either NP or AF tissue material were available in all patients. AF material was available in $n = 45$ patients, NP tissue samples were available from $n = 44$ patients, respectively.

The data showed that the histological degeneration as classified by the HDS was more advanced in the nucleus pulposus material (mean 11.4, range 7–14) in comparison to the degeneration of the annulus fibrosus (mean 7.6, range 4–12; Table 3). The difference between the degenerative changes in NP and AF material was highly significant ($p < 0.001$).

**Table 4** Overall clinical results for the entire study cohort of 51 patients with an average follow-up of 4 years (mean 50.5 months) following total lumbar disc replacement

| | Preoperative data | 3 months | 6 months | 12 months | 24 months | 36 months | 48 months | Overall improvement (difference preoperative vs. last FU) | Overall results at last FU |
|---|---|---|---|---|---|---|---|---|---|
| Number of patients | n = 51 | n = 34 | n = 33 | n = 30 | n = 34 | n = 24 | n = 15 | n = 51 | n = 51 |
| Oswestry Disability Index (ODI) | 39.3 ± 12.7 % | 18.5 ± 15.9 % | 17.3 ± 17.5 % | 20.2 ± 19.0 % | 15.9 ± 17.5 % | 15.0 ± 18.5 % | 11.5 ± 12.6 % | −24.1 ± 16.8 % | 15.2 ± 16.7 % |
| Visual Analogue Scale Scores (VAS) | 6.9 ± 1.6 | 2.6 ± 2.1 | 2.5 ± 2.4 | 2.7 ± 2.8 | 2.5 ± 2.5 | 2.6 ± 2.9 | 1.9 ± 1.8 | −4.1 ± 2.8 | 2.7 ± 2.6 |
| Subjective satisfaction rates | | | | | | | | | |
| Highly satisfied | – | 54.8 % (n = 17/31) | 62.1 % (n = 18/29) | 69.2 % (n = 18/26) | 70.0 % (n = 21/30) | 63.6 % (n = 14/22) | 65.5 % (n = 9/12) | n.a. | 75.6 % (n = 34/45) |
| Satisfied | – | 29.0 % (n = 9/31) | 31.0 % (n = 9/29) | 23.1 % (n = 6/26) | 16.7 % (n = 5/30) | 27.3 % (n = 6/22) | 25.5 % (n = 3/12) | | 17.8 % (n = 8/45) |
| Not satisfied | – | 16.1 % (n = 5/31) | 6.9 % (n = 2/29) | 7.7 % (n = 2/26) | 13.3 % (n = 4/30) | 9.1 % (n = 2/22) | 0 % (n = 0) | | 6.7 % (n = 3/45) |
| Satisfied + highly satisfied | – | 83.9 % (n = 26/31) | 93.1 % (n = 27/29) | 92.3 % (n = 24/26) | 86.7 % (n = 26/30) | 90.1 % (n = 20/22) | 100 % (n = 12/12) | n.a. | 93.3 % (n = 42/45) |

Mean values ± standard deviation (SD) are provided

*ODI* Oswestry Disability Index, *VAS* Visual Analogue Scale, *FU* follow-up
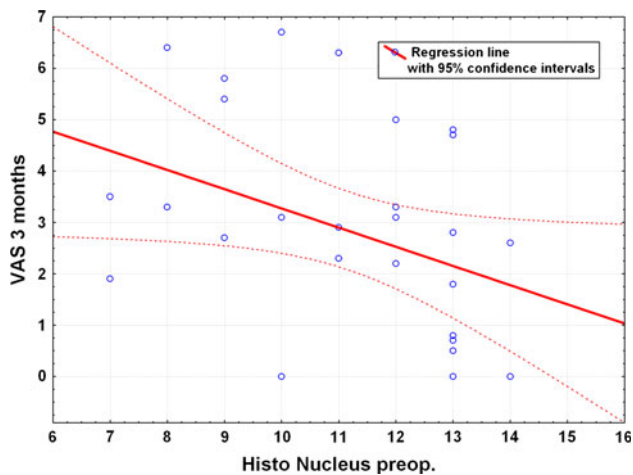
**Fig. 3** Patients with more severe preoperative histological nucleus pulposus degeneration scores demonstrated significantly lower VAS scores during the early postoperative course (3-month FU evaluation; $p = 0.02$, $r = -0.43$). *HDS* histological degeneration score, *AF* annulus fibrosus, *NP* nucleus pulposus

## Correlation between preoperative parameters of disc degeneration

A horizontal analysis between different parameters of lumbar DDD at the index segment revealed a highly significant correlation between the degeneration on MRI images as outlined by the Pfirrmann classification system with the disc space heights that were measured preoperatively ($p < 0.001$). A strong negative correlation was observed between both parameters ($r = -0.74$), indicating an increasing loss of DSH with advanced stages of disc degeneration on MRI images.

The parameters of $DSH_{anterior}$ and $DSH_{posterior}$ were highly significantly correlated with each other ($p < 0.001$, $r = 0.79$). Conversely, it was interesting to observe that this same strong interdependence was not observed between histological NP and AF samples ($p > 0.05$; $r = 0.3$).

## Preoperative DDD versus preoperative clinical symptomatology

The correlation between the MRI grading of DDD and the patient's preoperative symptomatology in terms of VAS or ODI scores was not statistically significant ($p = 0.06$).

Although patients with higher DSH values revealed lower preoperative VAS and ODI scores in comparison to the results from patients with more collapsed segments, statistical analysis similarly did not reveal any significant correlation between both parameters ($p > 0.05$).

Finally, there was no significant correlation between the preoperative histological changes of either nucleus or annulus material on the one hand with preoperative VAS or ODI scores, respectively ($p > 0.05$).

## Influence of preoperative DDD on postoperative outcome

Increasing stages of DDD in terms of lower DSH scores were not associated with inferior clinical results as outlined by postoperative VAS or ODI scores ($p > 0.05$). Furthermore, there was no significant correlation between the patient's satisfaction rates observed at the last FU examination and the degree of preoperative DSH ($p > 0.05$).

Conversely, patients with more severe preoperative histological NP scores demonstrated significantly lower VAS scores during the early postoperative course ($p = 0.02$, $r = -0.43$; Fig. 3).

Whilst patients with preoperative NP scores between 7 and 9 revealed an overall ODI improvement of only 16.8 %, an ODI improvement of 29.2 % was observed for patients with preoperative $HDS_{nucleus}$ scores ranging between 12 and 14 points. However, statistical testing did not reveal any significance ($p > 0.05$).

Although it was observed that increasing stages of DDD on preoperative MRI images were associated with lower VAS levels during the early postoperative course, statistical analysis similarly did not reveal any significance ($p = 0.057$).

## Discussion

### Lumbar degenerative disc disease

Clinically symptomatic low back pain (LBP) is multifactorially influenced. Degenerative changes resulting from lumbar degenerative disc disease (DDD) have been associated with a negative impact on the clinical manifestation of LBP. Hereditary as well as mechanical factors have been discussed in the pathogenesis of DDD, and experimental studies demonstrated that the degenerative cascade can be initiated with a mere needle puncture into the disc [27, 38, 40, 43–46, 61–63]. Once initiated, the degenerative process is progressive, irreversible and closely associated with a mechanical dysfunction of the affected segment. A quantitative assessment of the degree of DDD has been performed via invasive and non-invasive means, including X-ray, MRI as well as histological evaluations.

### Sequelae of lumbar disc degeneration

The first degenerative structural changes in human lumbar intervertebral discs can be observed histologically. As a consequence of diminished blood supply, clefts and tears within the disc become evident from the age of 15 years, the cell density decreases, accompanied by a steady increase in structural defects which extend into the annulus

[38, 57, 58, 64]. The initial stages of the degenerative cascade can first be observed in the endplates, followed by nucleus and finally annulus tissue [38, 57–59].

Secondary stages of DDD are characterized by a loss of fluid content which can be detected on MRI images [39, 53, 56, 65]. Thereafter, the degenerative cascade will result in a loss of intervertebral disc space height (DSH) which from then on can be observed on X-ray images. Depending on the degree of DDD, these degenerative changes have been shown to have a significant influence on the biomechanics and kinematics of a lumbar motion segment [38, 39, 41, 45, 65–71].

The goal of this current study was therefore to analyze the above mentioned parameters of DDD and to establish their influence on motion preserving technologies with total lumbar disc replacement.

## Interdependence between parameters of DDD

In accordance with these above mentioned studies and as a consequence of the degenerative cascade of disc degeneration, our results demonstrated a significant correlation and interdependence between the various parameters of DDD.

The degenerative changes in NP tissue samples were significantly more pronounced in comparison to those of AF material ($p < 0.001$) [38, 57–59].

X-ray evaluation of anterior and posterior DSH revealed a significant and strong correlation between each other ($p < 0.001$, $r = 0.79$). Interestingly, this homogenous progression of disc degeneration was not confirmed in our histological analysis between NP and AF tissue samples ($p > 0.05$). These results indicate that the degenerative cascade in the AF follows NP degenerative changes at delayed time intervals and to a varying extent, and that different underlying pathomechanisms may initiate and sustain the degenerative cascade within the AF and NP material.

## DDD versus preoperative clinical symptomatology

The question as to whether the degree of DSH and disc degeneration corresponds with the patient's symptomatology has been the subject of previous studies [52, 69, 72–75]. None of these studies were able to find a significant correlation between the DSH and the patient's complaints. Our study similarly confirms that the preoperative DSH was not correlated with the patient's pain severity in terms of VAS or ODI scores ($p > 0.05$).

Furthermore, we investigated whether MRI and histological parameters of DDD were correlated with preoperative VAS and ODI scores in order to establish whether morphological degenerative changes have an impact on the patient's pain severity. Since histological and cellular investigations have previously demonstrated neural innervations in NP and AF tissue samples, it was one of the aims of this study to assess whether progressive histological degenerative changes, in particular those of AF tissue samples, are associated with increasing pain levels preoperatively [38, 76]. This hypothesis was not confirmed, and the current data did not provide a significant correlation between the clinical data and the histological results ($p > 0.05$).

In summary, none of the statistical tests performed in this study demonstrated any significant correlation between the morphological degenerative changes and the patient's clinical symptomatology ($p > 0.05$).

## Total lumbar disc replacement

Fusion of lumbar motion segments has been associated with a variety of early and late complications in a considerable number of patients [1–12]. In an attempt to avoid these fusion-related negative side effects, motion preserving technologies such as total lumbar disc replacement (TDR) procedures have been introduced. Their clinical efficacy has been demonstrated by a variety of class I to class IV studies worldwide [13–26].

Despite the widespread clinical application of TDR, the adequate extent of preoperative DDD remains controversially debated, the number of previously published studies is scarce and the limited data available reveal contradictory results. The fact that access to in vivo human histological tissue samples is challenging explains the paucity of currently available studies that have investigated the influence of DDD on the patient's symptomatology in a clinical setting. To date, no study has specifically investigated the influence of different parameters of DDD and their possible role as a predictor of outcome in a prospective clinical trial setting for a cohort of TDR candidates.

## Contraindications against TDR

Moore et al. [27] were able to show delayed but significant changes of the facet joints at the index and adjacent levels during the progressive stages of DDD in a standardized animal model of disc degeneration. Significant preoperative facet joint degeneration remains a commonly agreed upon contraindication against TDR [28–31]. Thus, well-justified concern arises from possible degenerative changes in the facet joints with increasing stages of disc degeneration. Furthermore, advanced stages of disc space collapse may also require more excessive intraoperative release, which similarly bears the potential to impair the postoperative outcome. Freeman et al. [77] therefore concluded that TDR may be limited to the treatment of DDD at the early stages.

Based on these concerns, different study groups have independently defined various contraindications against TDR. Zeh et al. and Lemaire et al. reported that a reduction in DSH of >50 % was considered a contraindication against TDR [20, 32]. Other authors defined an absolute DSH value of 4 mm as inclusion/exclusion criteria [30, 31, 33]. A disc space height of more or less than 4 mm was considered one of the criteria for prime, good, borderline or poor indication for TDR by Bertagnoli et al. [34].

### Influence of preoperative DDD on the outcome of TDR

Since their introduction, these previously defined contra-indications have not been evaluated or confirmed with evidence based data. Yaszai et al. [78] recently reported that optimal pre or postoperative disc height did not translate into an improved clinical outcome in a 2-year FU study. Other studies did not report a significant influence of preoperative DSH on postoperative VAS and ODI scores, and patients with more collapsed DSH even revealed higher patient satisfaction rates [55].

Similarly, the data compiled from this study did not reveal a negative impact of increasing stages of preoperative disc degeneration on postoperative outcome. In particular, there was no preoperative DDD threshold value for any one of the parameters investigated from which an inferior postoperative outcome could have been deduced.

Conversely, patients with more severe preoperative HDS scores of NP samples demonstrated significantly lower VAS scores during the early postoperative course ($p = 0.02$, $r = -0.43$; Fig. 3).

Although not statistically significant, patients with advanced HDS-NP scores also showed signs of greater overall improvement from preoperative ODI levels ($p = 0.056$), whilst patients with advanced stages of disc degeneration (MRI grading) revealed lower VAS-levels during the early postoperative course ($p = 0.057$).

### Clinical implications

In a previous study it has been hypothesized that more rigid and collapsed segments could potentially compensate for increased axial rotational instability, one of TDR's perceived negative side effects [55, 79–81].

Biomechanical studies have furthermore demonstrated that destabilizing effects following PLL resection can be reversed using a higher implant [82, 83]. According to the authors, the increased laxity is taken up by disc space restoration [83], and the prosthesis height seemed to be more crucial than PLL preservation to maintain the primary stability after TDR [82]. Since the vast majority of all patients ($n = 47/51$; 92.2 %) were treated with the same

implant heights (10 mm), stabilizing effects in this particular cohort can furthermore be explained by means of increasing distraction in patients with smaller preoperative disc space heights.

Thus, the clinical data obtained from this study did not confirm a negative effect of increasing stages of DDD on the postoperative outcome following TDR, and, contrary to our primary working hypothesis, revealed some advantageous effects postoperatively. These positive effects can possibly be referred to increasing segmental rigidity resulting from morphological changes with increasing stages of DDD on the one hand as well as restabilizing effects from slightly more distraction in degenerated segments on the other hand.

In accordance with the results published by Moore et al. who demonstrated delayed degenerative changes of the facet joints during progressive stages of DDD, our data reveal a therapeutic window for TDR in a cohort of patients with various stages of DDD as long as preoperative facet joint complaints or degenerative facet arthropathies can be excluded and stringent preoperative decision making criteria are adhered to. This implies that previously published absolute disc space heights which have been defined as threshold values and contraindications against TDR should be reconsidered.

### Conclusion

Histological, X-ray and MRI parameters of disc degeneration demonstrated a significant interdependence amongst each other preoperatively but showed no correlation with the patient's clinical symptomatology.

Increasing stages of disc degeneration did not negatively impact the outcome following TDR in a highly selected patient population. No preoperative DDD threshold value was identified from which an inferior postoperative outcome could have been deduced. Conversely, potential advantageous effects on the postoperative outcome were detected in patients with advanced stages of DDD. The combined effects of increasing morphological structural rigidity of the index segment and restabilizing effects from larger distraction in degenerated segments may compensate for increasing axial rotational instability, one perceived disadvantage of TDR procedures.

Our data reveal a "therapeutic window" for TDR in a cohort of patients with various stages of DDD as long as preoperative facet joint complaints or degenerative facet arthropathies can be excluded and stringent preoperative decision making criteria are adhered to. Previously published absolute DSH values as a contraindication against TDR should be reconsidered.

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