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Associations between Vertebral Body Fat Fraction and Intervertebral Disc Biochemical Composition as assessed by Quantitative MRI

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Abstract

Background—There is an interplay between the intervertebral disc (IVD) and the adjacent bone marrow that may play a role in the development of IVD degeneration and might influence chronic lower back pain (CLBP).

Purpose—To apply novel quantitative MR imaging techniques to assess the relationship between vertebral bone marrow fat (BMF) and biochemical changes in the adjacent IVD.

Study Type—Prospective.

Subjects—46 subjects (26 female and 20 male) with a mean age of 47.3±12.0 years.

Field Strength/sequence—3 Tesla MRI; a combined $T_{1\rho}$ and T_2 mapping pulse sequence and a 3D SPGR sequence with six echoes and iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) reconstruction algorithm.

Assessment—Using quantitative MRI, vertebral BMF fraction was measured as well as the biochemical composition (proteoglycan and collagen content) of the IVD. Furthermore, clinical Pfirrmann grading, Oswestry disability index (ODI), and Visual Analog Scale (VAS) was assessed.

Statistical Tests—Mixed random effects models accounting for multiple measurements per subject were used to assess the relationships between disc measurements and BMF.

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Results—The relationships between BMF (mean) and $T_{1\rho}/T_2$ (mean and SD) were significant with $p<0.05$. Significant associations ($p<0.001$) where found between clinical scores (Pfirrmann, ODI, and VAS) with $T_{1\rho}/T_2$ (mean and SD). BMF mean was significantly related to ODI ($p=0.037$) and VAS ($p=0.043$) but not with Pfirrmann ($p=0.451$). In contrast, BMF SD was significantly related to Pfirrmann ($p=0.000$) but not to ODI ($p=0.064$) and VAS ($p=0.13$).

Conclusion—Our study demonstrates significant associations between BMF and biochemical changes in the adjacent IVD both assessed by quantitative MRI; this may suggest that the conversion of hematopoietic bone marrow to fatty bone marrow impairs the supply of available nutrients to cells in the IVD and may thereby accelerate disc degeneration.

Keywords

Chronic Lower Back Pain; Bone Marrow Fat; Intervertebral Disc Degeneration; Spine

Introduction

Intervertebral disc (IVD) degeneration is often considered a primary cause of chronic low back pain (CLBP), which is one of the most common health problems worldwide (1,2). Because the relationship between IVD degeneration and CLBP is not well understood, this limits the development of prevention and treatment strategies. The intervertebral disc is the largest avascular tissue in the body, and its health depends on nutritional transport from capillaries in the adjacent vertebral bodies. However, vertebral perfusion decreases as much as 75% with age (3) and the conversion of hematopoietic bone marrow to bone marrow fat (BMF) may account for these age-related perfusion changes (4). Studies also suggest that inflammatory constituents from the IVD may trigger an autoimmune response which can result in bone marrow lesions in the adjacent vertebrae (5,6). Thus, the interplay between the disc and the adjacent vertebral marrow may play a role in the development of IVD degeneration and influence CLBP.

Traditionally, qualitative methods have been used to assess vertebral body fat content and IVD health, however, recent advances in MRI have facilitated quantitative analysis of vertebral BMF and biochemical composition of the IVD. Modic et al. introduced a qualitative rating scheme (Modic changes) in 1988 which is based on qualitative evaluation of bone marrow using clinical T_1 and T_2 weighted MR images (7). Multiple independent studies found that Modic Type I and II changes are among the most specific (70%-100%) MRI observations for predicting CLBP (8-13). However, the sensitivity of these changes to predict CLBP was only 15%-65% (8,13,14). This might be due to the qualitative nature of an observer based grading system which is categorical and subjective (15). Other studies demonstrated strong relationships between bone marrow perfusion and BMF (3) using the Ricci grading score (16) which is another subjective BMF evaluation system. Similarly, qualitative methods have been used to assess IVD degeneration, most notably, by the Pfirrmann grading system (17) which is a numerical grading system from one (healthy disc) to five (severely degenerated disc).

In order to overcome the qualitative nature of these grading systems, recent advances in MRI pulse sequence development have introduced novel quantitative assessment tools for both

vertebral BMF (18,19) and biochemical disc composition (20,21). BMF fraction maps can be obtained with high resolution and high accuracy from chemical shift encoding based water–fat MRI (18,22). This approach has been previously evaluated (22) and clinically applied (23). An advantage of this method includes the higher spatial resolution compared to ^{1}H MR spectroscopy and thus the ability to also look at BMF variations (18). $T_{1\rho}$ and T_2 relaxation time measurements have been used in several studies for the assessment of IVD health (20,21,24). $T_{1\rho}$ and T_2 demonstrate high sensitivity for proteoglycan and collagen integrity, respectively, and thus, interest has grown in their utility as biomarkers for IVD degeneration (25,26). The objective of our study was to apply these novel quantitative MRI measures to investigate the relationships between vertebral BMF content and biochemical degeneration in the adjacent IVD as well as clinical symptoms. We hypothesized that increased vertebral BMF content and spatial variations are significantly associated with biochemical changes in the adjacent IVD.

Materials and Methods

Subject Selection

Our cross-sectional study obtained full institutional review board approval and written informed consent was obtained from each subject. Between January 2016 and November 2017, we enrolled 46 subjects with a mean age of 47.3±12.0 years. Participant characteristics are listed in Table 1. Male and non-pregnant female patients between 18 and 70 years of age were included. Thirty-seven subjects had LBP with a back pain score ≥ 40% on the ODI and ≥ 4 on the VAS and 9 subjects were healthy controls without pain. Subjects with lumbar vertebral abnormalities were excluded such as spondylolisthesis, spondylolysis, lumbar scoliosis with Cobb angle of greater than 15 degrees, evidence of prior fracture or trauma to the lumbar levels, and lumbar disc herniation comprising extrusion. Further exclusion criteria were motor strength deficit in the lower extremities as well as chronic disease (other than degenerated disc disease), chronic pain (other than CLBP), or psychological dysfunction.

MR imaging

MR imaging was performed on a Discovery MR 750 3T scanner using an 8-channel phased-array spine coil (GE Healthcare, Waukesha, WI). Clinical fast spin echo (FSE) images with T_1 and T_2 weighting were acquired in sagittal orientation with a field of view (FoV) of 26cm, slice thickness of 4mm. In addition, T_2-weighted FSE had an echo time TE=60ms, repetition time TR=4877ms, echo train length ETL=24, readout-bandwidth rBW=±50kHz, and an in-plane resolution of 0.6mm. T1-weighted FSE had an echo time TE=30ms, repetition time TR=511ms, echo train length ETL=4, bandwidth=±50kHz, and an in-plane resolution of 0.5mm.

A combined $T_{1\rho}$ and T_2 mapping pulse sequence with a segmented 3D-SPGR acquisition (MAPSS) (27) was used for the assessment of disc degeneration. The $T_{1\rho}$ magnetization preparation was performed using four spin-lock times (TSL=0, 10, 40, 80 ms) and 300 Hz spin lock frequency. T_2 preparation was executed with four echo times (TE=0, 8, 16, 64 ms). MAPSS acquisition parameters were: Repetition time TR=5.2ms, readout-bandwidth rBW=

±62.5kHz, field- of-view FoV=20cm, in-plane resolution=0.8mm, and slice thickness=8mm. Water-fat MRI consisted of a 3D SPGR sequence with six echoes and iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) reconstruction algorithm [4]. Imaging parameters include: TR=7ms, TE=2.1ms, flip angle=3°, rBW=±83.3kHz, FoV=22cm, in-plane resolution=1.3mm, and slice thickness=4mm. For Pfirmann grading, sagittal T2 weighted 3D FSE images were acquired (TR=4721ms, TE=60, rBW=±50 KHz, FoV=26cm, in-plane resolution=0.6mm, slice thickness=4mm).

Imaging Analysis

Images were transferred to a Linux Workstation and Matlab (Mathworks, Natick, MA) was used to manually segment all five lumbar vertebrae and adjacent discs. The whole disc (WD) as well as the nucleus pulposus (NP) and the annulus fibrosus (AF) were manually segmented. $T_{1\rho}$ and T_2 parametric maps were generated by performing mono-exponential fitting of all TSLs and TEs respectively on a pixel-by-pixel basis using the Levenberg-Marquardt algorithm: $S(TSL) \propto S_0 \times exp(-TSL/T_{1\rho})$ and $S(TE) \propto S_0 \times exp(-TE/T_2)$ where S is the decaying signal intensity starting at maximum signal S_0. The fitting procedure and examples of $T_{1\rho}$ and T_2 parametric maps are shown in Figure 1.

BMF fat fraction maps were generated on the scanner from the six acquired echoes using the IDEAL algorithm that accounts for multiple peaks in the fat spectrum and performs T_2* (28) and T_1 corrections (18). Examples of BMF fat fraction maps are shown in Figure 2 along with the corresponding T_1-weighted FSE images.

For our analysis, we focused on the relationships between the lumbar vertebrae and the IVD below each lumbar level. This ensured always five pairs of vertebrae/disc in our imaging field of view. Thus, when we refer to a certain lumbar level, we refer to that level and the IVD below that level as a vertebra/disc pair.

Clinical Grading

Pfirrmann grading (17) was performed by CO and ZM. Both are board-certified sub-specialists in Pain Medicine. CO has twenty years and ZM has seven years of experience reading and interpreting spine MRIs for both clinical and research purposes. Pfirrmann grading was based on the T_2-weighted clinical images and ranges from healthy grade one to severally degenerated disc grade five. The enrolled subjects also completed the Oswestry disability index (ODI) (29) and Visual Analog Scale (VAS) (30) to assess clinical symptoms such as pain.

Statistical Analysis

Mixed random effects models accounting for multiple measurements per subject were used to assess the relationships between BMF (mean and SD) and the adjacent IVD below ($T_{1\rho}$ / T_2 mean and SD) for all discs and adjacent vertebra independent of lumbar level and by lumbar level. Significance was defined as $p<0.05$.

Results

Clinical Evaluation

The mean age and BMI of all subjects were 47.3 years and 24.9, respectively. Table 1 shows the frequency of Pfirrmann grades for the discs. Most discs (41.74%) had a Pfirrmann grade of 2. Only 4.78% of discs were graded with Pfirrmann grade 5. Among all subjects, 37 reported clinically significant CLBP, which we defined as a VAS (30) ≥ 4 and an ODI (29) score ≥ 40%; nine subjects had no lower back pain.

Overall relationships between BMF, $T_{1\rho}$ / T_2 and clinical scores (Pfirrmann, ODI, and VAS)

The IVD was divided into WD, NP, and AF. The following results focus on the WD analysis. NP and AF showed similar trends with AF having weaker associations with BMF than WD and NP. Table 2 shows the overall relationships between BMF and $T_{1\rho}/T_2$ (mean and SD) with Pfirrmann, ODI, and VAS independent of lumbar level. Significant associations ($p<0.001$) where found between clinical scores (Pfirrmann, ODI, and VAS) with $T_{1\rho}/T_2$ (mean and SD).

BMF mean was significantly related to ODI ($p=0.037$) and VAS ($p=0.043$) but not with Pfirrmann ($p=0.451$). In contrast, BMF SD was significantly related to Pfirrmann ($p=0.000$) but not to ODI ($p=0.064$) and VAS ($p=0.13$). Figure 2 depicts examples of clinical T_1-weighted images and corresponding BMF maps. There was no significant difference between the patients with lower back pain and the healthy controls without back pain in respect to age, Pfirrmann grade, BMF mean, BMF SD, *$T_{1\rho}$ / T_2 mean and $T_{1\rho}$ / T_2 SD*.

Overall relationships between BMF and $T_{1\rho}$ / T_2

Table 3 shows the overall relationships (independent of lumbar level) between BMF (mean and SD) with $T_{1\rho}/T_2$ (mean and SD) in the adjacent disc. All relationships were significant ($p<0.05$) and inverse. Thus, higher BMF mean and SD were associated with lower $T_{1\rho}/T_2$ mean and SD. Sensitivity analysis revealed similar significant relationships in the healthy control group versus the patient group.

Relationship of BMF and $T_{1\rho}$ / T_2 by lumbar level

Figure 3 shows BMF values at each lumbar level for all subjects. We found significant increases in mean BMF between each level from L1 to L5. For $T_{1\rho}/T_2$, we found significantly higher values for the upper three discs compared to the two lower discs. Analyzing the relationships between BMF (mean and SD) with $T_{1\rho}/T_2$ (mean and SD) for each lumbar level L1 to L5 separately, most relationships were found to be significant ($p<0.05$) for L1 to L4. Except for the relationship between BMF (mean and SD) and T_2 SD at L4 ($p=0.058$ and $p=0.075$) and the relationship between BMF mean and T_2 SD ($p=0.053$) at L1. For L5, only the relationship between BMF SD and T_2 mean was significant ($p=0.024$). There was a negative relationship for all pairs. The associations between BMF (mean and SD) and $T_{1\rho}/T_2$ mean are illustrated in Figure 4. The graph in Figure 4 represents modelled values of the relationships calculated from the mixed effects regression model sampled every 5 units of BMF. A linear model fit represented most appropriately the data fit as shown. In general, low BMF (mean and SD) values were associated with high $T_{1\rho}/T_2$

(mean and SD) values, while high BMF (mean and SD) values were associated with low $T_{1\rho}/T_2$ (mean and SD) values. Figure 5 shows examples of clinical T_2 weighted images, $T_{1\rho}/T_2$ and BMF maps that also illustrate these trends.

Discussion

Using novel quantitative MR imaging techniques, our study demonstrated significant associations between BMF and biochemical degeneration of the adjacent IVDs as assessed by $T_{1\rho}$ and T_2, which are MRI biomarkers sensitive to proteoglycan and collagen integrity of the disc, respectively (25,26). The overall relationships (independent of disc level) were all significant and inverse. The inverse relationships support the notion that diminished nutrient supply may influence IVD degeneration due to a conversion process from hematopoietic bone marrow to fatty bone marrow which impairs the supply of available nutrients to cells in the IVD. This mechanism might accelerate disc degeneration. However, the here suggested causality needs to be further investigated and confirmed in larger longitudinal studies.

Most significant relationships were found between BMF SD and $T_{1\rho}/T_2$ (mean and SD). As BMF SD is a measure of BMF variations, this result indicates that increasing variations in BMF might reflect different stages of IVD degeneration. When examining the individual lumbar levels, we found significant inverse relationships between BMF (mean and SD) with $T_{1\rho}/T_2$ mean and with $T_{1\rho}$ SD for levels L1 to L4. The above results suggest that BMF and IVD health are interrelated, and highlight the utility of novel quantitative MRI biomarkers for the detection of early disc degeneration.

It has been shown that qualitative grading systems such as Modic (7) or Ricci (16) are very specific to discogenic pain (31) but they have low sensitivity (8,13,14). Their low sensitivity might be due to the subjective nature of these grading systems (15). Thus, one of the goals of our study was to improve these subjective BMF evaluations with a quantitative fat fraction assessment tool based on MRI IDEAL and correlate with measures of early disc degeneration that are also quantitative ($T_{1\rho}$ and T_2). We found that the loss of proteoglycan and collagen was significantly associated with greater pain scores (VAS) and greater low back pain-related disability (ODI). BMF mean was also significantly positively associated with ODI and VAS. This finding underscores the role of IVD degeneration as a direct source of pain and disability as compared to BMF.

The significant inverse relationships found between $T_{1\rho}/T_2$ (mean and SD) with Pfirrmann grade were expected as Pfirrmann directly evaluates morphologic changes on clinical T_2 images. Similar relationships between $T_{1\rho}$ /T_2 mean with Pfirrmann grade were previously reported (24). However, in our study, we also found Pfirrmann grading to be significantly positively associated with BMF SD albeit not with BMF mean. This again underlines the importance of BMF variations in the context of IVD degradation of the adjacent discs.

For the level by level analysis, we found significant associations between BMF (mean and SD) with $T_{1\rho}/T_2$ (mean and SD) for L1 to L4 and adjacent IVD. However, there was no significant relationship at L5, which was also the lumbar level adjacent to the most degenerated discs. About 38% of S1/L5 discs had Pfirrmann grade 4 or 5 and significantly

lower $T_{1\rho}/T_2$ as compared to the upper lumbar levels. It has been previously reported, that both $T_{1\rho}/T_2$ mean and SD decreased during early degeneration before increasing again in later stages of severe degeneration (21). This behavior was attributed to morphological changes including the formation of nitrogen bubbles in severely degenerated discs (32) and could explain the lack of significant relationships for S1/L5 seen in this study. This result for the level by level analysis again indicates the potential importance of BMF as a biomarker for disc degeneration.

There are several limitations of this study. First, for the analysis we have focused on investigating relationships between lumbar vertebrae and the adjacent disc below. This ensured that we had always five pairs of vertebrae/disc for each subject. Our data suggested similar relationships for the adjacent discs above. Second, in this study we have focused on the analysis of the WD. However, as shown in Figure 5, the NP almost disappears in some severe cases and this might have contributed to the lower $T_{1\rho}/T_2$ values seen. Furthermore, our sample size might have been limited for the investigation of individual lumbar levels. This would explain the lower number of significant relationships compared to the overall analysis that included all IVDs independent of lumbar level. Another limitation is related to the lower number of subjects with severe disc degeneration (Pfirrmann 4 and 5). This is partly explained by the fact that we also included healthy controls. In addition, in most patients within our age range, the prevalence of severe degeneration is usually limited to 1 or 2 discs and thus most other IVD appear normal.

In conclusion, this study found significantly inverse associations between BMF variations and IVD degeneration (measured with MRI $T_{1\rho}/T_2$ as well as assessed by Pfirrmann grading) and between $T_{1\rho}/T_2$ values and pain and disability. Our data highlight the importance of studying BMF variations more closely using quantitative imaging approaches. Novel high-resolution MRI techniques such as IDEAL can be powerful tools to spatially interrogate BMF changes and eventually overcome the qualitative traditional classification systems. In summary, our findings suggest that quantitative MRI has the potential of becoming a clinically useful tool for diagnosis and treatment assessment of CLBP.

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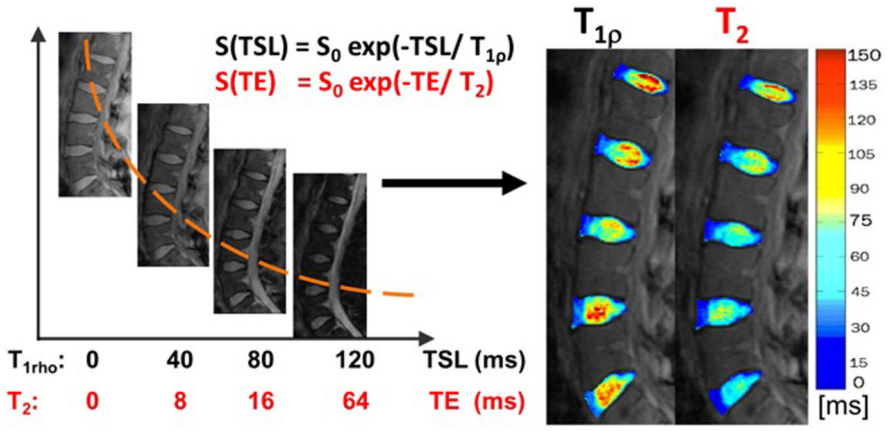

Figure 1:

Shown is an example of $T_{1\rho}$ and T_2 data fitting. Four data points were acquired for each method (4 TSL times for $T_{1\rho}$ and 4 TE times for T_2). Using the equations shown, a mono-exponential signal decay is fitted to the acquired data for each pixel. The resulting $T_{1\rho}$ and T_2 values from a 38 year old subject without LBP and Pfirrmann grade 1 for all discs are depicted on the color maps on the right.

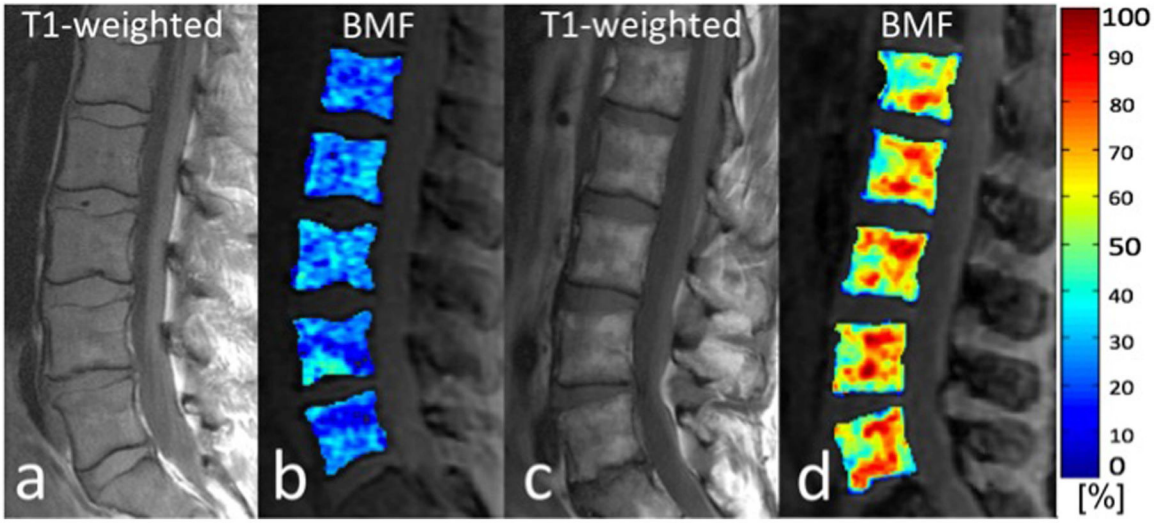

Figure 2:

Shown are T_1-weighted FSE images along with the corresponding BMF fat fraction maps of a subject with low Pfirrmann grading (a and b) and a subject with high Pfirrmann grading (c and d). The left image a) had grade 1 for all discs whereas the right image c) had grade 2,2,3,3, and 5 from L1 to L5. Absolute BMF content was assessed by IDEAL MRI and is reflected by the color maps in b and d. These color-coded maps reflect the fat fraction in the bone marrow on a pixel-by-pixel basis. Higher absolute BMF content as well as larger BMF variations can be appreciated in d compared to b. Although absolute fat content cannot be assessed by clinical T_1-weighted FSE, a larger variation in signal intensity that reflects BMF variations can also be qualitatively determined in c compared to a.

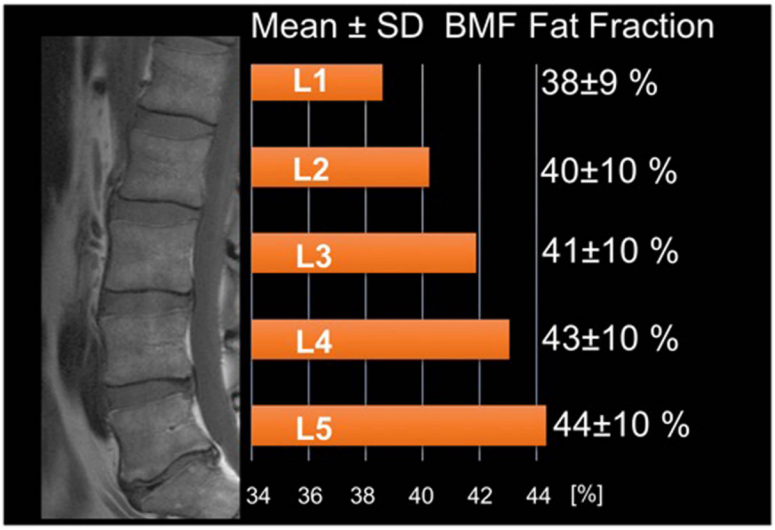

Figure 3:

This figure shows the mean and SD of BMF fat fraction for each lumbar level separately. A T_1-weighted FSE image is shown on the left to illustrate the different lumbar levels. A significant ($p<0.05$) increase in BMF was found between each level going from 38% fat fraction in L1 up to 44% fat fraction in L5.

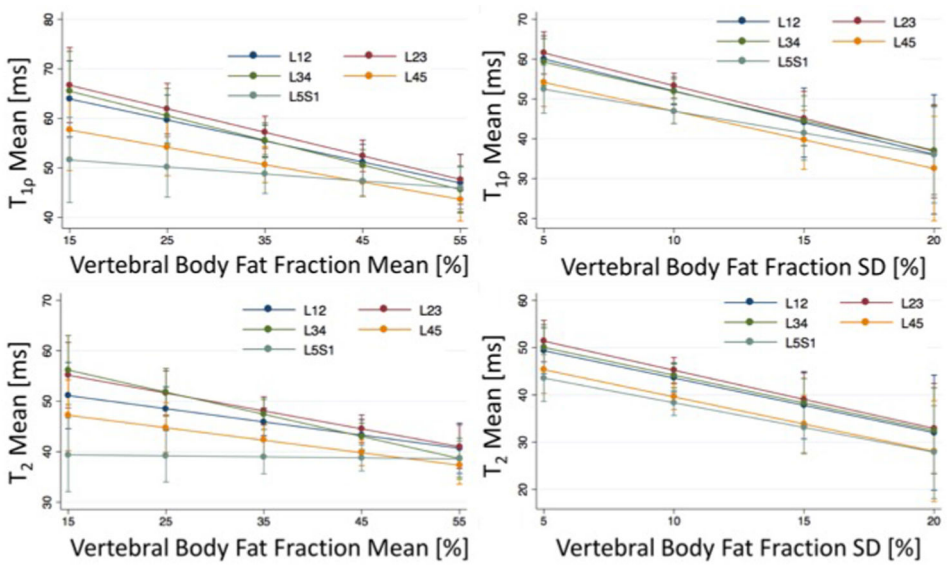

Figure 4:

The graph shows the associations between the vertebral body BMF mean and SD with $T_{1\rho}$ / T_2 mean for each lumbar level. An inverse relationship is clearly demonstrated for each level. Only at L5/S1 the $T_{1\rho}$ / T_2 mean values are low (degenerated disc) for different vertebral fat fractions. However, $T_{1\rho}$ / T_2 varied much more for different BMF variations (SD).

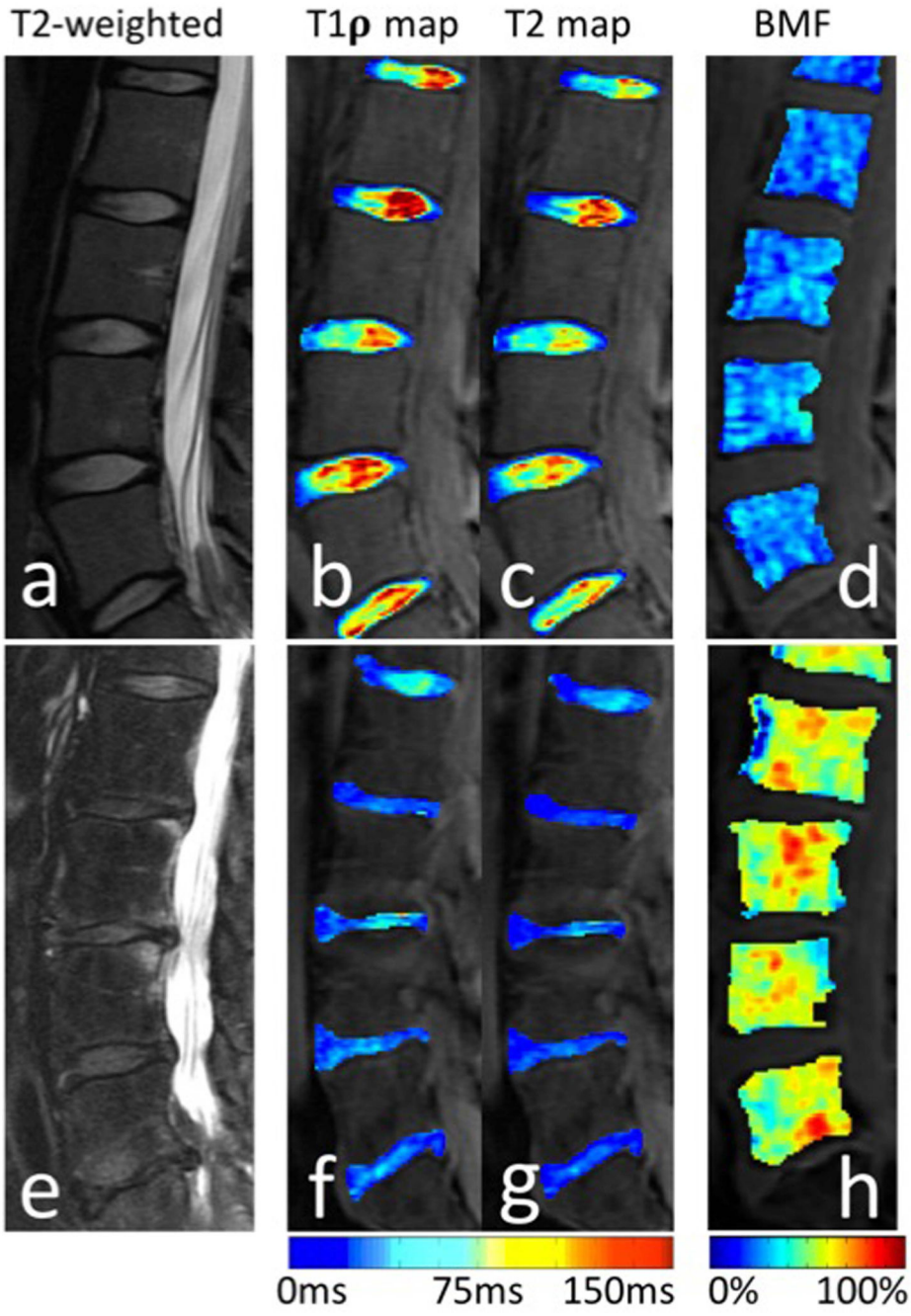

Figure 5:

This figure shows T_2-weighted FSE images, $T_{1\rho}$ and T_2 relaxation maps as well as corresponding BMF fact fraction maps of a subject with low Pfirrmann grading (a, b, c, and d) as well as a subject with high Pfirrmann grading (e, f, g, and h). The subjects with low Pfirrmann grading shows higher $T_{1\rho}$ and T_2 values as well as lower BMF fat fraction content compared to the subject with high Pfirrmann grading. These result reflect the inverse relationships found between $T_{1\rho}$ and T_2 values and BMF as well as the associations between Pfirrmann and BMF as well as Pfirrmann and $T_{1\rho}$ and T_2.

Table 1:

Participant Characteristics

	All Participants
n	46
Age (years)	47.3 ± 12.0
BMI (kg/m^2)	24.9 ± 4.8
Gender (female)	26 (56.5%)
ODI* (mean ± SD)	26.1 ± 19.4
VAS (mean ± SD)**	5.1 ± 3.3
Pfirrmann Grade	
1	55 (23.91%)
2	96 (41.74%)
3	45 (19.57%)
4	23 (10.00%)
5	11 (4.78%)

* ODI: Oswestry Disability Index

** VAS: Visual Analog Scale

Table 2:

Overall associations between Pfirrmann score, ODI, and VAS with BMF and $T_{1\rho}$ / T_2 (mean and SD) with p values and 95% confidence intervals (CI). Abbreviations: Coef. (Coefficient of relationship). Significant associations are highlighted in bold.

	Pfirrmann		ODI		VAS	
	Coef.	**p value (95% CI)**	**Coef.**	**p value (95% CI)**	**Coef.**	**p value (95% CI)**
BMF Mean	−0.14	0.451 (−0.50 0.22)	**0.60**	**0.037 (−0.04 1.16)**	**0.099**	**0.043 (0.00 0.20)**
BMF SD	**0.53**	**0.000 (0.30 0.76)**	2.95	0.064 (−0.18 6.08)	0.41	0.130 (−0.13 0.96)
$T_{1\rho}$ Mean	**−3.70**	**0.000 (−5.05 −2.34)**	**−1.03**	**0.001 (−1.62 −0.45)**	**−0.20**	**0.000 (−0.30 −0.11)**
$T_{1\rho}$ SD	**−2.82**	**0.000 (−3.87 −1.77)**	**−1.34**	**0.001 (−2.07 −0.60)**	**−0.26**	**0.000 (−0.38 −0.14)**
T_2 Mean	**−3.07**	**0.000 (−4.15 −1.98)**	**−1.27**	**0.000 (−1.94 −0.609)**	**−0.23**	**0.000 (−0.34 −0.12)**
T_2 SD	**−2.21**	**0.000 (−3.09 −1.34)**	**−1.58**	**0.000 (−2.43 −0.73)**	**−0.30**	**0.000 (−0.44 −0.16)**

Table 3:

Overall associations between BMF mean and SD with $T_{1\rho}$ / T_2 (mean and SD) of the intervertebral disc with p values and 95% confidence intervals (CI). Significant associations are highlighted in bold.

	$T_{1\rho}$ Mean		$T_{1\rho}$ SD		T_2 Mean		T_2 SD	
	Coef.	**p value (95% CI)**	**Coef.**	**p value (95% CI)**	**Coef.**	**p value (95% CI)**	**Coef.**	**p value (95% CI)**
BMF Mean	**−0.37**	**0.000 (−0.58 −1.62)**	**−0.28**	**0.001 (−0.45 −0.12)**	**−0.26**	**0.007 (−0.45 −0.07)**	**−0.19**	**0.013 (−0.34 −0.04)**
BMF SD	**−1.43**	**0.000 (−2.11 −0.74)**	**−0.99**	**0.000 (−1.52 −0.44)**	**−1.15**	**0.000 (−1.71 −0.59)**	**−0.91**	**0.000 (−1.36 −0.46)**