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T1rho MRI Relaxation in Knee OA Subjects with Varying Sizes of Cartilage Lesions

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Abstract

Objective—The purpose of this investigation is to evaluate the $T_{1\rho}$ relaxation times of articular cartilage surrounding focal defects of the tibiofemoral joint.

Materials and Methods—Quantitative assessment of cartilage was performed using 3T MRI with $T_{1\rho}$ mapping in 19 healthy individuals and 44 OA patients. Sagittal T_2-weighted fast spin echo (FSE) fat-saturated images were acquired for cartilage and meniscal lesion assessment. Western Ontario and McMaster University (WOMAC) scores were obtained to assess clinical symptoms. Differences between quantitative measures were determined using analysis of variance (ANOVA).

Results—Cartilage lesions were found in 37% of controls, and 93% of OA patients. Meniscal tears were found in 16% of controls and 57% of OA patients. We observed no difference in $T_{1\rho}$ relaxation times when comparing cartilage immediately surrounding a focal defect, and the remaining cartilage within that compartment. The medial femoral condyle (MFC) had the highest incidence of cartilage defects. A high incidence of medial meniscal lesions were observed in subjects without MFC lesions (18/45). MFC and medial meniscus posterior horn $T_{1\rho}$ were higher in subjects having multiple focal lesions ($p=0.048$, $p<0.001$ respectively) and extensive full thickness lesions ($p=0.009$, $p<0.001$ respectively) compared to subjects with no MFC defects. Significant elevations in $T_{1\rho}$ of the adjacent compartment (medial tibia) and medial meniscus were observed in subjects with MFC lesions.

Conclusions—Increased relaxation times in the involved compartment as well as the adjacent compartment and associated meniscus underscores the interdependence of the these structures at bearing load. However, no differences in cartilage composition immediately surrounding a defect

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CONFLICT OF INTEREST STATEMENT

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was noted. Finally, there was a close association between cartilage defects and meniscal damage in advanced disease.

Keywords

osteoarthritis; cartilage lesions; T1rho; magnetic resonance imaging

Introduction

Cartilage lesions within the knee joint are commonly found in healthy subjects, and patients with osteoarthritis (OA).[1-5] The medial compartment is more commonly implicated in OA, and an increased rate of lesion growth has been reported in the medial compartment of subjects with OA.[6] Cartilage lesions are associated with the severity of OA, and are predictors for cartilage loss and knee joint replacement surgery.[2,5,7-8] Furthermore, the severity of cartilage lesions has been observed to be associated with meniscal degeneration.[9-10] However, treatment options for individual with meniscal lesions are limited to debridement in a majority of cases.

Microfracture, mosaicplasty, and autologous chondrocyte implantation are some of the current treatment options for patients with cartilage lesions. While each of these treatment options have their strengths and limitations, one challenge for all of them is addressing the lesion and surrounding tissue. It has been stated that the quality of the rim of the lesion is critical for clot stability following microfracture.[11] Pre-surgical quantitative evaluation of this tissue would be very valuable in surgical planning. However, standard clinical MRI can give some details about cartilage pathology but lacks the detail to evaluate tissue composition and ultimately determine surrounding cartilage viability. Advanced MR relaxation time mapping techniques for evaluating cartilage composition have received considerable attention recently.[12-17] $T_{1\rho}$ relaxation times of cartilage have been suggested as technique that provide a non-invasive means of detecting early OA prior to morphological or clinical changes. A decline in the proteoglycan content during early osteoarthritis may be quantified using $T_{1\rho}$ relaxation times.[12,18] Cartilage $T_{1\rho}$ relaxation times have been investigated in subjects with OA both *in vitro*[13-14] and *in vivo.*[15-17] Several studies have found that subjects with early or moderate OA based on radiographic changes have elevated $T_{1\rho}$ relaxation times.[15-17] Stahl and colleagues[6] reported elevated relaxation times in the surrounding cartilage of subjects with focal cartilage lesions in several compartment. Additionally, Li and colleagues[16] reported a trend toward increasing $T_{1\rho}$ times with each increasing grade of radiographic disease severity but did not statistically analyze this relationship due to limited sample sizes. Furthermore, in another study which used visual inspection to grade disease severity on a limited number of cartilage specimen, Regatte and colleagues[13] reported significant increase in $T_{1\rho}$ times between mild and advanced disease. Taken together, $T_{1\rho}$ relaxation time mapping of cartilage appears to be a valuable technique for evaluating tissue composition and identifying early disease.

The purpose of this investigation is to evaluate the $T_{1\rho}$ relaxation times of articular cartilage surrounding focal defects of the tibiofemoral joint. We hypothesized that the cartilage immediately surrounding (within 1 cm) of the injured area will have elevated relaxation time values when compared to control subjects, but that the remaining compartment and adjacent structures (meniscus, tibia) will be unaffected.

MATERIALS AND METHODS

Subjects

The patient recruitment for the study was a combination of referral by UCSF orthopaedic surgeons and recruitment from the general public. The inclusion criteria for OA patients were frequent clinical symptoms of OA over the last 6 months prior to the study and radiographic evidence of OA. The control cohort was recruited through posted flyers in the surrounding community and included subjects that had no history of diagnosed OA, no clinical OA symptoms (pain, stiffness, or swelling) requiring regular medication usage or modification of activities, and no previous knee injuries. Standard standing anteroposterior radiographs of the knee were obtained in all subjects at baseline to determine K-L grade.[20] All controls were only enrolled in the study if they received a KL score of 0 indicating no signs of radiographic OA. Subjects included in the study were in good health as assessed by a medical history and physical examination and had no contraindications to MR imaging. Subjects were asked to complete the Western Ontario and McMasters University (WOMAC) questionnaire to assess pain, stiffness, and function through a 5-point scale.[21] Subject characteristics are presented in Table 1. The study was approved by the Committee on Human Research at the University of California, San Francisco, and subjects gave written informed consent to participate in the study.

Magnetic Resonance Imaging Protocol

MRI of the knee was performed using a 3T GE Excite Signa MR Scanner (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array knee coil (Invivo, Orlando, FL, USA). In the OA subjects, the knee with more severe radiographic findings was imaged. In control subjects, the dominant leg was imaged. Parallel imaging was performed with an array spatial sensitivity technique (ASSET) using acceleration factor (AF) = 2. High spatial resolution volumetric fat-suppressed spoiled-gradient-echo (SPGR) sequences (TR/TE = 15/6.7 ms, flip angle = 12, FOV =14 cm, matrix = 512 × 512, slice thickness = 1 mm, BW = 31.25 kHz, number of excitations = 0.75, acquisition time = 7 m 37 s) were acquired for cartilage segmentation and image registration of the relaxation time maps. A T_2-weighted fat-saturated FSE sequence (TR/TE = 4300/51ms, FOV = 14 cm, matrix = 512 × 256, slice thickness = 2.5 mm, gap = 0.5 mm) was used to assess lesions of the cartilage and the menisci.

Sagittal three-dimensional (3D) $T_{1\rho}$ sequences were used to assess cartilage relaxation times. The $T_{1\rho}$-weighted images were obtained using a spin-lock technique followed by SPGR acquisition using transient signals evolving towards steady-state (TR/TE = 9.3/3.7 ms, time of recovery = 1500ms, FOV = 14 cm, matrix = 256 × 192, slice thickness = 3 mm, BW = 31.25 kHz, views per segment = 48, time of spin-lock (TSL)= 0/10/40/80 ms, FSL= 500 Hz, acquisition time of approximately 13 min).[22]

MRI Analysis

Morphological Analysis—The clinical assessment of cartilage and meniscus was performed using a sagittal T_2-weighted FSE fat-saturated image by two experienced radiologists. The radiologists were blinded to subject information and relaxation time data, and performed separate readings, with a consensus in the case of disagreement. Analysis was performed separately for four cartilage regions: medial femoral condyle (MFC), lateral femoral condyle (LFC), medial tibia (MT), and lateral tibia (LT).

Cartilage and meniscal lesions were graded using a modified Whole Organ Magnetic Resonance Imaging Score (WORMS) of the knee.[23] Cartilage lesions were graded as follows: 0 = normal thickness, 1 = normal thickness, increased signal intensity in T_2-

weighted FSE images, 2 = partial thickness focal lesion less than 1cm of greatest width, 2.5 = full thickness focal lesion less than 1 cm of greatest width, 3 = multiple areas partial lesion less than 1 cm of greatest width, or grade 2 lesion wider than 1cm but less than 75% of the region, 4 = diffuse partial thickness loss greater than 75% of the region, 5 = multiple areas of full thickness lesion greater than 1 cm but less than 75% of the region, 6 = diffuse full thickness loss greater than 75% of the region.[23] Subjects were then stratified into four ordinal categories for analysis: No lesions (WORMS 0-1); Focal lesions (WORMS grades 2-2.5); Multiple focal lesions (WORMS grades 3-4); and Extensive full thickness lesions (WORMS grades 5-6).

Meniscal lesions were graded as follows: 0 = no lesion, 1 = intrasubstance abnormality, 2 = non-displaced tear, 3 = displaced or complex tear without deformity, and 4 = maceration of the meniscus.[23] Meniscal scores of 2 through 4 were collapsed into one category to represent the group with a meniscal tear. The meniscus compartments analyzed included the following: anterior horn lateral meniscus (AHLAT), anterior horn medial meniscus (AHMED), posterior horn lateral meniscus (PHLAT), and posterior horn medial meniscus (PHMED).

Lesion Assessment—For all tibiofemoral cartilage plates that were observed via clinical assessment to have focal lesions, size of defects were measured in mm. In addition, the cartilage segmentation of these compartments were subdivided into: Surrounding Cartilage – all tissue within 1 cm of the defect, but not including any cartilage that remained under the defect; and Remaining Cartilage – the rest of the cartilage within the compartment after removal of the defect and Surrounding Cartilage.

Quantitative Assessment—All MR images were transferred to a Sun Workstation (Sun Microsystems, Palo Alto, CA) for data processing and quantification of $T_{1\rho}$ relaxation times. Cartilage compartments were segmented semi-automatically in high resolution SPGR images using in-house software developed with Matlab (Mathworks, Natick, MA, USA) based on edge detection and Bezier splines. Cartilage segmentation was performed by investigators with extensive experience and included the following regions: LFC, MFC, LT, and MT.

The menisci were segmented using a $T_{1\rho}$ image with TSL = 40 ms, which was rigidly registered to the SPGR image using the VTK CISG Registration Toolkit. Anatomical landmarks defined for meniscus segmentation have been previously described in detail.[24] Additional studies from our laboratory utilizing the same techniques and protocols for cartilage and meniscus quantification have reported good reproducibility and precision.[24-25]

$T_{1\rho}$ maps were reconstructed by fitting the $T_{1\rho}$-weighted images voxel by voxel using a Levenberg-Marquardt mono-exponential fitting algorithm developed in-house using the equations below:

$$S\ (TSL) \propto \exp\left(-TSL/T_{1\rho}\right) \text{for} T_{1\rho}$$

For cartilage, all four $T_{1\rho}$-weighted images were used to reconstruct the maps. For meniscus, only the first three $T_{1\rho}$-weighted images were used. $T_{1\rho}$-weighted images with TSL = 80 ms had a very low SNR (<5) for meniscus due to short $T_{1\rho}$ and T_2 times of meniscus, and therefore were not used during map reconstruction. Unpublished data from our lab suggests that this strategy gives a better approximation of the actual tissue relaxation time. The reconstructed $T_{1\rho}$ maps were then rigidly registered to the SPGR image using VTK CISG Registration Toolkit.[26] Three-dimensional cartilage and meniscus contours after

segmentation were overlaid on $T_{1\rho}$ maps. Mean $T_{1\rho}$ values were calculated in defined regions. $T_{1\rho}$ measures were compared between subjects with varying severity of lesions.

Statistical Analysis

All statistical analyses were conducted using JMP software, version 8.0 (SAS Institute, Cary, NC, USA). All analyses were conducted using 2-tailed tests and a p-value of less than 0.05 was considered significant. Analysis of variance (ANOVA) was used to assess the differences between the subject characteristics and relaxation measurements by lesion severity grade. Post-hoc comparisons were made with Fischer's protected least significant difference test. In cases where the ANOVA test was significant, the p-values for the post-hoc analysis are reported. Spearman correlation coefficient measurements were conducted to assess the correlations of cartilage lesion grades and meniscal lesion grades.

RESULTS

Subject Characteristics

A total of 63 subjects (29 men and 34 women) participated in the study. All controls subjects received a KL score of 0. Of the 44 knee OA subjects, 26 received a KL score of either 1 or 2, and 18 received a score of 3 or 4. Table 1 shows the subject characteristics of all subjects enrolled in the study stratified by K-L grade. The mild OA subjects were older than the controls ($p<0.001$), while severe OA subjects were older than controls ($p<0.001$) and mild OA subjects ($p=0.002$). The BMI and clinical WOMAC scores for pain, stiffness, and function were higher in severe OA subjects compared to controls ($p<0.001$ for BMI and WOMAC) and mild OA ($p=0.028$ for BMI, $p<0.001$for WOMAC). However, there was no difference in BMI or WOMAC scores between controls and mild OA, with each group having, on average, low levels of pain, stiffness, and function restrictions.

The highest incidence of lesions were noted in the MFC. Therefore, analyses that compared between subjects (those with large vs. small lesions), only subjects with MFC lesions were used as we did not have the statistical power to conduct an analysis for every cartilage compartment. Furthermore, previous studies have indicated that the medial compartment has the highest incidence of cartilage damage and cartilage loss in OA.[27-29] For analyses that made comparisons within a subject (immediately surrounding area vs. remaining areas), all lesions of the tibiofemoral compartment were included.

Table 2 shows the subject characteristics of the subjects stratified by lesion severity of the MFC with 4 subdivisions. Subjects having no MFC cartilage lesions were younger and had lower WOMAC scores compared to subjects with multiple focal lesions ($p<0.001$ for age, pain, and function, $p=0.001$ for stiffness) and extensive full-thickness lesions ($p=0.001$ for age, $p<0.001$ for all WOMAC). The BMI was higher in the subjects extensive full-thickness lesions compared to subjects with no cartilage lesions ($p=0.003$).

$T_{1\rho}$ Times Stratified by Cartilage Lesion Severity—Table 3 shows the cartilage and meniscus $T_{1\rho}$ measurements in subjects stratified by lesion severity of the MFC. Subjects with multiple focal lesions or extensive full-thickness lesions (WORMS: > 2.5) had higher MFC $T_{1\rho}$ ($p=0.048$, $p=0.009$ respectively) when compared to subjects with no MFC cartilage lesions. No significant difference was observed in $T_{1\rho}$ times of the MFC between subjects with multiple focal lesions (WORMS: 3-4) and those with extensive full-thickness lesions (WORMS: 5-6).

When analyzing the adjacent cartilage compartment – MT, subjects with extensive full-thickness lesions (WORMS: 5-6) had higher $T_{1\rho}$ times compared to subjects with no MFC

cartilage lesions ($p<0.001$ for both) or focal cartilage lesions (WORMS: 2-2.5; $p=0.035$ for $T_{1\rho}$). Subjects with multiple focal lesions or extensive full-thickness lesions (WORMS: > 2.5) had higher PHMED $T_{1\rho}$ ($p<0.001$) when compared to subjects with no MFC cartilage lesions. Furthermore, subjects with multiple focal lesions or extensive full-thickness lesions (WORMS: > 2.5) also had a higher PHMED $T_{1\rho}$ compared to subjects with small lesions (WORMS: 2–2.5; $p<0.001$ for both).

$T_{1\rho}$ Times in Compartments with Cartilage Defects—When evaluating the cartilage in all compartments with defects, the overall T1rho times in the entire affected compartments were significantly higher than cartilage in compartments without defects ($p<0.03$). When comparing the tissue within 1 cm surrounding the defect with that the remaining cartilage within that compartment, there was no difference in T1rho times (41.4 vs. 40.9 ms respectively, $p=0.335$) when lesions of all sizes were combined. Additionally, small defects (<1 cm), medium defects (1-2 cm) and large defects (2-2.5 cm) all behaved similarly without significant difference between the relaxation time surrounding the defect, and that of the remaining cartilage (Table 4). When evaluating the defects within femoral condyles only (excluding tibiae), only those with large defects (2-2.5 cm) showed significantly elevated cartilage surrounding the defect, when compared to compartments with no defects, although a similar trend was seen in compartments with smaller defects.

Cartilage and Meniscus WORMS Assessment—The percentages of subjects having cartilage lesions of any severity (cartilage WORMS>1) in the femorotibial compartment were as follows: 30.2% in the LFC, 22.2% in the LT, 39.7% in the MFC, and 19.0% in the MT. Stratifying by MFC lesion severity reveals interesting patterns of meniscal lesions in the PHMED. While 89% of control subjects did not have evidence of lesions in the MFC, 37% had clinical abnormalities of the PHMED (Table 5). In the mild OA group, 77% of subjects were free of lesions to the MFC, but a large majority (73%) had evidence of meniscal pathology. Finally, in the severe OA group, a small minority (6%) lacked evidence of lesions to the MFC, and most had involvement of pathology in the PHMED (89%), with a large group possessing full meniscal tears (72%, Table 5).

DISCUSSION

Quantitative MRI was used to evaluate cartilage $T_{1\rho}$ relaxation times in subjects with differing severity of cartilage lesions. As expected, subjects with more advanced disease were poorer functioning. Subjects with larger lesions to the MFC had significant elevations in $T_{1\rho}$ relaxation times in the MFC, MT, and in the adjacent meniscus. The relationship noted between lesion severity of the MFC and degeneration of the adjacent MT compartment as well as the PHMED underscores the strong biomechanical interdependence of these structures.

Our data indicate that compartments with cartilage defects have significantly elevated relaxation times when compared to healthy compartments, but that there is no difference in the cartilage immediately surrounding the defect when compared to the remaining tissue in that compartments. These data suggest that the cartilage composition (particularly the proteoglycan content) immediately adjacent to defects is no worse than that of the remaining compartment and interventions such as microfracture or autologous condrocyte implantation do not need to remove additional cartilage surrounding the defect for compositional reasons (tissue instability may warrant additional removal). However, within a small sample of large defects (2-2.5cm) within the femoral condyles, significant elevations were observed in the tissue immediately surrounding the defect, but not in the remaining tissue, suggesting that patients with these lesions may have more progression towards generalized OA.

It was observed that $T_{1\rho}$ times of the MFC are higher in subjects with multiple focal lesions (WORMS: 3-4) or extensive full-thickness lesions (WORMS: 5-6) compared to subjects with no MFC cartilage lesions. While the majority of controls and mild OA subjects had no lesions in the MFC, a relatively higher percentage of subjects showed lesions to the PHMED.

Subjects with multiple focal lesions or extensive full-thickness lesions were older and had higher WOMAC scores compared to subjects with no MFC cartilage lesions (Table 2). Previous studies report a positive correlation between age and cartilage lesion severity, regardless of OA status.[30] Although the only statistically significant difference in BMI was between subjects with extensive full-thickness lesions and subjects with no cartilage lesions, there was a trend of increasing BMI associated with increasing severity of cartilage lesions.

Similar to others, we report that 76% of subjects had cartilage lesions with the highest prevalence in the medial compartment.[1-2,31-32] Specifically, the MFC had the highest incidence of cartilage lesions.[1,31] The high incidence of cartilage lesion in the medial compartment may be attributed to the fact that the medial compartment withstands a greater compressive force and transmits a greater proportion of the total intrinsic compressive load across the joint than the lateral compartment.[32-33] Medial meniscal damage may also contribute to the high incidence of medial cartilage lesions.[9,34] Specifically, 57% of OA patients had a meniscal tear, with the highest incidence occurring in the PHMED. Furthermore, there was a direct association between the MFC lesion severity and incidence of PHMED damage.[32] The meniscus plays a central role in maintaining the integrity of articular cartilage by reducing the contact impact forces between the articular surfaces. Damage to the meniscus increases the contract stress on the articular cartilage surfaces and alters the biomechanical loading of the joint, putting the patient at increased risk of cartilage degeneration.[35]

One of the interesting findings of the current study is that we observed a high incidence of meniscal damage in subjects without MFC cartilage lesions. Specifically, 31% of controls and 46% of mild OA subjects had meniscal damage despite having no MFC cartilage lesions (Table 5). These findings lead us to speculate whether meniscal damage precedes the development of cartilage lesions. However, longitudinal studies are needed to confirm this hypothesis.

Subjects with more advanced cartilage disease (multiple focal lesions or extensive full-thickness lesions) of the MFC had significantly elevated $T_{1\rho}$ relaxation times of the remaining cartilage in the MFC when compared to subjects without lesions, suggesting that $T_{1\rho}$ relaxation time mapping can be useful not only for monitoring early changes within the cartilage matrix prior to morphological damage, but also at tracking further damage to the proteoglycan-collagen matrix that occur with increased lesion severity. However, it should be noted that in our cohort we did not observe significant differences between those with small focal lesions and those without lesions. While the reason for this lack of difference remains unclear, one explanation may be that changes to the cartilage proteoglycan content remain fairly unchanged in the presence of small focal lesions, and it is not until more extensive damage occurs that the cartilage composition breaks down further. Additionally, we did not observe differences in $T_{1\rho}$ relaxation of the MFC between the subjects with multiple focal lesions and subjects with extensive full-thickness lesions. These data suggest that the remaining cartilage in subjects with more advanced disease does not continue to undergo compositional changes as is observed in the early and moderate diseased cartilage. Based on these results, it is important to always include clinical grading of cartilage morphology along with more advanced quantitative imaging in subjects with OA.

In this group of subjects stratified by lesion severity of the MFC, we observed elevations in cartilage relaxation times of the adjacent cartilage plate (MT). Specifically, we observed that the MT of subjects with extensive full-thickness lesions had significantly greater $T_{1\rho}$ values when compared to subjects with no lesions or compared to those with small focal lesions. These data suggest that the adjacent cartilage surfaces may be sensitive to cartilage lesions, likely due to the altered biomechanical loads that are imposed. Consistent with the framework proposed by Andriacchi and colleagues[36], cartilage lesions will change the local biomechanical environment, unloading areas of the MT within the MFC lesion site, and increasing load in the remaining contact areas. Support for this idea comes from Pena and colleagues[37] who used finite element analysis to evaluate joint stresses and strains with MFC lesions. These authors reported no differences in stresses or strains with smaller defects (<1 cm^2), but significant elevations in these variables with larger lesions.

There was a significant correlation between MFC cartilage lesion severity and meniscal lesion severity of the PHMED (Spearman ρ=0.638, $p<0.001$), underlining the association between cartilage and meniscal damage.[32] Previous studies have shown that meniscal $T_{1\rho}$ measures are associated with the severity of OA.[24] Our findings indicate that the magnitude of PHMED $T_{1\rho}$ times were directly related to the severity of the MFC cartilage lesion. PHMED $T_{1\rho}$ elevations in subjects with multiple focal lesions or extensive full-thickness lesions parallel the trends in MFC $T_{1\rho}$, illustrating that cartilage and meniscus degeneration are tightly linked with one another in this cohort. Furthermore, previous studies have reported strong relationships between physical examination findings and meniscal damage on MRI, particularly in more advance knee OA.[38] Determining the initiating cascade of events in knee OA onset will help focus intervention studies to slow the disease process.

When we compare the findings of the current study to those of the previous investigation by Zarins and colleagues[19] using this same cohort of patients, several important relationships are observed. Zarins and colleagues reported that subjects with medial meniscal tears had significantly higher meniscal $T_{1\rho}$ and T_2 values in the posterior horn of the corresponding meniscus. Furthermore, they reported significantly higher $T_{1\rho}$ values in the MT, but not in the adjacent MFC.[19] In the current study, we observed elevated $T_{1\rho}$ relaxation times of the MFC, MT, and both posterior and anterior horns of the meniscus in subjects with the most extensive cartilage lesions. Taken together, these investigations suggest that meniscal tears are observed often in subjects with relatively limited adjacent pathology. However, extensive cartilage lesions are frequently observed in advanced OA pathology including compositional deterioration of the adjacent cartilage plates and the local menisci.

The potential limitations of this study are the cross-sectional design and relatively small sample size. The relatively small number of subjects limited our analysis to cartilage lesions of the MFC. Additional studies need to evaluate the effects of lesions in other cartilage plates in the knee to better determine their influence. Additionally, we did not measure knee alignment because we did not take long-limb radiographs and we did not include a physical activity level assessment. Previous studies have reported associations of malalignment and physical activity with knee cartilage lesions.[6,32,39-40] Future longitudinal studies involving a larger cohort with measures of alignment and physical activity levels are needed to confirm the present findings.

CONCLUSION

We observed no difference in $T_{1\rho}$ relaxation times when comparing cartilage immediately surrounding a focal defect, and the remaining cartilage within that compartment. We did however, observed higher $T_{1\rho}$ times of the MFC in the subjects with MFC cartilage lesions and observed significant elevations in $T_{1\rho}$ times of the adjacent cartilage plate (MT) and the

medial meniscus owing to the strong mechanical interactions of these structures. While the majority of controls and mild OA subjects had no lesions in the MFC, a relatively higher percentage of subjects showed damage to the PHMED, suggesting perhaps that meniscal lesions may precede cartilage lesions in this population.

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Table 1

Subject Characteristics stratified by KL grade.

					WOMAC		
	Age (yrs)	**Height (cm)**	**Weight (kg)**	**BMI**	**Pain**	**Stiffness**	**Function**
Controls (n=19)							
Mean	39.10	172.50	70.79	23.47	3.26	1.63	6.79
SD	10.15	9.09	12.66	3.44	3.26	1.67	8.98
Mild OA (n=26)							
Mean	52.27 *	170.04	75.28	26.00	3.19	1.88	10.42
SD	10.30	9.05	13.49	4.01	3.13	1.24	11.11
p-value (vs. controls)	<0.0001			0.087	0.948	0.578	0.300
Severe OA (n=18)							
Mean	62.61 *#	166.58	80.89	29.33 *#	10.72 *#	4.67 *#	35.55 *#
SD	10.33	8.48	16.67	6.78	4.48	1.64	14.15
p-value (vs. controls)	<0.0001			0.0005	<0.0001	<0.0001	<0.0001
p-value (vs. mild OA)	0.0017			0.028	<0.0001	<0.0001	<0.0001
ANOVA Prob>F	<0.0001	0.137	0.106	0.002	<0.0001	<0.0001	<0.0001

*Significantly different than control ($p<0.05$).

#Significantly different than mild OA ($p<0.05$).

BMI=body mass index; KL= Kellgren-Lawrence; WOMAC=Western Ontario and McMasters Universities Arthritis Index. Controls are defined as subjects having a KL score of 0, Mild OA are defined as subjects with a KL score of 1 or 2, and Severe OA are defined as subjects having a KL score of 3 or 4.

Table 2

Subject characteristics stratified by lesion severity of the MFC.

	Age (yrs)	Height (cm)	Weight (kg)	BMI	WOMAC Pain	WOMAC Stiffness	WOMAC Function
MFC no lesion (n=38)							
Mean	46.00	171	72.79	24.63	3.05	1.74	8.31
SD	12.86	9.13	13.26	4.25	2.71	1.48	9.66
Focal lesions (WORMS grades 2-2.5) (n=5)							
Mean	49.20	165	75.28	27.3	5.80	3.20	19.6
SD	7.26	10.39	11.50	1.26	6.83	1.79	21.14
p-value (vs. grades 0-1)	0.568			0.262	0.151	0.073	0.077
Multiple lesions (WORMS grades 3-4) (n=9)							
Mean	64.44 *#	165	75.16	27.63	9.22 *	3.89 *	30.22 *
SD	10.25	4.84	17.21	6.89	4.32	1.27	11.75
p-value (vs. grades 0-1)	<0.0001			0.108	<0.0001	0.001	<0.0001
p-value (vs. grades 2-2.5)	0.023			0.904	0.127	0.466	0.154
Extensive full thickness lesions (WORMS grades 5-6) (n=11)							
Mean	59.54 *	169.37	85.39	29.88 *	10.00 *	4.27 *	32.18 *
SD	9.54	10.04	15.31	6.27	5.65	2.45	19.73
p-value (vs. grades 0-1)	0.001			0.003	<0.0001	<0.0001	<0.0001
p-value (vs. grades 2-2.5)	0.107			0.338	0.054	0.242	0.082
p-value (vs. grades 3-4)	0.356			0.317	0.664	0.614	0.742
ANOVA Prob> F	0.0001	0.207	0.090	0.018	<0.0001	<0.0001	<0.0001

*Significantly different than MFC grades 0-1 ($p<0.05$).

#Significantly different than MFC grades 2-2.5 ($p<0.05$).

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Table 3

Cartilage and Meniscus T1rho stratified by lesion severity of the MFC.

	CARTILAGE		MENISCUS	
	MFC	MT	AHMED	PHMED
MFC no lesion (WORMS grades 0-1) (n=38)				
Mean	41.43	34.92	12.62	16.11
SD	4.81	4.10	2.14	5.77
Focal lesions (WORMS grades 2-2.5) (n=5)				
Mean	41.13	35.06	11.49	15.92
SD	3.10	3.43	1.91	2.65
p-value (vs. grades 0-1)	0.894	0.954	0.338	0.943
Multiple lesions (WORMS grades 3-4) (n=9)				
Mean	44.85 *	38.00	13.21	23.23 *#
SD	3.08	4.11	2.43	6.53
p-value (vs. grades 0-1)	0.048	0.122	0.521	0.0009
p-value (vs. grades 2-2.5)	0.150	0.324	0.215	0.021
Extensive full thickness lesions (WORMS grades 5-6) (n=11)				
Mean	45.65 *	41.24 *#	15.49 *#^	23.33 *#
SD	5.03	9.22	3.64	4.11
pvaue (vs. 0-1)	0.009	0.0009	0.002	0.0005
p value (vs. 2-2.5)	0.071	0.035	0.004	0.017
p value (vs. 3-4)	0.695	0.179	0.049	0.967
ANOVA Prob> F	0.024	0.007	0.008	0.0002

*Significantly different than MFC grades 0-1 ($p<0.05$).

#Significantly different than MFC grades 2-2.5 ($p<0.05$).

^Significantly different than MFC grades 3-4 ($p<0.05$).

Table 4

Surrounding and Remaining Cartilage T1rho times in subjects with Cartilage Defects.

	Surrounding Cartilage	Remaining Cartilage	P-value
No Defects	N/A	37.1	
Defects 0- 1cm (n=15)	41.5	41.0	0.919
Defects 1-2 cm (n=9)	39.4	39.7	0.472
Defects 2-2.5 cm (n=4)	45.8	43.4	0.355

Table 5

Interrelationship between the incidence of MFC cartilage defects and posterior horn medial meniscus (PHMED) damage as assessed by meniscal WORMS grade and stratified by KL group (control, mild, and severe OA).

	CONTROLS	MILD OA	SEVERE OA	TOTAL
MFC no lesion				
PHMED grade 0	11 (58 %)	8 (31%)	1 (6%)	20
PHMED grade 1	4 (21%)	6 (23%)	0 (0%)	10
PHMED grades 2-4	2 (10 %)	6 (23%)	0 (0%)	8
Total percent per KL group	89%	77%	6%	38
Focal lesions (WORMS grades 2-2.5)				
PHMED grade 0	1 (5%)	1 (4%)	0 (0%)	2
PHMED grade 1	1 (5%)	1 (4%)	1 (6%)	3
PHMED grades 2-4	0 (0%)	0 (0%)	0 (0%)	0
Total percent per KL group	10%	8%	6%	5
Multiple lesions (WORMS grades 3-4)				
PHMED grade 0	0 (0%)	0 (0%)	1 (6%)	1
PHMED grade 1	0 (0%)	1 (4%)	1 (6%)	2
PHMED grades 2-4	0 (0%)	1 (4%)	5 (28%)	6
Total percent per KL group	0%	8%	40%	9
Extensive full thickness lesions (WORMS grades 5-6)				
PHMED grade 0	0 (0%)	0 (0%)	0 (0%)	0
PHMED grade 1	0 (0%)	1 (4%)	1 (6%)	2
PHMED grades 2-4	0 (0%)	1 (4%)	8 (44%)	9
Total percent per KL group	0%	8%	50%	11
Total number of subjects	19 subjects	26 subjects	18 subjects	63 subjects

MFC=medial femoral condlye, PHMED=posterior horn of the medial meniscus, WORMS=Whole-Organ Magnetic Resonance Imaging Score, KL= Kellgren-Lawrence. The number in parenthesis represents the percentage of controls, mild OA or severe OA with a given cartilage defect grade.