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The Shear Modulus of the Nucleus Pulposus Measured Using MR Elastography: A Potential Biomarker for Intervertebral Disc Degeneration

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Summary

Purpose—This study aims to: 1) measure the shear modulus of nucleus pulposus (NP) in intact human vertebra-disc-vertebra segments using a magnetic resonance elastography (MRE) setup for a 7T whole-body scanner, 2) quantify the effect of disc degeneration on the NP shear modulus measured using MRE, and 3) compare the NP shear modulus to other MR-based biomarkers of disc degeneration.

Methods—Thirty intact human discs segments were classified as normal, mild, or severely degenerated. The NP shear modulus was measured using a custom-made setup that included a novel inverse method less sensitive to noisy displacements. T_2 relaxation time was measured at 7T. The accuracy of these parameters to classify different degrees of degeneration was evaluated using ROC curves.

Results—The MRE measure of shear modulus in the NP was able to differentiate between normal, mild degeneration, and severe degeneration. The T_2 relaxation time was able to differentiate between normal and mild degeneration, but it could not distinguish between mild and severe degeneration.

Conclusion—This study shows that the NP shear modulus measured using MRE is sensitive to disc degeneration and has the potential of being used as a clinical tool to quantify the mechanical integrity of the intervertebral disc.

Keywords

Intervertebral disc; magnetic resonance elastography; degeneration biomarkers

Introduction

Intervertebral disc degeneration is characterized by a progressive change in structure, composition and mechanical properties of the annulus fibrosus, nucleus pulposus (NP) and end plates (1–4). Structural and biochemical changes are first noticeable and more severe in

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the NP (4,5). In early degeneration, proteoglycan depletion in the NP leads to a decrease of water content, osmotic pressure and stiffness (3,4). Advanced stages of degeneration are characterized by a disc height loss and the presence of fissures and tears in the annulus fibrosus (1). The changes with advanced degeneration are permanent due to the slow matrix turnover of disc cells (6–9). Therefore, early diagnosis of disc degeneration is critical for the success of any molecular or biological treatment strategy.

Although there is no gold-standard method to diagnose early disc degeneration, several techniques are used to evaluate degenerative changes in the disc. The Pfirrmann score is used to evaluate the severity of disc degeneration based on the morphology and brightness of the disc in a T_2 -weighted MR images (10). The Pfirrmann score ranges from 1 to 5 for normal to severely degenerated discs, respectively. Even though this score is widely used, it cannot be considered as a gold standard for diagnosis of early degeneration because it is a subjective classification that may be susceptible to observer bias. Additionally, it is difficult to detect changes during early degeneration using the Pfirrmann score (11). Quantitative MR parameters, such as $T_{1\rho}$ and T_2 relaxation times, have been proposed as biomarkers of disc degeneration. $T_{1\rho}$ and T_2 correlate to Pfirrmann score, NP mechanics, NP water and NP proteoglycan content (12–14). While an improvement compared to degenerative scores, these parameters may not be sensitive to structural and organizational changes of the components of the disc. For example, the T_2 relaxation time of unloaded discs does not change significantly after digesting the NP using trypsin, even though the mechanical properties are altered (15–17). This suggests that the MR parameters may be more sensitive to composition than to the disc structure. Other MR methods such as magnetization transfer ratio, and sodium-23 imaging have also been applied to the disc (18,19). NP mechanical properties measured in-vitro are sensitive to both biochemical and structural changes during early degeneration (20–22). For example, the NP compressive modulus decreases significantly with degeneration (22). Additionally, the NP torsional shear modulus increases with early degeneration (20). Therefore, mechanical properties can be used to evaluate the mechanical integrity of the NP and have the potential to quantify early changes in the degeneration cascade.

The shear modulus of soft tissues can be measured non-invasively using magnetic resonance elastography (MRE) (23). MRE has been successfully used to diagnose and localize diseases that involve changes in the stiffness of the tissue such as liver fibrosis, breast cancer tumors and brain injuries (24–31). However, the mechanical properties of the intervertebral disc have not been measured non-invasively using MRE. The objectives of this study were: 1) to measure the NP shear modulus in intact human vertebra-disc-vertebra segments using a newly designed MRE setup for a 7T whole-body scanner, 2) to quantify the effect of degeneration on the NP shear modulus measured using MRE, and 3) to compare the shear modulus to other MR biomarkers of disc degeneration.

Methods

MRE setup

An electromechanical actuator was designed and fabricated to apply vibrations to human intact disc segments (vertebra-disc-vertebra) (Figure 1). The actuator consisted of a solenoid

coil of 24-gauge magnet-litz wire wound in layers of 20 mm inner diameter, 50 mm outer diameter, and a height of 25mm. The coil had a DC resistance of 5 Ohms. This coil was mounted on an acrylic shaft that had a ceramic tip to transmit the motion to the upper vertebra of the disc segment. The acrylic shaft was pivoted in a 100 mm diameter acrylic tube that was also used to hold the sample. The actuator was driven by a function generator (AWG2005, Tektronix, Beaverton, OR) coupled to a DC current amplifier (DC-300A II, Crown, Mishawaka, RD), making use of the static B_0 field to create torque via the Lorentz force. The sample was placed inside in a single-loop transmit/receive coil without any fixation. The motion actuator was then placed on top of the coil and the sample was held in place by sand bags. The sand bags kept the actuator from tipping over and applied a small amount of compression to the sample through the ceramic tip. When the actuator was activated, vibration was applied to whole disc segment. The single-loop transmit/receive RF surface coil was tuned to 297.2 MHz (Figure 1).

A 3D gradient echo pulse sequence was modified to include a motion sensitizing gradient (MSG) block, consisting of a series of oscillating polarity trapezoidal gradient pulses, with a frequency equal to the driving frequency of the electromechanical actuator. The amplitude of the gradients was 23 mT/m with rising time of 150 μ s. The number of cycles in the MSG was chosen according to the frequency and the TE time (12 cycles were used in the human disc measurements with a frequency 1250Hz and TE of 16 ms). In Siemens MR scanners the gradients must start and end at integer multiples of the raster time (10 μ s) which limits the possible oscillation frequencies of the MSG to values including 100, 200, 250, 500, 625, 1000, 1250 and 2500 Hz. The MSG was included on each of the gradient channels to measure the three components of the tissue displacement. Displacement data were acquired twice with opposite polarities of the MSG to cancel the background phase (32). Since the electromechanical actuator was run continuously during the entire data acquisition, there was a restriction on the timing of the sequence. The TR value was chosen to be an integer multiple of the period of the mechanical oscillation. In this way, the sequence was phase-locked to the mechanical oscillation. The start time of the MSG with respect to the slice-selective RF pulse determined the phase offset between the MSG and the mechanical oscillation. According to the Nyquist sampling theorem, the sampling frequency should be at least twice the highest frequency of the signal. Consequently, for MRE, two time points (i.e., phase offsets) were sufficient to avoid aliasing. In this study, the displacements were acquired for four different phase offsets separated by $\pi/2$ radians, which is twice the minimum sampling frequency. Therefore, the entire k-space was acquired 24 times (2 MSG polarities $\times$ 3 MSG directions $\times$ 4 MSG phase offsets). Additionally, ten dummy TR cycles were applied before any data acquisition to reach steady-state of the longitudinal magnetization.

Displacement Calculation

displacements were calculated from the phase data using the following equation (23):

$$\varphi(\mathbf{r}, \theta) = \frac{2\gamma NT(\mathbf{G} \cdot \boldsymbol{\xi}_0)}{\pi} \sin((\mathbf{k} \cdot \mathbf{r} + \theta)). \quad [1]$$

Where ϕ is the phase shift of the MR signal, γ is the gyromagnetic ratio, N is the number of cycles of the MSG, T is the time period of the MSG, $\mathbf{G}$ is the MSG vector, ξ_0 is the displacement vector, θ is the phase offset between the MSG and the mechanical vibration, $\mathbf{k}$ is wave vector, and $\mathbf{r}$ is position vector. A Fourier transformation was applied to the displacement vector field in the region of interest (ROI). A Helmholtz decomposition was then applied to obtain the divergence-free component of the displacement field, which is related to the shear waves generated by the motion actuator (33). The shear modulus was obtained by analyzing the motion equation and considering the divergence-free component of the displacement field as shown in the following section.

Inverse Method

Inverse methods that use second-order spatial derivatives are very sensitive to noise in the displacement (34,35). Therefore a method to calculate the shear modulus was developed to use first-order spatial derivatives of the displacement. The method is based on finding the weak formulation of the wave equation. The NP was considered to be a linear isotropic solid material. Several studies in other tissues have used more advanced models for the inverse method, including biphasic and viscoelastic (24,27,29,36–41). The assumption of a linear isotropic solid material is justified here since small deformations and strains were applied to the tissue, the same frequency was used for all the human samples, and any potential relative displacements between the NP fluid and solid components at the test frequency were unknown. The wave equation for linear isotropic materials is:

$$\lambda \nabla (\nabla \cdot \mathbf{u}) + \mu \nabla^2 \mathbf{u} = \rho \frac{\partial^2 \mathbf{u}}{\partial t^2} \quad [2]$$

Where μ and λ , are the Lamé elastic constants, ρ is the density, and $\mathbf{u}$ is the displacement vector. Considering the divergence-free component of the displacement field in the Fourier domain, Eq (2) is expressed as:

$$\mu \nabla^2 \bar{\mathbf{u}} = -\rho \omega^2 \bar{\mathbf{u}}, \quad [3]$$

where $\bar{\mathbf{u}}$ is the transformed displacement vector, and ω is the angular frequency. To reduce the order of the spatial derivatives, the weak form of Eq (3) was obtained using the displacements as weight functions. To do this, Eq (3) was multiplied by $\bar{\mathbf{u}}$ and integrated over a volume of interest (Ω):

$$\mu \int_{\Omega} \bar{\mathbf{u}} \cdot \nabla^2 \bar{\mathbf{u}} d\Omega = -\rho \omega^2 \int_{\Omega} \bar{\mathbf{u}} \cdot \bar{\mathbf{u}} d\Omega. \quad [4]$$

The left term of Eq (4) was re-written as:

$$\mu \int_{\Omega} [\nabla (\bar{\mathbf{u}} \cdot \nabla \bar{\mathbf{u}}) - \nabla \bar{\mathbf{u}} : \nabla \bar{\mathbf{u}}] d\Omega = -\rho \omega^2 \int_{\Omega} \bar{\mathbf{u}} \cdot \bar{\mathbf{u}} d\Omega. \quad [5]$$

Applying the divergence theorem to the first term of the left-hand side of Eq (5) a formulation of the motion equation with only first order derivatives was obtained:

$$\mu \left(\int_{\Gamma} \bar{\mathbf{u}} \cdot \nabla \bar{\mathbf{u}} \cdot \mathbf{n} d\Gamma - \int_{\Omega} \nabla \bar{\mathbf{u}} : \nabla \bar{\mathbf{u}} d\Omega \right) = -\rho \omega^2 \int_{\Omega} \bar{\mathbf{u}} \cdot \bar{\mathbf{u}} d\Omega. \quad [6]$$

where Ω and Γ are the volume and the surface of the region of interest and $\mathbf{n}$ is a unit vector normal to the surface Γ . From Eq (6) the shear modulus was calculated as:

$$\mu = \rho \omega^2 \frac{\int_{\Omega} \bar{\mathbf{u}} \cdot \bar{\mathbf{u}} d\Omega}{\int_{\Omega} \nabla \bar{\mathbf{u}} : \nabla \bar{\mathbf{u}} d\Omega - \int_{\Gamma} \bar{\mathbf{u}} \cdot \nabla \bar{\mathbf{u}} \cdot \mathbf{n} d\Gamma} \quad [7]$$

Validation

The MRE setup and the inverse method were validated by comparing the shear modulus of agarose gels measured using both MRE and torsion tests. Agarose (Molecular Biology Grade, Benchmark Scientific, Edison NJ) was dissolved in phosphate buffered saline (PBS) at 1, 1.5, 2, 2.5, 3, 3.5, and 4% w/v. Samples were tested using the MRE setup described above. Since the wavelength increases with the stiffness of the gel, the frequency of the mechanical excitation was increased to have more than one wavelength along the length of the sample (35 mm diameter and 40mm length). The frequency at which the motion was applied varied as function of the gel concentration (625 Hz for 1% and 1.5% gel, 1000 Hz for 2% and 2.5%, 1250 Hz for 3% and 3.5%). The changes in wavelength between test and retest data in agarose gels were negligible in preliminary studies. Consequently, only one sample was tested using MRE. Conversely, torsion tests were not as repeatable. Therefore, eight torsion samples and one MRE sample were prepared and tested from the same agarose batch for each concentration. Torsion tests were applied to samples of 8 mm diameter and 1.5 mm thickness. Torsion was applied at 10 Hz using a dynamic tester (ElectroForce 3200, Bose, Framingham MA). The shear modulus was calculated from the recorded torque and rotation data. The inverse method described above was compared to a another commonly used inverse method for MRE: algebraic inversion of the differential equations (AIDE) (23,34). The AIDE expression used to calculate the shear modulus from the divergence-free, Fourier-transformed displacements was:

$$\mu = \rho \omega^2 \frac{\bar{u}_1}{\nabla^2 \bar{u}_1} \quad [8]$$

where $\bar{u}_1$ is the main component of displacements in the gel. Since one value of the shear modulus can be obtained per voxel, the mean and standard deviation within the ROI were calculated.

Human Sample Preparation and Imaging at 3 Tesla for Degeneration Score

Sixteen cadaveric human lumbar spines T12 through L5 were obtained through an approved tissue source (NDRI, Philadelphia, PA). The age of the donors ranged from 46 to 81 years old, no distinction was made for gender. Each intact spine was imaged using a 3T whole-body scanner (Tim Trio, Siemens Healthcare, Germany) to determine the Pfirrmann degeneration score and the $T_{1\rho}$ and T_2 relaxation times (10,12,13). For the Pfirrmann score, a T_2 -weighted mid-sagittal image was acquired using a turbo spin echo sequence (Turbo-

factor = 7, TE/TR = 26/3000 ms, matrix = 256×256, thickness = 5mm, voxel = 1.37×1.37×5 mm³). Each disc was scored by three independent evaluators and the most common score was assigned to the disc. Quantitative T_{1ρ} and T₂ relaxation times have been used as MR biomarkers for disc degeneration (12,13,18,42). Since the relaxation times depend on the strength of the B₀ field, all spines were imaged at 3T to obtain MR parameters comparable to other studies. T_{1ρ} and T₂ maps were calculated in the mid-sagittal plane using an established protocol (12,13). An average relaxation time of a region of 5 mm diameter in the central NP was used for each disc.

The spine was then dissected into disc segments (vertebra-disc-vertebra) with posterior elements removed. Disc segments were frozen at -20 °C until the day of the test. Based on a power analysis from data relating mechanical properties and degeneration in human discs (22), an initial set of 30 discs from T12 to L5 levels were tested. The discs were classified in terms of degeneration as Normal (Pfirrmann score 1 and 2), Mild degeneration (Pfirrmann score 3) and Severe degeneration (Pfirrmann score 4 and 5). Normal discs present no major changes of morphology and signal intensity. Discs with mild degeneration present a substantial decrease of signal intensity and minor changes in morphology. Finally, discs with severe degeneration present major changes in morphology and signal intensity. A similar classification system has been used in other studies (20,43,44). The number of spines used in this study was chosen to include sufficient normal discs for statistical analysis. There was an abundance of discs with mild degeneration. However, for the objectives of this study, there was no need to perform MRE on all the discs with mild degeneration and only 11 were used. On the day of the test, discs were thawed and wrapped in plastic to prevent dehydration. Changes in disc mechanical properties are statistically significant only after the 4th freeze-thaw cycle (45–47). Consequently, no changes in mechanical properties are expected with the protocol used in this study.

Imaging disc segments at 7Tesla

The T₂ relaxation time and NP shear modulus were measured using a 7T whole-body scanner (Magnetom, Siemens Healthcare, Germany). A T₂ map in one axial slice of the disc was measured using a spin echo sequence (TR = 3000ms, TE = 12, 24, 48, 98, 192 ms, matrix = 64×64, thickness = 2mm, voxel = 1×1×2 mm³). An area of 64×64 mm was chosen to exceed the typical axial area of human intervertebral discs. The average T₂ relaxation time in a region of 8×8 mm was used as a representative value for the NP. The 3D displacement data were measured in the disc using the modified sequence described above (TE/TR = 16/100 ms, 6 slices of 1 mm of thickness, matrix = 64×64×6, flip angle = 30°, voxel = 1×1×1 mm³). To avoid changes in the NP shear modulus due to viscoelastic effects, the mechanical motion was applied at only one frequency (1250 Hz). The amplitude of the MSG was 23 mT/m and 12 cycles were used. The height of field of view (6 mm) was chosen to be smaller than the typical disc height (~10 mm) to avoid artifacts from the bone. Since a central difference algorithm was used to calculate spatial derivatives of displacements and the curl operation, edge voxels at the periphery of the field of view (1st and 6th slices) were not included because their values are less accurate than those of internal voxels in the field of view. For this reason, NP shear modulus was calculated in a ROI (Ω) of 8×8×4 mm³. The size of this ROI was smaller than the average dimension of the NP (lateral width ~27 mm,

anterior-posterior width ~ 20 mm) (48). In both cases (MRE and T_2), the ROI was manually placed at the center of the disc so that the all pixels were located inside the NP.

Statistical Analysis

For the validation with agarose gels, the coefficient of determinations was calculated to evaluate the relationship between the shear modulus measured using MRE and torsion. This coefficient describes how well a regression line fits a set of data, and, for single-variable functions, it is defined as the square of the Pearson's coefficient. Since the human shear modulus data did not pass a normality test (did not follow a Gaussian distribution), the shear modulus and T_2 relaxation time were calculated using median and interquartile range. To evaluate the ability of MRE-measured shear modulus and T_2 relaxation time to differentiate between the degeneration groups, the areas under the ROC (receiver operating characteristic) curves were used. The accuracy of the MRE shear modulus and T_2 relaxation time was classified as excellent (area under the curve between 1.0 and 0.9), acceptable (area under the curve between 0.9 and 0.7) and poor (area under the curve lower than 0.7). Correlations between MRE shear modulus and T_2 relaxation times at 7 Tesla, and between $T_{1\rho}$ and T_2 relaxation times at 3 Tesla were performed.

Results

Validation of the MRE methods developed in this study was performed by comparing the MRE-derived shear modulus of agarose gels to those directly measured from torsion tests. The shear modulus measured from these two techniques was highly correlated ($p < 0.01$, $r^2 = 0.88$) (Table 1). The AIDE inverse method had a large variance in the shear modulus (Table 1). This was caused by the noise in the displacement data and could be reduced by applying imaging filters (e.g., Gaussian smoothing) to decrease the noise of the data.

The Pfirrmann scores for the discs used in this study ranged between 1 and 5. One disc with a Pfirrmann score of 4 and all the discs with score of 5 were excluded from the study because the discs height was smaller than the height of the ROI, leaving a total of 26 segments used in the study. The numbers of samples for each Pfirrmann score were I ($n=1$), II ($n=10$), III ($n=11$), IV ($n=4$). When further grouped, the number of samples per degeneration group was Normal ($n=11$), Mild degeneration ($n=11$), and Severe degeneration ($n=4$). The samples were distributed across the following disc levels T12-L1 ($n=4$), L1-L2 ($n=10$), L2-L3 ($n=9$), L3-L4 ($n=1$), L4-L5 ($n=2$).

Measurements at 7 Tesla

Typical displacement fields for normal and degenerated discs are shown in Figure 2. Based on the amplitude of the displacements and the observed wavelength, shear deformations are estimated to be less than 1.0° . The MRE-derived NP shear modulus decreased with degeneration: normal (661 kPa, interquartile range 234-980), mild degeneration (135 kPa, interquartile range 48-316), and severe degeneration (71 kPa, interquartile range 51-106) (Figure 3A) and was weakly correlated with T_2 relaxation time ($r^2 = 0.30$, $p = 0.007$, Figure 3B). There was also a significant decrease of T_2 with degeneration: normal (median: 43.7 ms, interquartile range: 42.3-46.6 ms), mild degeneration (median: 37.0 ms, interquartile

range: 36.1-38.4 ms), and severe degeneration (median: 37.7 ms, interquartile range: 36.8-40.0 ms) (Figure 3C). The area under the ROC curves indicated that MRE had an acceptable accuracy for differentiating between normal, mild, and severe degeneration (Figure 4A). T_2 had an excellent accuracy for differentiating between normal and mild degeneration, but it could not distinguish between mild and severe degeneration (Figure 4B).

Measurements at 3 Tesla

There was a significant decrease of T_2 relaxation time with degeneration. Compared to 7T measurements, T_2 relaxation time had a lower area under the ROC curve for the normal and mild degeneration groups, indicating less accuracy differentiating between these groups. Additionally, T_2 time was not able to differentiate between mild and severe degeneration (Figure 4C). The T_2 relaxation times measured at 3T and 7T were moderately correlated ($p < 0.0001$, $r^2 = 0.57$). Additionally, the $T_{1\rho}$ and T_2 relaxation times were highly correlated ($p < 0.001$, $r^2 = 0.81$, Figure 4C). Other studies have shown a similar decrease in the T_2 values with degeneration at 3T (12,14). There was no significant correlation between NP shear modulus and $T_{1\rho}$ ($p = 0.560$, $r^2 = 0.014$) or T_2 ($p = 0.222$, $r^2 = 0.07$).

Discussion

The objectives of this study were to measure the NP shear modulus in intact disc segments using MRE, to quantify the effect of degeneration on the NP shear modulus, and to compare the shear modulus to other MR-based biomarkers of disc degeneration. The NP shear modulus was measured using MR elastography for the first time. The shear modulus was able to differentiate between degeneration groups. Therefore, the NP shear modulus has the potential of serving as a biomarker for disc degeneration. Additionally, the NP shear modulus is a property that describes the mechanics of the tissue and can be coupled to models relating composition, structure and mechanical behavior to directly evaluate the integrity of the intervertebral disc.

Validation of the MRE used agarose gels of different concentrations (Table 1) and demonstrated proportionality between MRE and mechanical tests. The differences between MRE properties and those measured directly using mechanical tests can be attributed to differences in the frequency and amplitude of the applied displacements (23,41). The inverse method used to calculate the shear modulus was less sensitive to noise in the displacement data compared to the more commonly used AIDE method. The large variation of the shear modulus calculated using AIDE can be reduced by applying noise filters to the displacement data.

Importantly, the MRE set up designed for this study was able to generate wave propagation in the disc (Figure 2). MRE measurements on disc segments showed that the NP shear modulus significantly decreased with degeneration (Figure 3A). It was not possible to measure the shear modulus of discs with Pfirrmann score 5 due to the reduced disc height. However, the goal of applying MRE to the intervertebral disc is to use the NP shear modulus as a biomarker for early degeneration. Other degeneration markers are obvious in discs with a Pfirrmann score of 5 rendering MRE unnecessary at this stage.

The areas under the ROC curves showed that MRE has an acceptable accuracy differentiating between normal, mild and severe degeneration. This indicates that the NP shear modulus has the potential of serving as a sensitive biomarker to disc degeneration. In terms of T_2 relaxation time at 7T, the areas under the ROC curves indicate an excellent accuracy differentiating between normal and mild degeneration. This was not surprising since the main difference between the discs classified as normal and with mild degeneration is a change in the intensity in the T_2 -weighted images. Similarly, the T_2 at 3T was able to differentiate between normal and mild degeneration. However, the lower area under the ROC curve for T_2 time measured at 3T versus that measured at 7T suggests that the accuracy of T_2 increases with the strength of the magnet. In both cases (3T and 7T), the T_2 time was not able to differentiate between mild and severe degeneration. This suggests that T_2 time is more sensitive to changes in hydration than changes in the disc structure since disc morphology represents the primary difference between mild and severe degeneration scores. Similar observations about T_2 have been made in other studies (15,17).

The shear modulus of 660 kPa for normal discs measured using MRE was higher than the ~ 10 kPa that has been reported for torsion tests (20). Yet the shear modulus of 47 kPa for severely degenerated discs obtained using MRE was similar to the ~ 60 kPa measured using torsion (20). This difference may be explained by the contribution of osmotic pressure to the NP stiffness in disc segments. The osmotic pressure is known to contribute to shear stiffness in cartilage and meniscus (49,50). In an intact healthy disc, the NP is pressurized due to osmotic effects. However, in ex situ torsion tests, the pressure is lost when the sample is dissected out of the disc for testing. Therefore, a healthy NP may appear softer in torsion since the contribution of the osmotic pressure is greatly reduced. For degenerated discs, where the osmotic pressure is negligible, the two methods resulted in similar values of shear modulus. Thus the osmotic pressure in healthy NP may contribute to the MRE measurement of shear modulus. Future studies will address the effect of composition and osmotic pressure on the shear modulus measured using MRE.

This study has some limitations. The inverse method assumes wave propagation in an infinite medium. However, the disc has a finite size. Consequently, pressure waves may be also present in the NP during this experiment. Second, the NP was not modeled as a biphasic material. The analysis of wave propagation in biphasic materials has shown the existence of two types of waves, compression and transverse (51–53), and each wave type has fast and slow components (53). For a biphasic material the wavelength of these two type waves depends on many factors including frequency, fluid volume ratio, and the shape of the pores in the solid phase. As these parameters have not yet been reported for NP, it is difficult to establish the relative displacements between the solid and fluid components. Another limitation is that a Siemens 7T whole-body scanner, which is not widely used in clinical practice, was used in this study. However, the same MRE setup can also be used in 3T or 1.5T clinical scanners. The only parameter affected from applying MRE in 3T or 1.5T scanners would be the SNR of the displacements.

There are several advantages of using mechanical parameters as biomarkers of disc degeneration. The intervertebral disc is a tissue with a primarily mechanical function: transmitting forces through the spine while allowing a relative motion between the vertebrae

(21). The mechanical behavior of the disc is the result of the interaction between the NP, annulus fibrosus, and cartilaginous endplates. The biochemical and structural changes in the degeneration cascade are first detected in the NP and are arguably more severe in the NP (4,5). Therefore, the integrity of the disc during early degeneration may be better estimated by measuring NP mechanical properties. Another advantage of using mechanical properties over MR relaxation time parameters is that, unlike $T_{1\rho}$ and T_2 relaxation times, they are insensitive to the strength of the B_0 field. This facilitates comparison between different studies and sites. In this study, the shear modulus was selected as the mechanical biomarker of disc degeneration because it can be non-invasively measured using MRE. Additionally, there are mechanical models relating composition and structure to the shear modulus that can be used to evaluate the integrity of the intervertebral disc (22,54).

Future studies will focus on elucidating the contribution of biochemical composition and intradiscal pressure to the NP shear modulus, a comparison of the displacement SNR obtained in 7T and 3T, and implementing MRE for in-vivo measurements of disc mechanical properties. Although the pulse sequence used in this study was designed and optimized using disc segments, it satisfies safety standards regarding RF power deposition and nerve stimulation for whole body applications. Therefore, it can be safely applied to patients. For an in-vivo application, it would be necessary to design an electromechanical actuator to apply motion to the lumbar spine non-invasively. Additionally, a spine transmit/receive coil may also be necessary. The difference in coils may affect the SNR of the displacement data. This MRE method has tremendous potential as a biomarker to quantify early disc degeneration and evaluating the effectiveness of molecular and biological treatments for disc degeneration.

Conclusion

This study shows that the NP shear modulus measured using MRE is sensitive to disc degeneration and has the potential to be used as a clinical tool to quantify disc degeneration. The advantages of using the NP shear modulus as a biomarker of disc degeneration are that mechanical parameters are sensitive to both compositional and structural changes and that mechanical properties do not depend on the strength of the magnet.

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Figure 1. Electromechanical actuator composed of a solenoid coil, a pivoted shaft and an outer acrylic cylinder also used to hold the sample. A 7T transmit/receive RF surface coil was used to image the sample.

Figure 2.
Representative displacement fields for (A) normal and (B) degenerated discs.

Figure 3.

MRE measurements at 7T: (A) MRE-derived shear modulus decreased with degeneration. (B) The shear modulus was also significantly correlated with T_2 relaxation time. (C) T_2 relaxation time decreased with degeneration.

Figure 4.

Evaluation of the accuracy of differentiation between degeneration groups, using ROC curves: (A) MRE shear modulus shows an acceptable accuracy of differentiation between normal, mild and severe degeneration. (B) T_2 measured at 7T had an excellent accuracy of differentiation between normal and mild degeneration but it could not distinguish between mild and severe degeneration. (C) T_2 measured at 3T had an acceptable accuracy differentiating between normal and mild degeneration, but it could not distinguish between mild and severe degeneration.

Table 1

The validation of the inverse method proposed using agarose gels of different concentration shows a good correlation between shear modulus derived from MRE and that derived from torsion tests ($p < 0.05$, $r^2 = 0.88$). AIDE results show a large variation of the shear modulus due to noisy displacement data.

Gel concentration (%)	Shear Modulus of Agarose Gels (kPa)		
	Proposed Inverse Method (Eq. 7)	Torsion	AIDE
1	13.5	21.7± 2.9	2.7 ± 83.7
1.5	57.9	68.6± 3.4	-109.7 ± 2012.5
2	85.5	61.4± 12.2	19.1 ± 413.3
2.5	122.5	153.5± 24.9	-11.3 ± 457.1
3	146.0	148.7± 10.4	-18.9415 ± 384.8
3.5	215.3	258.1± 24.35	5.3 ± 579.5
4	190.6	156.0± 44.6	40.1 ± 265.4