

The Effect of Degeneration on Intervertebral Disc Herniation: A Human *ex vivo* Study with Multiscale Structural Analysis

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Study design: Human cadaveric structural investigation of mechanical load-induced acute disc herniation across degeneration grades.

Objective: To understand the structural effects of loading to failure in discs of different degeneration grades for inferring herniation mechanisms.

Summary of background data: Animal models have been extensively used to study disc herniation in non-degenerate discs, but their relevance to human pathology is unclear and validation in human discs is limited. Studying microstructural failure in human discs is therefore essential for investigating mechanisms of herniation and how these are affected by degeneration.

Methods: Human cadaveric intervertebral discs ($n = 16$) were imaged using MRI, graded for degeneration using the Pfirrmann classification and assigned to either loaded or unloaded groups. Loaded discs were flexed (13°) to physiological limits and loaded to failure ($\sim 90\%$ of disc height). Discs were sectioned and examined macroscopically and microscopically to quantify structural failures (graded ordinally 0–3), facilitating comparison across degeneration grades.

Results: Direct comparison of MRI, macroscopic, and microscopic images provided the most comprehensive depiction of the human disc to date. Loaded discs exhibited significantly increased damage scores across radial tears (ordinal rating: 1.46 vs 0.92, $P = 0.045$), lamellae separations (1.12 vs 0.78, $P = 0.043$), endplate tears (0.85 vs 0.50, $P = 0.033$), and nucleus clefts (1.51 vs 0.82, $P = 0.008$). Increased disc degeneration was associated with increased annulus bulging scores (0.42 vs 1.72, $P < 0.013$), and larger clefts being present in the discs.

Conclusions: The standardised mechanical loading applied produced consistent macrostructural and microstructural failure of the disc. The findings motivate a hypothesis that mechanisms of herniation may vary with degeneration. Mildly degenerate discs may herniate via extrusion of inner disc material, whereas more degenerate discs may herniate through posterior annulus disc bulging. Treatment strategies, including surgical timing and expectations for spontaneous resorption, may therefore be tailored by degeneration grade.

Keywords: intervertebral discs, mechanical loading, disc herniation, degeneration, nucleus pulposus, annulus fibrosus, endplate, Pfirrmann grading, structural injury, microstructural analysis, cadaveric

Introduction

Low back pain represents a major global health issue, affecting approximately 9–9.8% of the population at any time,^[1] and up to 80% of individuals over the course of their lives.^[2] Intervertebral disc degeneration is widely recognised as a major contributing factor,^[3–5] affecting up to 90% of individuals aged 50 years and

older in the general population.^[6] Among degenerated discs, lumbar disc herniation (LDH) represents a clinically significant subset of these degenerative conditions.^[7]

LDH occurs when disc material protrudes beyond the intervertebral space,^[8] potentially compressing adjacent neural structures, and triggering local inflammatory cascades, leading to pain, numbness, or weakness.^[9] Conservative treatment options are effective for most (95%+) patients,^[10,11] but some require surgery. Understanding the structural causes and mechanisms of disc failure is therefore crucial to improve preventative strategies and treatments.

LDH is thought to be driven, at least in part, by elevated intradiscal pressure. Observations in astronauts indicate that microgravity-induced disc swelling, followed by high acceleration on return to Earth, is associated with increased intradiscal pressure and a higher incidence of disc herniation, supporting a potential pressure-related mechanism.^[12] Two resulting mechanical pathways have been described: 1) mid-span failure which results from rupture of the annulus fibrosus (AF), and 2) endplate junction failure (EPJF), in which failure occurs at the endplate (EP) or within the adjacent vertebral body (VB). Mechanistically, mid-span herniation occurs centrally and typically begins with compaction of the posterolateral AF, leading to fissures that allow nucleus pulposus (NP) extrusion through weakened lamellae and eventual rupture of the outer disc

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layers.^[13,14] EPJF in contrast, may occur through failure at the AF-EP interface,^[15,16] or via VB fracture pathways, permitting extrusion of inner disc material.^[17,18] These insights mainly come from animal models,^[19] which do not fully reflect human spinal geometry, degeneration, or variability.

Intervertebral disc degeneration accompanies ageing and is associated with marked biochemical and mechanical alterations.^[20,21] Reduced water content in the nucleus pulposus alters load transmission within the disc, shifting a greater proportion of mechanical loading to the AF and facet joints,^[21] and is often accompanied by osteophyte formation.^[22] Consequently, the hypothesised pressure-driven mechanism of herniation may not be applicable to degenerated discs, which are still capable of herniating.^[23]

To address these gaps, this study aims to investigate acute herniation mechanisms in human intervertebral discs across a range of degeneration levels, using multiscale imaging to capture both macro- and microstructural features, allowing microstructural tissue damage to be linked with whole-disc failure.

Materials and Methods

Specimen preparation

Seven human lumbar spines (L1–S1; 57 ± 15 y) were obtained and stored frozen (ethics number: R24001-1A). Prior to dissection, spines were thawed, and soft tissues removed, leaving only the intervertebral discs and anterior and posterior longitudinal ligaments intact. Disc hydration was maintained by wrapping specimens in phosphate-buffered saline soaked tissue. Between preparation steps specimens were refrozen at -20°C , undergoing a maximum of three freeze-thaw cycles.

MR imaging

Thawed specimens were MRI-scanned (Magnetom Skyra 3T, Siemens) using a T2-weighted sequence (TR 4,540 ms, TE 124 ms, $0.97 \times 0.97 \times 5$ mm resolution), which took approximately 20 minutes allowing discs to be graded for degeneration (Pfirrmann classification) and visualised.

Functional spinal unit (FSU) preparation

Cranial and caudal VBs were cut parallel to the disc mid-transverse plane, verified via fluoroscopy (Fluoroscanner Insight Mini C-arm, Hologic, Marlborough, MA). The facet joints were removed prior to embedding FSUs in polymethyl methacrylate (PMMA) for mounting to the testing rig. FSUs were potted at a 20° angle to the transverse plane to introduce lateral bending during forward-bending (Fig. 1B).

Disc degeneration grading

Disc degeneration was graded using the Pfirrmann scale (1–5) on mid-sagittal MRI slices.^[24] Three independent raters (CF, KR, NN) graded each disc, and discrepancies were resolved via consensus. Only mildly degenerate discs (Pfirrmann grades 2–3) were included, as herniated discs are most prevalent in individuals aged 30–50,^[25,26] whose discs most commonly fall within these grades.^[27] Discs were allocated non-randomly to loaded or unloaded groups to balance donors, Pfirrmann grades, and disc levels (Table 1).

Geometric measurements

Disc height was measured on the mid-sagittal MRI slice as the mean of anterior, middle, and posterior disc heights, defined as

the shortest distance between the superior and inferior EPs at each location. Disc cross-sectional area was manually outlined on reconstructed axial images. All measurements were performed using MicroDicom DICOM Viewer (2024.3) by two independent researchers (TS and CF). Differences between the two raters were expressed as the percentage difference relative to the mean of their measurements, with agreement values of $1.2 \pm 0.9\%$ for disc height and $2.4 \pm 2.6\%$ for cross-sectional area.

Mechanical loading

FSUs were subjected to nine hours of 0.06 MPa (80–120 N) axial preload (Model 8874, Instron, High Wycombe, UK) and then flexed to 13° (approximately the limit of lumbar flexion),^[28] and axially rotated 2° using a motor-driven, gimbal-based rig (Fig. 1A). A compressive ramp load was then applied at 40 mm min^{-1} (corresponding to a strain rate between 0.06 and 0.11 s^{-1}), until failure, which was defined as a displacement equal to 90% of the anterior disc height. Apparent failure stress was calculated by dividing the peak force by the MRI-calculated disc cross-sectional area. Unloaded discs were subjected to axial preload only and did not undergo subsequent loading to failure.

Fixation and sectioning

After mechanical loading, FSUs were fixed in 4% formalin for one week, decalcified in 10% formic acid for two weeks, and cut into four regions (Fig. 1C, D). The four regions (anterior, posterior center, and posterior left and right) were chosen to maintain AF layers approximately perpendicular to the sectioning plane, whilst also accounting for the greater curvature of the posterior disc. Regions were mounted on a cryo-cutter (NX70, Thermo Fisher, USA) and serially sectioned into $30 \mu\text{m}$ slices. Eight evenly spaced macroscopic images taken per region, throughout sectioning to document gross morphology. For microscopic imaging, five evenly spaced sections were imaged per region in brightfield, with a $10\times$ objective (MICA, Leica, Japan). This resulted in 20 micro- and 32 macroscopic images per disc, providing comprehensive coverage.

In some degenerated specimens, the NP was not retained within the section. Despite careful handling, this is attributed to degeneration-associated weakening of NP-EP integration,^[29,30] resulting in reduced NP cohesion, rather than a sectioning artefact.

Microscopic and macroscopic damage examination

Microscopic and macroscopic damage categories were developed using structural damage literature,^[15,31–33] and through preliminary examination of images from three FSUs (one unloaded, two loaded). The resulting categories are illustrated in Fig. 2. For each category, damage was scored per image on a 0–3 scale (0 = none, 3 = extensive, Appendix C, Supplemental Digital Content 3, <http://links.lww.com/SPINEOPEN/A56>). Regional scores were normalised to the maximum possible, and whole-disc scores were calculated as the mean of the four regions; with absent regions (e.g., NP detachment) being scored as N/A and excluded. Aggregated macroscopic and microscopic damage metrics were calculated by averaging category-level mean scores within loaded and unloaded groups.

Damage categories were classified according to whether they were expected to be primarily driven by mechanical loading or by degeneration, based on known degenerative effects^[33,34] and

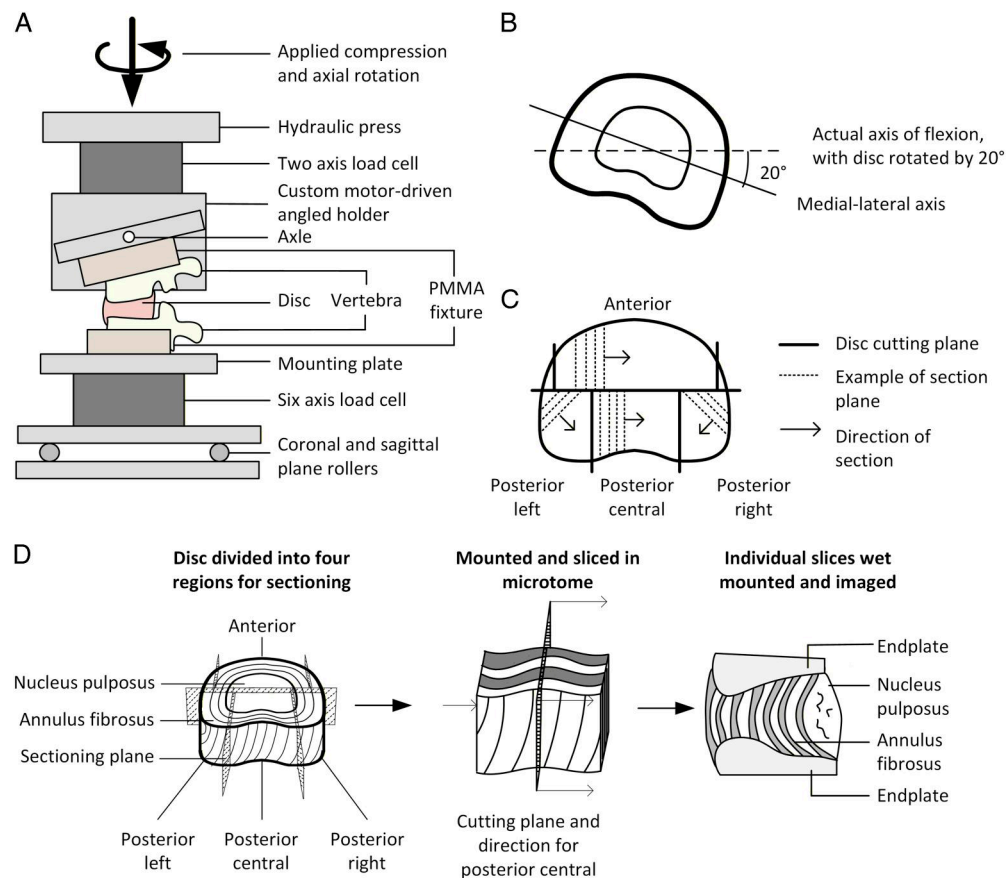


Figure 1. Experimental loading and sectioning geometry. (A) Lateral view of the mechanical testing setup. The disc was flexed at 13°, but due to a 20° axial offset, the applied bending resolved as an anterolateral moment. (B) Axial diagram illustrating the 20° axial offset that established the anterolateral bending axis, combining flexion and lateral bending. (C) Orientation of cutting slices for post-test sectioning: central and anterior regions were sectioned in the sagittal plane, while corner regions were sectioned at 45° to the sagittal plane. (D) Sectioning approach for the functional spinal unit (FSU), showing the cutting planes relative to the disc.

acute loading induced damages.^[15,31,32,35] Features considered degeneration-related were those reflecting chronic structural remodelling that cannot be acutely induced by loading: AF bulging, osteophyte formation, EP sclerosis, intrinsic changes to AF fibers, and calcification.

Statistical analyses

Inter-rater reliability (IRR) for macroscopic and microscopic imaging was assessed using Cohen's weighted kappa (κ).^[36,37] One disc was rated in conference to clarify scoring, then the remaining discs were rated independently by both assessors (TS and CF). κ values were calculated per damage category with quadratic weighting for ordered scales. Categories with $\kappa < 0.60$ were excluded from quantitative analysis (Appendix B, Supplemental Digital Content 2, <http://links.lww.com/SPINEOPEN/A55>).

Differences in the aggregate damage scores were assessed using a Mann-Whitney U test to assess whether mechanical loading had an overall effect on disc damage. Then, damage scores (from 0–3) for individual macro- and microstructural categories (Fig. 2) were analysed using ordinal generalised linear mixed-effects models (GLMM) with a cumulative logit link in SPSS (v30). Two separate models were implemented according

to the previously defined classifications. Loading-related features were analysed with disc type (loaded vs unloaded) as the fixed effect, whereas degeneration-related features were analysed with degeneration grade as the fixed effect. Testing degeneration-related damage for a loading effect (or vice versa) would have unnecessarily inflated the number of multiple comparisons. In both models, donor number and disc level were included as random intercepts to account for repeated measures and donor-level clustering. This conservative approach accounts for non-independence between discs from the same donor, reducing Type I error risk at the cost of reduced statistical power. Due to multiple comparisons, *P* values were adjusted using the Benjamini-Hochberg FDR method, with significance set at $P < 0.05$.

Results

Loaded discs had a peak force of 6.0 ± 1.1 kN, apparent failure stress of 3.9 ± 0.8 MPa, and a mean anterolateral torque of 65 ± 15 Nm (Fig. 3). The IRR analysis showed substantial to near-perfect Cohen's kappa values for all included macroscopic and microscopic damage categories (Appendix B, Supplemental Digital Content 2, <http://links.lww.com/SPINEOPEN/A55>).

Table 1
Details of lumbar discs from seven donors, including disc level, Pfirrmann grade, donor age, disc area, and disc height

Donor number	Disc level	Pfirrmann	Age / years	Area / mm ²	Disc height / mm
Loaded discs					
1	L4-L5	3	67	1750	8.66
2	L3-L4	3	68	1695	8.06
3	L2-L3	2	69	1461	9.03
4	L1-L2	2	58	1457	8.28
4	L4-L5	3	58	1758	10.16
5	L2-L3	3	59	1658	7.90
5	L3-L4	2	59	1406	8.82
6	L1-L2	2	29	1326	7.34
Mean ± standard deviation		2.5 ± 0.5	58 ± 13	1600 ± 230	8.53 ± 0.80
Unloaded discs					
7	L1-L2	2	25	1545	7.98
2	L2-L3	3	68	1746	7.08
2	L4-L5	3	68	1730	8.65
3	L1-L2	2	69	1347	8.18
4	L2-L3	2	58	1709	8.97
4	L3-L4	2	58	1735	11.28
5	L1-L2	3	59	1566	8.04
6	L2-L3	2	29	1447	8.26
Mean ± standard deviation		2.4 ± 0.5	54 ± 16	1560 ± 200	8.56 ± 1.15

Discs are grouped as test or control, with mean ± standard deviation shown for each relevant measurement per group.

Three of 12 macroscopic categories were excluded because they did not meet the $\kappa < 0.60$ threshold, while all 12 microscopic categories were retained. Macroscopic κ values averaged 0.71 (range 0.61–0.85), and microscopic κ values averaged 0.86 (range 0.82–0.95), indicating strong reliability across assessors.

Mechanically induced structural damage

Four disc sections are shown, including unloaded and loaded discs, across degeneration grades in Fig. 4. Sagittal plane disc shape, internal disc macrostructures (NP, AF); and fractures were present across multiscale imaging modalities. Microscopic imaging revealed microstructural damages, including radial tears and inter-lamellar matrix (ILM) disruptions; whereas macroscopic imaging showed NP features in regions where this tissue was not retained in the microscopic sections.

Pfirrmann 3 specimens displayed greater macro- and micro-structural damage than Pfirrmann 2 specimens, irrespective of testing condition (Fig. 4). Pfirrmann 3 discs showed extensive clefts in the AF and NP, radial AF tearing, and endplate sclerosis. Cumulatively, these changes resulted in near-total disconnection between the superior and inferior vertebral endplates, leaving the disc held together only by the outer AF tissue. In Pfirrmann 2 discs, macroscopic assessment showed intact AF and NP regions, however the microscopic imaging still demonstrated radial tears and ILM separations.

Loaded discs exhibited higher aggregated damage scores than unloaded discs, but differences were not significant (macro: 0.96 vs 0.53 $P=0.093$; micro: 0.81 vs 0.65 $P=0.442$, Fig. 5). Additionally, damage scores were lower in the posterior corners than in the anterior and posterior regions (loaded discs, micro-structural damage score: 0.80 and 0.82, in posterior left and right, vs 1.20 and 1.23 in the anterior and posterior regions, respectively).

The macroscopic damages increased by loading were clefts in the NP, (loaded: 1.51 vs unloaded: 0.82, $P=0.008$), and radial

tears (1.36 vs 0.64, $P=0.020$). Other commonly observed macroscopic damages, although not made more severe through mechanical loading, included clefts in the AF (1.14 vs 0.65, $P=0.062$) and reversal of AF orientation (1.17 vs 0.69, $P=0.067$). Microscopically, radial tears and ILM separations were frequently observed and showed a significant increase in damage with loading (radial tears: loaded 1.46 vs unloaded 0.92, $P=0.045$; ILM separations: 1.12 vs 0.78, $P=0.043$). A significant increase was also observed for EP tears (0.85 vs 0.50, $P=0.033$).

Impact of degeneration on mechanically induced damage

Mechanically induced damages appeared more pronounced in Pfirrmann 3 discs compared with Pfirrmann 2 (Fig. 6). Macroscopically, in Pfirrmann 3 discs, the NP was largely absent, leaving the central region fragmented with numerous clefts, whereas Pfirrmann 2 discs retained more NP tissue, and as a result had smaller clefts within the NP (Pfirrmann 3 score: 1.52 vs Pfirrmann 2 score: 0.89). Microscopically, radial tears and ILM disruptions differed with degeneration in morphology, and severity (Fig. 6). Pfirrmann 3 radial tears were wider, more irregular, and showed minimal central tissue displacement, while radial tears in Pfirrmann 2 discs were narrower, more linear, and showed outward tissue displacement (1.90 vs 0.64). ILM disruptions were also degeneration dependent: in Pfirrmann 3, failures often spanned the length of the AF, whereas in Pfirrmann 2, disruptions were localised, with partial interconnection of annular layers (1.35 vs 0.65).

Disc damage features associated with degeneration

Macro- and microstructural damage features hypothesised to result from disc degeneration were compared between Pfirrmann grade 2 and 3 discs (Fig. 7). Bulging of the AF increased significantly from Pfirrmann 2 to Pfirrmann 3 (0.42 vs 1.72, $P<0.013$). The remaining damage features showed no

Macroscopic damage features				Microscopic damage features			
Clefts in NP Donor 2 L3-L4 PC		Bulging of AF Donor 2 L2-L3 AC		Nuclear extrusion Donor 4 L2-L3 AC		EP tear / fracture Donor 5 L1-L2 PC	
Radial tears Donor 2 L2-L3 PL		Herniation of disc (extrusion) Donor 2 L4-L5 PL		Radial tears Donor 5 L3-L4 PL		Continuous separation Donor 4 L4-L5 PL	
Clefts in AF Donor L4-L5 PC		Herniation of disc (protrusion) Donor 1 L4-L5 PR		ILM damage (lamellae separations) Donor 5 L1-L2 AC		Loss of fibre differentiation Donor 3 L2-L3 PR	
Reversal of AF fibers Donor 5 L2-L3 PC		Sclerosis of EP Donor 2 L3-L4 PC		Disorganisation of AF Donor 2 L2-L3 PC		Amorphous tissue formations in NP Donor 3 L2-L3 PR	
				AF-EP rupture Donor 2 L2-L3 PC		Perforation of AF Donor 3 L2-L3 AC	
				NP-EP rupture Donor 3 L1-L2 PC		Calcification of disc Donor 1 L4-L5 PC	

Figure 2. Representative macroscopic and microscopic images for the respective damage features. Each image is labelled with the donor number, disc level, and the specific region of the disc shown. PC = posterior-central; AC = anterior-central; PL = posterior-lateral; PR = posterior-right. AF = annulus fibrosus; NP = nucleus pulposus; EP = endplate; ILM = Inter-lamellar matrix.

significant differences between degeneration grades and had broadly similar scores between loaded and unloaded discs.

Discussion

This is the first study to comprehensively assess the structure of the whole human intervertebral disc across MR, macroscopic, and microscopic images. Human discs sustain both macroscopic and microscopic damage under flexed, compressive loading, with failure patterns varying by degeneration grade. Macroscopic failures included clefts in the NP (Fig. 5); radial tears (Fig. 5); and bulging of the AF (Fig. 7). Microscopic examination revealed ILM tears, radial tears of the AF, and EP tears (Fig. 4, Fig. 5). More degenerate discs

exhibited more extensive NP clefting (Fig. 6) and bulging of the AF, often extending beyond normal disc boundaries (Fig. 4, Fig. 7).

Together, these findings suggest that Pfirrmann 2 and 3 discs may be associated with distinct patterns of structural failure that could reflect different mechanisms of disc herniation. In less degenerate discs, internal hydrostatic pressure helps distribute load evenly,^[21] whereas in more degenerate discs, altered load distribution could lead to a hypertrophied peripheral AF tissue, a structural change that could contribute to lumbar disc herniation symptoms.

Macrostructural damage in disc herniation

Loaded discs had significantly more NP clefts, and radial tears in the AF (Fig. 5). This highlights that NP and AF structures are primary

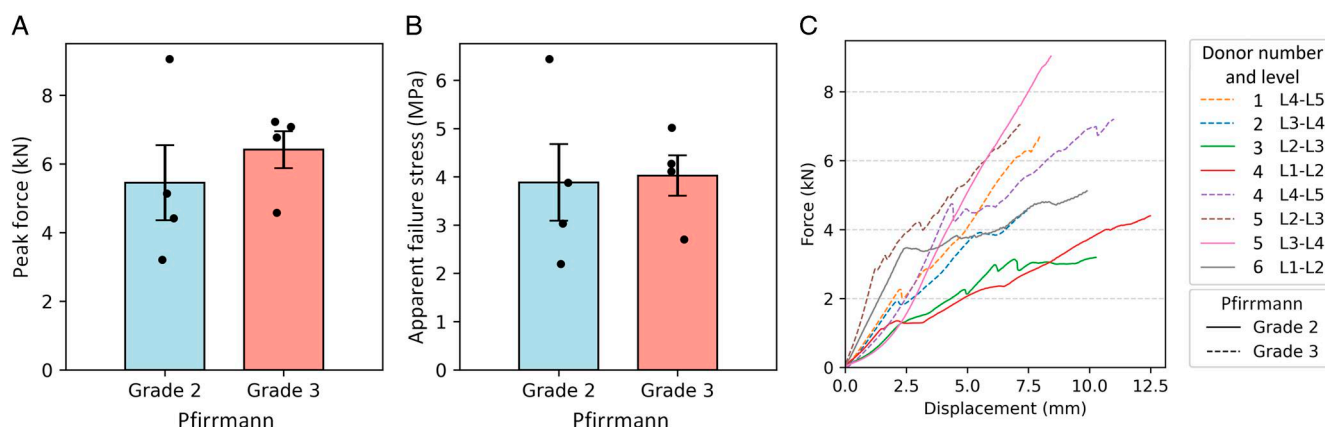


Figure 3. (A) Bar charts with individual data points showing peak force, and (B) Apparent failure stress, for Pfirrmann 2 and 3 discs during ultimate complex loading. (C) Force-displacement plots for all loaded specimens.

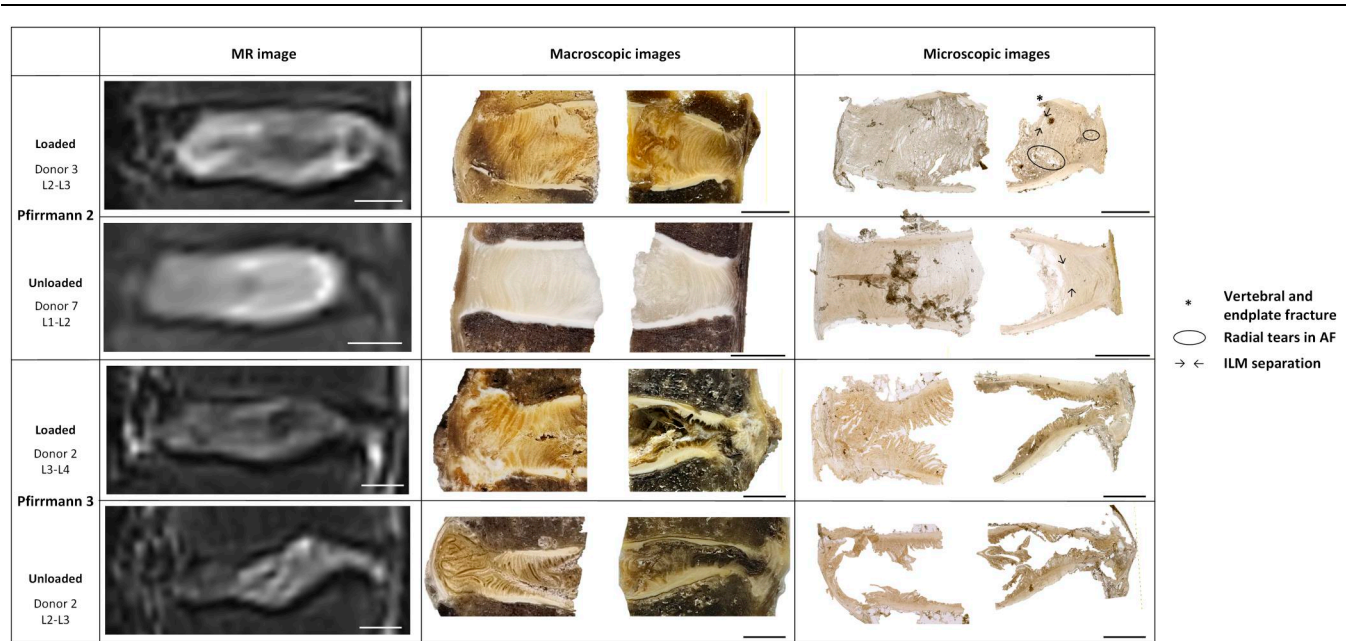


Figure 4. MR, macroscopic, and microscopic images of Pfirrmann 2 and 3 discs, showing examples from both loaded and unloaded groups. Macroscopic and microscopic images were stitched together using images from the central anterior and posterior regions. Damages are outlined in Pfirrmann 2 discs. In Pfirrmann 3 discs, extensive structural damage is present and is not highlighted. All scale bars represent 5 mm.

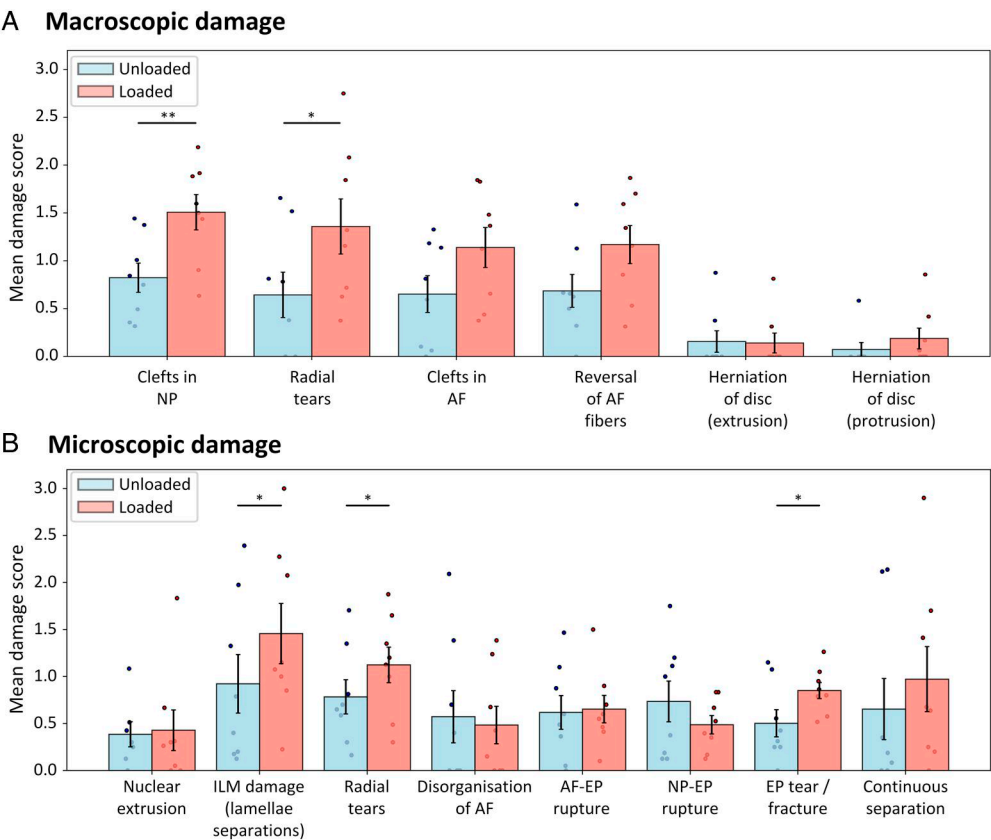


Figure 5. Quantitative assessment of (A) macroscopic and (B) microscopic tissue damages; by loaded (pink) or unloaded (blue) discs. Note, the maximum possible damage score, based on the grading system utilised, was three. Error bars indicate standard error across the discs in each category. * Represents $P < 0.05$, ** represents $P < 0.01$.

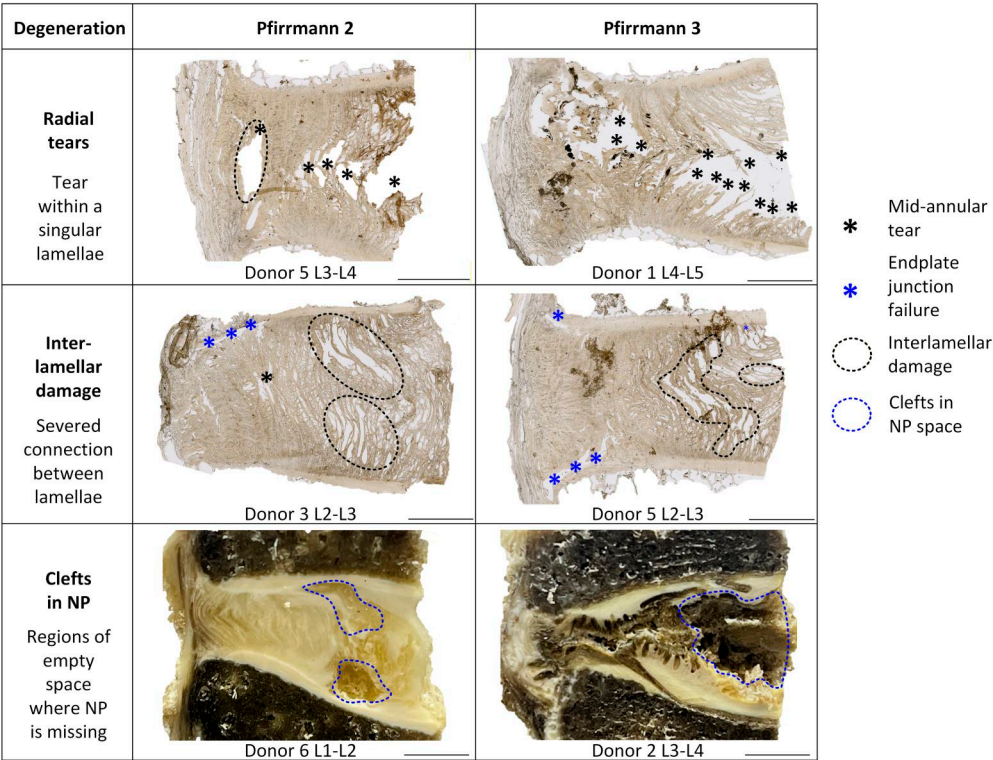


Figure 6. Representative images of mechanically loaded Pfirrmann 2 and 3 FSUs, illustrating how severity changes with degeneration. Four anterior regions (microscopic) and two posterior-central regions (macroscopic) are shown, highlighting radial tears, ILM damage, and clefts in the NP caused by mechanical loading. Scale bars are 5 mm.

sites of mechanical failure under flexion-compression. Other damage types were also observed but did not differ significantly between loaded and unloaded discs, suggesting that loading may have amplified pre-existing structural failures rather than creating entirely new damage, consistent with prior MRI and macroscopic studies showing AF fiber reversal and clefts in unloaded discs.^[38,39]

Microstructural damage in disc herniation

Radial tears, ILM damage and EP tears were observed more frequently in loaded discs (Fig. 6). Radial tears,^[15,16,31] and ILM damage^[40] have previously been observed in animal studies and are therefore likely to be key factors in the gradual buildup of herniation damage. This study’s human disc results indicate that

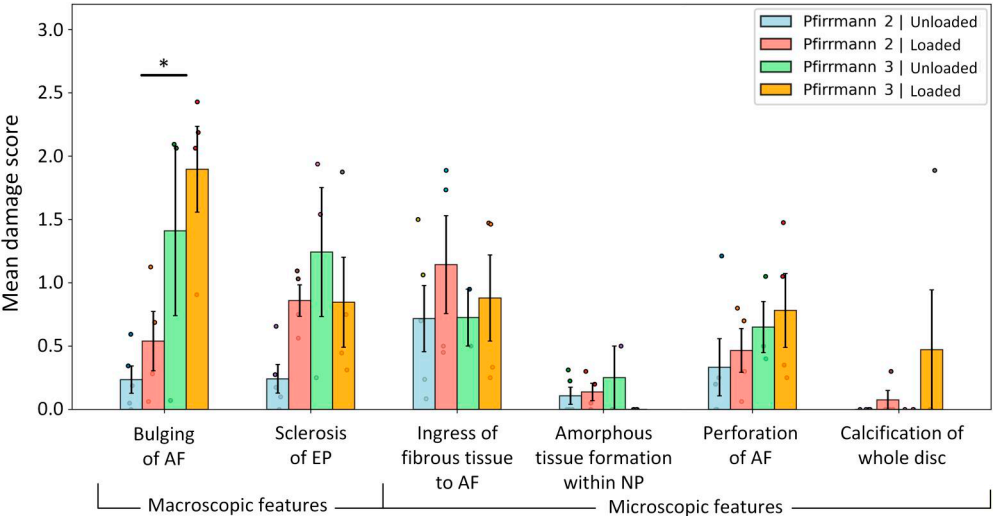


Figure 7. Bar charts showing disc damage features hypothesised to be predominantly affected by the degeneration of the disc. The bars are grouped by both degeneration grade and loading condition (loaded vs unloaded). Note, the maximum possible damage score, based on the grading system utilised, was three. Statistical comparisons were performed only between degeneration grades, with unloaded and loaded discs analysed together (n=8 per group). * denotes $P < 0.05$.

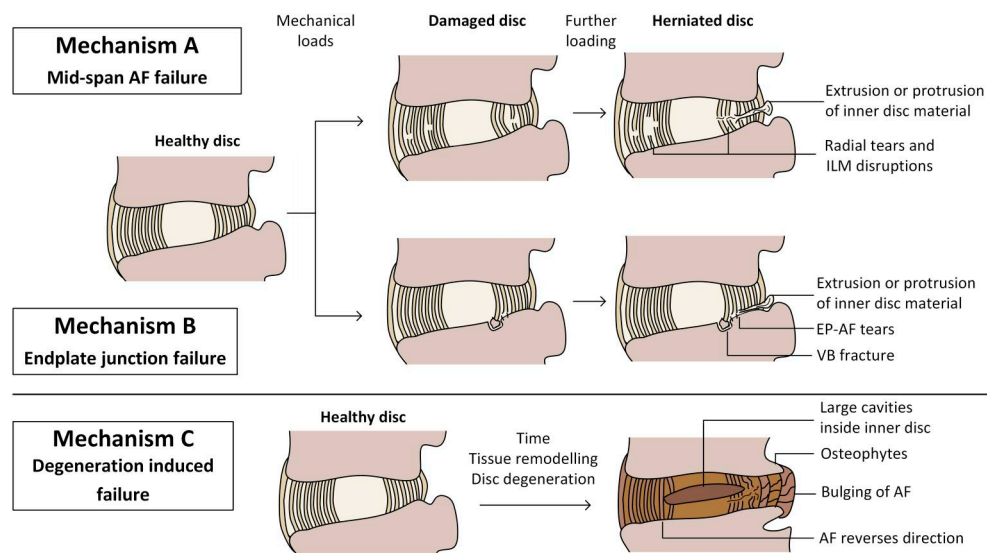


Figure 8. Herniation mechanisms in lumbar intervertebral discs. Mechanism (A) AF mid-span failure, from radial tearing and lamellar delamination. Mechanism (B) EPJF characterised by failure at the endplate or within the adjacent VB. Mechanism (A) and (B) were proposed for non-degenerate discs, where pressurisation of the NP can cause elevated stresses and structural failure. Mechanism (C) is proposed as a degeneration-induced mechanism, where osteophyte formation alongside bulging of peripheral fibrocartilaginous tissue, results in a herniated disc.

AF lamellae remain a structure prone to failure across species and under sufficient load.

Degeneration of the human disc

This study presents the first Pfirrmann grading of excised human intervertebral discs combined with comprehensive whole-disc macrostructural and microstructural analysis. The most prominent morphological changes observed with increasing degeneration were: (1) increased bulging of the outer AF; (2) increased perforation of the AF tissue and (3) the emergence of large internal cavities and associated loss of NP tissue (Fig. 6, Fig. 7, Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SPINEOPEN/A54>). Together, these changes are consistent with a damage-cascade model, arising from maladaptive load distribution and biochemical degenerative processes.^[20]

Degenerative changes reduce proteoglycan content, water retention, and nutrient transport within the disc,^[41] reducing internal pressurisation, resulting in AF fibers buckling inward.^[14,38] These structural changes progressively shift load-bearing to the AF and facet joints.^[21] Consistent with this, Pfirrmann 3 discs here showed outer AF bulging (Fig. 7, Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SPINEOPEN/A54>), potentially reflecting a Davis's Law response, where chronic in vivo mechanical loading stimulated compensatory extracellular matrix deposition.^[42] Meanwhile, the presence of vertebral osteophytes may represent a Wolff's Law adaptation of bone to altered mechanical stress.^[43]

Pfirrmann scale for classifying degeneration

Only Pfirrmann 2 and 3 discs were studied, yet they exhibited variability in NP loss, fibrosity, and AF bulging (Fig. 4, and Appendix A, Supplemental Digital Content 1, <http://links.lww.com/SPINEOPEN/A54>). Although the Pfirrmann scale defines five grades,^[33] the structural variation observed within a single grade, compounded by age differences (25–69 y), may be too

broad for reliable clinical stratification. MRI signal intensity reflects tissue hydration,^[44] so water-filled cavities may appear healthy, obscuring degeneration.

Mechanisms of herniation in the human disc

Herniation occurs in both young and older discs,^[45] and the failure mechanisms may differ between non-degenerate and degenerate discs. Many ex vivo herniation models rely on non-degenerate animal discs, biasing current mechanistic understanding towards the healthy spine.^[19] Based on our findings, we propose a hypothesis for distinct, degeneration-dependent mechanical pathways of herniation in human discs (Fig. 8).

In non-degenerate discs, acute herniation is likely pressure-driven: a hydrated, NP generates high internal pressure that induces stress in the AF.^[12] We observed radial AF tears, ILM disruption, and EP tears (Fig. 5), each providing a structural route for inner disc material to move outwards. These failures align with mid-span AF and EPJF herniation mechanisms.^[15,31,46,47] Our findings provide supporting structural evidence (radial tearing, EP tears, Fig. 6) consistent with these mechanisms in human discs under flexion-compression loading (Mechanisms A and B in Fig. 8).

In degenerate discs, internal pressure is diminished and loads are redistributed towards the outer AF and facet joints.^[21,48] Here, we hypothesise that herniation may not be NP-driven, but may instead reflect peripheral AF bulging driven by this load redistribution (Fig. 5, AF bulging), which is distinct from bulging induced by small radial tears and internal disc pressure.^[49] Our imaging of degenerate discs suggests that the hypertrophied AF and osteophytes extend beyond the native disc boundary, even in the absence of NP extrusion or VB fracture.^[33,50,51] In this hypothesised mechanism, encroachment may represent an alternative structural pathway in degenerate discs, though this requires in vivo validation (Mechanism C in Fig. 8). Interestingly, prior studies report that herniated material

comprises predominantly AF in up to 78% of cases,^[52,53] which has not previously been mechanistically explained, and contrasts with the prevailing view that NP extrusion is the most common mode of herniation. Our observation of bulging AF in degenerate discs may offer a potential structural explanation for this phenomenon, though this warrants further investigation.

Limitations

Disc failures were induced by ramping to an ultimate load, representing an acute herniation. While relevant to adolescent herniation,^[54] this does not capture the gradual, repetitive loading in typical herniation, limiting generalisability of the findings.^[13] Such a load also fails to replicate the biological changes occurring within the disc during the period prior to herniation, including inflammation, proteoglycan degradation, and neovascularisation of the disc, which likely influence structural failure behaviour.^[55] The load was applied at a fixed angle near the physiological limit of human bending,^[28] ensuring standardisation, but not replicating the range of in vivo motions.^[56] Nevertheless, the standardised loading protocol enabled controlled comparisons, highlighting degeneration-dependent differences in disc failure patterns, without altering the degenerative changes that had occurred in vivo.

Human cadaveric samples vary in baseline disc condition and damage susceptibility due to age, genetics, and lifestyle,^[57,58] and imaging techniques have inherent constraints, including MRI resolution, microscopic tissue loss, and undetected microscopic failures in macroscopic imaging. The combined use of these techniques mitigates the limitation.

Specimens underwent three freeze-thaw cycles prior to testing, which may have influenced disc biomechanical properties (e.g., a potential ~30% increase in range of motion)^[59] and could have affected tissue microstructure. Nevertheless, previous work on animal cadaveric discs indicates that microstructural integrity remains robust to freeze-thaw cycles supporting the validity of the results.^[35]

Low sample sizes limited statistical power and prevented detailed analysis of interactions between degeneration and mechanical loading in the ordinal GLMMs used to analyse macro- and microstructural damage scores. To increase group sizes for statistical purposes ($n = 8$ per group), specimens were stratified by degeneration and loading, which does not account for the possibility that degeneration may amplify loading effects, or vice versa. However, because the proposed herniation mechanism reflects in vivo tissue remodelling, this stratification is unlikely to affect interpretation of degeneration-dependent failure patterns. The proposed herniation mechanism remains a hypothesis, and further studies including larger sample sizes, and a wider range of degeneration grades are needed to explore whether similar pathways occur across a broader spectrum of degeneration.

Clinical implications

If validated in prospective studies, structural differences between degenerate and non-degenerate discs may inform surgical decisions. In less degenerate discs, herniation may be driven by NP extrusion, which may partially resorb. In contrast, in older, more degenerate discs (where herniation may be associated with peripheral tissue bulging and osteophyte formation, although this has not been demonstrated in vivo) spontaneous resorption is less likely (Fig. 8).^[60,61] Specifically, patients with more

degenerate discs might benefit from a shorter period of conservative therapy before surgery, minimizing prolonged pain while still allowing time for potential resorption in discs likely to recover spontaneously. Further research is needed to determine whether tailoring surgical timing to the degree of disc degeneration could improve functional outcomes, expanding upon the current consensus that earlier surgical intervention improves functional recovery.^[62]

Conclusions

Our findings suggest that herniation mechanisms differ with degeneration: mildly degenerate discs (Pfirrmann 2) tend to fail through extrusion of inner disc material, whereas more degenerate discs (Pfirrmann 3+) may herniate through annular bulging, intruding on the spinal canal. These degeneration-dependent failure patterns have direct clinical implications: recognising the structural differences can inform management decisions, guiding the appropriateness of a conservative approach or limited discectomy in less degenerate discs, and more extensive intervention in severely degenerate discs.

Ethical approval

Research Ethics Committee: This study was ethically approved through the Imperial College Healthcare Tissue and Biobank (ICHTB) under Wales REC3 (22/ WA/0214), with human disc samples issued for project R24001-1A from sub-collection BIO_SM_14_034. ICHTB is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. Tissue was supplied by ScienceCare (Phoenix, USA) in accordance with national and institutional consent requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Conflicts of interest

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KEY POINTS

- Multiscale imaging (MR, macroscopic, microscopic) enabled detailed visualisation of human disc structure and damage not previously captured in mildly degenerate discs.
- Standardised ultimate flexion-compression loading reproducibly generated structural failures in human discs, including radial tears, endplate lesions, and nucleus pulposus clefts.
- A new mechanism for disc herniation in degenerate discs is proposed due to the bulging of degenerate outer annulus fibrosus tissue.
- Clinical and surgical herniation management should be tailored based on disc degeneration grade.

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