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Longitudinal evaluation of $T_{1\rho}$ and T_2 spatial distribution in osteoarthritic and healthy medial knee cartilage

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SUMMARY

Objective—To investigate longitudinal changes in laminar and spatial distribution of knee articular cartilage magnetic resonance imaging (MRI) $T_{1\rho}$ and T_2 relaxation times, in individuals with and without medial compartment cartilage defects.

Design—All subjects (at baseline n = 88, >18 years old) underwent 3-Tesla knee MRI at baseline and annually thereafter for 3 years. The MR studies were evaluated for presence of cartilage defects (modified Whole-Organ Magnetic Resonance Imaging Scoring – mWORMS), and quantitative $T_{1\rho}$ and T_2 relaxation time maps. Subjects were segregated into those with (mWORMS ≥2) and without (mWORMS ≤1) cartilage lesions at the medial tibia (MT) or medial femur (MF) at each time point. Laminar (bone and articular layer) and spatial (gray level co-occurrence matrix – GLCM) distribution of the $T_{1\rho}$ and T_2 relaxation time maps were calculated. Linear regression models (cross-sectional) and Generalized Estimating Equations (GEEs) (longitudinal) were used.

Results—Global $T_{1\rho}$, global T_2 and articular layer T_2 relaxation times at the MF, and global and articular layer T_2 relaxation times at the MT, were higher in subjects with cartilage lesions compared to those without lesions. At the MT global $T_{1\rho}$ relaxation times were higher at each time point in subjects with lesions. MT $T_{1\rho}$ and T_2 became progressively more heterogeneous than control compartments over the course of the study.

Conclusion—Spatial distribution of $T_{1\rho}$ and T_2 relaxation time maps in medial knee OA using GLCM technique may be a sensitive indicator of cartilage deterioration, in addition to whole-compartment relaxation time data.

Keywords

GLCM; Texture; Quantitative MRI; Cartilage defects; Laminar

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Author contributions

Conception and design: Schooler, Kumar, Link, Majumdar; Acquisition of data: Schooler, Kumar; Analysis and interpretation of the data: Schooler, Kumar, Nardo, McCulloch, Li, Link, Majumdar; Statistical expertise: McCulloch; Drafting of article or critical revision of the article for important intellectual content: Schooler, Kumar, Nardo, McCulloch, Li, Link, Majumdar; Final approval of the article: Schooler, Kumar, Nardo, McCulloch, Li, Link, Majumdar.

Conflicts of interest No author has any conflict of interest to disclose.

Introduction

Knee osteoarthritis (OA) most commonly affects the medial compartment[1] and degenerative cartilage lesions associated with knee OA have been reported more frequently at the medial compartment of the knee[2–4]. Early degenerative changes in OA consist of reduction in the proteoglycan content and disruption of the collagen network[5]. $T_{1\rho}$ and T_2 relaxation time mapping magnetic resonance imaging (MRI) techniques, among others, have been proposed for quantitative evaluation of early changes associated with OA in knee hyaline cartilage[6–10]. An increase in $T_{1\rho}$ and T_2 relaxation times indicates loss of proteoglycans and disruption of collagen matrix respectively[7–9,11–13]. T_2 relaxation time has also been inversely correlated with proteoglycan concentration[14], suggesting that this metric is sensitive to both collagen and proteoglycan concentration. Previous studies have demonstrated differences between superficial and deep layers of articular cartilage using laminar analyses, for mean $T_{1\rho}$[10] and T_2[15] relaxation times, possibly due to spatial differences in collagen orientation and content throughout the cartilage matrix. It has also been shown that individuals with greater number and severity of cartilage lesions in the medial femur (MF) have higher $T_{1\rho}$ relaxation times at the MF[4]. However, longitudinal analysis of changes in $T_{1\rho}$ and T_2 relaxation times for the superficial and deep layers of articular cartilage, and their association with medial knee cartilage defects, has not been performed.

Haralick *et al.*[16] developed a method of texture analysis based on the gray level co-occurrence matrix (GLCM) that is used to evaluate spatial distribution of pixel intensities in an image along a corresponding angle or direction. Spatial analysis of $T_{1\rho}$ and T_2 relaxation times in cartilage has been shown to provide supplementary information about specific patterns of degeneration when compared to standard metrics alone (compartment mean values and standard deviations)[17,18]. Techniques to flatten regions of interest after image acquisition to more accurately classify tissues with well-defined layers have been proposed[19]. Carballido-Gamio *et al.*[20] reported significant increases in $T_{1\rho}$ GLCM parameter reproducibility with flattened cartilage maps compared to non-flattened maps. Flattening of $T_{1\rho}$ and T_2 cartilage maps allows for quantification of GLCM spatial heterogeneity both along (parallel to the bone–cartilage interface, corresponding to the A–P axis) and through (perpendicular to the bone–cartilage interface, corresponding to the S–I axis) the natural lamina present in articular cartilage. Longitudinal changes in knee articular cartilage GLCM parameters for both $T_{1\rho}$ and T_2 relaxation times, using flattened cartilage maps, and their association with cartilage defects, have not been investigated to date.

The goals of this study were to (1) compare global, laminar (bone and articular layer), and flattened texture parameters of $T_{1\rho}$ and T_2 relaxation times between medial knee compartments with and without cartilage lesions (cross-sectional), and (2) to compare the changes in global, laminar (bone and articular layer), and flattened texture parameters of $T_{1\rho}$ and T_2 relaxation times in medial knee compartments with and without cartilage lesions over 3 years (longitudinal). We hypothesized that longitudinally, knee compartments with cartilage lesions will display elevated $T_{1\rho}$ and T_2 relaxation times and will become increasingly more heterogeneous compared to compartments without cartilage lesions.

Materials and methods

Subjects

Patients with OA and control subjects without OA were recruited from UCSF orthopedic surgeons and the communityas part of a natural evolution study on knee OA. The data in this study include ongoing analyses from these previouslycollected data. The inclusion criteria for OA patients were frequent clinical symptoms of OA (including pain, stiffness and

dysfunction) and demonstration of typical signs of OA in radiographs [Kellgren–Lawrence (KL)grade>0][21]. The controlshad no history of diagnosed OA, clinical OA symptoms, previous knee injuries, or signs of OA on radiographs. Standard standing antero-posterior radiographs of the knee were obtained in all subjects at baseline to determine the KL grade and OA severity[22]. At baseline, the 88 subjects (41 men, 47 women) that participated in this study had a mean age of 50.1 ± 14 years and a mean BMI of 26.1 ± 4.6 kg/m^2.

MRI

All subjects underwent MR imaging of the knee at baseline, and at 1 year intervals for 3 more years. MR data were acquired on a 3 T Signa HDx MR (GE Healthcare, Piscataway, NJ) scanner with a dedicated 8-channel phased array knee coil. Clinical scoring of cartilage lesions was performed on a sagittal T_2 fast-spin echo (FSE) sequence (repetition time (TR)/ echo time (TE) = 4300/51 ms, field of view (FOV) = 6–8 cm, matrix = 512 × 256, slice thickness (ST) = 1 mm, echo train length = 9, bandwidth (BW) = 31.25 kHz, NEX = 2, acquisition time = 4 min). A fat-saturated 3D spoiled gradient-echo (SPGR) sequence (TR/ TE = 15/6.7 ms, flip angle = 12, FOV = 6–8 cm, matrix = 512 × 512, ST = 1 mm, BW = 31.25 kHz, number of excitations (NEX) = 1, acquisition time = 8 min 30 s) was acquired for the purposes of cartilage segmentation. Cartilage $T_{1\rho}$ and T_2 maps were generated using 3D $T_{1\rho}$ mapping techniques[20] based on a gradient echo sequence (TR/TE = 9.3/3.7 ms, FOV = 6–8 cm, matrix = 256 × 128, ST = 2 mm, BW = 31.25 kHz, views per segment = 64, Trec = 1.5 s, spin-lock time (TSL) = 0, 10, 40, 80 ms, spin-lock frequency (FSL) = 500 Hz, acquisition time = 13 min)[23]. T_2-weighted images were acquired using sagittal 3D T_2 mapping (TR = 3700 ms, TE = 4.1, 14.5, 25, 45.9 ms, FOV = 6–8 cm, matrix = 256 × 128, ST = 2 mm, BW = 31.25 kHz, views per segment = 64, time of recovery (Trec) = 1.5 s, acquisition time = 13 min). Parallel imaging was used on all imaging sequences utilizing Array Spatial Sensitivity Encoding Technique (ASSET) with an acceleration factor of 2. Fig. 1 displays representative $T_{1\rho}$ relaxation time color overlays of baseline and year 2 time points for both groups.

Clinical grading

UCSF modified Whole-Organ Magnetic Resonance Imaging Score (mWORMS)[24] was used to assess cartilage morphology at each time point, on a sagittal intermediate-weighted FSE fat-saturated image (Fig. 2) by board certified radiologists (TML with 20 and LN with 4 years of experience with musculoskeletal MRI). The radiologists were blinded to subject information and performed separate readings, with a consensus in case of disagreement. Cartilage was graded as follows: 0: normal signal and thickness; 1: normal thickness and elevated signal; 2: partial-thickness focal defect less than 1 cm in width; 2.5: full-thickness focal defect less than 1 cm in width; 3: multiple areas of partial-thickness focal defects mixed with areas of normal thickness or a grade 2 defect wider than 1 cm but less than 75% of the region; 4: diffuse partial thickness loss (≥75% of region); 5: multiple areas of full-thickness cartilage loss less than 1 cm or a full-thickness lesion greater than 1 m but less than 75% of the region; 6: diffuse full-thickness cartilage loss. Subjects were stratified into those with cartilage lesions (mWORMS ≥2) and those without cartilage lesions (mWORMS ≤1) at each time point.

Image processing

Cartilage compartments were segmented on multiple slices semi-automatically in high resolution SPGR images using the in-house software developed with Matlab (Mathworks, Natick, MA, USA) based on edge detection and Bezier splines[25]. The cartilage compartments analyzed for this study included the MF and medial tibia (MT). $T_{1\rho}$ and T_2

maps were reconstructed by fitting $T_{1\rho}$- and T_2-weighted images pixel-by-pixel to the equations below using in-house developed software:

$$S\left(\mathrm{TSL}\right) \infty S_0 \exp\left(\frac{\mathrm{TSL}}{T1_\rho}\right) \quad (1)$$

$$S\left(\mathrm{TE}\right) \infty S_0 \exp\left(\frac{\mathrm{TE}}{T_2}\right) \quad (2)$$

Post-processing of $T_{1\rho}$ and T_2 maps for this study was identical to that of previous studies from our group which used the same dataset[26,27]. MF and MT ROIs were further partitioned into two equal layers: bone (closer to the subchondral bone) and articular (closer to articular surface) lamina automatically using in-house developed software[25].

Cartilage $T_{1\rho}$ and T_2 maps were flattened before quantification of the GLCM contrast, entropy, and variance parameters in the horizontal (corresponding to the A–P axis) and vertical (corresponding to the S–I axis) directions, for the regions of interest[20]. Flattening was achieved using a Bezier spline, non-linear warping technique setting the bone–cartilage interface spline as the reference for warped flattening. Relaxation times were analyzed at a one pixel offset. Elevated contrast indicates a greater number of adjacent pixels of differing values. Entropy is a measure of pixel orderliness with elevated entropy indicating a more uniform histogram (i.e., equal numbers of each pixel value). Variance is a measure in reference to how much pixel values vary from the compartment mean. Equations (3)–(5) denote three representative GLCM measurements[16].

$$\mathrm{Entropy}=\sum_{i=1}^{N}\sum_{j=1}^{N} P\left(i,j\right)\left(-\ln\left[P\left(i,j\right)\right]\right) \quad (3)$$

$$\mathrm{Variance}=\sum_{i,j=0}^{N=1} P_{i,j}\left(i-\mu_{i,j}\right)^2 \quad (4)$$

where $\mu_{i,j}=\#_{i,j=0}^{N''1} i\left(P_{i,j}\right)$

$$\mathrm{Contrast}=\sum_{i=1}^{N}\sum_{j=1}^{N} P\left(i,j\right)\left(i-j\right)^2 \quad (5)$$

P indicates the probability of pixel values *i* and *j* co-occur in an image and *N* indicates the total number of pixel co-occurrences in each region of interest. A pixel offset of one pixel was chosen based on the fact that approximately three to four pixels span the cartilage thickness. Methods of using these specific representative measurements from each GLCM group have been widely applied in the study of $T_{1\rho}$ and T_2 mapping of auricular cartilage[18,28–30].

Statistical analysis

Independent two-tail Student's *t* tests were carried out to compare differences in subject age and BMI for compartments in the presence and absence of cartilage lesions at baseline. Similarly, chi-square tests were employed to calculate gender differences between the two

groups. For cross-sectional statistics, a linear regression model was fit to each outcome, adjusting for age, gender and BMI. To evaluate whether lesion and control groups changed differentially over time, we utilized Generalized Estimating Equations (GEEs) to accommodate the repeated measures. All analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC).

Results

Subject characteristics

Age, BMI and gender distribution at each time point for both groups are presented in Table I. Subjects with lesions tended to be older and heavier. Overall, there were 27 subjects with lesions in both MF and MT compartments, eight subjects with a lesion in the MF but not in the MT compartment, 0 subject with a lesion in the MT but not in the MF compartment, and 53 subjects without a lesion in either MF or MT compartments.

MF

Mean values (95% confidence intervals (CI), estimated model differences) for $T_{1\rho}$ and T_2 global, laminar, and GLCM texture data for MF are shown in Table II. For the global $T_{1\rho}$ relaxation times, the subjects with lesions displayed higher $T_{1\rho}$ at year 1 and 2 ($P < 0.05$) but not at baseline and year 3. For laminar $T_{1\rho}$ the subjects with lesions had higher articular layer $T_{1\rho}$ at year 1 ($P = 0.015$) and higher deep layer $T_{1\rho}$ at year 3 ($P = 0.001$). For the GLCM measures at baseline, the subjects with lesion had higher contrast, entropy, and variance in both directions ($P < 0.05$). At year 1, the subjects with lesions had higher vertical contrast ($P = 0.03$) as well as higher entropy and variance in both directions ($P < 0.05$). At year 2, the subjects with lesions had higher horizontal entropy ($P = 0.02$), higher contrast and variance in both directions ($P < 0.05$). At year 3, there were no differences between the groups for any of the GLCM measures. Longitudinal change in global mean $T_{1\rho}$ relaxation time between the two groups approached a significant difference ($P = 0.056$) (Table IV). The lesion group global mean displayed increasingly longer relaxation time until year 2, experiencing the largest drop-off from year 2 to year 3 (Fig. 3). Meanwhile, the control cartilage group experienced a slight yet consistent decrease in global mean $T_{1\rho}$ relaxation time (roughly 2 ms throughout the course of the study) (Fig. 3).

For MF global T_2, the subjects with lesions had higher relaxation times at years 1, 2 and 3 ($P < 0.05$) (Table II). For laminar T_2, the subjects with lesions had higher articular and deep layer T_2 relaxation times at years 1 and 3 ($P < 0.05$). For T_2 GLCM measures at baseline, the subjects with lesions had higher vertical contrast ($P = 0.0007$), and higher variance in both directions ($P < 0.05$) (Table II). At year 1, the subjects with lesions had higher contrast and variance in both directions ($P < 0.05$) and higher horizontal entropy ($P = 0.003$). At year 2, the subjects with lesions had higher contrast and variance in both directions ($P < 0.05$). At year 3, the subjects with lesions had higher contrast in both directions ($P < 0.05$). Global T_2 relaxation time displayed significant longitudinal changes between lesion and control cartilage groups ($P = 0.042$) (Table IV). Lesion group global T_2 relaxation time remained relatively constant throughout the study, fluctuating less than 1 ms from baseline to year 3, while control compartment global mean T_2 relaxation time longitudinally decreased more than 2 ms (Fig. 3). Articular layer T_2 relaxation time for lesion and control compartment groups also showed significantly different longitudinal changes ($P = 0.043$). Similarly to global mean T_2, lesion group articular T_2 fluctuated very little throughout the course of the study (less than 0.5 ms) while the control group decreased roughly 1.5 ms throughout all time points (Fig. 3) (Table IV).

MT

Mean values (95% CI, estimated model differences) for $T_{1\rho}$ and T_2 global, laminar, and GLCM texture data for MT are shown in Table III. For global and laminar $T_{1\rho}$ relaxation times, the subjects with MT lesions had higher values for all parameters at all time points ($P < 0.05$). For $T_{1\rho}$ GLCM measures, at baseline and years 1 and 2, the subjects with lesions had higher contrast and variance in both directions ($P < 0.05$). Horizontal entropy was higher at years 1, 2 and 3, and vertical entropy was higher at years 2 and 3 ($P < 0.05$) (Table III). Subjects with lesions in the MT compartment also showed an increase in horizontal entropy ($P = 0.021$) and vertical entropy ($P = 0.0006$) over time compared to subjects without lesions (Table IV) (Fig. 4).

Global, bone and articular layer T_2 relaxation times were higher in subjects with lesions in the MT compartment at each time points (Table III). Subjects with lesions had greater contrast in the horizontal direction at each time point, and greater contrast in the vertical direction at each time point except year 3 (Table III). Subjects with lesions also had higher T_2 variance in both directions at each time point compared to subjects without lesions. Horizontal MT T_2 entropy in compartments with lesions was higher at year 1 ($P = 0.001$), year 2 ($P = 0.001$), and year 3 ($P = 0.017$) but was not significantly different at baseline. As observed in MF, articular layer T_2 relaxation time in MT showed significantly different longitudinal trends between the lesion and control compartment groups ($P = 0.01$) caused by increases in articular layer T_2 for the lesion group and decreases in the control group (Table IV) (Fig. 5). Similar longitudinal trends approaching significance were observed for global T_2 relaxation time ($P = 0.06$) although for this variable control compartment T_2 decreased while lesion T_2 remained relatively constant. Additionally, T_2 horizontal entropy of the two groups changed differently with time. T_2 entropy in compartments with lesions increased slightly, then decreased slightly from year 2 to year 3, while control compartments experienced a longitudinal decrease ($P = 0.043$) (Fig. 5) (Table IV).

Discussion

In this study we investigated longitudinal changes in global, laminar and flattened texture parameters of articular cartilage $T_{1\rho}$ and T_2 relaxation times in medial knee compartments with and without cartilage lesions. It is established that the prevalence of cartilage lesions due to OA is greater in the medial knee joint[31,32]. In the MF, baseline cross-sectional $T_{1\rho}$ global mean values were not significantly different between the two groups, but the lesion group $T_{1\rho}$ was significantly more heterogeneous. This trend is consistent with the other reports[29,33,34] of higher spatial variation of T_2 values in people with knee OA compared to controls, which predicts clinical deterioration over the long term. Additionally, there was no significant difference in global mean MF $T_{1\rho}$ relaxation times or GLCM texture measurements between the two groups at the year 3 time point, suggesting prolonged cartilage degeneration may reduce the capacity of the tissue to bind to motion-restricted water molecules.

Longitudinally, we discovered that lesion group MT $T_{1\rho}$ and T_2 relaxation times became progressively more heterogeneous than healthy control compartments, as measured by GLCM entropy. Longitudinal changes in MT $T_{1\rho}$ GLCM entropy were significantly different between the groups in both the horizontal and vertical directions. MT $T_{1\rho}$ entropy progressively increased in the lesion group and remained constant in the control group. Qazi *et al*. studied heterogeneity of T_1-weighted images of OA and control patients using entropy calculated from histogram signal intensities. They described increases in entropy as a widening bandwidth of pixel signal intensity values and a reduction of the more dominant pixel values seen in homogenous histograms. Our results suggest that over time MT cartilage with lesions will develop a progressively more diverse array of $T_{1\rho}$ values when

compared with control compartments. The longitudinal significance of this relationship in both the horizontal and vertical directions supplement previous studies displaying increasing entropy in $T_{1\rho}$ values in OA cartilage compared to controls[18], and show the utility of using this metric to supplement global mean $T_{1\rho}$ values. MT T_2 horizontal entropy in control cartilage became increasingly homogeneous over time while entropy in the lesion group remained higher (significantly higher at years 1, 2 and 3). This relationship displayed significant longitudinal differences in voxel heterogeneity between groups. These results are consistent with previous longitudinal studies that displayed elevated medial knee OA mean T_2 values along with increased entropy[30,35].

This study has several limitations. Firstly, the study focused on investigating the relationship between medial knee cartilage lesions and quantitative MR parameters of cartilage composition. Hence, the findings are not generalizable to the whole knee and pertain to individuals with cartilage lesions in the medial compartment, which are more common than lesions in the lateral compartment. Future studies would need to be done to investigate these relationships for lateral knee cartilage lesions. Secondly, there was a significant reduction in follow-up data collection due to late enrollment and subject attrition that may have limited the power to investigate differences at the year 2 and 3 time points, especially in the lesion group MT (n = 7 year 3). However, even with the limited sample size, we observed a large number of significant differences between the groups.

In summary, $T_{1\rho}$ and T_2 MRI provide some promising methods by which the classification of biochemical changes in medial knee joint OA is possible. MF $T_{1\rho}$ and T_2 global mean values were not significantly different at baseline, but GLCM contrast and variance were significantly higher in the lesion group indicating that GLCM calculations may provide a heightened level of sensitivity which may be undetectable via global mean analysis alone. MT $T_{1\rho}$ and T_2 entropy displayed progressive, longitudinal increases in the lesion group. Thus the longitudinal evolution of cartilage $T_{1\rho}$ and T_2, and the heterogeneity of these measures may be different at different stages of OA, and are strongly dependent on compartment and cartilage layer. The results presented here underscore the potential of using flattened $T_{1\rho}$ and T_2 cartilage GLCM calculations along with laminar analysis to provide a more detailed characterization of longitudinal biochemical and structural changes in medial osteoarthritic knee articular cartilage.

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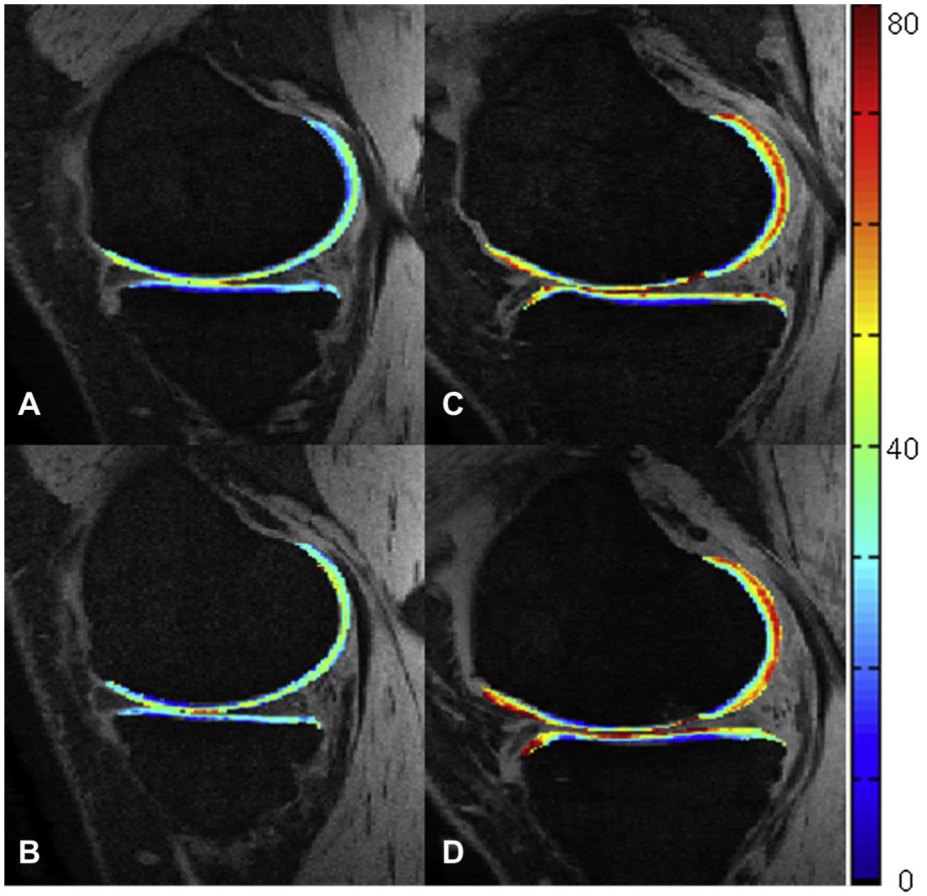

Fig. 1.

Representative sagittal SPGR images with $T_{1\rho}$ relaxation times superimposed on articular cartilage as a color overlay of a healthy control at (A) baseline and (B) at the 2-year follow-up. OA patient at (C) baseline and (D) at the 2-year follow-up. Qualitative OA spatial heterogeneity increases are visible near the anterior portion of the MF/MT. Color scale (right) measured in milliseconds.

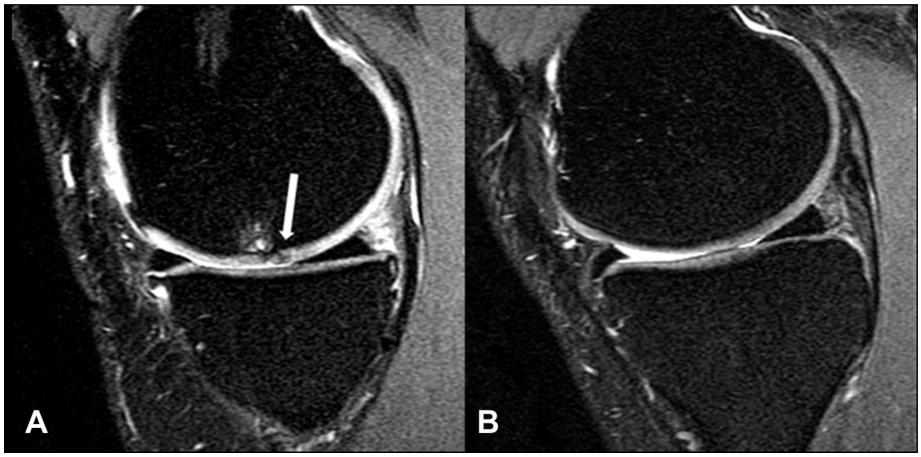

Fig. 2.
Sagittal T_2-weighted FSE images displaying (A) a MF osteoarthritic partial-thickness lesion (arrow) associated with underlying bone marrow edema mWORMS grade 2 (0.7 mm) and (B) a healthy control with intact cartilage.

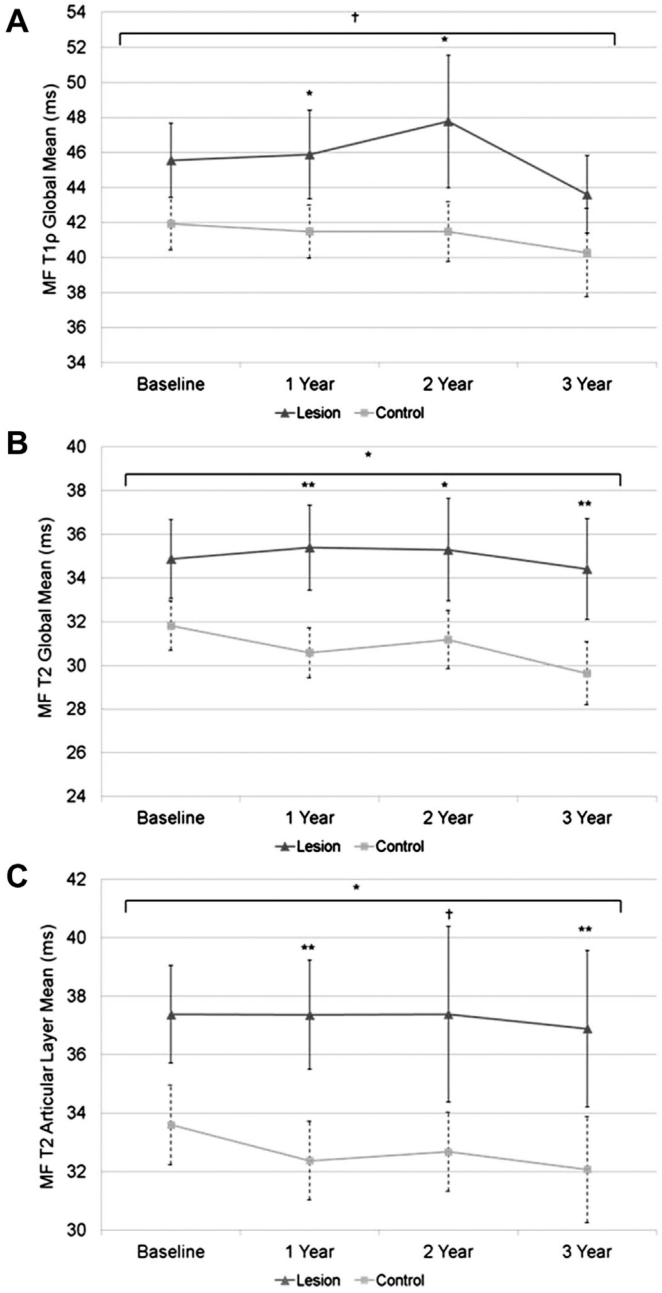

Fig. 3.

Global mean $T_{1\rho}$ and T_2 relaxation times (A and B) and mean articular layer T_2 relaxation times (C) in the MF. Single asterisk indicates $P < 0.05$, double asterisk indicates $P < 0.01$, and cross indicates $P = 0.07–0.051$ (approaching significance). Longitudinal significance between the groups is denoted above the horizontal bracket.

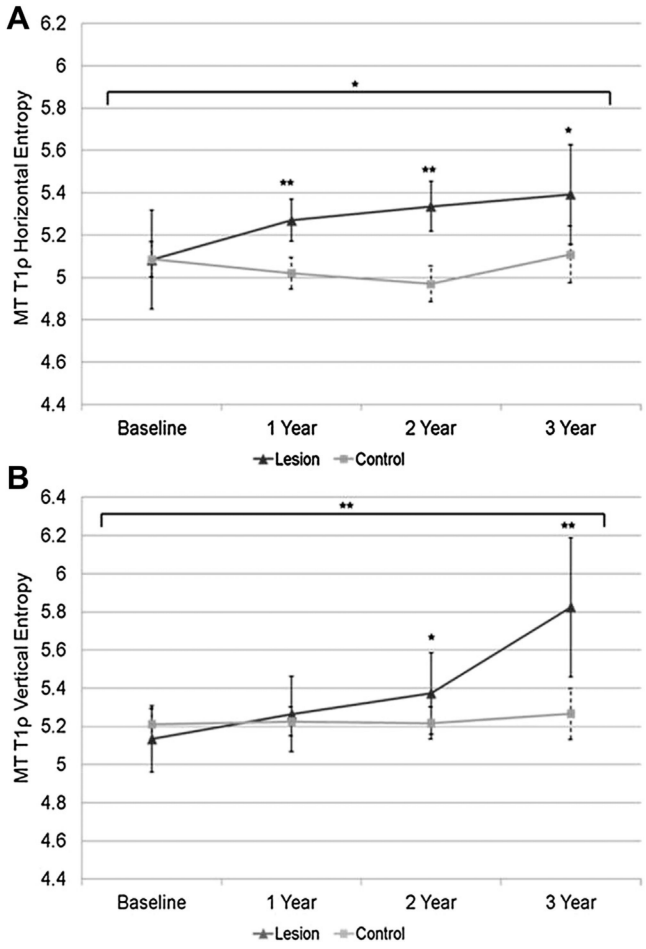

Fig. 4.

Mean $T_{1\rho}$ entropy (A and B) in the MT. Single asterisk indicates $P < 0.05$, double asterisk indicates $P < 0.01$. Longitudinal significance between the groups is denoted above the horizontal bracket.

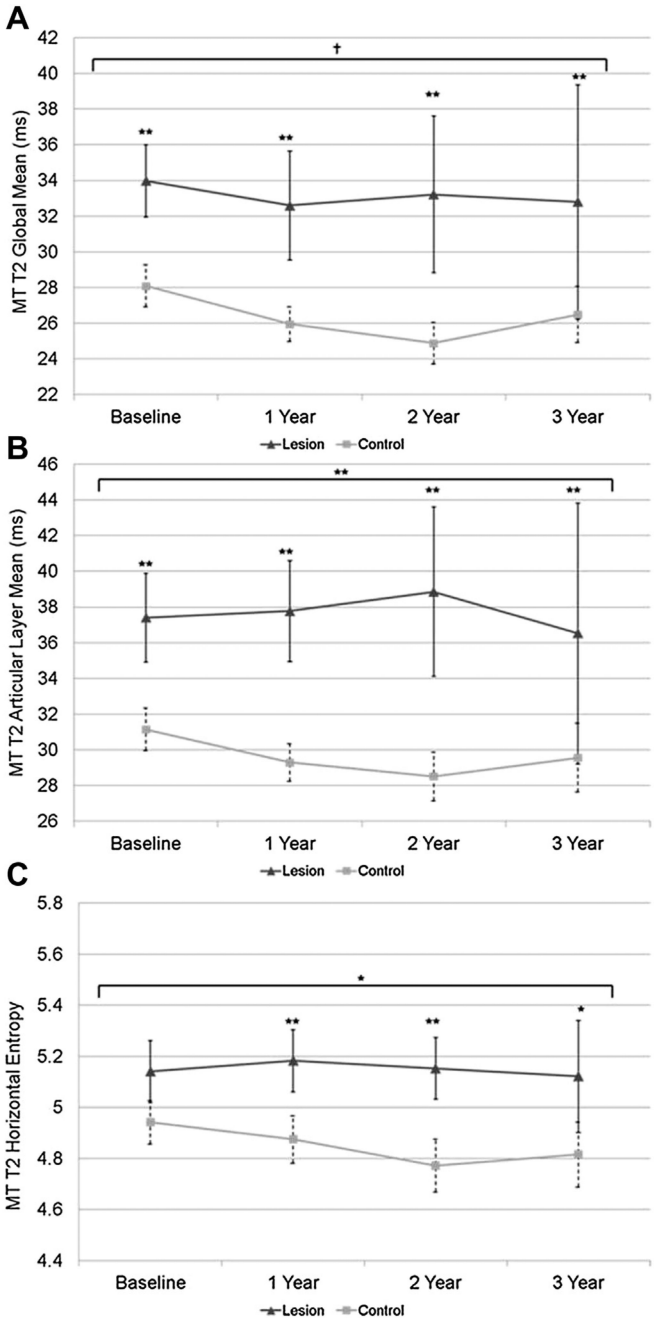

Fig. 5.

Global mean and articular T_2 relaxation times (A and B) and mean T_2 entropy in the MT. Single asterisk indicates $P < 0.05$, double asterisk indicates $P < 0.01$, and cross indicates $P = 0.07–0.051$ (approaching significance). Longitudinal significance between the groups is denoted above the horizontal bracket.

Table I

Age, BMI, and gender distribution for the groups. *P* values from independent samples *t*-tests for age and BMI, and from chi-square tests for gender distribution

	Baseline (*n* = *88*)		**1 Year (*n* = *60*)**		**2 Year (*n* = *38*)**		**3 Year (*n* = *27*)**	
	Control (*n* = *53*)	**Lesion (*n* = *35*)**	**Control (*n* = *37*)**	**Lesion (*n* = *23*)**	**Control (*n* = *28*)**	**Lesion (*n* = *10*)**	**Control (*n* = *15*)**	**Lesion (*n* = *12*)**
MF								
Age (years)	43.9 (12.3)	59.5 (11)	45.3 (12.4)	55 (10.7)	45.3 (12)	57.5 (7)	47.8 (13.6)	51.3 (10.4)
P-value	**<0.0001**		**0.002**		**0.001**		0.461	
BMI (kg/m^2)	25.1 (4.6)	27.5 (4.4)	24.8 (4.4)	26.9 (4.1)	24 (3.1)	26.4 (6.3)	22.6 (2.7)	24.4 (3.6)
P-value	**0.021**		0.074		0.279		0.173	
Gender (F:M)	26:27	21:14	16:21	12:11	10:18	4:6	8:7	6:6
P-value	0.385		0.500		0.810		0.863	
	Control (*n* = *61*)	**Lesion (*n* = *27*)**	**Control (*n* = *43*)**	**Lesion (*n* = *17*)**	**Control (*n* = *29*)**	**Lesion (*n* = *9*)**	**Control (*n* = *20*)**	**Lesion (*n* = *7*)**
MT								
Age (years)	44.4 (11.9)	61.9 (9.9)	46 (11.8)	56.5 (11.5)	46.1 (11.9)	56.2 (9.5)	49.2 (12.5)	49.9 (12.1)
P-value	**<0.0001**		**0.004**		**0.018**		0.898	
BMI (kg/m^2)	25.3 (4.5)	27.8 (4.8)	24.9 (4.1)	27.5 (4.5)	24.1 (3.1)	26.2 (6.6)	23.3 (2.9)	23.7 (4.3)
P-value	**0.022**		**0.050**		0.396		0.830	
Gender (F:M)	30:30	16:11	20:23	8:9	11:18	3:6	12:8	2:5
P-value	0.422		0.970		0.802		0.148	

The bold indicates significance at $P < 0.05$.

Table II

MF mean values (95% CI, estimated differences) of each variable cross-sectionally (linear regression models adjusting for age, gender, BMI)

		$T_{1\rho}$ Global (ms)	**Estimated difference**	**95% CI**	***P*-value**	**$T_{1\rho}$ Articular layer (ms)**	**Estimated difference**	**95% CI**	***P*-value**	**$T_{1\rho}$ Bone layer (ms)**	**Estimated difference**	**95% CI**	***P*-value**
Baseline	Control	41.93	0.811	–1.926, 3.5	0.56	47.16	1.082	–1.94, 4.1	0.48	36.43	0.387	–2.7, 3.4	0.8
	Lesion	45.55				51.62				39.31			
1 Year	Control	41.48	3	0.553, 5.5	**0.017**	47.37	3.4	0.69, 6.2	**0.015**	35.26	2.5	–0.61, 5.5	0.11
	Lesion	45.88				52.55				38.99			
2 Year	Control	41.48	3.9	0.664, 7.2	**0.02**	47.40	3.4	–0.25, 7.0	0.067	35.28	3.8	–0.59, 8.2	0.088
	Lesion	47.77				54.20				41.01			
3 Year	Control	40.28	2.3	–0.274, 4.9	0.077	47.37	1.321	–2.69, 5.3	0.5	32.82	4.60	2.1, 7.2	**0.001**
	Lesion	43.60				50.04				37.24			
		$T_{1\rho}$ Contrast-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Contrast-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	10.62	23	8.6, 37	**0.002**	81.84	41	8.4, 73	**0.014**				
	Lesion	35.32				148.90							
1 Year	Control	9.43	16	–3.76, 36	0.11	81.23	36	4, 69	**0.028**				
	Lesion	30.09				137.36							
2 Year	Control	6.22	22	4.8, 40	**0.015**	85.65	81	29, 134	**0.0034**				
	Lesion	33.88				202.60							
3 Year	Control	9.51	10.2	–7.38, 28	0.24	95.41	–5.678	–37.66, 26	0.72				
	Lesion	22.37				100.51							
		$T_{1\rho}$ Entropy-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Entropy-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	5.26	0.211	0.039, 0.382	**0.017**	5.55	0.225	0.07, 0.34	**0.004**				
	Lesion	5.56				5.84							
1 Year	Control	5.21	0.258	0.102, 0.414	**0.0016**	5.61	0.251	0.11, 0.40	**0.001**				
	Lesion	5.54				5.89							
2 Year	Control	5.13	0.271	0.057, 0.484	**0.015**	5.64	0.13	–0.10, 0.36	0.25				
	Lesion	5.52				5.83							
3 Year	Control	5.28	0.047	–0.183, 0.277	0.68	5.74	0.031	–0.22, 0.28	0.8				
	Lesion	5.41				5.84							
		$T_{1\rho}$ Variance-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Variance-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	72.35	85	55, 116	**<0.0001**	66.05	77	48, 106	**<0.0001**				
	Lesion	185.54				167.22							
1 Year	Control	75.92	73	43, 103	**<0.0001**	68.04	57	32, 82	**<0.0001**				
	Lesion	167.96				141.72							

		$T_{1\rho}$ Global (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Articular layer (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Bone layer (ms)	Estimated difference	95% CI	*P*-value
2 Year	Control	80.14	127	67, 187	**0.0001**	71.43	85	39, 130	**0.0006**				
	Lesion	232.83				183.11							
3 Year	Control	97.18	32	–43.08, 107	0.39	85.56	24	–31.89, 80	0.38				
	Lesion	148.24				125.27							
		T_2 Global mean (ms)	Estimated difference	95% CI	*P*-value	T_2 Articular layer (ms)	Estimated difference	95% CI	*P*-value	T_2 Bone layer (ms)	Estimated difference	95% CI	*P*-value
Baseline	Control	31.82	1.349	–0.929, 3.6	0.24	33.60	1.753	–0.699, 4.2	0.16	29.93	1.003	–0.97, 3.2	0.42
	Lesion	34.88				37.38				32.33			
1 Year	Control	30.58	3.8	1.781, 1.551	**0.0004**	32.37	3.7	1.551, 5.8	**0.001**	28.67	4	1.52, 6.4	**0.002**
	Lesion	35.39				37.37				33.32			
2 Year	Control	31.18	2.6	0.162, 5.1	**0.038**	32.68	2.4	–0.048, 4.9	0.054	29.60	2.9	–0.30, 6.1	0.074
	Lesion	35.30				37.39				33.16			
3 Year	Control	29.64	4.1	1.74, 6.5	**0.0016**	32.07	3.7	0.985, 6.4	**0.0098**	27.05		2.3, 6.8	**0.0004**
	Lesion	34.41				36.89				31.80	4.60		
		T_2 Contrast-horizontal	Estimated difference	95% CI	*P*-value	T_2 Contrast-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	10.66	11.9	–2.284, 26	0.099	59.12	63	28, 99	**0.0007**				
	Lesion	25.26				139.79							
1 Year	Control	4.08	8.4	3.5, 13.3	**0.0012**	53.76	42	19.1, 65	**0.0006**				
	Lesion	13.60				100.70							
2 Year	Control	3.35	9.9	3.5, 16.3	**0.0035**	48.85	47	8.4, 86	**0.019**				
	Lesion	13.92				113.73							
3 Year	Control	3.16	2.2	0.299, 4	**0.025**	45.14	16.2	1.878, 31	**0.028**				
	Lesion	5.70				66.65							
		T_2 Entropy-horiizontal	Estimated difference	95% CI	*P*-value	T_2 Entropy-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	5.09	0.094	–0.05, 0.24	0.19	5.48	0.056	–0.11, 0.22	0.49				
	Lesion	5.32				5.61							
1 Year	Control	4.90	0.25	0.09, 0.41	**0.003**	5.45	0.134	–0.01, 0.28	0.064				
	Lesion	5.27				5.66							
2 Year	Control	4.84	0.166	–0.05, 0.38	0.13	5.48	–0.087	–0.26, 0.09	0.31				
	Lesion	5.13				5.48							
3 Year	Control	4.86	0.107	–0.07, 0.29	0.23	5.47	0.083	–0.10, 0.28	0.36				
	Lesion	5.07				5.66							
		T_2 Variance-horizontal	Estimated difference	95% CI	*P*-value	T_2 Variance-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	73.12	78	39, 117	**0.0001**	67.09	50	22, 78	**0.0006**				
	Lesion	186.63				146.76							

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		$T_{1\rho}$ Global (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Articular layer (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Bone layer (ms)	Estimated difference	95% CI	*P*-value
1 Year	Control	68.57	61	30, 92	**0.0002**	61.54	47	22, 73	**0.0005**				
	Lesion	139.81				116.40							
2 Year	Control	63.52	101	32, 169	**0.0056**	57.00	59	11.9, 107	**0.016**				
	Lesion	180.03				136.00							
3 Year	Control	64.19	18.1	–6.19, 42	0.14	56.86	12.3	–5.936, 31	0.18				
	Lesion	92.75				78.23							

The bold indicates significance at $P < 0.05$.

Table III

MT mean values (95% CI, estimated differences) of each variable cross-sectionally (linear regression models adjusting for age, gender, BMI)

		$T_{1\rho}$ Global (ms)	**Estimated difference**	**95% CI**	***P*-value**	**$T_{1\rho}$ Articular layer (ms)**	**Estimated difference**	**95% CI**	***P*-value**	**$T_{1\rho}$ Bone layer (ms)**	**Estimated difference**	**95% CI**	***P*-value**
Baseline	Control	34.57	5.5	2.5, 8.6	**0.0005**	41.02	4.5	1.056, 8	**0.011**	28.04	5.9	2.2, 9.6	**0.0024**
	Lesion	40.66				47.28				33.75			
1 Year	Control	34.52	8	4.2, 11.9	**0.0001**	41.13	10.1	5.4, 14.9	**<0.0001**	27.68	5.8	1.579, 10	**0.0079**
	Lesion	42.40				51.55				33.47			
2 Year	Control	35.38	6.6	2.7, 10.6	**0.0017**	42.30	6.3	1.864, 10.8	**0.0069**	28.33	5.1	0.4, 9.8	**0.034**
	Lesion	41.46				49.23				32.21			
3 Year	Control	33.58	6.2	2.6, 9.7	**0.0018**	40.33	8.3	2.3, 14.4	**0.0091**	26.71	5.8	1.55, 10	**0.0099**
	Lesion	38.11				47.38				30.12			
		$T_{1\rho}$ Contrast-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Contrast-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	13.14	28	15, 41	**<0.0001**	106.24	118	63, 173	**<0.0001**				
	Lesion	42.96				260.12							
1 Year	Control	13.68	55	18.8, 91	**0.0035**	94.21	183	112, 253	**<0.0001**				
	Lesion	64.90				307.70							
2 Year	Control	8.59	50	19.4, 81	**0.0023**	106.12	110	33, 187	**0.0064**				
	Lesion	57.93				256.48							
3 Year	Control	13.83	–2.187	–10.35, 6	0.58	98.72	–7.996	–40.63, 25	0.62				
	Lesion	10.87				97.71							
		$T_{1\rho}$ Entropy-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Entropy-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	5.09	–0.045	–0.279, 0.188	0.7	5.21	–0.07	–0.28, 0.14	0.51				
	Lesion	5.08				5.14							
1 Year	Control	5.02	0.248	0.101, 0.395	**0.0014**	5.23	0.058	–0.125, 0.24	0.53				
	Lesion	5.27				5.26							
2 Year	Control	4.97	0.355	0.188, 0.522	**0.0001**	5.22	0.187	–0.006, 0.38	**0.05**				
	Lesion	5.34				5.37							
3 Year	Control	5.11	0.267	0.024, 0.51	**0.033**	5.27	0.524	0.207, 0.841	**0.0024**				
	Lesion	5.39				5.82							
		$T_{1\rho}$ Variance-horizontal	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Variance-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	97.44	124	70, 179	**<0.0001**	84.71	89	44, 134	**0.0002**				
	Lesion	262.71				212.65							
1 Year	Control	95.14	201	138, 264	**<0.0001**	87.72	159	104, 215	**<0.0001**				
	Lesion	315.53				257.53							

		$T_{1\rho}$ Global (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Articular layer (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Bone layer (ms)	Estimated difference	95% CI	*P*-value
2 Year	Control	100.03	133	79, 187	**<0.0001**	86.38	120	71, 169	**<0.0001**				
	Lesion	258.85				226.33							
3 Year	Control	103.72	30	–3.777, 64	0.079	95.90	24	–13.87, 62	0.2				
	Lesion	139.75				122.61							
		T_2 Global mean (ms)	Estimated difference	95% CI	*P*-value	T_2 Articular layer (ms)	Estimated difference	95% CI	*P*-value	T_2 Bone layer (ms)	Estimated difference	95% CI	*P*-value
Baseline	Control	28.09	3.7	1.216, 6.3	**0.0042**	31.15	4.1	1.301, 6.9	**0.0045**	24.97	3.6	0.017, 7.2	**0.049**
	Lesion	33.97				37.40				30.76			
1 Year	Control	25.96	6.6	4, 9.2	**<0.0001**	29.30	7.9	5.4, 10.4	**<0.0001**	22.56	5.5	1.765, 9.3	**0.0047**
	Lesion	32.60				37.77				27.74			
2 Year	Control	24.89	7.9	4.8, 11	**<0.0001**	28.52	9.3	5.9, 12.6	**<0.0001**	21.17	6.8	3.2, 10.5	**0.0006**
	Lesion	33.22				38.86				27.88			
3 Year	Control	26.50	7.3	3.8, 10.8	**0.0003**	29.56	6.9	2.2, 11.6	**0.0056**	23.28	8	3.7, 12.3	**0.0009**
	Lesion	32.80				36.53					29.30		
		T_2 Contrast-horizontal	Estimated difference	95% CI	*P*-value	T_2 Contrast-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	15.86	23	6.6, 40	**0.0066**	115.95	123	52, 194	**0.001**				
	Lesion	41.70				262.36							
1 Year	Control	11.06	14.2	8, 20	**<0.0001**	80.42	173	106, 240	**<0.0001**				
	Lesion	25.00				285.26							
2 Year	Control	6.96	11.6	2.1, 21	**0.019**	73.21	127	68, 186	**0.0001**				
	Lesion	23.57				241.23							
3 Year	Control	7.05	12.7	3.8, 22	**0.0073**	108.58	68	–33.1, 169	0.18				
	Lesion	21.21				172.17							
		T_2 Entropy-horizontal	Estimated difference	95% CI	*P*-value	T_2 Entropy-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	4.94	0.146	–0.033, 0.326	0.11	5.18	–0.005	–0.23, 0.22	0.97				
	Lesion	5.14				5.14							
1 Year	Control	4.88	0.313	0.135, 0.491	**0.0009**	5.15	0.154	–0.05, 0.35	0.13				
	Lesion	5.18				5.31							
2 Year	Control	4.77	0.372	0.162, 0.582	**0.0011**	5.19	0.242	–0.02, 0.51	0.071				
	Lesion	5.15				5.38							
3 Year	Control	4.82	0.25	0.051, 0.45	**0.017**	5.17	0.226	–0.02, 0.47	0.068				
	Lesion	5.12				5.46							
		T_2 Variance-horizontal	Estimated difference	95% CI	*P*-value	T_2 Variance-vertical	Estimated difference	95% CI	*P*-value				
Baseline	Control	108.51	137	77, 197	**<0.0001**	96.96	106	54, 158	**0.0001**				
	Lesion	287.60	198			238.24							

		$T_{1\rho}$ Global (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Articular layer (ms)	Estimated difference	95% CI	*P*-value	$T_{1\rho}$ Bone layer (ms)	Estimated difference	95% CI	*P*-value
1 Year	Control	82.89		143, 254	**<0.0001**	73.23	152	108, 196	**<0.0001**				
	Lesion	304.81				240.65							
2 Year	Control	75.31	118	66, 171	**<0.0001**	64.60	96	54, 139	**<0.0001**				
	Lesion	229.27				190.26							
3 Year	Control	89.83	110	43, 177	**0.0026**	77.43	92	37, 147	**0.0022**				
	Lesion	205.07				172.35							

The bold indicates significance at $P < 0.05$.

Table IV

Longitudinal interactions for variables approaching or displaying significantly divergent interactions using GEE models. Data adjusted for age, gender, BMI

Variable	95% CI	Estimated difference	*P*-value
MF $T_{1\rho}$ global mean (ms)	–0.019, 1.596	0.788	0.056
MF T_2 global mean (ms)	0.03, 1.576	0.803	**0.042**
MF T_2 articular layer mean (ms)	0.027, 1.6	0.813	**0.043**
MT T_2 global mean (ms)	–0.073, 2.706	1.317	0.063
MT T_2 articular layer mean (ms)	0.474, 3.482	1.978	**0.0099**
MT T_2 horizontal entropy	0.002, 0.117	0.059	**0.043**
MT $T_{1\rho}$ vertical entropy	0.017, 0.212	0.114	**0.021**
MT $T_{1\rho}$ horizontal entropy	0.058, 0.21	0.134	**0.0006**

The bold indicates significance at $P < 0.05$.