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RESEARCH ARTICLE

Correlation study between facet joint cartilage and intervertebral discs in early lumbar vertebral degeneration using T2, T2\* and T1p mapping

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# Abstract

Recent advancements in magnetic resonance imaging have allowed for the early detection of biochemical changes in intervertebral discs and articular cartilage. Here, we assessed the feasibility of axial T2, T2\* and T1p mapping of the lumbar facet joints (LFJs) to determine correlations between cartilage and intervertebral discs (IVDs) in early lumbar vertebral degeneration. We recruited 22 volunteers and examined 202 LFJs and 101 IVDs with morphological (sagittal and axial FSE T2-weighted imaging) and axial biochemical (T2, T2\* and T1p mapping) sequences using a 3.0T MRI scanner. IVDs were graded using the Pfirrmann system. Mapping values of LFJs were recorded according to the degeneration grades of IVDs at the same level. The feasibility of T2, T2\* and T1p in IVDs and LFJs were analyzed by comparing these mapping values across subjects with different rates of degeneration using Kruskal-Wallis tests. A Pearson's correlation analysis was used to compare T2, T2\* and T1p values of discs and LFJs. We found excellent reproducibility in the T2, T2\* and T1p values for the nucleus pulposus (NP), anterior and posterior annulus fibrosus (PAF), and LFJ cartilage (intraclass correlation coefficients 0.806–0.955). T2, T2\* and T1p mapping (all P<0.01) had good Pfirrmann grade performances in the NP with IVD degeneration. LFJ T2\* values were significantly different between grades I and IV ( $P_L = 0.032$ ,  $P_R = 0.026$ ), as were T1p values between grades II and III ( $P_{\rm I} = 0.002$ ,  $P_{\rm B} = 0.006$ ) and grades III and IV  $(P_{\rm L} = 0.006, P_{\rm B} = 0.001)$ . Correlations were moderately negative for T1p values between LFJ cartilage and NP ( $r_{\rm L} = -0.574$ ,  $r_{\rm R} = -0.551$ ), and between LFJ cartilage and PAF ( $r_{\rm L} =$ -0.551,  $r_{\rm B} = -0.499$ ). T1p values of LFJ cartilage was weakly correlated with T2 (r = 0.007) and T2\* (r = -0.158) values. Overall, we show that axial T1p effectively assesses early LFJ cartilage degeneration. Using T1p analysis, we propose a link between LFJ degeneration and IVD NP or PAF changes.

### Introduction

Low back pain (LBP) is a common disease that limits the activities of daily living, and is thus a major economic burden on health care systems. It is widely accepted that intervertebral lumbar discs (IVDs) and lumbar facet joints (LFJs) are the main sources of LBP[1, 2].

Degeneration changes in the IVD are characterized by a loss of hydrated proteoglycanrich matrix of the nucleus pulposus (NP) and collagen, both of which affect the mechanics of the IVD[3]. In facet joint (FJ) osteoarthritis, patients demonstrate a loss of articular cartilage matrix, morphological reconstruction of the subchondral bone, and local tissue inflammation [2, 4, 5]. IVD degeneration may also change the mechanical integrity of the local lumbar spine, which may cause LFJ disorder, leading to FJ osteoarthritis[6]. Particularly in the early stages of IVD degeneration, it can be difficult to detect the small morphological changes of the LFJ on plain radiography, computed tomography, or conventional magnetic resonance imaging (MRI) [4]. In addition, morphological MRI grading systems for LFJ dysfunction (e.g., Weishaupt grading) tend to have poor inter-rater agreement[7].

With the improvements in MRI over the past two decades, new quantitative functional techniques-T2, T2\* and T1p mapping, diffusion-weighted imaging, and delayed gadolinium-enhanced MRI have been used to reveal early biochemical changes in IVDs and in articular cartilage[8–11]. In IVDs and cartilage, T2 relaxation times are dependent on the quantity of water and the integrity of the proteoglycan(PG)-collagen matrix[12, 13]. During early disc degeneration, T2 mapping shows a decrease in water and glycosaminoglycan(GAG) content. When collagen degradation occurs in the LFJs, the increase in the water molecule content or an increased motion can be reflected as an increase of the T2 relaxation time, which indicates early damage[14]. In contrast, the T2\* relaxation time reflects the "true" transverse relaxation time. Theoretically, T2\* mapping and T2 mapping should similarly evaluate degeneration; however, some researchers report discrepant results for T2\* values in degenerative articular cartilage as a result of different patterns of cartilage degeneration such as via fibrocartilage replacement or synovial fluid invasion[15]. Most recent studies have shown that T2\* values decrease with an increase in cartilage degeneration, and these findings have suggested that T2\* mapping could be used as a clinical diagnostic protocol for identifying cartilage and disc degeneration[15–18].

T1 $\rho$  mapping, however, uses a "spin lock" pulse to change the relaxation rates of water associated with large macromolecules, such as PGs and GAGs. Decreased GAG content may lead to an increased mobile proton density in bulk water and an increased in T1 $\rho$  relaxation times. Therefore, T1 $\rho$  mapping could be a reliable method for quantitatively assessing PG content in IVDs and cartilage without the need for a contrast agent[3, 19–21].

To the best of our knowledge, only a few articles have explored the relevance of biochemical parameters, such as T2 values for assessing LFJs and IVDs[7, 22]. The aims of this study were to explore whether axial T2, T2<sup>\*</sup> and T1 $\rho$  mapping are feasible for evaluating early changes in LFJ, and to determine if there is an association of the T2, T2<sup>\*</sup>, or T1 $\rho$  relaxation time between the LFJ and IVD in the degenerative process of the lumbar spine.

#### Materials and methods

The study was approved by our institution's research ethics committee of Xiangya Hospital, Central South University (NO. 201301008), and all volunteers involved in this study signed informed consent and agreed to the use of their imaging information for this analysis.

#### Study subjects

This was a prospective study. A total of 22 volunteers, each with 5 lumbar IVDs and 10 LFJs, were recruited from September 2015 to March 2016. The inclusion criteria were healthy

volunteers or other adults with nonspecific acute LBP, which was defined as pain lasting < 2 h per day over a period of < 3 months in subjects aged 20 to 45 years. The exclusion criteria were chronic LBP > 3 months, LBP caused by injury, LBP with a visual analog scale (VAS, 0–10 points, 0 stand for pain-free and gradually serious pain feeling with increasing points, 10 stand for the most serious) score  $\geq$  4 points, disc herniation or spinal stenosis, lumbar spondylolisthesis, tuberculosis, tumor or any other spinal diseases that would affect the stability of the lumbar spine and the loading state of the FJ. Subjects with a body mass index (BMI) > 25 or having other conditions that might generate unreadable data were also excluded from our study. All volunteers were examined by MRI in the morning (i.e., not after a long work day) to maintain the intervertebral discs in a relatively stable physiological situation.

#### MR imaging protocol

All MR examinations were performed by a 3.0 T MR unit (Signa HDxt; GE Medical Systems, Waukesha, WI, USA) and a dedicated eight-channel spine coil. Morphological (sagittal and axial FSE T2-weighted imaging) and biochemical (axial T2, T2\* and T1p mapping) sequences were performed, covering the IVDs L1/2 to L5/S1.

T2 and T2\* mapping were carried out in the axial plane using a 2D multi-echo spin-echo (MESE) sequence and 2D multi-echo fast spoiled gradient-echo (ME-FSGRE) sequence, respectively (S1 Text). Five axial slabs with three slices each covered the five lumbar segments (discs and FJs L1/2 to L5/S1) in each patient for both techniques. Each two-dimensional slab (group of three slices) was aligned along the corresponding intervertebral disc. The central slice (slice 2 of 3), which covered the intervertebral disc and the slice caudal to the central slice (slice 3 of 3) were used for T2 and T2\* evaluation of the IVDs and the FJs respectively.

T1 $\rho$  mapping was performed in the axial plane by 3D spoiled gradient-echo (SPGR) sequence (S1 Text). The spin-lock frequency was set to 500 Hz and the spin-lock times (TSLs) of 0, 10, 40 and 80 ms were used for acquisition. Each three-dimensional slab (group of eight slices) was aligned along the corresponding intervertebral disc. The slice (slice 5 of 8) covering the intervertebral disc and the slice caudal to central slice (slice 6 of 8) were used for T1 $\rho$  evaluation of the IVDs and the FJs respectively. All sequences and sequence parameters are shown in Table 1.

#### Image analysis

Two experienced readers independently assessed the morphology of the IVDs from L1/2 to L5/S1 according to the Pfirrmann grading system on sagittal T2 FSE images. The Pfirrmann

Sequences Parameter	T2WI Sagittal	T2WI Axial	T2 mapping Axial	T2* mapping Axial	T1ρ mapping Axial	
Pulse sequence	FSE	FSE	2D MESE	2D MEFSGRE	3D SPGR	
Repetition time (ms)	2900 5080 1000 450		7.5			
Echo time or TSLs (ms)	(ms) 120 94 12.2; 24.4; 36.6; 48.9; 61.1; 73.3; 85.5; 97.7 5.1; 10.6; 16.1; 21.6; 27.1; 32.6; 38.1; 43.6		0; 10; 40; 80			
Flip angle (°)	-	-	-	30	60	
Field of view (mm) 320×320 180×1		180×180	180×180	180×180	140×140	
Matrix	416×320 320×320 256×256 256×256		256×128			
Slice thickness (mm)	4	3	4	4	3	
Interslice gap (mm)	1	0.3	2	2	-	
Number of slices/slab	11	8/5	3/5	3/5	8/5	
Acquisition time (min: s)	01:27	06:52	04:34	07:48	03:19	

Table 1. Parameters of the morphological and biochemical MRI sequences.

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grading system is primarily based on changes in signal intensity from the NP, the distinction between the NP and the annulus fibrosus, and disc height[23–25]. The distribution of the 101 IVDs with respect to the Pfirrmann grades was determined independently by an experienced musculoskeletal radiologist (XJP) with 15 years' experience, and a spinal surgeon (CYD) with 20 years' experience. A senior radiologist with 13 years' experience manually selected the regions of interest (ROIs) on the working station (Function Software, ADW 4.4 workstation, GE Medical Systems, Waukesha, WI, USA) to measure the mapping values (S1 Fig). The ROIs for the IVDs were drawn on T2, T2\* and T1 $\rho$  maps according to the subject's anatomic shape. In addition, one large, circular ROI was selected for the NP, and two smaller circular ROIs were selected for the anterior annulus fibrosus (AAF) and the posterior annulus fibrosus (PAF), respectively. The ROI of the NP in the mid-sagittal line was about 50% to 60% of the disc diameter. The ROIs of the LFJs were drawn on each map across both articular surfaces of each FJ. All ROIs were selected and calculated on the left and right sides.

#### Statistical analysis

Mean values were used for statistical analyses. The intraclass correlation coefficients (ICC) with 95% confidence intervals (95% CIs) were used to evaluate the reproducibility of T2, T2\* and T1p relaxation times, and an ICC>0.75 was considered excellent agreement. The Kruskal-Wallis and Nemenyi tests were used to compare the differences in the T2, T2\* and T1p values of discs and LFJs among the different Pfirrmann grades. A Pearson correlation analysis was performed to compare T2, T2\* and T1p values of the disc and LFJs. The absolute value of correlation coefficients *r* were used to indicate very strong correlation (r = 0.80 to 1.00), strong correlation (r = 0.60 to 0.79), moderate correlation (r = 0.40 to 0.59), weak correlation (r = 0.20 to 0.39) or no correlation (r < 0.20). All statistical evaluations were performed using PASW Statistics software (19.0, SPSS, Chicago, IL, USA). A *P* < 0.05 was considered statistically significant.

### Results

#### Volunteers characteristics

A total of 22 volunteers were recruited (12 women and 10 men; mean age, 33.2 years, range, 21 to 44 years). In all, 202 LFJs and 101 IVDs from L1/2 to L5/S1 were assessed. The morphological IVD Pfirrmann grades on sagittal T2WI are shown in <u>S1 Fig</u>. The reproducibility for the three methods was excellent and the data are presented in <u>Table 2</u>.

Differences in the T2, T2<sup>\*</sup> and T1 $\rho$  values for various anatomic areas of the IVDs among the four Pfirrmann grades. The images of the axial morphological sequence (FSE) and the T2, T2<sup>\*</sup>, and T1 $\rho$  mapping of the IVD and LFJ are shown in Fig 1. The T2, T2<sup>\*</sup> and T1 $\rho$  values of the NP, AAF and PAF with increasing Pfirrmann grade are shown in Fig 2 and Table 3. There were statistically significant differences in the T2, T2<sup>\*</sup> and T1 $\rho$  values for the

ROIs	T2	mapping	T2*	* mapping	T1p mapping		
	ICC	95% CI	ICC	95% CI	ICC	95% CI	
NP	0.908	0.870-0.928	0.899	0.854-0.922	0.892	0.849–0.916	
AAF	0.895	0.850-0.920	0.931	0.882-0.941	0.942	0.926-0.951	
PAF	0.941	0.925-0.951	0.955	0.942-0.967	0.951	0.938–0.964	
LFJ	0.807	0.785–0.820	0.831	0.808–0.847	0.825	0.805-0.842	

Table 2. The interclass correlation coefficients (ICC) with 95% confidence intervals (CIs) of T2, T2\* and T1p mapping.

Abbreviations: ROI, regions of interest; NP, nucleus pulposus; AAF, anterior annulus fibrosus; PAF, posterior annulus fibrosus; LFJ, lumbar facet joint.

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**Fig 1. Illustration of the intervertebral discs (IVDs) and lumbar facet joints (LFJs) in morphological sequence and T2/T2\*/T1p mapping in one volunteer.** (A-1) Morphology of the IVD in the FSE sequence with Pfirrmann grade I. (A-2 to A-4) Color-coded T2/T2\*/T1p map of the L3/4 IVD, respectively. (B-1) Morphology of the LFJ of the same segment adjacent to the L3/4 IVD. (B-2 to B-4) Color-coded T2/T2\*/T1p map of L3/4 LFJ respectively.

NP among the four grades (all P<0.001), especially in the T1 $\rho$  values between grades II (166.93 ±15.87 ms) and III (108.98±10.31 ms) (P = 0.000). There were no significant differences in the T2, T2\* and T1 $\rho$  values for the AAF (all P>0.05). Although there were differences in the T2, T2\* and T1 $\rho$  values for the PAF (Fig 2), we found no significant differences in the T2 values among the grades (P = 0.051, Fig 2A). However, a significant difference was found in the T2\* values between Pfirrmann grades II (34.34±7.28 ms) and III (28.79±4.04 ms) (P = 0.005, Fig 2B) and in the T1 $\rho$  values between Pfirrmann grades II (73.67±7.55 ms) and III (63.24±7.85 ms) (P = 0.000, Fig 2C) and grades III and IV (52.69±4.99 ms) (P = 0.006, Fig 2C).

**Correlations of T2, T2\* and T1p values between the LFJ cartilage and IVD.** The T2, T2\* and T1p values for the LFJ cartilage tended to change with an increase in Pfirrmann grade





(Figs <u>3A</u>, <u>4A</u> and <u>5A</u> and <u>Table 3</u>). The correlations between the T2, T2<sup>\*</sup> and T1p values for the LFJ and the IVD are shown in Figs <u>3</u>, <u>4</u> and <u>5</u>. For the T2 value of the LFJ, no significant differences were found among the four groups ( $P_L = 0.961$ ,  $P_R = 0.855$ , Fig <u>3A</u>). The T2 value also showed no correlation between the LFJ cartilage and the NP ( $r_L = 0.081$ ,  $r_R = 0.033$ , Fig <u>3B</u>), the AAF ( $r_L = -0.169$ ,  $r_R = 0.046$ , Fig <u>3C</u>), or the PAF ( $r_L = -0.004$ ,  $r_R = 0.047$ , Fig <u>3D</u>).

Table 3. T2, T2\* and T1p values and the distribution of IVD and LFJ.

	T2 values (ms)				T2* values (ms)				T1ρ values (ms)			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
NP	119.80	109.55	78.05	58.22	79.16	70.36	49.46	35.22	183.90	166.93	108.98	73.20
	±14.12	±14.57	±9.82	±6.10	±10.22	±13.54	±11.12	±5.52	±20.30	±15.87	±10.31	±12.39
AAF	52.55	50.29	49.39	46.61	30.97	30.31	27.67	25.99	72.31	71.59	68.62	63.82
	±5.74	±3.43	±4.68	±3.52	±7.51	±7.28	±2.33	±2.50	±7.68	±8.39	±7.41	±5.08
PAF	61.89	58.77	56.97	52.94	34.15	34.34	28.79	26.59	74.15	73.67	63.24	52.69
	±7.35	±5.80	±5.45	±4.09	±5.82	±7.28	±4.04	±2.90	±8.92	±7.55	±7.85	±4.99
L	57.17	57.62	57.01	58.15	22.02	20.62	20.01	19.33	49.37	50.70	55.08	60.80
LFJ	±6.00	±6.23	±5.03	±2.68	±3.48	±3.00	±3.11	±3.01	±4.67	±4.38	±3.69	±3.65
R	57.44	57.67	57.15	59.53	21.89	20.78	20.19	19.21	49.49	50.71	54.37	60.46
LFJ	±5.33	±7.13	±7.18	±5.31	±3.17	±3.35	±3.16	±2.88	±3.75	±4.36	±3.18	±4.32

Abbreviations: IVD, intervertebral discs; LFJ, lumbar facet joint; NP, nucleus pulposus; AAF, anterior annulus fibrosus; PAF, posterior annulus fibrosus.

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Fig 3. Changes in the T2 values of the lumbar facet joint (LFJ) with changes in the intervertebral discs (IVDs). (A) Changes in the T2 values of the LFJ with degeneration grade; (B-D) Correlations between the T2 values of the left/right LFJ cartilage and (B) the nucleus pulposus (NP), (C) the anterior annulus fibrosus (AAF), and (D) the posterior annulus fibrosus (PAF).

The T2\* values for the LFJs showed a significant difference among the four Pfirrmann grade groups and between grades I (left [L],22.02±3.48 ms; right [R], 21.89±3.17 ms) and IV (L, 19.33±3.01 ms; R,19.21±2.88 ms) ( $P_L = 0.032$ ,  $P_R = 0.026$ , Fig 4A). The NP T2\* values were weakly correlated with the LFJ T2\* value ( $r_L = 0.148$ , $r_R = 0.215$ , Fig 4B). Neither the AAF T2\* value ( $r_L = 0.021$ ,  $r_R = 0.087$ ) nor the PAF T2\* value ( $r_L = 0.082$ , $r_R = 0.160$ ) was correlated with that of the LFJ (Fig 4C and 4D).



**Fig 4.** Changes in the T2\* values of the lumbar facet joint (LFJ) with changes in the intervertebral discs (IVDs). (A) Changes in the T2\* values of the LFJ with degeneration grade. (B–D) Correlations between the T2\* values of the left/right LFJ cartilage and (B) the nucleus pulposus (NP), (C) the anterior annulus fibrosus (AAF), and (D) the posterior annulus fibrosus (PAF). \**P* <0.05.

Fig 5A shows the mean T1 $\rho$  values for the LFJ at different IVD Pfirrmann grades. There were statistically significant differences among the four groups and between grades II (L, 50.70±4.38 ms; R, 50.71±4.36 ms) and III (L, 55.08±3.69 ms; R, 54.37±3.18 ms) ( $P_L = 0.002$ ,  $P_R = 0.006$ ), and grades III and IV (L, 60.80±3.65 ms; R, 60.46±4.32 ms) ( $P_L = 0.006$ ,  $P_R = 0.001$ ). A moderately negative correlation was found between the LFJ and the NP ( $r_L = -0.574$ ,  $r_R = -0.551$ , Fig 5B) for the T1 $\rho$  value, as well as between the LFJ and the PAF ( $r_L = -0.551$ ,  $r_R = -0.499$ , Fig 5D). There was no correlation between the LFJ and the AAF ( $r_L = -0.173$ ,  $r_R = -0.200$ , Fig 5C).

**Correlations between T1p values and the T2 and T2\* values of the LFJ.** To avoid the mutual influence of the different methods, we next explored the relationships among the T1p value and the other two methods. Our results showed that the T1p values for LFJ were weakly correlated with the T2 (r = 0.007) and T2\* values (r = -0.158) (Fig 6).

#### Discussion

Quantitative MRI has attracted increasing attention over the past two decades as a way to evaluate articular cartilage and IVD[18, 26-29]. Many authors believe that T2, T2<sup>\*</sup> or T1 $\rho$ 



**Fig 5.** Changes in the T1p values of the lumbar facet joint (LFJ) with changes in the intervertebral discs (IVDs). (A) Changes in the T1p values of the LFJ with degeneration grade. (B–D) Correlations between the T1p values of the left/right LFJ cartilage and (B) the nucleus pulposus (NP), (C) the anterior annulus fibrosus (AAF), and (D) the posterior annulus fibrosus (PAF). \*\**P*<0.01.

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mapping are reliable for investigating early degeneration of cartilage[13, 15, 20, 30]. To the best of our knowledge, little research has been done to determine the T2, T2<sup>\*</sup> and T1 $\rho$  relaxation times of the LFJ and correlate changes in relaxation times of the IVD with degenerative changes.

Previous studies have reported the ranges of T2, T2\* and T1 $\rho$  values for healthy and osteoarthritis (OA) cartilage in knees[31–34]. We performed axial T2, T2\* and T1 $\rho$  mapping of the LFJ and the IVD (Table 3); the values of the LFJ are close to those for knee joint cartilage[7, 22]. The mean and range of T1 $\rho$  values for the FJ cartilage in our study are the first such measurements to be reported. T2, T2\* and T1 $\rho$  mapping performed well in evaluating the degeneration changes of the IVDs in our study, with significant differences noted for the T2, T2\* and T1 $\rho$  values for the NP between Pfirrmann grades, especially between grades II and III. Furthermore, we measured a significant difference in the T2\* values for the PAF between Pfirrmann grades II and III, as well as in the T1 $\rho$  values for the PAF between grades II and III and grades III and IV; these results are similar to those reported by others[3, 18].

The changes in the molecular biochemical components in degenerated IVDs can be accurately evaluated by T2, T2<sup>\*</sup> and T1 $\rho$  mapping. T2 mapping might be more sensitive to tissue hydration; however, T2<sup>\*</sup> mapping might be more sensitive to collagen integrity, and T1 $\rho$  mapping can show slow-motion interactions between macromolecules and bulk water in the extracellular matrix[7, 18, 21, 26, 28]. The main degenerative changes to the IVD are the loss of PG/GAG and dehydration[22, 23, 25]. Considering the load-bearing characteristics of IVDs, the NP and PAF may suffer more stress than the AAF and show earlier and more severe signs of degenerative change. In previous work, the T1 $\rho$  relaxation time was shown to be associated with the change of PG/GAG, and T1 $\rho$  mapping could also be used to detect early changes of PG/GAG composition in IVD[26, 27]. Here, we found that T1 $\rho$  mapping was more sensitive in detecting early changes in the IVD than T2 and T2<sup>\*</sup> mapping.

In this study, we noted different sensibilities for the T2, T2\* and T1 $\rho$  values of the FJ in detecting degeneration of the LFJ with increasing Pfirrmann grades of the IVD. T2\* and T1 $\rho$  values could detect LFJ changes with increasing Pfirrmann grades of IVD, but no significant results were found for T2 values. Stelzeneder D et al. reported comparable results regarding FJ

T2 values in segments with normal and abnormal Pfirrmann scores[7]. Compared with T2 and T2\*, T1 $\rho$  values showed better sensitivity for detecting early degenerative changes in the FJ cartilage. In the LFJ, the changes in degeneration as measured by T2, T2\* and T1 $\rho$  values were similar to previous results found in other joints[12, 31, 32, 35, 36]. LFJ cartilage degeneration is mainly associated with alterations in water, collagen and PG, which play important roles in different stages of degeneration[5, 8]. Previous studies in other joints have shown that at a very early stage of cartilage degeneration, the GAG content might change more obviously than the collagen content[10, 19], and this change could be detected by the T1 $\rho$  relaxation time. Therefore, in LFJ degeneration, T1 $\rho$  values seem to offer a more sensitive and reliable method to assess the early changes in the cartilage.

Another meaningful finding in this study was that the degenerative changes of the LFJ may correlate with IVD degeneration, as measured through T1p values, especially the NP and the PAF. We did not find any meaningful correlations for T2 and T2\* values for the LFJ. A previous study found that FJs were weakly correlated with T2 values for the PAF according to axial T2 mapping[7]. However, there is a lack of more direct studies that could prove the correlation between LFJ degeneration and the changes in the IVD measured using other mapping values. As described in the literature, changes in the lumbar spine mechanics environment during IVD degeneration may affect the loading distribution on the subchondral bone of the LFJ, and this would lead to functional and morphological changes in the cartilage [4, 37]. Changes in the biochemical values that reflect early degeneration of the IVD are dependent on interactions between free water and matrix molecules. T1p values that reflect dehydration and loss of the PG in the NP were negatively correlated with that of the LFJ, suggestive of increased water content and decreased GAG content of the LFJ cartilage. Degenerative discs can cause an increase in force transmission across the FJs and, in turn, a change in the orientation and stability of the FJ can affect the disc. Degeneration in the PAF causes a reduction of load-bearing capacity, which leads to degeneration of the LFJ cartilage and, later, a further change in the PAF. Our results also suggest that the NP and the PAF degenerate before the AAF, and that PAF degeneration is closely associated with FJOA. In this study, all of the volunteers who were recruited were less than 45 years old and the Pfirrmann grades of the IVDs for these subjects were mainly distributed within grades I to III. The biochemical changes in the LFJ in our study cohort were mainly due to the loss of PG/GAG content, as described before. Low GAG levels are represented by high T1p values, and the loss of PG/GAG results in an increase in the T1p relaxation time in articular cartilage[20]. However, in degenerated IVDs, the reduced water content is recognized as a contributing factor that causes a decrease in  $T1\rho$  values[27, 38]. Therefore, we found a negative correlation between LFJs and IVDs confirmed only by T1p values. T1p values for the LFJ were weakly correlated with the T2 and T2\* values, suggesting that changes to the LFJs are detected earlier by T1p, and that the sensitivity of T1p exceeds that of T2\* and T2 measurements.

The major limitation of our study was that there was no histological assessment of disc degeneration or LFJ cartilage. We should also point out that the T2, T2\* and T1p values of the LFJ cartilage do not remove the effect of joint fluid, and this may be a result of relatively poor resolution of the mapping. However, there appears to have been a limited effect of joint fluid on our results.

Our study uniquely assessed the feasibility of detecting IVD and LFJ degeneration using three quantitative biochemical methods on axial scanning. Our results demonstrated that T1p values are more sensitive than T2 and T2\* values for assessing the early degenerative changes in the LFJ cartilage, and showed that LFJ degeneration may be correlated with changes in the NP and PAF of the IVD.

## Supporting information

**S1 Text. The model assumed for data fitting in MRI mapping.** (DOCX)

S1 Fig. ROIs for the IVD and LFJ, and the Pfirrmann grade of IVD shown from grade I to grade IV. (DOCX)

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## **Author Contributions**

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### References

- Duan CY, Espinoza Orias AA, Shott S, An HS, Andersson GB, Hu JZ, et al. In vivo measurement of the subchondral bone thickness of lumbar facet joint using magnetic resonance imaging. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2011; 19(1):96–102. PubMed Central PMCID: PMC3011863.
- Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nature reviews Rheumatology. 2013; 9(4):216–24. PubMed Central PMCID: PMC4012322. <u>https://doi.org/10.1038/nrrheum.2012.199</u> PMID: 23147891
- Zhou Z, Jiang B, Zhou Z, Pan X, Sun H, Huang B, et al. Intervertebral disk degeneration: T1rho MR imaging of human and animal models. Radiology. 2013; 268(2):492–500. <u>https://doi.org/10.1148/radiol. 13120874</u> PMID: 23579049
- Cao Y, Zhang Y, Yin X, Lu H, Hu J, Duan C. 3D visualization of the lumbar facet joint after degeneration using propagation phase contrast micro-tomography. Scientific reports. 2016; 6:21838. PubMed Central PMCID: PMC4764819. https://doi.org/10.1038/srep21838 PMID: 26907889
- 5. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. Seminars in arthritis and rheumatism. 2007; 37(2):69–80. https://doi.org/10.1016/j.semarthrit.2007.01.007 PMID: 17379279

- Manchikanti L, Hirsch JA, Pampati V. Chronic low back pain of facet (zygapophysial) joint origin: is there a difference based on involvement of single or multiple spinal regions? Pain physician. 2003; 6 (4):399–405. PMID: 16871288
- Stelzeneder D, Messner A, Vlychou M, Welsch GH, Scheurecker G, Goed S, et al. Quantitative in vivo MRI evaluation of lumbar facet joints and intervertebral discs using axial T2 mapping. European radiology. 2011; 21(11):2388–95. https://doi.org/10.1007/s00330-011-2198-z PMID: 21748388
- Blumenkrantz G, Majumdar S. Quantitative magnetic resonance imaging of articular cartilage in osteoarthritis. European cells & materials. 2007; 13:76–86.
- Kijowski R, Chaudhary R. Quantitative magnetic resonance imaging of the articular cartilage of the knee joint. Magnetic resonance imaging clinics of North America. 2014; 22(4):649–69. https://doi.org/ 10.1016/j.mric.2014.07.005 PMID: 25442027
- Wang L, Regatte RR. Quantitative mapping of human cartilage at 3.0T: parallel changes in T(2), T(1) rho, and dGEMRIC. Academic radiology. 2014; 21(4):463–71. PubMed Central PMCID: PMC3949430. https://doi.org/10.1016/j.acra.2013.12.010 PMID: 24594416
- Singh A, Haris M, Cai K, Kogan F, Hariharan H, Reddy R. High resolution T1rho mapping of in vivo human knee cartilage at 7T. PloS one. 2014; 9(5):e97486. PubMed Central PMCID: PMC4022681. https://doi.org/10.1371/journal.pone.0097486 PMID: 24830386
- Hannila I, Lammentausta E, Tervonen O, Nieminen MT. The repeatability of T2 relaxation time measurement of human knee articular cartilage. Magma. 2015; 28(6):547–53. <u>https://doi.org/10.1007/s10334-015-0494-3 PMID: 26162930</u>
- Kim HK, Horn P, Dardzinski BJ, Kim DH, Laor T. T2 Relaxation Time Mapping of the Cartilage Cap of Osteochondromas. Korean journal of radiology. 2016; 17(1):159–65. PubMed Central PMCID: PMC4720804. https://doi.org/10.3348/kjr.2016.17.1.159 PMID: 26798229
- Chen C, Huang M, Han Z, Shao L, Xie Y, Wu J, et al. Quantitative T2 magnetic resonance imaging compared to morphological grading of the early cervical intervertebral disc degeneration: an evaluation approach in asymptomatic young adults. PloS one. 2014; 9(2):e87856. PubMed Central PMCID: PMC3912130. https://doi.org/10.1371/journal.pone.0087856 PMID: 24498384
- Newbould RD, Miller SR, Toms LD, Swann P, Tielbeek JA, Gold GE, et al. T2\* measurement of the knee articular cartilage in osteoarthritis at 3T. Journal of magnetic resonance imaging: JMRI. 2012; 35 (6):1422–9. PubMed Central PMCID: PMC4351813. <u>https://doi.org/10.1002/jmri.23598</u> PMID: 22314961
- Bittersohl B, Hosalkar HS, Miese FR, Schibensky J, Konig DP, Herten M, et al. Zonal T2\* and T1Gd assessment of knee joint cartilage in various histological grades of cartilage degeneration: an observational in vitro study. BMJ open. 2015; 5(2):e006895. PubMed Central PMCID: PMC4322206. <u>https://</u> doi.org/10.1136/bmjopen-2014-006895 PMID: 25667150
- Bittersohl B, Miese FR, Hosalkar HS, Herten M, Antoch G, Krauspe R, et al. T2\* mapping of hip joint cartilage in various histological grades of degeneration. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2012; 20(7):653–60.
- Welsch GH, Trattnig S, Paternostro-Sluga T, Bohndorf K, Goed S, Stelzeneder D, et al. Parametric T2 and T2\* mapping techniques to visualize intervertebral disc degeneration in patients with low back pain: initial results on the clinical use of 3.0 Tesla MRI. Skeletal radiology. 2011; 40(5):543–51. https:// doi.org/10.1007/s00256-010-1036-8 PMID: 20878155
- Regatte RR, Akella SV, Lonner JH, Kneeland JB, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. Journal of magnetic resonance imaging: JMRI. 2006; 23(4):547–53. https://doi.org/10.1002/jmri.20536 PMID: 16523468
- Wang L, Chang G, Xu J, Vieira RL, Krasnokutsky S, Abramson S, et al. T1rho MRI of menisci and cartilage in patients with osteoarthritis at 3T. European journal of radiology. 2012; 81(9):2329–36. PubMed Central PMCID: PMC3298732.
- Zhang X, Yang L, Gao F, Yuan Z, Lin X, Yao B, et al. Comparison of T1rho and T2\* Relaxation Mapping in Patients with Different Grades of Disc Degeneration at 3T MR. Medical science monitor: international medical journal of experimental and clinical research. 2015; 21:1934–41. PubMed Central PMCID: PMC4501651.
- Takashima H, Takebayashi T, Yoshimoto M, Terashima Y, Ida K, Shishido H, et al. Investigation of intervertebral disc and facet joint in lumbar spondylolisthesis using T2 mapping. Magnetic resonance in medical sciences: MRMS: an official journal of Japan Society of Magnetic Resonance in Medicine. 2014; 13(4):261–6.
- Rodrigues LM, Oliveira LZ, Pinhal MA. Expression of heparanase isoforms in intervertebral discs classified according to Pfirmann grading system for disc degeneration. Spine. 2013; 38(13):1112–8. <a href="https://doi.org/10.1097/BRS.0b013e3182894cf4">https://doi.org/10.1097/BRS.0b013e3182894cf4</a> PMID: 23370684

- Griffith JF, Wang YX, Antonio GE, Choi KC, Yu A, Ahuja AT, et al. Modified Pfirrmann grading system for lumbar intervertebral disc degeneration. Spine. 2007; 32(24):E708–12. https://doi.org/10.1097/BRS. 0b013e31815a59a0 PMID: 18007231
- Rim DC. Quantitative Pfirrmann Disc Degeneration Grading System to Overcome the Limitation of Pfirrmann Disc Degeneration Grade. Korean Journal of Spine. 2016; 13(1):1–8. PubMed Central PMCID: PMC4844654. https://doi.org/10.14245/kjs.2016.13.1.1 PMID: 27123023
- Blumenkrantz G, Zuo J, Li X, Kornak J, Link TM, Majumdar S. In vivo 3.0-tesla magnetic resonance T1rho and T2 relaxation mapping in subjects with intervertebral disc degeneration and clinical symptoms. Magnetic resonance in medicine. 2010; 63(5):1193–200. PubMed Central PMCID: PMC2988488. https://doi.org/10.1002/mrm.22362 PMID: 20432290
- Borthakur A, Maurer PM, Fenty M, Wang C, Berger R, Yoder J, et al. T1rho magnetic resonance imaging and discography pressure as novel biomarkers for disc degeneration and low back pain. Spine. 2011; 36(25):2190–6. PubMed Central PMCID: PMC4002043. https://doi.org/10.1097/BRS. 0b013e31820287bf PMID: 21358489
- Hoppe S, Quirbach S, Mamisch TC, Krause FG, Werlen S, Benneker LM. Axial T2 mapping in intervertebral discs: a new technique for assessment of intervertebral disc degeneration. European radiology. 2012; 22(9):2013–9. https://doi.org/10.1007/s00330-012-2448-8 PMID: 22544293
- Marinelli NL, Haughton VM, Anderson PA. T2 relaxation times correlated with stage of lumbar intervertebral disk degeneration and patient age. AJNR American journal of neuroradiology. 2010; 31(7):1278– 82. https://doi.org/10.3174/ajnr.A2080 PMID: 20360340
- Prasad AP, Nardo L, Schooler J, Joseph GB, Link TM. T(1)rho and T(2) relaxation times predict progression of knee osteoarthritis. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2013; 21(1):69–76. PubMed Central PMCID: PMC3596874.
- Bittersohl B, Hosalkar HS, Sondern M, Miese FR, Antoch G, Krauspe R, et al. Spectrum of T2\* values in knee joint cartilage at 3 T: a cross-sectional analysis in asymptomatic young adult volunteers. Skeletal radiology. 2014; 43(4):443–52. https://doi.org/10.1007/s00256-013-1806-1 PMID: 24425347
- **32.** Kim T, Min BH, Yoon SH, Kim H, Park S, Lee HY, et al. An in vitro comparative study of T2 and T2\* mappings of human articular cartilage at 3-Tesla MRI using histology as the standard of reference. Skel-etal radiology. 2014; 43(7):947–54. https://doi.org/10.1007/s00256-014-1872-z PMID: 24715200
- Kumar D, Souza RB, Singh J, Calixto NE, Nardo L, Link TM, et al. Physical activity and spatial differences in medial knee T1rho and t2 relaxation times in knee osteoarthritis. The Journal of orthopaedic and sports physical therapy. 2014; 44(12):964–72. PubMed Central PMCID: PMC4476033. https://doi. org/10.2519/jospt.2014.5523 PMID: 25353261
- Schooler J, Kumar D, Nardo L, McCulloch C, Li X, Link TM, et al. Longitudinal evaluation of T1rho and T2 spatial distribution in osteoarthritic and healthy medial knee cartilage. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2014; 22(1):51–62. PubMed Central PMCID: PMC3934359.
- Hirose J, Nishioka H, Nakamura E, Oniki Y, Yamashita Y, Mizuta H. T1rho and T2 mapping of the proximal tibiofibular joint in relation to aging and cartilage degeneration. European journal of radiology. 2012; 81(10):2776–82. https://doi.org/10.1016/j.ejrad.2011.11.019 PMID: 22153747
- 36. Souza RB, Kumar D, Calixto N, Singh J, Schooler J, Subburaj K, et al. Response of knee cartilage T1rho and T2 relaxation times to in vivo mechanical loading in individuals with and without knee osteoarthritis. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2014; 22(10):1367–76. PubMed Central PMCID: PMC4184934.
- 37. Fujiwara A, Tamai K, Yamato M, An HS, Yoshida H, Saotome K, et al. The relationship between facet joint osteoarthritis and disc degeneration of the lumbar spine: an MRI study. European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 1999; 8(5):396–401. PubMed Central PMCID: PMC3611192.
- Wang YX, Zhao F, Griffith JF, Mok GS, Leung JC, Ahuja AT, et al. T1rho and T2 relaxation times for lumbar disc degeneration: an in vivo comparative study at 3.0-Tesla MRI. European radiology. 2013; 23 (1):228–34. https://doi.org/10.1007/s00330-012-2591-2 PMID: 22865227