Joshua D. Auerbach
Wade Johannessen
Arijitt Borthakur
Andrew J. Wheaton
Carol A. Dolinskas
Richard A. Balderston
Ravinder Reddy
Dawn M. Elliott

In vivo quantification of human lumbar disc degeneration using $T_{1\rho}$ -weighted magnetic resonance imaging

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J. D. Auerbach · W. Johannessen
D. M. Elliott (✉)
Department of Orthopaedic Surgery,
McKay Orthopaedic Research Laboratory,
University of Pennsylvania,
424 Stemmler Hall, Philadelphia, PA
19104-6081, USA
E-mail: dellott@mail.med.upenn.edu
Tel.: +1-215-8988653
Fax: +1-215-5732133

A. Borthakur · A. J. Wheaton · R. Reddy
MMRCC, Department of Radiology,
University of Pennsylvania, Philadelphia,
PA, USA

C. A. Dolinskas
Department of Radiology,
Pennsylvania Hospital, Philadelphia
PA, USA

R. A. Balderston
Booth, Bartolozzi, and Balderston
Orthopaedics, Pennsylvania Hospital,
Philadelphia, PA, USA

Abstract Diagnostic methods and biomarkers of early disc degeneration are needed as emerging treatment technologies develop (e.g., nucleus replacement, total disc arthroplasty, cell therapy, growth factor therapy) to serve as an alternative to lumbar spine fusion in treatment of low back pain. We have recently demonstrated in cadaveric human discs an MR imaging and analysis technique, spin-lock $T_{1\rho}$ -weighted MRI, which may provide a quantitative, objective, and non-invasive assessment of disc degeneration. The goal of the present study was to assess the feasibility of using $T_{1\rho}$ MRI in vivo to detect intervertebral disc degeneration. We evaluated ten asymptomatic 40–60-year-old subjects. Each subject was imaged on a 1.5 T whole-body clinical MR scanner. Mean $T_{1\rho}$ values from a circular region of interest in the center of the nucleus pulposus were calculated from maps generated from a series of $T_{1\rho}$ -weighted images. The degenerative

grade of each lumbar disc was assessed from conventional T_2 -weighted images according to the Pfirmann classification system. The $T_{1\rho}$ relaxation correlated significantly with disc degeneration ($r = -0.51$, $P < 0.01$) and the values were consistent with our previous cadaveric study, in which we demonstrated correlation between $T_{1\rho}$ and proteoglycan content. The technique allows for spatial measurements on a continuous rather than an integer-based scale, minimizes the potential for observer bias, has a greater dynamic range than T_2 -weighted imaging, and can be implemented on a 1.5 T clinical scanner without significant hardware modifications. Thus, there is a strong potential to use $T_{1\rho}$ in vivo as a non-invasive biomarker of proteoglycan loss and early disc degeneration.

Keywords Intervertebral disc degeneration · Magnetic resonance imaging (MRI) · Spin lock · Nucleus

Introduction

Degenerative disc disease, which has been implicated as a potential source of low back pain [17, 24, 38], is characterized in its late stages by a loss of disc height, annular tears and rim lesions, and osteophyte formation [2, 13]. While lumbar spinal fusion is currently the gold standard for surgical treatment of low back pain with

advanced degeneration, earlier stages of disc degeneration may be amenable to emerging alternative treatments (e.g., nucleus replacement, total disc arthroplasty, cell therapy, growth factor therapy) that may preclude the morbidity associated with fusion [9, 10, 14]. These treatments will likely be targeted to the early stages of degeneration, which can be characterized by loss of proteoglycan in the disc nucleus pulposus. Proteoglycan

loss reduces the capacity to bind water and leads to a loss of hydration and pressure [5, 13, 37]. Diagnostic methods and a system for classification of these early degenerative changes are needed and will become more important as these emerging treatment technologies develop.

The ideal classification system for disc degeneration is quantitative, permits region-specific evaluation within the disc sub-structures, avoids observer bias, can detect early subtle changes, and correlates with clinical symptoms. The widely used classification system of Pfirrmann is based on conventional T_2 -weighted MR images: an integer grade (between I and V) is assigned to the disc based on signal intensity and structural morphology (e.g., homogeneity within the nucleus pulposus, distinction between the NP and the annulus fibrosus, and disc height) [29]. Although this classification system is among the most widely accepted and used [23], and provides excellent detection of advanced stage degeneration, integer-based classification systems cannot discriminate among early degenerative changes [8, 25, 28]. Moreover, integer-based classification systems are qualitative, susceptible to observer bias, and are not specific for disc sub-structures. Therefore, there continues to be a need for a quantitative method to detect early localized disc degenerative changes.

We have recently demonstrated an MR imaging and analysis technique, spin-lock $T_{1\rho}$ -weighted MRI, which may provide a quantitative, objective, and non-invasive assessment of degenerative changes [20]. We showed in cadaveric human discs that in the nucleus pulposus $T_{1\rho}$ strongly correlates with proteoglycan content (Fig. 1), and with the Pfirrmann classification grade [20]. $T_{1\rho}$ is defined as the spin-lattice relaxation in the rotating frame and is influenced by the relaxation of water protons in the presence of extracellular matrix molecules

[1, 31, 32, 41]. Matrix changes, such as loss of proteoglycan, may be reflected in the $T_{1\rho}$ relaxation time. In articular cartilage, $T_{1\rho}$ is strongly correlated with proteoglycan content and mechanical properties and is being studied for its potential as a biomarker of early osteoarthritis [1, 39]. The goal of the present study was to assess the feasibility of using $T_{1\rho}$ MRI in vivo to detect intervertebral disc degeneration. We evaluated asymptomatic 40–60-year-old subjects, an age range in which a broad spectrum of disc degeneration, possibly including early degeneration, was expected.

Materials and methods

Ten subjects (five males, five females) were recruited to undergo MRI of their lumbar spine following approval from our Institutional Review Board (IRB). Inclusion criteria consisted of (1) age between 40 and 60 years, (2) no prior back surgery, and (3) no significant back pain within the past 6 months (as determined by absence from work due to back pain, a period of bracing, or diagnostic/therapeutic injections). Subjects were excluded if they failed to meet the above criteria or if they had any complaints suggestive of sciatica or neurological involvement including leg weakness, numbness, or tingling.

Each subject was imaged on a 1.5 T whole-body clinical MR scanner (Sonata, Siemens Medical Solutions) according to two protocols. First, a conventional T_2 -weighted image was acquired using a standard spin-echo imaging sequence to assess degenerative grade. The scan was acquired with the following parameters: FOV = 28×28 cm; slice thickness = 4 mm; acquisition matrix = 256×256; and TE/TR = 127 ms/4,320 ms. Second, a series of $T_{1\rho}$ -weighted images was acquired using a turbo spin-echo based imaging sequence [12] with the following parameters: FOV = 28×28 cm; slice thickness = 4 mm; acquisition matrix = 512×512; and TE/TR = 12 ms/3,000 ms with 3 echoes per TR. Spin-lock pulse durations ranged from 15 to 75 ms with a spin-lock pulse amplitude set to correspond to a nutation frequency of 400 Hz. The body coil of the scanner was used to transmit RF pulses and three receivers of a spine-array coil were used to receive the signal from the lower spine.

The degenerative grade of each lumbar disc ($n = 50$) was assessed from T_2 -weighted images according to the classification system described by Pfirrmann et al. [29]. Grading was performed by three independent physicians: one board-certified musculoskeletal radiologist (CAD), one resident in orthopaedic surgery (JDA), and one physician research associate. In order to calculate intra-observer reliability, grading was performed by all three observers on 3 consecutive weeks. Inter- and intra-observer reliability of T_2 -weighted disc grading was then

Fig. 1 A strong correlation between $T_{1\rho}$ and nucleus pulposus s-GAG content has been previously established in human cadaveric samples [20]

Fig. 2 A representative set of images from an asymptomatic 41-year-old male subject. **a** Slight loss of signal intensity on the T₂-weighted image suggests degeneration at L4/L5 disc. **b** This is confirmed by a lower T_{1ρ} relaxation time (only 105 ms) on T_{1ρ} maps of the discs overlaid on a T_{1ρ} image. **c** Enlarged views of the maps which also schematically represent the region of interest (ROI) used for computing mean T_{1ρ} (white circles)

determined by calculating a kappa statistic (SAS Software, MKAPPA macro written by WESTAT Inc).

T_{1ρ} values were calculated from the spin-lock images by performing a linear regression of pixel intensity data to an exponential decay function of spin-lock time:

$S(TSL) = S_0 e^{-(TSL/T_{1\rho})}$. A spatial map of T_{1ρ} was generated from these data and a 5-mm circular region of interest was manually selected in the center of the nucleus pulposus in order to calculate mean T_{1ρ} (Fig. 2c). Region of interest selection was performed by two independent investigators. Linear regressions between T_{1ρ} and degenerative grade were performed using Graphpad Prism software (GraphPad Software, San Diego CA, USA). The correlation between mean quantitative T_{1ρ} values from both investigators was calculated to determine inter-observer reliability.

Results

Acquisition of T₂- and T_{1ρ}-weighted MR images was performed on all ten subjects. The average total scan time was 35 min. A representative T₂-weighted image from an asymptomatic 41-year-old male subject demonstrates evidence of early disc degeneration at the L4/L5 level (Fig. 2a). This qualitative observation is quantified in the T_{1ρ} map of the disc overlaid on the T_{1ρ} image (Fig. 2b) and the enlarged T_{1ρ} maps of each disc (Fig. 2c), where a broad range of T_{1ρ} values (105–151 ms) can be observed from L1 to S1, with a notably lower value of 105 ms at L4/L5. A similar set of representative images from an asymptomatic 58-year-old female (Fig. 3) demonstrates overall lower T_{1ρ} values (55–105 ms), with higher T_{1ρ} values at the less

Fig. 3 A representative set of images from an asymptomatic 58-year-old female subject. **a** T₂-weighted image, **b** T_{1ρ} map overlaid on a T_{1ρ} image, **c** T_{1ρ} map. The L1/L2 and L2/L3 discs are non-degenerate with relatively high T_{1ρ} times. In contrast, the L3/L4 and L4/L5 discs show a distinct loss of signal intensity on T₂ imaging and a dramatic decrease in T_{1ρ} time. The severely degenerate L5S1 disc was not included in analysis due to lack of tissue

Fig. 4 There was an inverse correlation between $T_{1\rho}$ relaxation and degenerative grade. Average degenerative grade, based on the Pfirrmann classification scale, was calculated as the mean from three independent observers

degenerate L1/L2 and L2/L3 discs and lower $T_{1\rho}$ values corresponding to the more degenerate L3/L4 and L4/L5 discs. The L5/S1 disc in this example was too degenerate to determine the $T_{1\rho}$ value.

The $T_{1\rho}$ values for all levels of all ten subjects were correlated with the Pfirrmann grade (Fig. 4). Linear regression analysis revealed a significant correlation between $T_{1\rho}$ relaxation time and degenerative grade ($r = -0.51$, $P < 0.01$). For each of the integer grades, Fig. 4 demonstrates a wide range of $T_{1\rho}$ values. There was an excellent agreement ($r = 0.95$) between investigators in selecting region of interest location for calculating $T_{1\rho}$ relaxation (Fig. 5). In comparison, for the integer grading among the three observers, the kappa values for intra-observer reliability ranged from 0.53 to 0.91, and the inter-observer reliability was moderate, ranging from 0.49 to 0.63. The $T_{1\rho}$ values determined in vivo in the 40–60-year-old population were on the same order of magnitude as the values previously measured in cadaveric samples with a wider age range of 15–81 years (Fig. 6) [20].

Discussion

This study demonstrates the feasibility of performing in vivo quantification of human lumbar disc degeneration in a 40–60-year-old asymptomatic population using $T_{1\rho}$ -weighted magnetic resonance imaging. $T_{1\rho}$ relaxation time correlated significantly with disc degeneration (Fig. 4) and the values were consistent with our previous in vitro cadaveric study (Fig. 6) [20]. In that study we demonstrated correlation between $T_{1\rho}$ and proteoglycan content of the nucleus pulposus (Fig. 1) [20]. This suggests a strong potential to use $T_{1\rho}$ in vivo as a

Fig. 5 Two independent investigators calculated mean $T_{1\rho}$ from a user-selected circular region of interest within the center of the nucleus pulposus. A correlation of mean values indicates excellent agreement ($r = 0.95$) between investigators

non-invasive biomarker of proteoglycan loss and early disc degeneration. The correlations of $T_{1\rho}$ and other quantitative measures, such as proteoglycan content, are stronger than with grading systems due to the inherent limitations of integer-based grading systems that do not distribute the data along a continuum.

Similar quantitative imaging studies investigating intervertebral disc degeneration have been performed previously, including T_1 - and T_2 -weighted relaxation [4, 8, 11], magnetization transfer [27], diffusion imaging [3, 15, 18, 21], and spectroscopy [19, 22]. Some techniques, while appropriate for basic science research, are less suitable for clinical in vivo applications. Other methods, such as dGEMRIC and sodium MRI [6, 7, 40, 42], which have been demonstrated for cartilage imaging, may not be readily applied to the disc due to the restricted diffusion of the contrast agent necessary for the technique. Potential advantages of $T_{1\rho}$ MRI as a biomarker over other techniques include the ability to provide quantitative spatial measurements of disc substructures on a continuous scale, the ability to detect early, subtle changes of disc degeneration, and ease of implementation on 1.5 T clinical MR scanners without the need for significant hardware modifications. Because $T_{1\rho}$ relaxation times are larger than T_2 relaxation times, $T_{1\rho}$ imaging has an increased dynamic range [30]. This advantage for $T_{1\rho}$ is likely to be critical for in vivo applications, where resolution is near the limit for current clinical scanners and imaging time of approximately 30 min is near the tolerance level for human subjects.

These findings suggest the potential for $T_{1\rho}$ MRI as a diagnostic tool to supplement or potentially replace conventional MRI and radiographs in the detection of

Fig. 6 $T_{1\rho}$ relaxation times from this in vivo study for subjects between 40 and 60 years old (*circles*) were within the range of values from a previous cadaveric in vitro experiment (*triangles*) [20]

Fig. 7 Spin-lock MRI techniques, such as $T_{1\rho}$ -weighted imaging, may have the potential to detect degenerative changes earlier than conventional MRI or radiography

early disc degeneration (Fig. 7). Diagnosis with $T_{1\rho}$ MRI is particularly suited for early stages of degeneration, when sufficient disc tissue is available to select a region of interest; conventional imaging techniques can detect late stages of degeneration such as significant loss of disc height. A quantitative assessment tool that is sensitive to early degeneration will be particularly important in light of continued development of emerging treatment modalities such as nucleus pulposus replacements, disc repair enhancement via injection or gene therapy-mediated growth factors, and stem cell transplantation therapy [26, 33–36]. Successful translation of these emerging modalities will depend upon better diagnosis of early degeneration and the ability to

non-invasively quantitatively evaluate their efficacy. Using $T_{1\rho}$ weighted MRI as a biomarker for disc degeneration and restoration may be a critical tool in this evaluation.

This initial feasibility study has limitations. First, the subjects were intentionally selected from an age range limited to 40–60 years. Future study, therefore, should be performed in a larger subject population with a broader range of ages and degrees of degeneration. We evaluated reproducibility of the grading methods individually, but did not perform a direct statistical comparison between the continuous $T_{1\rho}$ -weighted MRI and the nominal Pfirrmann grading classification. However, it is clear that there is an excellent reproducibility using the $T_{1\rho}$. In comparison, the nominal Pfirrmann classification was found to be only moderately reproducible. Additional studies to assess repeatability and the potential confounding role of diurnal disc hydration changes are also needed. This initial study in asymptomatic subjects did not explore the correlation between $T_{1\rho}$ and clinical symptoms. The relationship between low back pain and disc degeneration detected via any assessment tool remains controversial. Future studies should be directed toward evaluating the ability of $T_{1\rho}$ -weighted MRI to detect degeneration in patients with back pain.

Conclusions

This study demonstrated quantitative in vivo assessment of human lumbar disc degeneration using $T_{1\rho}$ -weighted magnetic resonance imaging. The $T_{1\rho}$ relaxation correlated significantly with disc degeneration and the values were consistent with our previous in vitro cadaveric study, in which we demonstrated correlation between $T_{1\rho}$ and proteoglycan content [20]. The technique allows for spatial measurements on a continuous rather than an integer-based scale, minimizes the potential for observer bias, has a greater dynamic range than T_2 -weighted imaging, and can be implemented onto a 1.5 T clinical scanner without significant hardware modifications. Thus, there is a strong potential to use $T_{1\rho}$ in vivo as a non-invasive biomarker of proteoglycan loss and early disc degeneration.

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