Quantitative Predictive Imaging Biomarkers of Lumbar Intervertebral Disc Degeneration

Rammohan Vadapalli¹, Raghavdutt Mulukutla², Abhinav Sriram Vadapalli³, Rajanikanth Rao Vedula⁴

¹Department of Radiology, Krishna Institute of Medical Sciences, Secunderabad, India
²Department of Spine Surgery, Uday Omni Hospitals, Hyderabad, India
³Department of Orthopaedics and Trauma, Medway Maritime Hospital, Gillingham, UK
⁴Department of Radiology and Imaging, Krishna Institute of Medical Sciences, Secunderabad, India

Study Design: Observational comparative study.

Purpose: To compare fractional anisotropy (FA) maps with T2 values of the nucleus pulposus (NP) and annulus fibrosus (AF) of intervertebral discs in healthy volunteers and patients to develop a predictive disc health scale.

Overview of Literature: T2-weighted magnetic resonance imaging (MRI) is not sensitive to early morphological changes and provides no quantitative biomarker profile for early degeneration.

Methods: We examined 59 healthy controls and 59 patients with back pain by MRI using T2 relaxometry and diffusion tensor imaging (DTI). Each group was divided into three age subgroups: A (<30 years, n=12); B (30–50 years, n=26); and C (>50 years, n=21). We obtained FA values for AF and NP and T2 values for NP for each intervertebral disc. Furthermore, we calculated the FA (AF/NP) ratios.

Results: We categorized 590 intervertebral discs from 118 participants, 566 of which were analyzed with T2 relaxometry and DTI. The T2 values were as follows: subgroup A, 55.8±4.4 ms; B, 48.5±6.9 ms; C, 45.8±8.7 ms (p<0.050). The T2 values for the healthy controls of the subgroups A, B, and C were >120 ms, 90–100 ms, and 70 ms, respectively (p<0.001). Control subgroup A had higher T2 values and AF/NP ratios than subgroups B and C; the AF values were not significantly different. Control subgroup B had higher T2 values and AF/NP ratios than subgroup C but lower FA (NP).

Conclusions: FA maps of the AF/NP ratio and T2 values of NP are potential microstructure biomarkers of normal and degenerating discs and can help detect early degeneration using a predictive disc health score on a continuous scale.

Keywords: Annulus fibrosus; Diffusion tensor imaging; Fractional anisotropy; Nucleus pulposus; T2 relaxometry

Introduction

Detecting disc degeneration for the early diagnosis of patients with degenerative disc disease (DDD) is vital to facilitate optimal treatment, given therapies are most efficacious in the early stages of the disease. Numerous factors induce the breakdown of intervertebral discs in the spine, including osteoarthritis, disc herniation, spinal stenosis, and aging. Denervation resulting from spinal disc injury leads to muscle atrophy and loss [1]. Predicting the patient's disc health proximal and adjacent to the proposed surgical site is thus essential for proper surgical planning, improving functional outcomes, and abrogating the adverse effects of DDD.
To predict the severity of disc degeneration, intervertebral discs can be characterized either with T2 relaxometry to quantify the signal changes and evaluate disc health or with diffusion tensor imaging (DTI) for three-dimensional visualization [2]. The use of T2 relaxometry as a biomarker facilitates sensitive, quantitative magnetic resonance imaging (MRI) and helps identify the extent of disc damage [3,4]. Although MRI provides details of the spinal cord anatomy, conventional MRI using T2-weighted imaging is not sensitive to early morphological changes and provides no predictive quantitative biomarker profile of early degeneration. The limitations of conventional MRI also include prolonged acquisition time for multiple images.

DTI as a biomarker helps predict the severity of disc degeneration by providing qualitative information on the microstructural architecture of discs. DTI employs fiber tracking to display a ring or lamellar architecture of the annulus fibrosus (AF) that surrounds the soft inner core of the nucleus pulposus (NP). DTI also provides quantitative information using fractional anisotropy (FA) maps. The high FA values measured in the AF correlate with its highly organized, tension-resistant, fibrous collagen structure. The lower FA values measured in the NP reflect its less structured, compression-resistant, proteoglycan-rich gelatinous core [5].

The Thompson grading system is currently employed to classify the severity of intervertebral disc degeneration based on MRI into one of five stages of degeneration: stage 1 is a healthy intervertebral disc and rest of four stages depend on the other four characteristics. Characteristics have been used to stage disc degeneration into five stages are as follows: the number, disc height, disc fissure configuration, and distinctness of the boundary between the collagenous and the cartilaginous portions of the disc. The Thompson system was originally designed for use with anatomical slices used in experimental research [6]. Using T2-weighted images, the Pfirrmann system has shown acceptable intraobserver and interobserver reliability (0.84–0.90 and 0.69–0.81, respectively), with five grades of morphology and signal intensity: I–II (for apparently healthy discs of children and young adults), III (for disks with reduced T2 signal intensity), and IV–V (for disks with progressively decreased height and T2 signal) [7,8].

In this study, the extent of disc damage was determined by combining objective biomarkers using T2 relaxometry and DTI as functional tools for treating disc degeneration. We detected microstructural alterations before morphological changes and employed FA to detect morphological differences between the NP and AF, as well as degenerative changes in the NP. Finally, we propose a continuous scale with quantitative scoring to evaluate lumbar intervertebral disc degeneration.

Materials and Methods

After receiving approval from the institution review board of Vijaya Diagnostics Hyderabad (IRB approval no., 04/17/2014), we conducted an observational comparative study that included 59 patients (who provided their informed consent) and age-matched controls. All participants underwent lumbar spine MRI on a 3T MRI scanner (Philips Medical Systems, Amsterdam, The Netherlands) between 2014 and 2017. In all, we analyzed 295 healthy intervertebral discs (59 controls) and 59 patients with lumbar DDD (35 men [59.3%] and 24 women [40.6%]; male-to-female ratio, 1.4:1; age range, 29–69 years; mean±standard deviation age, 41.7±11.80 years). We evaluated all intervertebral lumbar discs from L1 to S1 according to morphological abnormality and degeneration grades. The patient population included participants with lower back pain, sciatica, and neurological deficits. We excluded patients with spinal infections or who had undergone trauma or spinal surgery. The control and patient groups were divided into three age subgroups each: A (<30 years, n=11); B (30–50 years, n=21); and C (>50 years, n=27). For each intervertebral disc, we obtained DTI-FA values for the AF and NP and T2 values for the NP in each of the three control and patient subgroups. We calculated and compared the ratios of the two parameters FA (AF/NP).

We employed the following imaging parameters: (1) 450/8 ms repetition time (TR)/echo time (TE); 372×328 matrix; 33.6×68.2 field of view; 4-mm slice thickness; 1.0-mm slice gap and one number of excitations (NEX) for T1 sagittal view; (2) 2,709/100 ms TR/TE; 336×255 matrix; 32.3×57.7 field of view; 4-mm slice thickness; 0.4-mm slice gap and 2 NEX for T2 at the intervertebral disc levels; (3) 6,248/60 ms TR/TE; 2-mm slice thickness; 0.5-mm slice gap; 2 number of signal averages; 112×112 matrix; 29.8 bandwidth; b-values of 0 and 800; 15 directions for DTI in sagittal; and (4) 15, 30, 60, 80, 90, 120 ms TE for T2 maps.
1. Data analysis

We generated FA maps using Fibre Track software (Philips Healthcare, BEST, The Netherlands) provided with the MRI equipment. FA maps of the AF and NP were co-registered with T2 images. We analyzed the T2 relaxometry maps by region of interest (ROI) in the NP at five disc levels using T2 Map Software (IntelliSpace Portal workstation, Philips Healthcare), which generated color-coded T2 maps. ROIs were placed in the NP, avoiding end-plate regions and the disc periphery to generate FA (AF/NP) ratios and T2 values for the NP. We calculated the T2 values and FA (AF/NP) ratios for the control and patient groups for the statistical analysis.

2. Statistical analysis

The T2 values and FA (AF)/FA (NP) ratios for the control and patient groups were calculated for the statistical analysis using Pearson’s correlation coefficient. We employed SPSS for Windows ver. 17.0 (SPSS Inc., Chicago, IL, USA) for the statistical analysis and performed the following correlations for both groups: age versus FA (AF/NP) ratio and T2 map versus FA (AF/NP) ratio.

We evaluated the degree of correlation using the $r$ absolute value as follows: $r>0.6$ was defined as strong; $0.5<r≤0.6$ as moderate; and $r≤0.3$ as weak. Statistical significance was set at $p<0.001$.

Results

We categorized the MRIs of 590 intervertebral discs of 118 participants (59 healthy volunteers and 59 patients). Of these, 566 discs were successfully measured on T2 relaxometry images (Fig. 1A, B) and FA maps (Fig. 2A, B).

We excluded 24 discs due to highly reduced disc height resulting from degeneration, those where an optimal ROI (n=17) was placed at L4–L5 and L5–S1 and those obscured due to susceptibility artifacts (n=7).

Among the healthy controls, subgroup A had a higher T2 and AF/NP ratio than subgroup B; however, the AF was not significantly different. Subgroups A and B had a higher T2 and AF/NP ratio than subgroup C but lower NP and AF values (Table 1).

Among the patients, there were no differences between subgroups B and C. Subgroup A showed higher T2 values than subgroup B and had a higher T2 and FA (NP) ratio than subgroup C (Table 2).
1. Healthy controls versus patients

Subgroup A of the healthy controls had a higher T2 and AF/NP ratio but lower NP than subgroup A of the patients. Subgroup B of the healthy controls had a higher T2 and AF/NP ratio but lower NP and AF values than subgroup B of the patients. Subgroup C of the healthy controls had a higher T2 and AF/NP ratio but lower FA (NP) values than subgroup C of the patients.

2. Correlations

AF/NP values were strongly correlated with age and with the T2 map (ms) in the healthy controls but not in the patients. In the healthy volunteers, there was no correlation between $R^2$ values $<0.300$ and FA (AF/NP), and there was a strong increasing correlation with increasing $R^2$ values $>0.300$ and a trend for $R^2$ values $>0.600$. AF/NP was strongly correlated with increasing age in the healthy con-
MRI Biomarkers of Disc Degeneration

The control group presented mean T2 values >120 ms in subgroup A, 90-100 ms in subgroup B and approximately 70 ms in subgroup C (p<0.001). The patient group presented mean T2 values of 55.8±4.4 ms in subgroup A, 48.5±6.9 ms in subgroup B and 45.8±8.7 ms in subgroup C (p<0.050). These results indicate a significant difference in T2 values in degenerated discs in patient subgroups A and B compared with the normal healthy controls in the corresponding subgroups.

Similarly, the DTI-FA values for the NP and AF expressed as a ratio (FA AF/NP) showed significant statistical differences (p<0.001), indicated by higher FA values in the NP and lower FA (AF/NP) ratios in the patient population than in the healthy controls in subgroups A and B. T2 values and DTI indices for subgroup C (controls and patients) were not statistically significant due to age-related microstructural changes in the NP, especially in subgroup C of the healthy controls, given that differences in the FA values for NP and AF are not specific to degeneration alone.

The T2 relaxometry scoring tool provides potential benefits for quantitatively grading the early stages of DDD, wherein T2 values decrease linearly with increased degeneration. DTI-FA values can characterize the amorphous NP showing low FA values and differentiate it from AF having high FA in a healthy disc. In a degenerated disc, the NP shows increased FA values. As the degeneration advances, the NP presents characteristics similar to the AF, including fibers in the fiber tracking. The FA (AF/NP) ratio can therefore act as a potential biomarker.

3. Predictive disc health score

We therefore propose the following simple predictive disc...
health scoring system based on T2 relaxometry and DTI indices.

H (healthy): T2 values >120 ms, FA (NP/AF) ratio >2, mean FA (NP) between 0.4 and 0.55.

DE (early degeneration): T2 values <100 ms, FA (NP/AF) ratio <1.5, mean FA (NP) between 0.6 and 0.65.

DA (advanced degeneration): T2 values <80 ms, FA (AF/NP) ratio <1.2, mean FA (NP) between 0.8 and 0.85.

Discussion

The present study examined the potential of combining biomarkers using T2 relaxometry and DTI to characterize intervertebral disc health in various age groups. The intervertebral disc is a fibrocartilaginous joint that supports spinal forces, facilitating joint movement. The disc consists of tension-resistant AF and compression-resistant NP, which together mechanically stabilize the disc [2]. Healthy intervertebral discs show high T2 signal intensity, while degenerated discs present lower T2 signal intensity. The criteria for classifying intervertebral disc degeneration are therefore based on inspecting T2-weighted images. MRI findings of disc degeneration include low T2 signal intensity, reduced height and annular fissures in the disc.

1. T2 relaxometry

The decay constant for MRI T2 signal intensity, known as the T2 relaxation time, is an intrinsic tissue property that reflects the disc’s molecular framework (consisting of water, proteins, collagen, and other solutes) and can be calculated from a series of images obtained with different echoes and recovery times or by relaxometry [4,7]. T2-weighted multiecho sequences provide T2 measurements in approximately 6 minutes with a 1.5-T system and in approximately 8 minutes on a 3T system with a 6-echo sequence [9]. Mwale et al. [10] reported that quantitative MRI indices (relaxation, magnetization transfer ratio, and apparent diffusion coefficient [ADC]) are driven by the disc matrix composition (water, proteoglycan, and collagen) and matrix integrity as represented by collagen denaturation. Different regions within the disc demonstrate varying signal intensity and T2 relaxation values. While the intranuclear cleft and the peripheral annulus show reduced T2 values due to their high fiber content, the NP shows higher T2 values due to its amorphous nature [11]. Diurnal variations in water content due to degeneration can be measured with T2 relaxometry [11-16].

2. Diffusion tensor imaging and disc disease

DTI illustrates the intervertebral disc microstructure based on diffusion-driven molecular mobility through diffusion tensor calculation. Diffusion represented by the ADC as a biomarker decreases in degenerated discs, correlating in a direction-dependent manner with intradiscal water and disc matrix integrity. ADC values might help with evaluating disc degeneration due to their sensitivity to water content and the geometrical packing of the collagen network structure [17]. Given that it is not truly quantitative, ADC characterizes a single scalar coefficient and is dependent on the number of directions used for measurements. Invariant indices are necessary for an accurate depiction of the intervertebral disc microstructure [18-21].

We observed a mean decrease in FA values in subgroups A, B, and C, with progressive degeneration. The NP has a high molecular weight with fixed negative charges and thereby induces osmosis [22]. The AF is composed of type I collagen fibers in the lamellae and limits the swelling of the NP and adjacent vertebral segmental motion. The swelling pressure of the NP is opposed by tensile forces in the collagen fibers of the AF [3,23]. Physiological degeneration of lumbar intervertebral discs usually starts in the second decade of life. The metabolic derangement of NP involves decreased water content, progressive loss of proteoglycan and damage to the collagen matrix [24,25]. Our data indicates that the use of T2 relaxometry provides a qualitative and quantitative diagnosis of DDD. Conventional MRI has acceptable qualitative accuracy in detecting morphological changes as part of the diagnostic characterization of disc disease due to aging and degeneration but is unable to identify the clinical significance in asymptomatic individuals [26,27]. Recent studies have suggested that MRI cannot provide information on the cause of back pain in DDD, given that similar morphological changes have been observed in patients with back pain and in asymptomatic individuals [6,28-30].

The relaxation times of the NP change by approximately 10% per decade in normal disks. A 20%–50% change has been shown in Pfirrmann grade III degeneration. T2 relaxation times in the intervertebral disc have been shown to decrease gradually with age and degeneration as a result
of diminishing water and glycosaminoglycan content in the disc [1,15]. Given that T2 correlates very closely with water content, T2 in theory could provide a continuous measure of hydration in the disc’s cartilage matrix.

The increased FA in the NP, in contrast to the unchanged FA in the AF of degenerated discs, indicates multiple changes in the NP and the AF that may not correlate with morphological changes seen in T2W images. Chan et al. [18] demonstrated that mean FA values in the AF were significantly higher than those in the NP and observed that mean FA values in the NP increased as the degeneration progressed from the early to advanced stage, with a relatively inert change in mean FA values in the AF. The authors concluded that early disc degeneration could be detected by including the quantitative DTI indices in the clinical imaging protocol [5,18].

The disadvantages of current grading scales are their subjectivity, a lack of specific criteria for characterizing distinct or indistinct boundaries and their ambiguity regarding degeneration versus age-related changes. These scales are discontinuous, rendering only obvious measurable changes in disc morphology and providing limited value in the short-term monitoring of the intervertebral disc signal. These scales are also unable to distinguish the progression of degeneration and repair without a major morphological change. Disc degeneration or regeneration is also not effectively demonstrated with discontinuous scales such as the Thompson and Pfirrmann scales.

A continuous scale or scoring system is therefore required to evaluate intervertebral disc disease [4,7]. Our scoring system is both qualitative and quantitative, using T2 relaxometry color maps and values for disc hydration and water content. FA values from the NP and AF and their ratio provide a structural correlation. This study is not only predictive but is also potentially reproducible.

3. Limitations

The study’s limitations include its small sample size. This study can be replicated with larger sample sizes from healthy populations and patients to create a quantitative atlas of disc degeneration indices.

Conclusions

This study shows that quantitative MRI with T2 maps and DTI provides objective evidence of disc degeneration (early/advanced) and facilitates the use of novel diagnostic quantitative imaging therapies for the early detection of disc degeneration. This method also helps predict the disc health of adjacent segments above and below the level of the proposed surgery or instrumentation. Given that instrumentation accelerates disc degeneration by increasing the loading on noninstrumented discs, it is vital to predict which disc adjacent to the proposed fusion level will degenerate early. Aging and disc tissue degeneration correlate with the transformation of the NP fluid-like structure to the cartilaginous fibrous structure (AF) scored by T2 relaxometry and DTI. This scale is relatively simple, practical, and objective and helps provide guidance on the level of surgery in avoiding unnecessary long segment fusions with short- and/or long-term complications.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Marinelli NL, Haughton VM, Munoz A, Anderson PA. T2 relaxation times of intervertebral disc tissue correlated with water content and proteoglycan content. Spine (Phila Pa 1976) 2009;34:520-4.
2. Wang C, Auerbach JD, Witschey WR, Balderston RA, Reddy R, Borthakur A. Advances in magnetic resonance imaging for the assessment of degenerative disc disease of the lumbar spine. Semin Spine Surg 2007;19:65-71.
3. Bernick S, Walker JM, Paule WJ. Age changes to the anulus fibrosus in human intervertebral discs. Spine (Phila Pa 1976) 1991;16:520-4.
4. Lotz JC, Haughton V, Boden SD, et al. New treatments and imaging strategies in degenerative disease of the intervertebral disks. Radiology 2012;264:6-19.
5. Marchand F, Ahmed AM. Investigation of the laminate structure of lumbar disc anulus fibrosus. Spine (Phila Pa 1976) 1990;15:402-10.
6. Thompson JP, Pearce RH, Schechter MT, Adams ME, Tsang IK, Bishop PB. Preliminary evaluation of a scheme for grading the gross morphology of the human intervertebral disc. Spine (Phila Pa 1976) 1990;15:411-5.
7. Haughton V. Imaging intervertebral disc degenera-
8. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976) 2001;26:1873-8.

9. Blumenkrantz G, Zuo J, Li X, Kornak J, Link TM, Majumdar S. In vivo 3.0-tesla magnetic resonance T1rho and T2 relaxation mapping in subjects with intervertebral disc degeneration and clinical symptoms. Magn Reson Med 2010;63:1193-200.

10. Mwale F, Iatridis JC, Antoniou J. Quantitative MRI as a diagnostic tool of intervertebral disc matrix composition and integrity. Eur Spine J 2008;17 Suppl 4:432-40.

11. Perry J, Haughton V, Anderson PA, Wu Y, Fine J, Mistretta C. The value of T2 relaxation times to characterize lumbar intervertebral disks: preliminary results. AJNR Am J Neuroradiol 2006;27:337-42.

12. Boos N, Wallin A, Gbedegbegnon T, Aebi M, Boesch C. Quantitative MR imaging of lumbar intervertebral disks and vertebral bodies: influence of diurnal water content variations. Radiology 1993;188:351-4.

13. Boos N, Wallin A, Schmucker T, Aebi M, Boesch C. Quantitative MR imaging of lumbar intervertebral disc and vertebral bodies: methodology, reproducibility, and preliminary results. Magn Reson Imaging 1994;12:577-87.

14. Kerttula L, Kurunlahti M, Jauhiainen J, Koivula A, Olkarien J, Tervonen O. Apparent diffusion coefficients and T2 relaxation time measurements to evaluate disc degeneration: a quantitative MR study of young patients with previous vertebral fracture. Acta Radiol 2001;42:585-91.

15. Marinelli NL, Haughton VM, Anderson PA. T2 relaxation times correlated with stage of lumbar intervertebral disk degeneration and patient age. AJNR Am J Neuroradiol 2010;31:1278-82.

16. Urban JP, McMullin JF. Swelling pressure of the lumbar intervertebral discs: influence of age, spinal level, composition, and degeneration. Spine (Phila Pa 1976) 1996;21:415-20.

17. Kealey SM, Aho T, Delong D, Barboriak DP, Provenzale JM, Eastwood JD. Assessment of apparent diffusion coefficient in normal and degenerated intervertebral lumbar disks: initial experience. Radiology 2005;235:569-74.

18. Chan Q, Anthony MP, Zhang Z, Cheung KM, Kim M. Quantitative evaluation of diffusion tensor imaging at 3T in human lumbar intervertebral disc degeneration. Proc Intl Soc Mag Reson Med 2010;18:538.

19. Niu G, Yu X, Yang J, Wang R, Zhang S, Guo Y. Apparent diffusion coefficient in normal and abnormal pattern of intervertebral lumbar discs: initial experience. J Biomed 2011;25:197-203.

20. Wu N, Liu H, Chen J, et al. Comparison of apparent diffusion coefficient and T2 relaxation time variation patterns in assessment of age and disc level related intervertebral disc changes. PLoS One 2013;8:e69052.

21. Zhang Z, Chan Q, Anthony MP, et al. Age-related diffusion patterns in human lumbar intervertebral discs: a pilot study in asymptomatic subjects. Magn Reson Imaging 2012;30:181-8.

22. Roberts S, Urban JP, Evans H, Eisenstein SM. Transport properties of the human cartilage endplate in relation to its composition and calcification. Spine (Phila Pa 1976) 1996;21:415-20.

23. Adams MA. Biomechanics of back pain. Acupunct Med 2004;22:178-88.

24. Majumdar S. Magnetic resonance imaging and spectroscopy of the intervertebral disc. NMR Biomed 2006;19:894-903.

25. Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. Spine (Phila Pa 1976) 2004;29:2700-9.

26. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: a prospective investigation. J Bone Joint Surg Am 1990;72:403-8.

27. Borenstein DG, O’Mara JW Jr, Boden SD, et al. The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects: a seven-year follow-up study. J Bone Joint Surg Am 2001;83-A:1306-11.

28. Boos N, Dreier D, Hilfiker E, et al. Tissue characterization of symptomatic and asymptomatic disc herniations by quantitative magnetic resonance imaging. J Orthop Res 1997;15:141-9.

29. Elfering A, Semmer N, Birkhofer D, Zanetti M, Hodler J, Boos N. Risk factors for lumbar disc degeneration: a 5-year prospective MRI study in asymptomatic individuals. Spine (Phila Pa 1976) 2002;27:125-4.

30. Jarvik JG, Deyo RA. Diagnostic evaluation of low back pain with emphasis on imaging. Ann Intern Med 2002;137:586-97.