Noninvasive Assessment of Biochemical and Mechanical Properties of Lumbar Discs Through Quantitative Magnetic Resonance Imaging in Asymptomatic Volunteers

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Intervertebral disc degeneration is a prevalent phenomenon associated with back pain. It is of critical clinical interest to discriminate disc health and identify early stages of degeneration. Traditional clinical T2-weighted magnetic resonance imaging (MRI), assessed using the Pfirrmann classification system, is subjective and fails to adequately capture initial degenerative changes. Emerging quantitative MRI techniques offer a solution. Specifically, T2 mapping images water mobility in the macromolecular network, and our preliminary ex vivo work shows high predictability of the disc's glycosaminoglycan content (s-GAG) and residual mechanics. The present study expands upon this work to predict the biochemical and biomechanical properties in vivo and assess their relationship with both age and Pfirrmann grade. Eleven asymptomatic subjects (range: 18–62 yrs) were enrolled and imaged using a 3T MRI scanner. T2-weighted images (Pfirrmann grade) and quantitative T2* maps (predict s-GAG and residual stress) were acquired. Surface maps based on the distribution of these properties were generated and integrated to quantify the surface volume. Correlational analyses were conducted to establish the relationship between each metric of disc health derived from the quantitative T2* maps with both age and Pfirrmann grade, where an inverse trend was observed. Furthermore, the nucleus pulposus (NP) signal in conjunction with volumetric surface maps provided the ability to discern differences during initial stages of disc degeneration. This study highlights the ability of T2* mapping to noninvasively assess the s-GAG content, residual stress, and distributions throughout the entire disc, which may provide a powerful diagnostic tool for disc health assessment. [DOI: 10.1115/1.4037549]*

Introduction and Background

Back pain is one of the most prevalent musculoskeletal disorders with an estimated lifetime prevalence of 70–85%, creating significant disability and financial burden with annual costs greater than \$100 billion [1–4]. Intervertebral disc degeneration, widely regarded as a primary underlying mechanism of low back pain, presents as a loss of proteoglycan content, water, and mechanical integrity, resulting in diminished disc competency and often spinal instability [5–7]. Disc degeneration is a natural phenomenon of aging and although it accompanies low back pain, the relationship between degeneration and pain is not causal [8,9]. Therefore, understanding the natural course of disc degeneration, especially during the initial stages, provides a strong rationale to investigate and identify those individuals that may progress into back pain.

Clinically, disc degeneration is assessed with magnetic resonance imaging (MRI) using a sagittal T2-weighted imaging sequence in conjunction with the Pfirrmann classification system [10]. This subjective system grades disc health on a scale of 1 (healthy) to 5 (degenerative) based on key morphological features: signal intensity, transition from annulus fibrosus to nucleus pulposus (NP), and disc height [10]. Although this allows for the categorization of disc health, the subjective nature and the substantial morphological changes that occur between each grade limit

accuracy and consistent identification of early stage disc degeneration (i.e., subtle changes within a given grade encapsulate multiple important steps, therefore a finer scale is needed) [11–16].

Experimentally, the gold standard for assessing disc health is resection of the disc for biochemical and biomechanical analyses. However, because of the invasive nature of this procedure, it is not clinically viable. Hence, quantification of the biochemical content and biomechanical properties of the disc through diagnostic imaging may assist in advancing clinical assessment. Specifically, there is a need to objectively quantify disc degeneration that is both noninvasive and sensitive to early changes of disc health based on key morphological features and the biochemical and mechanical integrity of the disc.

Recent advances in quantitative MRI techniques offer potential solutions to this unmet need. Particularly, quantitative T2* (T2-star) MRI, a multi-echo gradient-echo sequence, images the interaction of water within the macromolecular network [17]. Our previous ex vivo work has demonstrated a strong relationship between T2* relaxation times and the glycosaminoglycan content and residual stress of the disc across the degenerative spectrum [18]. The ability of T2* relaxation times to predict biochemical and biomechanical properties demonstrates the sequence's potential to identify early stages of disc degeneration and even the ability to track the effectiveness of emerging treatments including rehabilitation, advanced surgical techniques, and biologics.

Previous studies have implemented T2* sequences to investigate disc changes associated with low back pain [14,19,20]; however, to the authors' knowledge, no studies have investigated the natural progression of degeneration throughout aging in an

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Fig. 1 Axial T2* map of a healthy intervertebral disc with ROIs identified: aAF, pAF, oAF, iAF, and NP. The iAF and oAF were obtained from the left and right lateral sides of the disc. (Reprinted with permission from Ellingson et al. [18]. Copyright 2014 by Wiley.)

asymptomatic population. Additionally, no one has used this sequence to noninvasively examine the disc's biochemical and biomechanical properties in vivo, which are the critical next steps toward clinical application. Toward this end, the purpose of this study was to predict glycosaminoglycan content and residual stress using axial T2* maps across the disc in asymptomatic volunteers to understand the natural progression of disc degeneration.

Materials and Methods

Subject Data Acquisition. Eleven asymptomatic volunteers (six females; five males) with mean age of 38.8 ± 15.5 yrs (range 18–62) with no prior history of chronic or lingering back pain, spinal abnormalities (scoliosis, herniation, etc.), or spinal surgeries were included in the study. Two additional volunteers were

recruited, but excluded from the analysis: one due to an undiagnosed spinal abnormality (19-yr old male) and the other due to motion artifact during the scan (51-yr old female). This study was approved by the local Institutional Review Board (IRB: 1701M05441).

Each subject underwent an MRI of the lumbar spine in the supine position for investigation of the L4–L5 disc. All scans were completed on a 3 T scanner (MAGNETOM Prisma; Siemens Healthcare, Erlangen, Germany) using a dedicated Siemens spine matrix coil. The imaging protocol included a clinical T2-weighted sequence acquired in the sagittal plane (TR (ms): 3220; TE (ms): 91; pixel size (mm): 0.4688×0.4688 ; slice thickness (mm): 3.0; and scan time (min:s): 3:47) and quantitative T2* axial maps (TR (ms): 500; TE (ms): 4.18, 11.32, 18.46, 25.60, 32.74, 39.88; pixel size (mm): 0.625×0.625 ; slice thickness (mm): 3.0; and scan time (min:s): 4:18). Seven circular regions of interest (ROIs) of 5 mm diameter were isolated across the transverse plane of the L4–L5 disc and mean T2* relaxation times were measured using OsiriX Imaging Software (Pixmeo, Geneva, Switzerland) (Fig. 1). The following ROIs were investigated: anterior annulus fibrosus (aAF), posterior annulus fibrosus (pAF), outer lateral annulus fibrosus (oAF), inner lateral annulus fibrosus (iAF), and NP. The iAF and oAF were obtained from each side of the disc, the left and right. The iAF encompasses the transition zone from the NP to the AF, while the oAF contains only the outer most annular layer. The location of each ROI was chosen based on anatomically scaled dimensions: aAF and pAF were the most anterior and posterior locations in the midsagittal plane, oAF was the most lateral position in the midcoronal plane, NP was at the center, and iAF was halfway between the NP and oAF.

Assessment of Intervertebral Disc Health. Previously published work by our lab determined the correlation between quantitative T2* relaxation times and the corresponding biochemical and biomechanical properties in a cadaveric model [18]. The current study expands on this work to define the linear relationships using regression analyses. Briefly, the prior study comprised eighteen osteoligamentous lumbar spines (range 21–71 yrs) that were imaged using quantitative T2* mapping by a 3T MRI scanner. Following imaging, the discs were biomechanically tested through a series of stress relaxation tests using a hybrid confined/in situ indentation methodology to obtain the residual stress at various ROIs (aAF, iAF, oAF, pAF, and NP). This technique left the cartilaginous endplate intact, thus not disrupting the innate structure below [21]. Next, each ROI was excised and sulfated-glycosaminoglycan (s-GAG) content was measured and normalized by dry weight ($\mu\text{g}/\mu\text{g}$).

The present study developed and utilized linear regression equations to predict each subject's s-GAG content and residual stresses based on their quantitative T2* maps at each ROI

Table 1 Linear regression equations for predicting s-GAG content and residual stress from T2* relaxation times. Standard error (Std. error) of the slope and y-intercept, correlation coefficients, and p-values are displayed. (Relationships reprinted with permission from Ellingson et al. [18]. Copyright 2014 by Wiley.)

Location	s-GAG linear regression ($\mu\text{g}/\mu\text{g}$)	Std. error (slope)	Std. error (intercept)	Correlation coefficient	p-value
Anterior AF	$\text{s-GAG} = 1.015 \times 10^{-2} (\text{T2}^*) - 1.235 \times 10^{-1}$	3.668×10^{-3}	1.233×10^{-1}	0.569	0.014
Inner AF	$\text{s-GAG} = 9.935 \times 10^{-3} (\text{T2}^*) - 4.553 \times 10^{-2}$	1.980×10^{-3}	5.883×10^{-2}	0.782	<0.001
NP	$\text{s-GAG} = 6.681 \times 10^{-3} (\text{T2}^*) - 9.399 \times 10^{-2}$	5.831×10^{-4}	3.094×10^{-2}	0.944	<0.001
Outer AF	$\text{s-GAG} = 9.955 \times 10^{-3} (\text{T2}^*) + 2.707 \times 10^{-2}$	2.932×10^{-3}	4.850×10^{-2}	0.647	0.004
Posterior AF	$\text{s-GAG} = 5.915 \times 10^{-3} (\text{T2}^*) + 1.881 \times 10^{-2}$	2.750×10^{-3}	1.042×10^{-1}	0.474	0.047
Location	Stress linear regression (MPa)	Std. error (slope)	Std. error (intercept)	Correlation coefficient	p-value
Anterior AF	$\text{Stress} = 1.115 \times 10^{-3} (\text{T2}^*) - 1.562 \times 10^{-3}$	1.115×10^{-3}	3.751×10^{-2}	0.242	0.332
Inner AF	$\text{Stress} = 2.540 \times 10^{-3} (\text{T2}^*) - 1.295 \times 10^{-2}$	1.004×10^{-3}	2.983×10^{-2}	0.535	0.022
NP	$\text{Stress} = 2.069 \times 10^{-3} (\text{T2}^*) - 6.107 \times 10^{-2}$	3.115×10^{-4}	1.653×10^{-2}	0.857	<0.001
Outer AF	$\text{Stress} = 6.846 \times 10^{-3} (\text{T2}^*) - 6.046 \times 10^{-2}$	1.905×10^{-3}	3.151×10^{-2}	0.668	0.002
Posterior AF	$\text{Stress} = 3.315 \times 10^{-3} (\text{T2}^*) - 7.678 \times 10^{-2}$	1.335×10^{-3}	5.058×10^{-2}	0.527	0.025

Fig. 2 Representative axial T2* map of a healthy (top) and severely degenerated (bottom) intervertebral disc with corresponding surface maps of T2* relaxation times, s-GAG, and residual stress. Healthy: Pfirrmann grade 1; severe: Pfirrmann grade 5. Figure partially adapted from Ellingson et al. [18].

(Table 1). Then, these data, along with the T2* relaxation time at each location (iAF and oAF, right and left, were treated independently), were extrapolated using a surface curve fitting approach with a thin plate spline function to estimate s-GAG and residual stress throughout the entire disc (Fig. 2). The generated surface maps were then integrated using a trapezoidal method and normalized by each disc's area. This surface volume metric was then calculated for T2* signal, s-GAG content, and residual stress across the disc.

Additionally, each disc was graded in accordance with the Pfirrmann scale (AME) using the mid-sagittal slice of the T2-weighted images [10].

Data and Statistical Analysis. A correlational study design was used to define the relationship between each metric of disc health derived from the quantitative T2* maps (T2* relaxation times, s-GAG content, residual stress, and surface volumes) with age and Pfirrmann grade. The 95% prediction intervals for each predicted s-GAG content and residual stress at the NP and iAF were calculated. Only the NP and iAF (right and left averaged) were investigated to preserve statistical power, as our lab's previous work indicated that these ROIs had the strongest relationships between T2* relaxation times and the biochemical and biomechanical properties [18]. Pearson's correlation tests were performed with a level of significance set to 0.05. The cohort's age and Pfirrmann grade were assessed for normality using the Shapiro–Wilks test. Statistical tests were performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria)².

Results

The investigated asymptomatic cohort exhibited the full degenerative spectrum with Pfirrmann grades from 1 to 5, which was normally distributed based on age ($W=0.92$; $p=0.32$) and Pfirrmann grade ($W=0.90$; $p=0.18$). The correlational summary statistics are displayed in Table 2. The NP T2* relaxation time was significantly and negatively correlated with both Pfirrmann grade and age ($p<0.01$). A similar trend was observed between the iAF T2* relaxation time and Pfirrmann grade ($p=0.082$), but was not significantly correlated with age ($p=0.154$). Since predicted s-GAG content and residual stress were directly proportional to the mean T2* relaxation time, these values exhibited the same linear relationship with Pfirrmann grade and age, depicted in Fig. 3. Prediction intervals were found for each subject's predicted s-GAG content and residual stress: the NP was within $0.11 \mu\text{g}/\mu\text{g}$ and 0.06 MPa of the prediction (Fig. 3), and the iAF was within $0.24 \mu\text{g}/\mu\text{g}$ and 0.13 MPa of the prediction.

Pearson correlation coefficients for the relationship of surface volumes with age and Pfirrmann grade are displayed in Table 2. As shown in Fig. 4, age was significantly correlated with T2* surface volumes ($p=0.036$); a strong trend was observed with s-GAG surface volumes ($p=0.051$), but not with residual stress surface volumes ($p=0.341$). A significant linear relationship was observed between Pfirrmann grade and surface volumes for T2* and s-GAG ($p<0.037$); however, the data demonstrated a more curvilinear relationship. Therefore, a post-hoc second-order polynomial regression was applied (Fig. 5). The additional coefficient improved the fit of our data, as shown in Table 3, with a greater R^2 and adjusted R^2 value compared to the linear regression. A significant fit of the polynomial model was detected for T2* and s-GAG surface volumes ($p<0.006$), with residual stress surface volume approaching significance ($p=0.061$).

Discussion

Quantitative T2* MRI has been shown to convey information on water mobility within the macromolecular network [17]. Pertaining to the intervertebral disc, this sequence has a high predictability of the biochemical content (glycosaminoglycan) and mechanical integrity (residual stress) throughout the disc [18,22]. This multi-echo gradient-echo sequence has the advantage of short acquisition time, high signal-to-noise ratio, and implementation on clinical scanners; these are ideal qualities for individuals with back pain due to the increased risk of motion artifact with long acquisition times [17]. The purpose of this study was to investigate the distribution of biochemical and biomechanical

²<https://www.R-project.org/>

Table 2 Summary of correlation statistics between metrics of disc health with age and Pfirrmann grade

	T2* relaxation time		Surface volume		
	NP (ms)	iAF (ms)	T2* (ms)	s-GAG ($\mu\text{g}/\mu\text{g}$)	Residual stress (MPa)
Age					
Correlation coefficient (r)	-0.768	-0.461	-0.634	-0.599	-0.318
p -value	0.006	0.154	0.036	0.051	0.341
Pfirrmann					
Correlation coefficient (r)	-0.751	-0.547	-0.670	-0.632	-0.491
p -value	0.008	0.082	0.024	0.037	0.125

Note: Predicted s-GAG content and residual stress are directly proportional to T2* relaxation time. Therefore, these values exhibited the same linear relationship with age and Pfirrmann grade.

Fig. 3 Correlation plots between metrics of disc health (T2* relaxation time, s-GAG, and residual stress) and age (left) and Pfirrmann grade (right) in the NP. s-GAG content is represented in red with one side of the prediction interval displayed below the prediction. Residual stress is represented in blue with one side of the prediction interval displayed above the prediction. Pearson's correlation coefficient (r) and p -value are displayed.

Fig. 4 Correlation plot of age and T2* surface volume of the disc with corresponding correlation coefficient (r) and p -value

Fig. 5 Correlation plot of Pfirrmann grade and T2* surface volume of the disc with the linear and second-order polynomial regression; R^2 , adjusted R^2 , and p -value

Table 3 Comparison between simple linear and second-order polynomial regression models for fitting the relationship between surface volume and Pfirrmann grade

	Surface volume		
	T2* (ms)	s-GAG ($\mu\text{g}/\mu\text{g}$)	Residual stress (MPa)
Simple linear regression			
R^2	0.448	0.399	0.241
Adjusted R^2	0.387	0.332	0.157
p -value	0.024	0.037	0.125
Polynomial regression			
R^2	0.737	0.721	0.503
Adjusted R^2	0.672	0.651	0.379
p -value	0.005	0.006	0.061

properties of the L4-L5 disc of asymptomatic individuals through noninvasive quantitative T2* MRI and establish the relationship with age and degeneration (Pfirrmann grade).

In the present study, T2* relaxation times decreased with both advancing degeneration and increasing age in an asymptomatic population. Previous studies have found a similar inverse relationship between Pfirrmann grade and T2* relaxation times; however, these studies focused on a cohort of symptomatic individuals [14,19,20,23]. To the authors' knowledge, only one previous study examined an asymptomatic population with T2* MRI who were all under the age of 30, to establish a baseline cohort of healthy discs [24]. Past work with T2* MRI has not investigated the relationship of T2* relaxation time with age in an asymptomatic population to comprehend the natural course of disc degeneration. Previous studies with T2 signal have investigated the relationship between degeneration and age in an asymptomatic population; however, T2 signal is limited to measures of hydration [15,25–27]. To better understand the natural aging process, the current study evaluated T2* relaxation times and utilized derived regression equations to predict biochemical and biomechanical properties of the disc in an asymptomatic population.

Predicted s-GAG content ranged from -0.014 to 0.513 s-GAG per dry weight ($\mu\text{g}/\mu\text{g}$) in the NP and 0.117 to 0.607 $\mu\text{g}/\mu\text{g}$ in the iAF, which are within range of the previously reported in vitro s-GAG content of the disc found to be less than 0.65 $\mu\text{g}/\mu\text{g}$

[6,18,28,29]. An inverse association with age and Pfirrmann grade was observed in the current study; this relationship is consistent with the previous studies done in vitro with excised discs [6,18,29]. Johannessen et al. reported values of the NP in healthy (0.44 ± 0.085 $\mu\text{g}/\mu\text{g}$) and degenerated discs (0.148 ± 0.112 $\mu\text{g}/\mu\text{g}$), with similar correlations for both age and degeneration ($r = -0.75$ and $r = -0.69$, respectively) to the current findings [6]. Previous observations from our lab have ranged from 0.104 to 0.539 $\mu\text{g}/\mu\text{g}$ in the NP and 0.039 to 0.523 $\mu\text{g}/\mu\text{g}$ in the iAF, decreasing as a function of degeneration [18]. The current study demonstrates a noninvasive technique for predicting s-GAG content in vivo that is consistent with these previous in vitro studies.

Predicted residual stresses ranged from -0.036 to 0.127 MPa in the NP and 0.029 to 0.154 MPa in the iAF; both inversely associated with age and Pfirrmann grade. Prior studies on individuals without low back pain used an invasive technique to measure intradiscal pressures prone (0.09 – 0.1 MPa), sitting (0.46 – 0.8 MPa), and standing (0.33 – 0.54 MPa) [30–32]. Sato et al. reported a decrease in intradiscal pressures, while prone, with advancing stages of degeneration: healthy 0.089 ± 0.027 MPa, mild 0.072 ± 0.042 MPa, moderate 0.032 ± 0.045 MPa, and severe 0.010 ± 0.020 MPa [32]. The present study's predicted residual stresses displayed a similar trend to the findings of Sato et al. throughout degeneration and within the range of each stage of degeneration [32]. These results provide evidence of the robustness of the linear regression equations to predict biochemical and biomechanical properties within the disc in vivo and in vitro using the quantitative T2* MRI sequence.

Surface maps obtained through an axial T2* slice demonstrated the ability to quantitatively assess surface volumes and distribution of the biochemical and biomechanical properties, which may offer additional details to detect early stages of disc degeneration. The results revealed that an individual with a healthy disc is represented by a discrete, highly centralized T2* signal (Fig. 6). During the initial stages of degeneration, there is a diminished signal intensity of the NP accompanied by an expansion of the NP signal, resulting in an increased surface volume (Fig. 5). This is potentially explained by a loss of mechanical integrity of the inner annulus allowing for the spread of proteoglycans. This phenomenon is supported by a rapid decrease of proteoglycans in the nucleus accompanied by weakening of the inner annulus and a less distinct transition between the nucleus and annulus with

Fig. 6 Depiction of the continuum of early degeneration with sagittal T2-weighted images with corresponding Pfirrmann grade, axial T2* maps with NP T2* relaxation time, and T2* surface maps with quantified surface volume

progressive aging [5, 33–36]. This pronounced change captured by the surface maps is a key morphological feature in the assessment of disc degeneration, which is difficult to identify through traditional T2-weighted imaging and the Pfirrmann classification system. After the initial stages of degeneration, the signal continues to decrease and the surface volume begins to decrease. This suggests that the integration of the NP signal with the surface map is capable of detecting early stages of degeneration by analyzing the distribution through the disc.

The current study has limitations. First, a small sample size of asymptomatic individuals was included; however, they were normally distributed across an appropriate age range. Also, this study did not control for the time of day nor the subjects' activities prior to the scan. Utilization of ex vivo derived linear regression models is an inherent limitation of our study, as directly obtaining these measurements in vivo is invasive—highlighting the important need to develop noninvasive assessment techniques. The linear regression equations were limited to the T2* relaxation time range (NP: 27.1–91.6 ms) from which the equations were created. Only one subject was outside of this range and data needed to be extrapolated; this subject was at the most advanced stage of degeneration and resulted in negative s-GAG and residual stress predictions. An uncertainty propagation was conducted via prediction intervals to adequately assess the variability in the predicted measurements, thus resulting in inherently larger variability compared with confidence intervals, as it accounts for the variability of the conditional distribution in addition to the conditional mean.

In conclusion, the present study demonstrated the ability to noninvasively predict site-specific biochemical and biomechanical properties in asymptomatic individuals based on quantitative T2* MRI. Incorporation of surface volumes to assess disc health provides insight into the initial stages of degeneration, which may play a vital role in clinical assessment of disc health and the ability to track the effectiveness of emerging treatments.

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Nomenclature

aAF = anterior annulus fibrosus
 iAF = inner lateral annulus fibrosus
 min = minutes
 mm = millimeters
 ms = milliseconds
 MPa = megapascal
 MRI = magnetic resonance imaging
 NP = nucleus pulposus
 oAF = outer lateral annulus fibrosus
 pAF = posterior annulus fibrosus
 ROI = region of interest
 s = seconds
 s-GAG = sulfated glycosaminoglycan
 T2* = T2-star
 μ g = microgram

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