Spine Publish Ahead of Print
DOI: 10.1097/BRS.0000000000000389

Mechanical Influences in Progressive Intervertebral Disc Degeneration.

Manos Stefanakis PhD*, Jin Luo PhD**, Phillip Pollintine PhD

Patricia Dolan PhD, Michael A. Adams PhD

Centre for Comparative and Clinical Anatomy,

University of Bristol, Bristol, U.K.

* School of Science and Engineering, University of Nicosia, Cyprus

** University of Roehampton, London, U.K.

Corresponding author:

Professor Michael A. Adams

Centre for Comparative and Clinical Anatomy,

University of Bristol,

Southwell Street,

Bristol BS2 8EJ,

U.K.

Tel: +44 (0) 117 9288363;

E-mail: M.A.Adams@bris.ac.uk

Acknowledgements: We thank Adam Truss and Charles Finnan for help with data analysis. Study approved by Frenchay NHS Research Ethics Committee, Bristol, U.K.

Running title: Mechanical progression of disc degeneration

The Manuscript submitted does not contain information about medical device(s)/drug(s).

BackCare, Action Medical Research, and the Greek Institute of Scholarships funds were received to support this work.

Relevant financial activities outside the submitted work: grants/grants pending, payment for lectures, royalties and travel/accommodations/meeting expenses.

Abstract

Study Design: Mechanical study on cadaver motion segments.

Objective: To determine if high *gradients* of compressive stress within the intervertebral disc are associated with progressive disc degeneration.

Summary of Background Data: Mechanical loading can initiate disc degeneration, but may be unimportant in disease progression because degenerative changes cause the disc to be increasingly "stress-shielded" by the neural arch. However, the most typical feature of advanced disc degeneration (delamination and collapse of the annulus) may not depend on absolute values of compressive stress, but on *gradients* of compressive stress which act to shear annulus lamellae.

Methods: 191 motion segments (T8-9 to L5-S1) were dissected from 42 cadavers aged 19-92 yrs. Each was subjected to approximately 1 kN compression, while intradiscal stresses were measured by pulling a pressure transducer along the disc's mid-sagittal diameter. "Stress gradients" in the annulus were quantified as the average rate of increase in compressive stress (MPa/mm) between the nucleus and the region of maximum stress in the anterior or posterior annulus. Measurements were repeated before and after creep loading, and in simulated flexed and erect postures. Disc degeneration was assessed macroscopically on a scale of 1 to 4.

Results: As grade of disc degeneration increased from 2 to 4, nucleus pressure decreased by an average 68%, and maximum compressive stress in the annulus decreased by 48-64%, depending on location and posture. In contrast, stress *gradients* in the annulus increased by an average 75% in the anterior annulus (in flexed posture), and by 108% in the posterior annulus (in erect posture). Spearman rank correlation showed that these increases were statistically significant.

Conclusion: Despite stress-shielding by the neural arch, *gradients* of compressive stress increase with increasing grade of disc degeneration. Stress gradients act to shear adjacent lamellae, and can explain progressive annulus delamination and collapse.

Key words: disc degeneration; delamination; progression; cadaveric; motion segments; stress gradient; shear; nucleus pressure; annulus compressive stress; stress-shielding.

Level of Evidence: N/A

Precis [48 words]

With increasing grade of disc degeneration, stress-shielding of the disc by the neural arch reduces nucleus pressure and peak compressive stresses on the annulus. Nevertheless, *gradients* of compressive stress in the annulus increase substantially. Stress gradients act to shear adjacent lamellae, and can explain progressive annulus delamination and collapse.

Key Points

1. Cadaver experiments showed that, with increasing grade of disc degeneration, nucleus pressure and maximum stress in the annulus both decrease markedly. However, stress *gradients* in the annulus increase.
2. Stress gradients are influenced by posture: they are greatest in the anterior annulus in flexion, and greatest in the posterior annulus in erect (lordotic) postures.

3. Gradients of compressive stress act to shear adjacent lamellae of the annulus, and could explain progressive annulus delamination and collapse.

Introduction

Excessive mechanical loading can play a major role in the *initiation* of intervertebral disc degeneration. Longitudinal studies have shown how premature degeneration can be precipitated by injury to the disc or vertebral endplate,[1,2] and animal experiments confirm that physical disruption of the annulus or endplate leads inexorably to disc degeneration.[3-5] Underlying mechanisms have been demonstrated by laboratory experiments which show how physical damage decompresses the disc nucleus,[6,7] alters disc cell metabolism,[8-10] and increases annulus susceptibility to nerve and blood vessel ingrowth.[11]

The role of mechanical loading in the *progression* of disc degeneration remains unclear. Loss of proteoglycans and water from a degenerating disc[12] decompresses the nucleus[13] and increases load-bearing by the annulus.[14] Consequently, the annulus bulges outwards,[15] and inwards,[16,17] causing the disc to lose height, typically by 3-4% per year.[18] Neural arch load-bearing increases, especially in erect postures, thereby reducing the compressive load on the annulus.[19,20] Such 'stress-shielding' by the neural arch, combined with age-related reductions in muscle forces,[21] might be expected to limit disc height loss, and prevent the severe disc narrowing which is strongly associated with pain.[22] Perhaps genetic susceptibility[23] and matrix-degrading enzymes[24] drive later stages of disc degeneration, rather than mechanical loading? This question is important, because it raises the possibility that moderate disc degeneration might be halted, or reversed, by inhibiting matrix-degrading enzymes.

However, the influence of mechanical loading in progressive disc collapse may be greater than just suggested. Overall compressive loading of the disc will decrease because of stress-shielding,[19] but

other forms of loading may not. Degenerated discs typically show high *concentrations* of compressive stress[25,26] which create high shear stresses in the annulus. In homogeneous elastic solids, shear stresses are proportional to the rate of change of compressive stress with distance, and even in a complex material such as the annulus, the stress gradient (shown by the heavy solid line in Figure 2) will be directly related to the shear stresses which cause adjacent lamellae to slide past each other.[27] Interlamellar movements create the circumferential tears which increase in degenerated discs.[28-30] Furthermore, delamination of the annulus prevents individual lamellae from supporting each other, and is a precursor to the gross structural defects that characterize severe disc degeneration.[16,17,31-33]

For mechanical loading to cause annulus delamination, it must be severe enough to break the discrete radial 'translamellar bridges' [34,35] which bind lamellae together. And if shear stresses are to be considered a driving force behind *progressive* disc degeneration, their magnitude must increase as degeneration progresses, even though overall compressive loading of the disc falls because of stress-shielding by the neural arch.

The present study aims to quantify annulus stress gradients in loaded cadaveric spines, and to determine how their location and magnitude vary with disc degeneration. We hypothesise that stress gradients, unlike maximum compressive stresses or nucleus pressure, *increase* with increasing grade of disc degeneration.

Materials and Methods

Cadaveric material Spines from 42 donors, aged 19-96 yrs, with no history of trauma or prolonged bed rest, were dissected into "motion segments" comprising 2-3 vertebrae with intervening discs and ligaments. These were stored in sealed plastic bags at -20^{0}C for up to six months until required for testing [36]. 191 specimens were obtained, ranging from T7-8 to L5-S1 (**Table 1)**.

Mechanical testing Methods have been described and justified previously.[36] Each specimen was mounted in cups of dental plaster, and loaded on a hydraulic materials testing machine (Dartec-Zwick-Roell Ltd, U.K). Variable-height low-friction rollers attached to the upper cup enabled specimens to be compressed in flexed or extended (i.e. lordotic or erect standing) postures (**Figure 1)**. Initially, each specimen was compressed for 15 minutes at 300 N to counteract post-mortem super-hydration.[37]

'Stress profilometry' A miniature pressure transducer, side-mounted in a 1.3 mm-diameter needle, was pulled along the antero-posterior diameter of the disc while it was subjected to a mean compressive force of 1.1 kN for 20s. (The compressive force was as low as 0.75 kN, or as high as 2 kN, in a few exceptionally small or large specimens.) A displacement transducer attached to the needle indicated transducer position within the disc, enabling 'stress profiles' to be plotted (**Figure 2)**. Rotating the pressure transducer needle about its long axis enabled the distribution of vertical stress (parallel to the spine's long axis) and horizontal stress to be measured in successive tests. Profiles were repeated in a simulated erect standing or lordotic posture ($0\text{-}4^0$ of extension, depending on spinal level and mobility, mean 1.1^0) and a moderately flexed posture ($2\text{-}8^0$ of flexion, mean 5.0^0).

After the initial measurements, specimens were 'creep' loaded at 1kN for two hours in order to simulate diurnal variation in disc hydration and mechanics.[37] Stress profiles were repeated immediately. After testing, specimens were dissected, and intervertebral disc degeneration graded on a scale of 1-4.[25,38]

Analysis of 'stress profiles' All intradiscal stress measurements were normalised (scaled) for an applied compressive force of 1kN. Profiles of horizontal and vertical compressive stress were aligned on the same axes, and the functional 'nucleus' defined as that region where they differed from each other by less than 10%, and varied <10% with location (Figure 2). Maximum stresses in the anterior and posterior annulus, and their distance from the disc periphery, were recorded, as were the stress gradients in the anterior and posterior annulus. The straight line marking the stress gradient joined

the edge of the nucleus with the point of maximum stress in the annulus, as defined above, and so was an averaged rather than instantaneous measure of rate of change of stress with distance. All subsequent analyses refer to stress gradients measured from the vertical (axial) stress profile, which is simpler to interpret. Stress profiles from 10 discs were analysed on two separate days by two examiners, in order to assess inter- and intra-examiner reliability.

Statistical analysis Each motion segment was considered to be independent because 'cadaver number' had a negligible effect on the outcomes over and above the major influences of age, gender, and disc degeneration. Spinal level was scored from 1 (T7-T8) to 11 (L5-S1). Several outcome measures, including stress gradients, were marginally non-Normally distributed, so non-parametric 'Spearman rank' correlation was used to calculate correlation coefficients between these parameters. Accordingly, information concerning both median and mean values are included in the bar charts. Mean and median values were compared using Analysis of Variance (ANOVA) and Kruskal-Wallis, respectively. Analyses were performed using SPSS (v.19). Significance was accepted at the 5% level.

Results

Reproducibility of stress profiles Intraclass correlation coefficients ranged from 0.64 to 0.99 for both between- and within-examiner comparisons.

Nucleus pressure Nucleus pressure was similar for non-degenerated grade 1 and 2 discs, but fell by 68% between grades 2 and 4 ($P<0.001$, **Figure 3)**. 'Creep' loading for 2 hrs also decreased nucleus pressure, by 20% and 13% in flexed and erect (lordotic) postures respectively, with the decrease being proportionally larger in more degenerated discs (Figure 3). Flexed posture increased nucleus pressure compared to erect posture, by 15% before creep, and by 8% after creep (data not shown).

Maximum compressive stresses in the annulus Maximum compressive stresses in the annulus also decreased between disc degeneration grades 2 and 4 (**Figure 4**), confirming the stress-shielding

effect of the neural arch on narrowed discs. In the anterior annulus, the effect was greatest in erect (lordotic) posture (mean fall in maximum compressive stress: 64%), and in the posterior annulus it was greatest in flexed posture (mean fall: 48%). The distance of maximum annulus stress from the disc periphery generally increased as degeneration progressed. If this distance was expressed as a % of the disc's antero-posterior diameter, and averaged over all four loading conditions (posture, creep), then the location of the anterior peak stress moved inwards from 17.6% (in grade 2 discs) to 22.3% in grade 4 discs ($P<0.002$). In the posterior annulus, this inward shift was non-significant.

Stress gradients in the annulus In contrast to the above results, stress gradients increased progressively with disc degeneration (**Figure 5**). In the anterior annulus, the effect was greater in flexed posture (for example, mean increase between disc grades 2 and 4 was 75%), and in the posterior annulus, the effect was greater in erect (lordotic) posture (mean increase 108%).

Correlation between variables Spearman correlation coefficients shown in Table 2 refer to results obtained (on all 191 specimens) after creep loading, and in flexed posture. All four equivalent data sets (before/after creep, flexed/erect posture) gave broadly similar results, but this combination was chosen because it is most typical of substantial spinal loading in-vivo: 'after creep' results are applicable to living discs during most of the day, after the extra water imbibed during sleep has been expelled, and 'flexed posture' is the functional posture for many manual labouring tasks. [9] Disc degeneration increased with age, but degeneration generally had the stronger influence on disc stresses and stress gradients. Among the highly significant correlations with disc degeneration were: decreasing nucleus pressure ($r_s = -0.58$), decreasing maximum stress in the posterior annulus ($r_s = -0.42$), and increasing stress gradients in the anterior and posterior annulus ($r_s = 0.30$ and $r_s = 0.16$ respectively). Broadly similar results were obtained in the other three loading conditions, although there were some notable postural effects: in *erect* posture after creep loading, increasing degeneration was associated with reducing maximum stress in the anterior annulus ($r_s = -0.35$, $P<0.01$) as well as in the posterior annulus and nucleus.

Influence of spinal level and gender Nucleus pressure and annulus stresses generally decreased at lower spinal levels (Table 2) presumably because the applied compressive load was distributed over a larger disc. Results in Table 2 refer to flexed posture, but in erect posture also, lower spinal levels (cranio-caudally) were associated with reducing IDP (r_s = -0.27, P<0.01) and reducing maximum stress in the posterior annulus (r_s = -0.30, P<0.01). Intradiscal stresses were also lower in male specimens compared to female (data not shown), presumably for the same reason. In flexed posture (Table 2) posterior stress gradients increased at lower spinal levels (r_s =0.20, P<0.01).

Discussion

Summary of results With increasing grade of disc degeneration, nucleus pressure and peak compressive stresses in the anterior and posterior annulus all decreased, because of increasing stress-shielding by the neural arch. However, stress gradients in the annulus *increased*. Most of these changes were large and highly significant, and were still evident when comparing between discs with moderate (grade 3) and severe (grade 4) degeneration.

Strengths and weaknesses of the study Cadaver studies can give reliable mechanical information concerning spinal tissues, because the effects of death and post-mortem storage are slight.[39-41]. The stress profilometry technique has been validated, and transducer output shown to approximate to the average axial compressive stress acting perpendicular to its membrane, even in degenerated annulus tissue.[19,42] The main strength of the study is that a sufficiently large number of human spine specimens were tested, complete with their neural arch, to justify extensive sub-group analyses. The main limitation of the study is that it was cross-sectional, so it can show only that increasing stress gradients and increasing grade of disc degeneration are strongly associated with each other.

Relationship to previous work Nucleus pressure is known to fall with age and disc degeneration, both in living people[13] and cadaveric spines,[25]as compressive load-bearing is transferred increasingly

to the neural arch.[19,20] Most of this extra load on the neural arch is resisted by the apophyseal joints,[43] predisposing them to osteoarthritis.[44] In comparison, little is known about age-related changes in load-bearing by the annulus. It has traditionally been assumed that annulus loading must increase as nucleus pressure falls,[45] and direct measurements have shown that high concentrations of compressive stress can appear in the annulus of degenerated discs, especially posteriorly.[25] Such stress concentrations are known to depend on posture,[46] to increase in dehydrated discs,[14] and to be related to increased tissue strain,[47]and to pain.[26] However, stress concentrations do not imply that overall loading of the annulus is increased. Indeed, the only previous measurements of "maximum compressive stress" acting on the annulus showed that it either decreased, or remained constant with increasing age and degeneration.[25]

Annulus stress gradients have not previously been measured, but the resulting shear strains (deformations) have been quantified from high resolution MRI scans of cadaveric spine specimens loaded in compression.[48] These previous experiments showed that shear strains are particularly large in the inner annulus, and are greater in the anterior than posterior annulus, in agreement with stress gradient data in Figures 2 and 5. Later results showed that high annulus shear strains induce high radial tensile strains that act to pull lamellae apart, and that this effect a) increases when nucleus pressure is reduced following nucleotomy,[49] and b) is greatest in the region of the annulus that is compressed most by the bending,[50] as are stress gradients (compare Figures 4 and 5). More invasive techniques have shown that spinal bending movements generate large shear strains in the posterior and posterolateral annulus,[51] which is the region most affected by annulus tears.[52] Torsion also can cause delamination of the annulus,[53] but only after gross damage to the neural arch.[54] Mathematical models also predict that interlaminar shear stresses are high in the posterolateral annulus, and following annulus injury or degeneration.[27,55,56] Experimental investigations of the physical process of annulus delamination have shown that large shearing deformations are required to separate adjacent lamellae[57] and that the force required to 'peel' lamellae apart is higher in the outer than

inner annulus.[58] The present results are consistent with all of this work, and show for the first time that large stress gradients can be generated in discs during physiological loading, despite the major stress-shielding action of the neural arch.

Interpretation of results With increasing disc degeneration, redistribution of compressive stress occurs in two stages: initially, from nucleus to annulus; and then (following disc narrowing) from disc to neural arch. As a result, stress gradients in the annulus increase even though maximum compressive stresses decrease. The major influence of posture can be explained in terms of vertical deformations of the annulus: flexion compresses the anterior annulus most, causing this region to exhibit the highest stresses (Figure 4A) and stress gradients (Figure 5A) when the disc is degenerated. Conversely, extension (lordotic posture) compresses the posterior annulus most, causing it to exhibit the highest stresses (Figure 4A) and stress gradients (Figure 5B). Increased stress-shielding by the neural arch in extended (lordotic) postures ensures that maximum stresses in the posterior *and* anterior annulus decrease in the presence of disc degeneration (Figure 4).

Stress gradients (Figure 2) arise in the annulus whenever it is compressed unevenly. Uneven compression generates shearing stresses in the direction of the spine's long axis, encouraging lamellae to move vertically relative to their neighbours. Inter-lamella sliding is resisted by collagenous 'bridging elements' which bind the lamellae together,[35] so shear stresses probably have to exceed some threshold value before annulus delamination occurs. Experimental delamination of small samples of pig cervical annulus suggests that the maximum (threshold) value of shear resistance is followed by substantial (though reducing) resistance to shear,[57] possibly caused by reorientation of inter-lamellar fibres, and by fibre-matrix interactions.[60] Delamination can be followed by inwards and outwards collapse of the isolated unsupported lamellae,[16,33] and diverging lamellae may also disrupt the cartilaginous endplate to which they are anchored.[61] Delamination mechanisms have been demonstrated in living animals by bending rats' tails backwards for long periods and noting how the lamellae of the posterior annulus become disrupted.[62] Applying uneven

compression to human discs in organ culture[10] also causes lamellar disruption. The present study has one important advantage over this previous work: the experiments were on human spine specimens that retained the neural arch, so that measured stress gradients in the annulus took full account of the protective action of the neural arch in spines with narrowed discs.

Shear loading arising from stress gradients can also affect the cells in cartilage, causing them to synthesise more collagen[63] while increasing the risk of oxidative cell damage.[64] Shear has little effect on tissue volume, or fluid flow through the matrix, so these biological effects probably arise directly from cell deformation.

Scientific and clinical relevance Results show that, as disc degeneration progresses, the primary mechanical stimulus responsible for delamination and collapse of the annulus continues to increase, even though nucleus pressure and peak annulus stresses decrease. Occupational loading appears to have little influence on disc degeneration,[65] presumably because spinal tissues strengthen in response to moderate habitual loading.[9] Spinal degeneration, like back pain, is more likely to be associated with sudden overloading events.[66] Genetic inheritance[23] and ageing[67] are also major risk factors for spinal degeneration, probably because they influence the quality and strength of spinal tissues. When these considerations are taken into account, the present results make it difficult to argue that mechanical factors are important only in the initiation of disc degeneration, and that cell-mediated factors largely determine its progression. It follows that attempts to improve the metabolic characteristics of degenerated discs must be accompanied by steps to improve the worsening mechanical environment in which their cells operate, if healing or regeneration is to be achieved.

A second implication of the present results concerns discogenic back pain. Back pain is strongly associated with specific structural changes to intervertebral discs, including annulus fissures,[68,69] annulus collapse,[67,70] and endplate damage.[71] Pain is also associated with inflammatory changes which can sensitise nerves to mechanical stimuli.[72] High stress gradients in the annulus have the potential to cause high local distortions of annulus tissue which could provoke a painful response,

and this probably explains why high stress concentrations and gradients have been associated with discogenic pain reproduction in surgical candidates.[26] The fact that annulus stress gradients increase, even when the disc becomes narrowed and protected by the neural arch, could explain why back pain tends to increase in proportion to the severity of disc degeneration.[22,67,73]

References

1. Kerttula LI, Serlo WS, Tervonen OA, Paakko EL, Vanharanta HV. Post-traumatic findings of the spine after earlier vertebral fracture in young patients: clinical and MRI study. Spine. 2000;25(9):1104-8.

2. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino J, Herzog R. ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: a ten-year matched cohort study. Spine 2009;34(21):2338-45.

3. Osti OL, Vernon-Roberts B, Fraser RD. 1990 Volvo Award in experimental studies. Annulus tears and intervertebral disc degeneration. An experimental study using an animal model. Spine. 1990;15(8):762-7.

4. Holm S, Holm AK, Ekstrom L, Karladani A, Hansson T. Experimental disc degeneration due to endplate injury. J Spinal Disord Tech. 2004;17(1):64-71.

5. Pfeiffer M, Griss P, Franke P, Bornscheuer C, Orth J, Wilke A, et al. Degeneration model of the porcine lumbar motion segment: effects of various intradiscal procedures. Eur Spine J. 1994;3(1):8-16.

6. Przybyla A, Pollintine P, Bedzinski R, Adams MA. Outer annulus tears have less effect than endplate fracture on stress distributions inside intervertebral discs: Relevance to disc degeneration. Clin Biomech. 2006;21(10):1013-9.

7. Dolan P, Luo J, Pollintine P, Landham PR, Stefanakis M, Adams MA. Intervertebral disc decompression following endplate damage: implications for disc degeneration depend on spinal level and age. Spine 2013;38(17):1466-74.

8. Ishihara H, McNally DS, Urban JP, Hall AC. Effects of hydrostatic pressure on matrix synthesis in different regions of the intervertebral disk. J Appl Physiol. 1996;80(3):839-46.

9. Adams MA, Bogduk N, Burton K, Dolan P. The Biomechanics of Back Pain (3rd Edition). Churchill Livingstone, Edinburgh; 2013.

10. Walter BA, Korecki CL, Purmessur D, Roughley PJ, Michalek AJ, Iatridis JC. Complex loading affects intervertebral disc mechanics and biology. Osteoarthritis Cartilage 2011;19(8):1011-8.

11. Stefanakis M, Al-Abbasi M, Harding I, Pollintine P, Dolan P, Tarlton J, Adams MA. Annulus fissures are mechanically and chemically conducive to the ingrowth of nerves and blood vessels. Spine 2012;37(22):1883-91.

12. Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. J Clin Invest. 1996;98(4):996-1003.

13. Sato K, Kikuchi S, Yonezawa T. In vivo intradiscal pressure measurement in healthy individuals and in patients with ongoing back problems. Spine. 1999;24(23):2468-74.

14. Adams MA, McMillan DW, Green TP, Dolan P. Sustained loading generates stress concentrations in lumbar intervertebral discs. Spine 1996;21(4):434-8.

15. Schmidt H, Shirazi-Adl A, Galbusera F, Wilke HJ. Response analysis of the lumbar spine during regular daily activities--a finite element analysis. J Biomech. 2010;43(10):1849-56.

16. Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. Spine 2000;25(13):1625-36.

17. Yasuma T, Koh S, Okamura T, Yamauchi Y. Histological changes in aging lumbar intervertebral discs: their role in protrusions and prolapses. J Bone Joint Surg Am. 1990;72(2):220-9.

18. Hassett G, Hart DJ, Manek NJ, Doyle DV, Spector TD. Risk factors for progression of lumbar spine disc degeneration: the Chingford Study. Arthritis Rheum. 2003;48(11):3112-7.

19. Pollintine P, Przybyla AS, Dolan P, Adams MA. Neural arch load-bearing in old and degenerated spines. J Biomech. 2004;37(2):197-204.

20. Luo J, Skrzypiec DM, Pollintine P, Adams MA, Annesley-Williams DJ, Dolan P. Mechanical efficacy of vertebroplasty: Influence of cement type, BMD, fracture severity, and disc degeneration. Bone 2007;40(4):1110-9.

21. Sinaki M, Nwaogwugwu NC, Phillips BE, Mokri MP. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil. 2001;80:330-8.

22. Cheung KM, Karppinen J, Chan D, Ho DW, Song YQ, Sham P, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine 2009;34(9):934-40.

23. Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Genetic and environmental effects on disc degeneration by phenotype and spinal level: a multivariate twin study. Spine 20081;33(25):2801-8.

24. Le Maitre CL, Freemont AJ, Hoyland JA. Localization of degradative enzymes and their inhibitors in the degenerate human intervertebral disc. J Pathol. 2004;204(1):47-54.

25. Adams MA, McNally DS, Dolan P. 'Stress' distributions inside intervertebral discs. The effects of age and degeneration. J Bone Joint Surg Br. 1996;78(6):965-72.

26. McNally DS, Shackleford IM, Goodship AE, Mulholland RC. In vivo stress measurement can predict pain on discography. Spine 1996;21(22):2580-7.

27. Goel VK, Monroe BT, Gilbertson LG, Brinckmann P. Interlaminar shear stresses and laminae separation in a disc. Finite element analysis of the L3-L4 motion segment subjected to axial compressive loads. Spine 1995;20(6):689-98.

28. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: Volvo Award in basic science. Spine 2002;27(23):2631-44.

29. Haefeli M, Kalberer F, Saegesser D, Nerlich AG, Boos N, Paesold G. The course of macroscopic degeneration in the human lumbar intervertebral disc. Spine 2006;31(14):1522-31.

30. Schollum ML, Robertson PA, Broom ND. How age influences unravelling morphology of annular lamellae - a study of interfibre cohesivity in the lumbar disc. J Anat. 2010;216(3):310-9.

31. Pezowicz CA, Schechtman H, Robertson PA, Broom ND. Mechanisms of anular failure resulting from excessive intradiscal pressure: a microstructural-micromechanical investigation. Spine 2006;31(25):2891-903.

32. Gunzburg R, Parkinson R, Moore R, Cantraine F, Hutton W, Vernon-Roberts B, et al. A cadaveric study comparing discography, magnetic resonance imaging, histology, and mechanical behavior of the human lumbar disc. Spine 1992;17(4):417-26.

33. Meakin JR, Redpath TW, Hukins DW. The effect of partial removal of the nucleus pulposus from the intervertebral disc on the response of the human annulus fibrosus to compression. Clin Biomech. 2001;16(2):121-8.

34. Schollum ML, Robertson PA, Broom ND. A microstructural investigation of intervertebral disc lamellar connectivity: detailed analysis of the translamellar bridges. J Anat. 2009;214(6):805-16.

35. Schollum ML, Robertson PA, Broom ND. ISSLS prize winner: Microstructure and mechanical disruption of the lumbar disc annulus: Ppart I: a microscopic investigation of the translamellar bridging network. Spine 2008;33(25):2702-10.

36. Zhao F, Pollintine P, Hole BD, Dolan P, Adams MA. Discogenic origins of spinal instability. Spine 2005;30(23):2621-30.

37. McMillan DW, Garbutt G, Adams MA. Effect of sustained loading on the water content of intervertebral discs: implications for disc metabolism. Ann Rheum Dis. 1996;55(12):880-7.

38. Adams MA, Dolan P, Hutton WC. The stages of disc degeneration as revealed by discograms. J Bone Joint Surg [Br] 1986;68(1):36-41.

39. Adams MA. Mechanical testing of the spine. An appraisal of methodology, results, and conclusions. Spine 1995;20(19):2151-6.

40. Dhillon N, Bass EC, Lotz JC. Effect of frozen storage on the creep behavior of human intervertebral discs. Spine 2001;26(8):883-8.

41. Panjabi MM, Krag M, Summers D, Videman T. Biomechanical time-tolerance of fresh cadaveric human spine specimens. J Orthop Res. 1985;3(3):292-300.

42. Chu JY, Skrzypiec D, Pollintine P, Adams MA. Can compressive stress be measured experimentally within the annulus fibrosus of degenerated intervertebral discs? Proc Inst Mech Eng [H]. 2008;222(2):161-70.

43. Dunlop RB, Adams MA, Hutton WC. Disc space narrowing and the lumbar facet joints. J Bone Joint Surg [Br]. 1984;66(5):706-10.

44. Robson-Brown K, Pollintine P, Adams MA. Biomechanical implications of degenerative joint disease in the apophyseal joints of human thoracic and lumbar vertebrae. Am J Phys Anthropol. 2008;136(3):318-26.

45. Nachemson A. In vivo discometry in lumbar discs with irregular nucleograms. Some differences in stress distribution between normal and moderately degenerated discs. Acta Orthop Scand. 1965;36(4):418-34.

46. Adams MA, May S, Freeman BJ, Morrison HP, Dolan P. Effects of backward bending on lumbar intervertebral discs. Relevance to physical therapy treatments for low back pain. Spine 2000;25(4):431-7; discussion 438.

47. Tsantrizos A, Ito K, Aebi M, Steffen T. Internal strains in healthy and degenerated lumbar intervertebral discs. Spine 2005;30(19):2129-37.

48. O'Connell GD, Johannessen W, Vresilovic EJ, Elliott DM. Human internal disc strains in axial compression measured noninvasively using magnetic resonance imaging. Spine 2007; 32(25):2860-8.

49. O'Connell GD, Malhotra NR, Vresilovic EJ, Elliott DM. The effect of nucleotomy and the dependence of degeneration of human intervertebral disc strain in axial compression. Spine 2011;36(21):1765-71.

50. O'Connell GD, Vresilovic EJ, Elliott DM. Human intervertebral disc internal strain in compression: the effect of disc region, loading position, and degeneration. J Orthop Res. 2011;29(4):547-55.

51. Costi JJ, Stokes IA, Gardner-Morse M, Laible JP, Scoffone HM, Iatridis JC. Direct measurement of intervertebral disc maximum shear strain in six degrees of freedom: motions that place disc tissue at risk of injury. J Biomech. 2007;40(11):2457-66.

52. Vernon-Roberts B, Moore RJ, Fraser RD. The natural history of age-related disc degeneration: the pathology and sequelae of tears. Spine 2007;32(25):2797-804.

53. Farfan HF, Cossette JW, Robertson GH, Wells RV, Kraus H. The effects of torsion on the lumbar intervertebral joints: the role of torsion in the production of disc degeneration. J Bone Joint Surg [Am] 1970;52(3):468-97.

54. Adams MA, Hutton WC. The relevance of torsion to the mechanical derangement of the lumbar spine. Spine 1981;6(3):241-8.

55. Iatridis JC, Ap Gwynn I. Mechanisms for mechanical damage in the intervertebral disc annulus fibrosus. J Biomech. 2004;37(8):1165-75.

56. Michalek AJ, Buckley MR, Bonassar LJ, Cohen I, Iatridis JC. The effects of needle puncture injury on microscale shear strain in the intervertebral disc annulus fibrosus. Spine J. 2010;10(12):1098-105.

57. Gregory DE, Veldhuis JH, Horst C, Wayne Brodland G, Callaghan JP. Novel lap test determines the mechanics of delamination between annular lamellae of the intervertebral disc. J Biomech. 2011;44(1):97-102.

58. Gregory DE, Bae WC, Sah RL, Masuda K. Anular delamination strength of human lumbar intervertebral disc. Eur Spine J. 2012;21(9):1716-23.

59. Michalek AJ, Buckley MR, Bonassar LJ, Cohen I, Iatridis JC. Measurement of local strains in intervertebral disc anulus fibrosus tissue under dynamic shear: contributions of matrix fiber orientation and elastin content. J Biomech. 2009;42(14):2279-85.

60. Adams MA, Green TP. Tensile properties of the annulus fibrosus. I. The contribution of fibre-matrix interactions to tensile stiffness and strength. European Spine Journal. 1993;2:203-8.

61. Rodrigues SA, Wade KR, Thambyah A, Broom ND. Micromechanics of annulus-end plate integration in the intervertebral disc. Spine J. 2012;12(2):143-50.

62. Lindblom K. Intervertebral disc degeneration considered as a pressure atrophy. J Bone Joint Surg [Am]. 1957;39:933-45.

63. Jin M, Frank EH, Quinn TM, Hunziker EB, Grodzinsky AJ. Tissue shear deformation stimulates proteoglycan and protein biosynthesis in bovine cartilage explants. Arch Biochem Biophys. 2001;395(1):41-8.

64. Martin JA, Brown TD, Heiner AD, Buckwalter JA. Chondrocyte Senescence, Joint Loading and Osteoarthritis. Clinical Orthopaedics and Related Research. 2004;427:S96-S103.

65. Videman T, Battie MC, Ripatti S, Gill K, Manninen H, Kaprio J. Determinants of the progression in lumbar degeneration: a 5-year follow-up study of adult male monozygotic twins. Spine 2006;31(6):671-8.

66. Magora A. Investigation of the relation between low back pain and occupation. IV. Physical requirements: bending, rotation, reaching and sudden maximal effort. Scand J Rehabil Med. 1973;5(4):186-90.

67. de Schepper EI, Damen J, van Meurs JB, Ginai AZ, Popham M, Hofman A, et al. The association between lumbar disc degeneration and low back pain: the influence of age, gender, and individual radiographic features. Spine 2010;35(5):531-6.

68. Videman T, Nurminen M. The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography. Spine. 2004;29(23):2668-76.

69. Peng B, Hao J, Hou S, Wu W, Jiang D, Fu X, et al. Possible pathogenesis of painful intervertebral disc degeneration. Spine 2006;31(5):560-6.

70. Videman TMDP, Battie MCP, Gibbons LEP, Maravilla KMD, Manninen HMDP, Kaprio JMDP. Associations between back pain history and lumbar MRI findings. Spine 2003;28(6):582-8.

71. Peng B, Chen J, Kuang Z, Li D, Pang X, Zhang X. Diagnosis and surgical treatment of back pain originating from endplate. Eur Spine J. 2009;18(7):1035-40.

72. Olmarker K. Puncture of a lumbar intervertebral disc induces changes in spontaneous pain behavior: an experimental study in rats. Spine 2008;33(8):850-5.

73. Bendix T, Kjaer P, Korsholm L. Burned-out discs stop hurting: fact or fiction? Spine 2008;33(25):E962-7.

Figure Captions

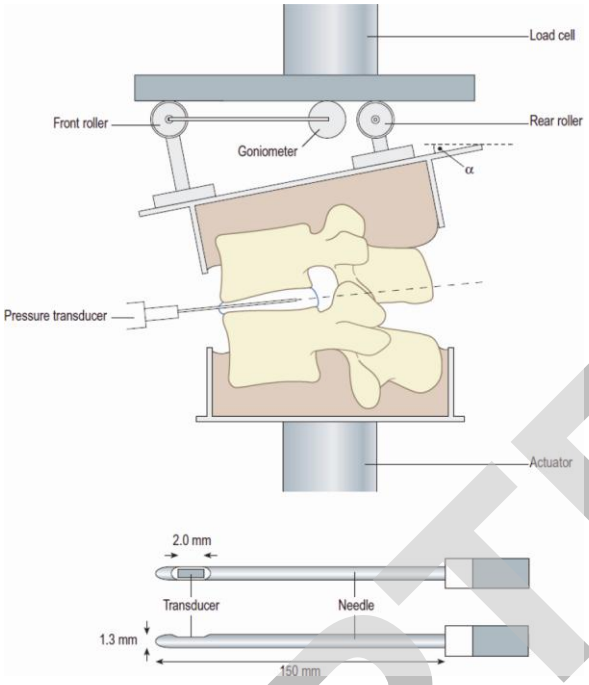

Figure 1 Apparatus for loading cadaveric motion segments. Adjusting the height of the rear roller enabled the specimen to be compressed evenly while positioned in moderate flexion (as shown) or in a simulated erect (lordotic) posture. A miniature pressure transducer was pulled across the antero-posterior diameter of the loaded disc. Dimensions of the transducer are shown in the lower diagram.

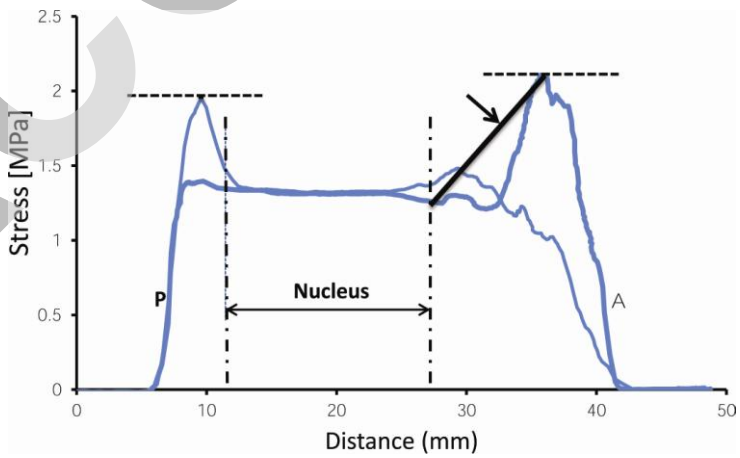

Figure 2 **"**Stress profiles" show how compressive stress varies across the sagittal diameter of intervertebral discs. Stresses acting in the vertical and horizontal directions are denoted by the thick

and thin lines, respectively. The functional nucleus is here defined as the region between the vertical broken lines, in which vertical and horizontal stresses vary by less than 10% in orientation or location. Horizontal dashed lines depict the maximum compressive stress in the anterior (A) and posterior (P) annulus. The arrow indicates the "stress gradient" measured in the anterior annulus from the profile of vertical stress: the line joins the anterior edge of the nucleus, as defined above, with the location of maximum stress in the anterior annulus.

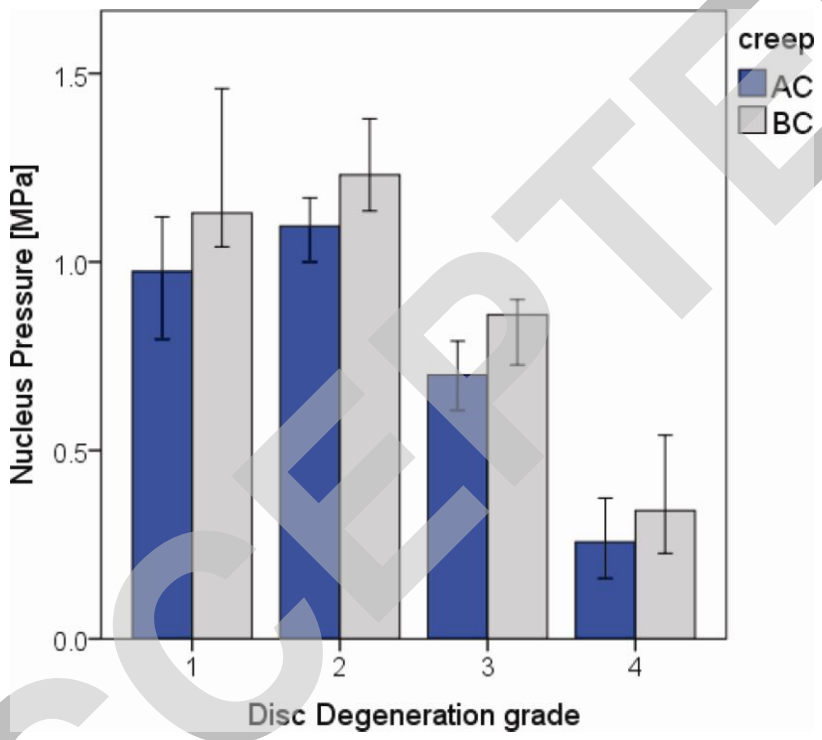

Figure 3 Nucleus pressure is shown for discs of different degeneration grades, both before and after sustained 'creep' loading (BC=before creep, AC = after creep). Data for 191 specimens have been averaged for flexed and erect postures. Bars represent median values, and error bars represent 95% CI about the *mean*.

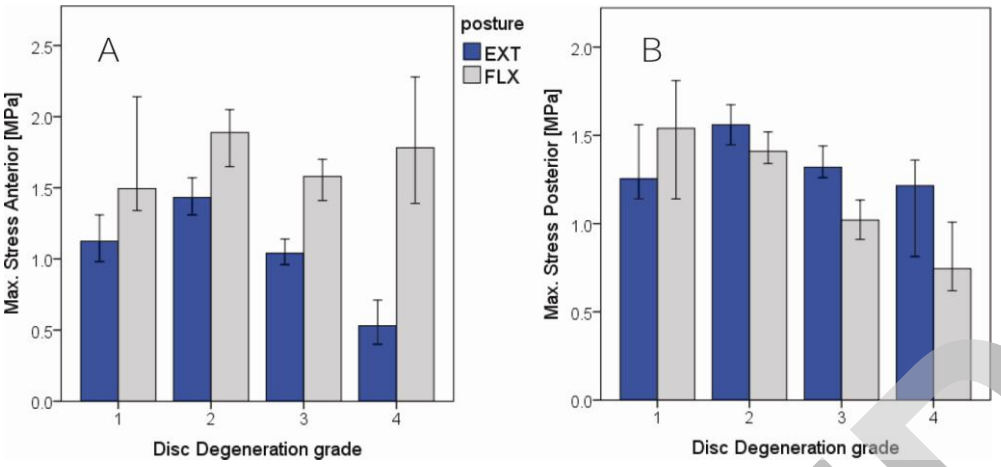

Figure 4 Maximum compressive stress in the anterior (A) and posterior (B) annulus is shown for discs of different degeneration grades, both in flexed (FLX) and erect/lordotic (EXT) postures. Data for 191 specimens have been averaged before and after sustained 'creep' loading. Bars represent median values, and error bars represent 95% CI about the *mean*.

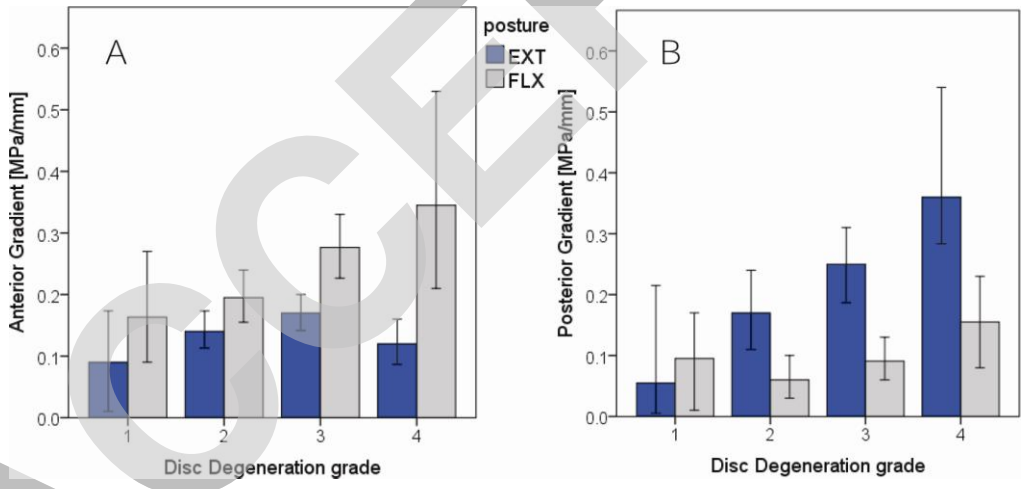

Figure 5. Stress gradients in the anterior (A) and posterior (B) annulus are shown for discs of different degeneration grades, for both flexed (FLX) and erect/lordotic (EXT) postures. Data for 191 specimens have been averaged before and after sustained 'creep' loading. Bars represent median values, and error bars represent 95% CI about the *mean*.

Table 1. Details of the 191 spine specimens tested**.**

		Disc degeneration grade (1-4)				Gender	
	Total	1	2	3	4	Female	Male
Thoracic	65	1	25	30	9	27	38
Upper lumbar	83	4	35	37	7	37	46
Lower lumbar	43	4	15	20	4	19	24

Table 2 Correlations between variables. Spearman rank correlation coefficients (r_S) are presented for data obtained in flexed posture after creep loading. * P<0.05; **P<0.01.

	Age (yr)	Disc degen. (grade1-4)	IDP (MPa)	Spinal level (1-12)	Gradient - anterior (MPa/mm)	Gradient - posterior (MPa/mm)	Max. stress - anterior (MPa)	Max. stress - posterior (MPa)
Age (yr)	1.00	0.39**	-0.42**	-0.18*	0.23**	0.18*	0.05	-0.38**
Disc degen (grade 1-4)		1.00	-0.58**	-0.07	0.30**	0.16*	0.04	-0.42**
IDP (MPa)			1.00	-0.12	-0.25**	-0.31**	0.23**	0.70**
Spinal level (1-11)				1.00	-0.14	0.20**	-0.41**	- 0.05
Gradient - anterior					1.00	0.08	0.47**	-0.11

Gradient - posterior						1.00	-0.21**	0.12
Max. stress - anterior							1.00	0.20**
Max. stress - posterior								1.00