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***In-vivo* Intervertebral Disc Characterization using Magnetic Resonance Spectroscopy and T_{1ρ} Imaging: Association with Discography and Oswestry Disability Index and SF-36**

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Abstract

Study Design—An *in vivo* study of intervertebral disc degeneration using quantitative MRI and MRS.

Objective—To quantify water and proteoglycan (PG) content in the intervertebral disc using *in vivo* magnetic resonance spectroscopy (MRS), and to evaluate the relationship between MRS-quantified water/PG content, T_{1ρ}, Pfirrmann score, clinical self-assessment, and discography.

Summary of Background Data—Previous *in vitro* studies have investigated the relationship between MRS-quantified water/PG content, and degenerative grade using cadaveric intervertebral discs. T_{1ρ} has been shown to relate to Pfirrmann grade and clinical self-assessment. However, the associations between MRS-quantified water/PG content, MR imaging-based T_{1ρ}, self-assessment of health status and clinical response to discography have not been studied *in vivo*.

Methods—MRS and MR imaging were performed in 26 patients (70 discs) with symptomatic intervertebral degenerative disc (IVDD) and 23 controls (41 discs). Patients underwent evaluation of intervertebral discs with provocative discography. All subjects completed the SF-36 Health Survey and Oswestry Disability Index questionnaires.

Results—The water/PG peak area ratio was significantly elevated in a) patients (compared to controls) and in b) discs with positive discography (compared to negative discography). MR T_{1ρ} exhibited similar trends. A significant association was found between T_{1ρ} and normalized PG content ($R^2 = 0.61$, $p < 0.05$), but not between T_{1ρ} and normalized water content ($R^2 = 0.24$, $p > 0.05$). The water/PG peak area ratio, normalized water, normalized PG, and Pfirrmann grade were significantly associated with patient self-assessment of disability and physical composite score, while disc height was not.

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The manuscript submitted does not contain information about medical device(s)/drug(s). The authors have not received benefits in any form from a commercial party related directly or indirectly to the subject of this manuscript.

This study was approved by the UCSF IRB.

Conclusion—This study demonstrated a relationship between *in vivo* MRS spectroscopy (water content, PG content), imaging parameters ($T_{1\rho}$, Pfirrmann Grade), discography results, and clinical self-assessment, suggesting that MRS-quantified water, PG and MR $T_{1\rho}$ relaxation time may potentially serve as biomarkers of symptomatic IVDD.

Keywords

intervertebral disc degeneration; magnetic resonance spectroscopy; water; proteoglycan; $T_{1\rho}$; clinical self-assessment; discography

INTRODUCTION

Intervertebral disc degeneration (IVDD) is a leading cause of low back pain, affecting 60 to 80% of aging Americans¹. The prevalence of disc degeneration increases with age² and even young adults have high rates of IVDD³.

IVDD involves metabolic changes (i.e. matrix synthesis), biochemical degeneration (i.e. loss of proteoglycans (PG), dehydration) and morphologic changes (i.e. annular tears, radial bulging, endplate damage)⁴. Clinicians often use magnetic resonance imaging (MRI) to evaluate disc degeneration; however, disc degeneration and pain do not always correspond, as subjects may have pain without the presence of structural abnormalities, and patients with significant IVDD may have limited clinical disability^{5,6}. Provocative discography is a technique to identify symptomatic IVDD. It is an invasive procedure that involves injecting x-ray contrast into the discs to determine the source of the pain and may yield up to 10% false positives⁷. A recent study reported that discography accelerated progression of degeneration changes in the disc⁸.

Since IVDD is initiated by biochemical changes (i.e. loss of cellularity and degradation of the extracellular matrix), followed by morphological degeneration, it would be important to identify early biochemical markers for IVDD. A semi-quantitative assessment of morphologic degeneration in IVDD can be performed using the Pfirrmann Grading, which is a 5-point scale system assessed from T_2 -weighted MR images⁹. Pfirrmann Grading is effective in identifying late-stage morphologic disc degeneration; however, it is insensitive to early biochemical degenerative changes. MRI, for example, T_2 relaxation time have been associated with collagen breakdown and dehydration^{10,11}, while MR $T_{1\rho}$ is sensitive to PG content and water loss in the disc¹². Both $T_{1\rho}$ and T_2 relaxation times decrease with disc degeneration^{10,13–18}. $T_{1\rho}$ is correlated with patient-reported physical activity and disability as assessed by clinical questionnaires (SF-36 and ODI)¹⁷. Significant correlation was found between nucleus pulposus osmotic pressure and $T_{1\rho}$ in a recent *ex vivo* study¹⁹, suggesting $T_{1\rho}$ maybe a possible biomarker to evaluate symptomatic IVDD.

In addition to morphologic and biochemical assessment of tissues using MRI, proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive method that may be used to evaluate the relative concentration of metabolites in tissues, in particular those related to PG. A recent study, using 1H-MRS in bovine and human cadaver discs, reported changes in metabolic concentration with increasing grade of disc degeneration and a relationship between metabolic concentration and PG content²⁰. While NMR spectroscopy and MRS have been used to study disc degeneration *in vitro*^{20–23}, MRS has not been used to study the intervertebral disc *in vivo*.

The purpose of this study is to demonstrate the feasibility of quantifying water and PG content using *in vivo* MRS in controls and subjects with symptomatic IVDD. The specific goals of the study are to determine the association between water/PG peak area ratio

quantified using *in vivo* MRS, and a) disc degenerative grade b) positive and negative discography in patients c) T_{1ρ} and Pfirrmann Grade and d) clinical presentation as quantified by clinical questionnaires SF-36 and ODI questionnaires^{24,25}.

MATERIALS AND METHODS

Subjects

This study was performed in accordance with the rules and regulations the Committee for Human Research (CHR) at our institution. Twenty-six pre-screened patients with symptomatic IVDD (mean age = 44.8±8.7years, 15 males and 11 females) were recruited based on radiologic screening and MRI confirmation of IVDD in the lumbar spine at one or more levels, and clinical symptoms of that were persistent despite non-operative care management for more than 3 months. Twenty-three healthy subjects without clinical symptoms of back pain (mean age: 35.1±12.6years, 12 males and 11 females) were recruited and classified as controls. Five discs from 4 control subjects (mean age = 28±4years, 2 males and 2 females) were scanned 3 times with repositioning between the scans to evaluate the reproducibility of spectroscopy. Subjects completed the SF-36 and ODI questionnaires prior to MR scanning. Provocative discography was performed on patients, and the patient was asked to rate whether the pain experienced was concordant (familiar pain location) or not and to rate the intensity of the pain. A disc was assigned to the positive discography group if the intensity and/or concordance values from discography were both greater than 6 on a 10-point scale²⁶. A summary of the subject cohort is provided in Figure 1.

Image and Spectroscopic Acquisition Methods

MR imaging was performed in each subject using a 3.0-Tesla GE Excite Signa MR scanner (General Electric Healthcare, Waukesha, WI) with an eight-channel CTL spine coil (GE).

Sagittal T₂-weighted images were acquired in all subjects using a fast spin echo (FSE) sequence for Pfirrmann grading⁹, single-slice sagittal images for T_{1ρ} mapping were acquired using a FSE sequence. A single voxel point-resolved spectra selection (PRESS) sequence with a three-pulse chemical shift selective (CHESS) saturation for water suppression was chosen to quantify water and PG content. Localized shimming was performed automatically followed by manual shimming to improve field homogeneity. Spectra were acquired with a full width at half maximum (FWHM) <15Hz at 3T, corresponding to 0.12ppm. A 4×18×16mm³ voxel was placed at the center of the disc (the voxel size can be modified according to the size of the actual imaging disc to avoid lipid contamination from neighboring tissues). The scan parameters for each sequence are shown in Table 1.

Image and Spectral Analysis

Pfirrmann grading was performed on T₂-weighted FSE images by an experienced musculoskeletal radiologist. Disc height was measured from the same images (central slice, middle of the disc) and was normalized with each subject's body mass index (BMI).

T_{1ρ} maps were created by fitting the signal intensity pixel-by-pixel to the following equation using a Levenberg Marquardt mono-exponential fitting algorithm developed in-house: $S(TSL) \propto \exp(-TSL/T_{1\rho})$. Median T_{1ρ} values were calculated in a 5mm-diameter section that was drawn manually in the center of the discs in each subject. For spectroscopy scans, only the N-acetyl resonance (2.04ppm) that is associated with PG and the water resonance (4.7ppm) can be robustly quantified, the other metabolites cannot be accurately quantified due to the limitation of the SNR in *in vivo* scans (Figure 2). The PG peak and the water peak were quantified from water-suppressed and non-water-suppressed spectra, respectively. The spectra data acquired were processed using a previously-developed method^{20,27}. A peak-

fitting program developed in-house²⁸ was further applied to provide an estimation of the peak areas of water and PG. The measured peak areas of water and PG were then normalized with the prescribed voxel volume and the noise. The noise was calculated as the standard deviation of peak heights from the flat noise baseline region (the last 200 points from the spectrum, corresponding to $-2.5 \sim 0.4$ ppm).

Signal to noise ratio (SNR) was examined in 12 discs (three discs each from Pfirrmann grade 1–4. Four discs were from controls and 8 discs from patients). The SNR of the water or PG peaks were calculated as the ratio of water or PG peak height to the noise and were normalized to the prescribed voxel volume.

Statistical Analysis

The coefficient of variation (CV) was employed to evaluate the reproducibility of spectroscopic measurements, namely the robustness of the measurement, as described by Glüer et al²⁹. Statistical analysis was performed using JMP software (SAS Institute, Cary, NC).

The differences in MRS (Water, PG) and MRI ($T_{1\rho}$) parameters between a) patients and controls, and between b) positive and negative discography were assessed using mixed-effect models with subject-specific random effects to account for multiple discs measured within one subject. The differences between MR parameters among the Pfirrmann Grade groups and within each Pfirrmann grade were assessed using analysis of variance with subject-specific random effects. The associations between MRS and MRI parameters were also assessed using mixed-effect models. The association between MRS parameters and clinical questionnaire scores were assessed using mixed-effect models. The output value from JMP, R^2 , is the percent of variation in the response variable that can be explained by the mixed-effect regression model. A P-value < 0.05 was considered significant.

RESULTS

Signal to Noise Ratio (SNR) and Reproducibility

The SNR values for water and PG are listed in Table 2. A trend of decreasing SNR with increasing grade of degeneration was evident for both water and PG. The reproducibility study indicated that the water/PG peak area ratio demonstrated the smallest mean CV (7.50%), followed by normalized water content (10.83%), and normalized PG content (14.03%).

MR Parameters in Patients vs. Controls

A summary of the water/PG ratios measured in discs that were classified by Pfirrmann grades in controls and patients is listed in Table 3. Note that two discs did not have spectroscopy data due to insufficient scan time. Figure 3 illustrates that the water/PG peak area ratio increased significantly as Pfirrmann Grade increased in both patients and controls. When subdividing the analysis by Pfirrmann Grade, the water/PG Peak area ratio was significantly elevated in patients as compared to controls in only the Pfirrmann Grade 3 group. When analyzing all subjects, the water/PG peak area ratio and $T_{1\rho}$ were both significantly different in patients vs. controls (even after adjusting for Pfirrmann grade, Figure 4).

In addition to the water/PG peak area ratio, this study evaluated the individual water and PG content in patients and controls. PG was significantly lower in patients compared to controls; however, this trend was not significant after adjusting for Pfirrmann Grade. Water content was lower in patients compared to controls; however, this was not significantly

different. Other MR parameters including disc height were not significantly different between patients and controls.

MR Parameters in Discs with Positive and Negative Discography

Discs with positive discography had significantly elevated the water/PG peak area ratio than discs with negative discography (even after adjusting for Pfirrmann grade) (Figure 5). Lower mean $T_{1\rho}$ were found in discography positive discs ($T_{1\rho} = 58\text{ms}$) compared to discography negative discs ($T_{1\rho} = 86\text{ms}$), but the difference was not significant. This analysis was restricted to only patients because controls did not have discs with positive discography. Figure 6 depicts the water and PG spectroscopy peaks in two patients who have positive and negative discography discs. The figure illustrates that the water/PG peak area ratio is elevated in discs with positive discography. Note in Figure 6b only the disc with positive discography has elevated water/PG peak area ratio, despite that all discs were graded as Pfirrmann Grade 2.

In addition to the water/PG ratio, this study evaluated the differences in the individual water and PG contents in discs with positive and negative discography. PG was significantly lower in positive discs as compared to negative discs; however, this trend was not significant after adjusting for Pfirrmann Grade. Water content was not significantly different between positive discs and negative discs (although water was lower in positive discs). Other MR parameters including disc height were not significantly different between positive and negative discography groups.

The relationship between $T_{1\rho}$ and Spectroscopy Parameters

Based on the regression model that accounts for multiple discs per subject, a significant correlation was evident between $T_{1\rho}$ and water/PG peak area ratio ($R^2=0.54$, $p<0.05$). Additionally, a significant association was found between $T_{1\rho}$ and PG content ($R^2=0.61$, $p<0.05$), but not between $T_{1\rho}$ and water content ($R^2=0.24$, $p>0.05$).

MR Parameters vs. Clinical Findings Based on Oswestry Disability index and SF-36

The association between clinical questionnaire scores (ODI and SF-36 Physical Health) and MR parameters (water/PG peak area ratio, Pfirrmann Grade, disc height) are listed in Table 4. Overall, an elevated water/PG ratio was related to decrease physical health (SF-36) and increased disability (ODI). The relationship between clinical questionnaire scores and $T_{1\rho}$ has been reported in a previous study³⁰: the relationship between $T_{1\rho}$ and ODI was $R^2=0.56$ ($p<0.05$) and the relationship between $T_{1\rho}$ and SF-36 was $R^2=0.55$ ($p<0.05$).

DISCUSSION

This study investigated the feasibility of *in vivo* MR spectroscopy of the intervertebral disc, and evaluated the associations between spectroscopic parameters and imaging parameters (Pfirrmann Grade, $T_{1\rho}$, and disc height), discography status, and clinical assessment (SF-36 and ODI). The reproducibility of the water/PG, normalized water content, and normalized PG content was comparable to spectral metabolite reproducibility found in single-voxel 1H spectroscopic studies of the human brain^{31,32}. Additionally, elevated water/PG peak area ratio was evident in patients (compared to controls), and in discs with positive discography (compared to negative discography). $T_{1\rho}$ exhibited similar trends between patients and controls, despite that fewer patients had $T_{1\rho}$ data available due to insufficient scan time.

Both water loss and PG depletion increase with disc degeneration, so as the water and PG content decreases the water and PG signal goes down; the noise in the system, and body noise in MR remains the same, thus reducing the SNR of water and PG with disc

degeneration. This trend was reflected in our measurements. Additionally, having sufficient SNR is imperative for quantification of intervertebral disc metabolic concentrations using *in vivo* spectroscopy. In this study, the SNR of PG decreased with increasing grade of degeneration and ranged from 32 in discs with Pfirrmann Grade 1 to 7 in discs with Pfirrmann Grade 4. These SNR values are greater than those that have been reported in other studies of different anatomic regions^{33–36}, which used a threshold ranging from 2 to 4. Thus, this study considered an SNR>5 as adequate for the detection of an identifiable PG peak in the intervertebral disc.

Correlations between $T_{1\rho}$ and disc biochemical composition (water, PG content) have been previously assessed *in vitro* using biochemical assays in cadaveric human discs^{12,20}. Johannessen et al. reported that $T_{1\rho}$ was correlated with PG per dry weight ($r=0.67$, $p<0.01$) and with water content ($r=0.58$, $p<0.05$). The current study corroborated the *in vitro* results exhibiting similar associations between $T_{1\rho}$ and both water and PG content. Additionally, the association between water/PG peak area ratio and $T_{1\rho}$ suggests that these parameters may provide similar information regarding the biochemical composition of the intervertebral disc.

Links between morphologic changes that are detectable with traditional imaging techniques (radiographs, computed tomography, MRI) and painful IVDD are not well established in the literature³⁷. This study examined the relationship between both MR imaging and spectroscopic parameters and clinical symptoms in IVDD. While disc height was not significantly associated with clinical questionnaire scores, Pfirrmann Grade was significantly associated with SF-36 and ODI and water/PG peak area ratio was significantly associated with SF-36. In a previous study³⁰, $T_{1\rho}$ was found to be significantly related to clinical questionnaire scores, while Pfirrmann Grade was not. It is difficult to make comparisons about the relative strength of the association between imaging/spectroscopy parameters and clinical questionnaire scores due to the varying sample sizes for each imaging/spectroscopy parameter. However, this study does suggest that spectroscopic and imaging parameters are related to patient self-assessment of health status and clinical symptoms associated with low back pain.

It may be of interest to explore the links between the water/PG ratio and individual water and PG components with disc degeneration. The results demonstrate that both the water and PG concentrations are lower in patients compared to controls; however the water/PG peak ratio is higher. A similar trend was evident when comparing discs with positive and negative discography: the water and PG concentration was lower in positive discs compared to negative discs, however the water/PG ratio was higher. Both water loss and PG depletion increase with disc degeneration. The changes in PG and water content also affect the discs ability to withstand biomechanical loading, it is this mechanism that leads to the relationship between spectroscopy, pain and thus clinical symptoms and Oswestry grades. Our measurements imply that PG depletion was much faster than water loss in discogenic pain patients, which maybe consistent with loss of biomechanical properties, as well as being related to spectroscopy, and $T_{1\rho}$ imaging rather than simple T_2 weighted imaging. While the relative changes in metabolic concentrations are exploratory, the results highlight that water and PG concentrations are altered with degeneration and MRS may be useful in assessing disc biochemical composition *in vivo*. Further studies of quantifying disc composition changes using biochemical analysis to validate the MRS findings are warrant.

One of the limitations of this study is that it focused on the assessment of water and PG metabolic resonances due to the low SNR of other metabolites. Other metabolite resonances such as the carbohydrate region (Carb) (3.50–4.20ppm), the choline region (Cho) (3.15–3.30ppm) and the lactate region (Lac) (1.15–1.40ppm) have been quantified *in vitro* and

implicated with disc degeneration²⁰, their *in vivo* SNR was too low (approximately 1–2) for accurate quantification in this study. The low SNR may be potentially due to: a) the coil: while the *in vitro* study used an 8 channel phased array transmit/receive volume coil, this *in vivo* study used an 8 channel receive surface coil (only 6 elements were used for lower lumbar spine scans); b) physiological motion: *in vivo* MRS is challenged by the presence of lipid in adjoining body marrow and bone susceptibility induced line broadening³⁸, making the assessment of lactate imprecise. Another limitation of the study is the uneven distribution of discs with different Pfirrmann Grades, and an insufficient number of discs with Pfirrmann grades 1, 4 and 5. While the current study concentrated on studying mild to moderately degenerated discs (Pfirrmann grade 2 to 3), including of healthy and severely degenerated discs would provide a more comprehensive assessment of IVDD.

The overall goal of this study was to demonstrate the feasibility of characterizing disc biochemical composition using *in vivo* MRS and MR imaging in subjects with symptomatic IVDD. The water/PG peak area ratio was related to discography status as well as clinical assessment. While $T_{1\rho}$ demonstrated similar trends as water/PG peak area ratio, future studies with larger sample sizes would be necessary to compare the utility of both parameters. The increase in water/PG peak area ratio and decrease in $T_{1\rho}$ with degeneration and pain suggest that these parameters may be potential markers for degenerative disc disease and associated clinical impact.

Key Points

- The water/PG peak area ratio was significantly elevated in patients (compared to controls) as well as in discs with positive discography (compared to negative discography). $T_{1\rho}$ exhibited similar trends.
- MR $T_{1\rho}$ was significantly associated with MRS-quantified PG content but not MRS-quantified water content.
- MRS-quantified water, MRS-quantified PG, the water/PG ratio and Pfirrmann grade, were significantly associated with clinical self-assessment.

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Figure 1.
Flowchart of the subjects enrolled in this study.

Figure 2.

A representative MR spectrum acquired from a healthy human disc with the corresponding T_2 -weighted fast spin echo image shown at the top left corner.

Figure 3.

The Water/PG Peak Area Ratio increases with increasing grade of degeneration and is elevated in patients as compared to controls. There is a significant difference in Water/PG in patients vs. controls in discs categorized as Pfirrmann Grade 3. Note that two discs (one Pfirrmann grade 1 and one Pfirrmann grade 5) did not have spectroscopy data available).

Figure 4.

The water/PG Peak area ratio was higher in patients compared to controls, while the T_{1ρ} was lower in patients compared to controls (* p < 0.05).

Figure 5.

Discs with positive discography had significant higher water/PG Peak area ratio than discs with negative discography (* $p < 0.05$).

Figure 6.

A) Water/PG Peak Area Ratio is elevated in the disc with positive discography. B) While all discs are Pfirsman Grade 2, the disc with positive discography has elevated Water/PG peak Area Ratio. In this figure, the amplitude of water was reduced to 1/200 of original and then normalized to 1 in order to illustrate the differences in water/PG peak Area ratio between discs.

Table 1

The scan parameters used in each sequence.

Sequence Name	FOV (mm)	Matrix	TR/TE (ms)	Echo Train Length	Imaging Time	Other
Sagittal T ₂ -weighted FSE	200	320 × 224	5000/70	16	4'45"	NEX =4
Sagittal T ₁ FSE	200	256 × 192	2000/minimum	8	6'38"	TSL = 0/40/80/120ms, Spin Lock Power =300Hz, NEX = 2
PRESS (Single Voxel Spectroscopy)	4 × 18 × 16 (voxel size)	1 × 1 × 1	1000/28	N/A	6'44"	Spectral Width =2000Hz, 1024 Points, 384 Repetitions

Table 2

The SNR of water and PG averaged in 3 different discs per Pfirrmann Grade. The SNR of PG decreases with increasing grade of degeneration and ranges from about 32 to 7.

	Pfirrmann Grade 1	Pfirrmann Grade 2	Pfirrmann Grade 3	Pfirrmann Grade 4
SNR: Water	2901±882	1995±496	1605±455	751±433
SNR:PG	32±10	26±5	10±3	7±3

Summary of the water/PG ratios measured in intervertebral discs that were classified by Pfirrmann grades in controls and patients. Note that two discs (one Pfirrmann grade 3 and one Pfirrmann grade 5 did not have spectroscopy data available).

Table 3

	Pfirrmann Grade 1	Pfirrmann Grade 2	Pfirrmann Grade 3	Pfirrmann Grade 4	Pfirrmann Grade 5
Controls	299±62 (n = 10)	310±83 (n = 17)	525±178 (n = 14)	N/A (n = 0)	N/A (n = 0)
Patients	274±78 (n = 5)	382±163 (n = 27)	763±344 (n = 31)	1114±415 (n = 5)	1100 (n = 2)

Table 4

The relationship between MR/MRS parameters and clinical questionnaire scores (SF-36 and ODI).

	Normalized Disc Height	Pfirmann Grade	Water/PG Peak Area Ratio	Normalized Water	Normalized PG
Clinical Questionnaires					
Disability Index (ODI)	0.52	0.58*	0.38*	0.65*	0.68*
Physical Healthy (SF-36)	0.52	0.57*	0.37	0.61*	0.68*