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Research Article

Histological and Radiological Study of Lumbar Intervertebral Disc Degeneration

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Abstract

Background: It was believed that lumbar IVD degeneration is a main source of back pain. Understanding the exact association between degeneration and back pain is poorly established. Using histological scoring of degenerative changes and correlating these scores with MRI grading and pain duration can give an excellent awareness about the association between disc degeneration and back pain. ***Objective***: To characterize the degree of histologic degeneration in terms of modified Histological Degeneration Score (HDS) in correlation with MRI grading of IVD degeneration and the duration of back pain. This may provide a reliable understanding of the role of IVD degeneration in back pain from both histologic and MRI perspectives. ***Methods***: Excised tissue from the lumbar disc of 23 patients was graded according to the histological degeneration score (HDS). MRI images have been documented and graded, relying on the Pfirrmann grading system. The histologic grades were compared to MRI grades and back pain duration and disc level. ***Results***: Higher HDS scores in disrupted discs are highly correlated with higher MRI grades (grades IV and V). There was a trend of severe disc degeneration associated with longer back pain duration, although it was not statistically significant. Gender shows no statistical correlation to the degree of degeneration. ***Conclusions***: This study showed that histological IVD alterations in excised tissues can be graded in a reliable fashion based on HDS that positively coincides with MRI grades of IVD degeneration.

Keywords: IVD degeneration, Histologic degeneration score, MRI.

الدراسة النسيجية والإشعاعية لتنكس القرص الفقري القطني

الخلاصة

الخلفية: كان يعتقد أن تنكس الغضاريف القطنية هو مصدر رئيسي لآلام الظهر. إن فهم العلاقة الدقيقة بين التنكس وآلام الظهر غير مثبت. يمكن أن يؤدي استخدام التسجيل النسيجي للتغيرات التنكسية وربط هذه الدرجات بتصنيف التصوير بالرنين المغناطيسي ومدة الألم إلى إعطاء وعي ممتاز بالعلاقة بين تنكس القرص وآلام الظهر. **الهدف**: توصيف درجة التنكس النسيجي من حيث درجة التنكس النسيجي المعدلة (HDS) بالارتباط مع تصنيف التصوير بالرنين المغناطيسي لتنكس IVD ومدة آلام الظهر. قد يوفر هذا فهما موثوقا به لدور تنكس IVD في آلام الظهر من كل من المنظورين النسيجي والتصوير بالرنين المغناطيسي. **الطرائق**: تم تصنيف الأنسجة المستأصلة من القرص القطني ل 23 مريضا وفقا لدرجة التنكس النسيجي (HDS). تم توثيق صور التصوير بالرنين المغناطيسي وتصنيفها ، بالاعتماد على نظام الدرجات Pfirrmann. تمت مقارنة الدرجات النسيجية بدرجات التصوير بالرنين المغناطيسي ومدة آلام الظهر ومستوى القرص. **النتائج**: ان درجات التدهور النسيجي العالية كانت مطابقة لدرجات التصوير بالرنين المغناطيسي العالية (تدهور أكثر شدة). اتجاه غير حاسم: التدهور الغضروفي الشديد كان يرتبط بمدة ألم الظهر الأطول، ولكن هذا لم يكن ذا دلالة إحصائية. ولا يوجد ارتباط مع الجنس الذي لم يكن له تأثير على درجة التدهور. **الاستنتاجات**: أظهرت هذه الدراسة أن التغيرات النسيجية في الغضاريف القطنية يمكن تقييمها بشكل موثوق باستخدام نظام التقييم النسيجي، والذي يتوافق مع درجات التصوير بالرنين المغناطيسي لتدهور الغضاريف.

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INTRODUCTION

Back pain is the second leading cause of disability and the most common ailment of working adults, which in the US is established to cost $50 billion annually [1]. Back pain is associated with significantly greater depression, anxiety, and insomnia, and recent evidence indicates that it persists in old age [2]. Research on pain provocation revealed that severe and chronic back pain most often arises from lumbar IVD, often with marked degenerative changes in early middle age. Recent large imaging studies show a strong correlation between IVD degeneration and back pain; however, several studies have shown that not all degenerated discs are painful for reasons that are poorly understood [3]. The consequences of IVD degeneration are amongst the chief reasons for functional incapability in both genders and are a common source of back pain and chronic incapacity in the working years [4]. IVD degeneration-related structural defects have been associated in many studies with the incidence of back pain; annular defects (e.g., complete radial fissure, loss of annulus fibrosus height, nucleus pulposus structural defects (such as disc extrusions), and endplate defects are all linked to back pain [5]. IVD possesses a distinctive structure composed of three distinct regions: the inner nucleus pulposus (NP), which is a hydrated gel-like rich in aggrecan proteoglycans and type II collagen, encircled by concentric lamellae of annulus fibrosus

(AF) that have a high content of type I collagen and other types for a lesser degree; both NP and AF are sandwiched from superior and inferior by a hyaline cartilage endplate (CEP) [6]. Aging and disc degeneration result in considerable compositional alterations in the disc, with loss of aggrecan, hence water loss, and increased deposition of type I collagen fibers within the NP with increased collagen cross-linking [7]. These changes give rise to the dark disk on MRI and may lead to progressive structural failure [8]. Several etiological factors that might increase the incidence and progression of disc degeneration have been described: aging, mechanical, genetic, and disc factors; however, disc degeneration is mostly affected by occupational environments and genetic predispositions. In most cases, classification of IVD degeneration is carried out using imaging techniques, particularly MRI [9], while investigations on histological degenerative changes of IVD are sparse; however, most of the available studies on histologic changes are primarily based on cadaverous tissue [10]. Recently, Boos and colleagues have established a reliable classification system that permits an evaluation of histological alterations of disc degeneration in a complete disc. This system has been accustomed to cadaveric discs; however, it was validated for surgically excised discs. For the application of this histologic degeneration score (HDS) to the surgical samples, a modification has been made [11] (Table 1).

Table 1: Modified histological parameters collected for the HDS

Criteria	Score
Cell density/chondrocyte proliferation	0 = "No proliferation" 1 = "Increased cell density" 2 = "Connection of two chondrocytes" 3 = "Small size clones (i.e. several chondrocytes group together, i.e., 2-7 cells)" 4 = "Moderate size clones (i.e., >8 cells)" 5 = "Huge clones (i.e., 15 cells)" 6 = "Scar / tissue defect"
Structural alterations (tears and clefts)	0 = "Absent" 1 = "Rarely present" 2 = "Present in intermediate amount" 3 = "Abundantly present" 4 = "Scar / tissue defect"
Granular changes	0 = "Absent" 1 = "Rarely present" 2 = "Present in intermediate amount" 3 = "Abundantly present" 4 = "Scar tissue / defect"

Histological degeneration score (HDS) 0-14.

This study aims to characterize the degree of histologic degeneration in terms of the modified Histological Degeneration Score (HDS) in correlation with MRI grading of IVD degeneration and the duration of back pain, and this may provide a reliable understanding of the role of IVD degeneration in back pain from both histological and MRI perspectives.

METHODS

Study design and setting

The study employed a cross-sectional analytic design with statistical inference and was conducted in the Department of Human Anatomy at the College of Medicine, Mustansiriyah University. The study was performed on a sample of patients who were treated in 3 different spine-specialized centers (Neurological Sciences Hospital, Red Crescent Hospital, and Al-Amal Private Hospital). A total of 23 lumbar IVD specimens were collected during single-spinal level surgical procedures for chronic back pain and/or sciatic pain. Patients with a history of back trauma, tumor, or congenital disc pathology have been excluded from this study. The male-to-female ratio was 11:12. In all cases, there were two regions for the same disc, a disrupted and a non-disrupted region, because of the lack of a control group; an intra-discal comparison between the disrupted and non-disrupted regions has been applied in this study. An agreement consent form regarding the study has been agreed upon and signed by all the patients (or their relatives) to get informed and documented patients' age, gender, duration of low back pain, spinal level, and an image of the MRI, besides using the excised IVD tissue in this study.

MRI images

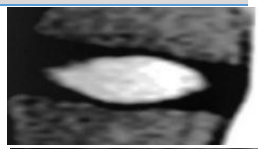
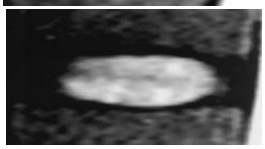
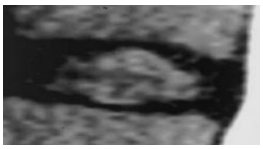
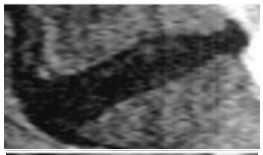
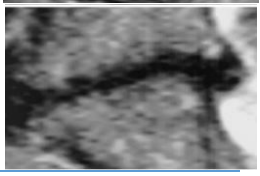
According to a standardized protocol, MRI data (T2-weighted sagittal scans) have been collected and documented for all the individuals to be assessed and graded by an experienced specialized spine surgeon. Five grades were described based on image homogeneity, distinction between nucleus and annulus, and disc height; nucleus pulposus was also checked for clarity and/or obscurity (Table 2) [12].

Tissue preparation

As agreed with the spine surgeon, all harvested discs should have included disrupted and non-disrupted parts. Immediately after excision, the removed disc tissue has been lightly washed with normal saline and carefully mobbed by gauze, then directly immersed in 10% formalin, where it is kept for 48 hours at room temperature. Fixed tissue specimens have been processed depending on Bancroft and Stevens criteria [12], following the sequence of dehydration, clearing, wax impregnation and embedding, sectioning, de-

waxing and hydration, staining, and mounting. The paraffin-embedded specimens were cut with a thickness set to 5 µm. Serial sections (3-5 sections/block) were taken from each block and put on a clean glass slide.

Table 2: The modified Pfirrmann grading of IVD degeneration

Grade	Structure	Distinction of NP and AF	Signal intensity	Height of IVD	MRI image
I	Homogeneous, bright white	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal	
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal	
III	Inhomogeneous, grey	Unclear	Intermediate	Normal to slightly decrease	
IV	Inhomogeneous, grey to black	Lost	Intermediate to hypointense	Normal to moderately decreased	
V	Inhomogeneous, black	Lost	Hypointense	Collapsed disc space	

NP: Nucleus Polposus, AF: Anullus Fibrosis, IVD: Intervertebral Disc

All specimens have been stained with routine hematoxylin and eosin stain according to standardized criteria [12] and evaluated by light microscope (Micros Austria® microscope with an LCD touch screen).

Data evaluation

Patient data are classified into two groups, disrupted and non-disrupted groups. In a set of 23 cases, evaluation of surgically removed IVDs was performed using the modified histologic degeneration score (HDS) [11]. Three histological parameters were used for scoring: cellularity/cellular proliferation (Figure 1), structural alterations (tears and clefts) (Figure 2), and granular changes (Figure 3).

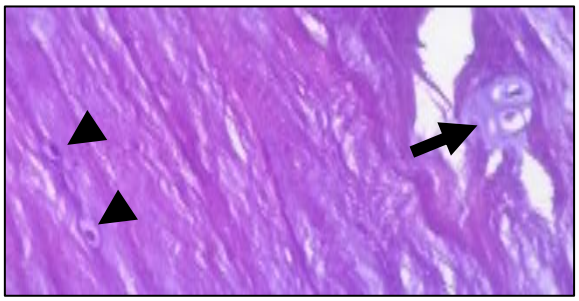


Figure 1: Annulus fibrosus with a pair of normal fibrocyte-like cells (arrow heads) and duplicated chondrocytes (arrow), L4-L5 disc for 55 years old female suffered from low back pain for 14 months duration; depicts. (H&E stain X400).

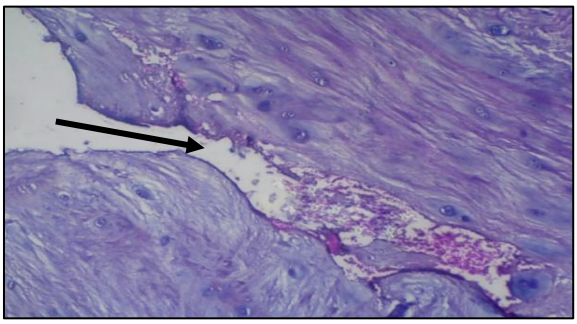


Figure 2: Structural alterations with annular tear (arrow), L5-S1 disc of 41 years old male patient suffered from 24 months of low back pain. (H&E stain, X100).

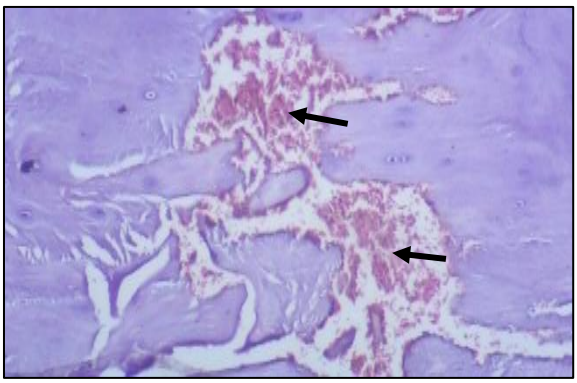


Figure 3: Severe occurrence of granular changes (arrows), L5-S1 disc of 46 years old female patient suffered from 24 months of low back pain. (H&E stain, X100).

Ethical considerations

The study protocol was approved by the local research ethics committee of the College of Medicine, Mustansiriyah University, and informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism 6®, and data was expressed in measures of means and standard deviations. The significance of the difference between the means was evaluated using Student's t-test and ANOVA test. The Pearson correlation was used to assess the correlation between two quantitative data. The probability value of $p<0.05$ was considered statistically significant and highly significant when the p value < 0.001 [13].

RESULTS

Assessment of the histological parameters was carried out on both disrupted and non-disrupted regions of the disc, applying an intra-discal comparison of both regions HDS. There was a highly significant difference between the means of HDS of disrupted compared to non-disrupted regions ($p<0.001$) (Figure 4), the mean HDS of the disrupted region was (8.8±1.6), while that of the non-disrupted region was (2.3±0.6).

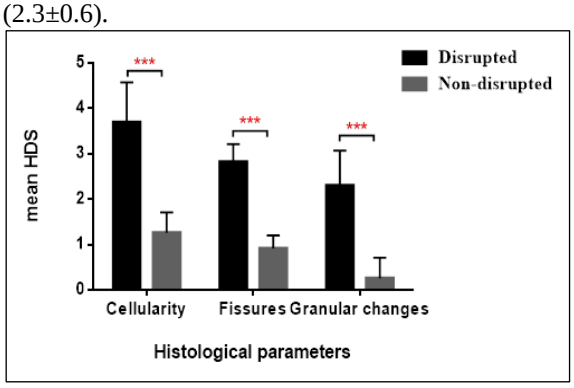


Figure 1: Comparison of HDS means for distinct histological parameters in both disrupted and non-disrupted parts of the intervertebral disc. (*** $p<0.001$, two-way ANOVA).

There is a significant correlation between disrupted discs HDS associated with increasing MRI grades (between grade IV and grade V $p<0.05$, while $p<0.005$ between grade III and both grade IV and V) (Figure 5).

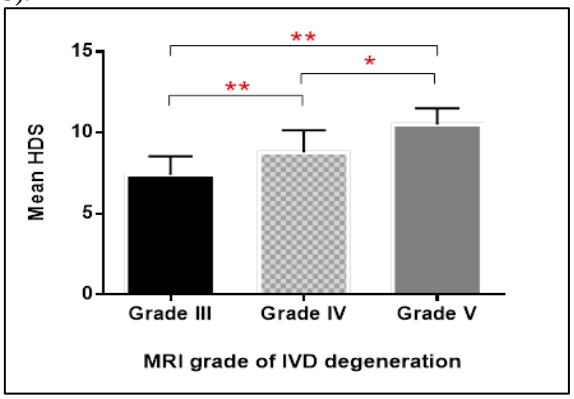


Figure 2: Comparison of HDS means of different MRI grades (** $p<0.005$, * $p<0.05$, One-way ANOVA test).

Disrupted discs with high HDS showed a trend with increasing back pain duration compared to that of non-disrupted discs (Figure 6).

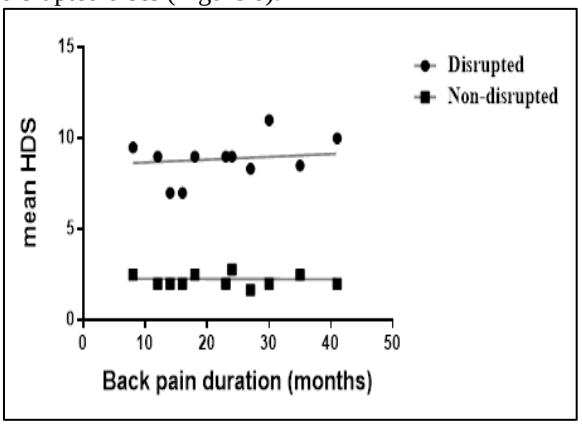


Figure 3: Linear correlation of HDS with the duration of back pain (months) in both disrupted and non-disrupted regions. HDS for disrupted region has insignificant ($p>0.05$) positive strong correlation with pain duration (r=0.8). However non-disrupted HDS has no correlation with pain duration (r=0.1).

DISCUSSION

IVD degeneration is a complex and progressive process. It has been found that many interactive factors (mechanical, nutritional, biological, and genetic) can play a role in the cascade of disc degeneration, implying a complex interaction of them. For the evaluation of the IVD degeneration and its severity, a variety of techniques have been applied, commonly MRI and, to a lesser extent, plain x-ray [14]; however, these techniques reflect the biochemical composition and water content alterations rather than exact histomorphological alterations. Previous data have shown insufficient evidence for defining the exact changes of IVD degeneration due to the significant heterogeneity and diversity within and between the different IVD regions [11]. Cells in the NP are rounded chondrocyte-like and stiffer than the ones in the AF. Excessive hydrostatic pressure, but small volumetric changes are predicted to occur for cells of the NP in response to axial compressive loading, where the tensile forces may be quite small. In contrast, cells within the lamellae of the AF are elongated, fibrocyte-like, and well adapted to experience tensile forces and volumetric changes to tensile stresses [15, 16]. In degenerated IVD, there is loss in the content of proteoglycans, particularly in the nucleus pulposus, leading to loss of hydrostatic pressure; this may contribute to applying an abnormal axial compressive load on the annulus fibrosus, creating areas of high and low stresses within the disc, leading to tissue damage [17]. Recurrent tissue damage is overcome by the process of adaptive remodeling, in which the tissue's cells try to improve the extracellular matrix so that it can encounter the mechanical demands placed upon it [18]. Thus, adapting the shape of cells to become more rounded and forming clusters (as shown in our current study) in the regions where high stresses happened [14]. This fact has been demonstrated in the current study in which intra-disc comparison has shown that disrupted regions have significantly higher

HDS compared to non-disrupted regions; these findings go with the observations of Stefanakis and colleagues [15]. In addition, cellularity parameters exhibited a considerable difference between the two regions, explaining the role of the cell-dependent remodeling process. There are a few studies that have correlated histological degenerative alterations with the duration of back pain (discogenic back pain). Chronic back pain is usually thought to be produced by nerve-root compression, but MRI often shows no compression of neural structures even with the existence of back pain and/or sciatica; moreover, back pain and sciatica can be reproduced by maneuvers that do not affect nerve roots, for instance, intra-discal saline injection or discography [16]. The present study showed that disrupted discs with high HDS displayed a trend with increasing back pain duration compared to that of non-disrupted discs (positive linear correlation). Although some researchers did not show the same correlation [17]. This could be explained by suggesting that the fissures are mechanically and chemically vulnerable to nerve ingrowth, hence inducing discogenic back pain [15]. Moreover, Freemont and colleagues have found that there is an association between the ingrowth of nerves expressing substance P (pain-transmitting neurotransmitter) and disc degeneration [19]. The findings of Peng and colleagues have stated that IVD degeneration may derive from the injury and subsequent repair of the annulus fibrosus. It has been suggested that proteoglycans (particularly glycosaminoglycan) depletion within posterior annular fissures leaves a scaffold for nerve ingrowth [20]. In our study, we found that there is a strong correlation between HDS and Pfirrmann MRI grades of disc degeneration, considering that the Pfirrmann grading system does not only take the signal intensity into account, but also disc structure, disc height, and annulus and nucleus distinction [16]. In addition to our three histological parameters (cellularity, clefts and tears, and granular changes). Cellularity parameters showed a highly significant correlation with the MRI grades than other parameters, indicating an association between cellular response to degenerative processes and MRI degeneration; to the best of our knowledge, this correlation has not been implicated in a previous study. These results coincide with the results of a recent study that was conducted on surgical specimens by Canbay and colleagues [21]. Moreover, many studies have been done on cadaveric disc tissue correlating histological and biochemical alterations with the signal intensity on T2-weighted MRI [22,23] and concluded that histological alterations were unrelated to signal intensity on MRI, and the reduction in signal intensity is probably due to loss in proteoglycans and water.

Study limitations

This study may have limitations, including a relatively small sample size and imbalance in the number of individuals allocated to both arms of the study, i.e., disturbed versus undisturbed. Besides, the study was based on individuals attending a single city (Baghdad) rather than attending multiple cities in Iraq, which could have led to a more reliable multicenter study.

Conclusion

This study revealed that histological disc alterations in surgically excised IVD tissues can be graded in a reliable manner based on HDS that positively coincides with MRI grades of disc degeneration. Histological alterations of disc degeneration showed a positive yet insignificant correlation with the duration of back pain.

Conflict of interests

No conflict of interest was declared by the authors.

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The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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