Title

Changes in MR relaxation times of the meniscal body with loading: an in vivo pilot study in knee osteoarthritis

Permalink

https://escholarship.org/uc/item/2dj7d1w9

Journal

Osteoarthritis and Cartilage, 21(2)

ISSN

1063-4584

Authors

Subburaj, K
Souza, RB
Wyman, BT
et al.

Publication Date

2013-04-01

DOI

10.1016/j.joca.2013.02.443

Peer reviewed

Changes in MR Relaxation Times of the Meniscus With Acute Loading: An In Vivo Pilot Study in Knee Osteoarthritis

Karupppasamy Subburaj, PhD[1],[*], Richard B. Souza, PT, PhD[1],[2], Bradley T. Wyman, PhD[3], Marie-Pierre Hellio Le Graverand-Gastineau, PhD[3], Xiaojuan Li, PhD[1], Thomas M. Link, MD, PhD[1], and **Sharmila Majumdar, PhD[1]**

[1]Musculoskeletal and Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California, USA

[2]Department of Physical Therapy and Rehabilitation Science, University of California San Francisco, San Francisco, California, USA

[3]Pfizer, Inc., Groton, Connecticut, USA

Abstract

Purpose—To prospectively evaluate changes in $T_{1\rho}$ and T_2 relaxation times in the meniscal body with acute loading using MRI in osteoarthritic knees and to compare these findings with those of age-matched healthy controls.

Materials and Methods—Female subjects above 40 years of age with ($N_1 = 20$) and without osteoarthritis (OA) ($N_2 = 10$) were imaged on a 3 Tesla MR scanner using a custom made loading device. MR images were acquired, with the knee flexed at 20°, with and without a compressive load of 50% of the subject's bodyweight. The subjects were categorized based on the radiographic evidence of OA. Three different zones (outer, middle, and inner) of meniscus body were defined (each occupying 1/3rd the width). After adjusting for age and body mass index in the general linear regression model, repeated measures analysis of variance was used to detect significant differences in $T_{1\rho}$ and T_2 with and without loading.

Results—In the unloaded condition, the average $T_{1\rho}$ and T_2 times were elevated in the outer and middle zones of the medial meniscus in OA subjects compared with the controls. In the loaded condition, $T_{1\rho}$ and T_2 times of the outer zone of the medial meniscus was significantly elevated in OA subjects compared with controls. Finally the change (from unloaded to loaded) was significantly higher in controls than OA subjects (15.1% versus 8.3%; $P = 0.039$ for $T_{1\rho}$, and 11.5% versus 6.9%, $P = 0.049$ for T_2).

Conclusion—These findings suggest that while the OA process appears to affect the relaxation times of all regions within the meniscus, it may affect some regions sooner or to a greater degree. Furthermore, the differences in the change in relaxation times between unloaded and loaded conditions may reveal evidence about load transmission failure of the outer zone of the medial

[*]Address reprint requests to: K.S., Musculoskeletal Quantitative Imaging Research, Department of Radiology and Biomedical Imaging, University of California San Francisco, 1700 4th Street, QB3, Suite-203, San Francisco, CA 94158. subburaj@radiology.ucsf.edu.

meniscus in subjects with knee OA. It is possible that these metrics ($T_{1\rho}$ and T_2) may be valuable as an early biomechanical biomarker, which could be used to predict load transmission to the underlying articular cartilage.

Keywords

THE MENISCUS, A fibrocartilaginous tissue found within the knee joint, is responsible for joint congruity, shock dissipation, load transmission, lubrication, and stability of the joint (1,2). The mechanical function of the meniscus largely depends on the structural and molecular integrity of its matrix, composed of a network of collagen fibers (type I and smaller amounts of type II) immobilizing proteoglycans (PG) (2,3). While PGs in the healthy meniscus resist large loads, it is the collagen fibrils arranged in fibrous lamellae that make meniscus efficient shock absorbers (4). Because of these functional roles, damage to or loss of the menisci affects the articular cartilage, as shown by the increased risk of developing osteoarthritis (OA) after meniscectomy (5). Traditionally, structural damage to the articular cartilage is considered as an initiator for the knee OA, but structural changes in the meniscus, which plays a critical role in the normal biomechanics and stability of the knee joint, may be a precursor to OA. Studies have also demonstrated that meniscal pathologies, such as meniscal degeneration and meniscal tears (6–8), are associated with change of the articular cartilage extracellular matrix (ECM) in patients in early or late stages of OA (9,10). The meniscus is increasingly being recognized as an important tissue in knee osteoarthritis (OA) (1–5). Morphological defects of meniscus and cartilage visualized with MRI are preceded by early degeneration of their ECM (8,10,11). In early stage osteoarthritis, the meniscal ECM exhibits increased proteoglycan content, loss of collagens, and less organized collagen fiber networks than those of normal menisci (12–18), and swelling, resulting in loss of mechanical properties. Changes in the matrix are an early and key finding in the evolution of OA as they likely alter the load distribution transmitted to the underlying articular cartilage. Thus, quantitative measures to detect and monitor changes that occur within the meniscus, both in unloaded and loaded conditions, could provide powerful diagnostic measurements for early-stage OA.

Recent studies have shown the potential of MR relaxation times ($T_{1\rho}$ and T_2) in studying biochemical composition of meniscus. This technology is promising for quantifying early meniscal degeneration and injury (15,19). These measures are highly sensitive to alterations in composition and structural integrity of collagen in the ECM of articular cartilage in vivo (20–22). Previous studies have shown that the collagen content and its orientation is the major factor in changes of cartilage T_2 relaxation times (21,22). T_2 relaxation time mapping is sensitive to a wide range of water interactions in tissue and in particular depends on the content, orientation and anisotropy of collagen and may therefore also play a role in assessing meniscal degeneration. While the exact contributor to $T_{1\rho}$ and T_2 relaxation times remain disputed it is generally agreed upon that these metrics are sensitive to alterations in ECM composition and macromolecular structure and integrity. Rauscher et al reported promising results using this technique to quantify degenerative changes in the meniscal matrix in subjects with early OA (15). While several studies have investigated use of

these quantitative measures ($T_{1\rho}$ and T_2) in assessing the effect of acute loading and physical exercise on articular cartilage (23–27), there is a lack of information regarding the affects of acute loading on meniscus relaxation times. Understanding the behavior of the meniscus relaxation times to acute loading may provide valuable information regarding the transmission of forces to the articular cartilage in persons with knee OA.

Thus the purpose of this study was to evaluate changes in MR ($T_{1\rho}$ and T_2) relaxation times in the meniscal body with acute loading in osteoarthritic knees and to compare these findings with those of age-matched healthy controls. The underlying hypothesis was that healthy knees will exhibit greater $T_{1\rho}$ and T_2 change with loading when compared with osteoarthritic knees.

MATERIALS AND METHODS

Subjects

Ten healthy controls ([mean ± SD (standard deviation): age = 52.9 ± 6.5 years; BMI = 28.0 ± 2.0 kg/m^2) and 20 patients (mean ± SD: age = 57.1 ± 4.7 years; BMI = 27.9 ± 2.6 kg/m^2]) with tibiofemoral OA affecting the medial compartment were included in the study (gender: female, age: 40–70 years and body mass index (BMI): 25–35 kg/m^2). For screening purposes, knee radiographic images were acquired for all subjects in a modified-Lyon-Schuss weight-bearing position using a Plexiglas Synaflexer (Synarc, CA) positioning device. None of the controls had a history of frequent knee pain, aching, or stiffness during the past year and were free of radiographic evidence of OA (Kellgren Lawrence [KL] score of 0 or 1) on both knees. The inclusion criteria for the patient cohort were knee pain, aching, or stiffness on most days of a month during the past year and radiographic evidence of OA (KL score of 2 or 3) on the study knee with either the same or less severe OA, on the contralateral knee. All OA subjects had medial joint space narrowing consistent with medial joint compartment degenerative disease. Prevalence studies have demonstrated the presence of sex differences in OA prevalence and incidence, with females generally at a higher risk. Females also tend to have more severe knee OA, particularly after menopausal age (28–31). Also medial knee OA in female subjects is more prevalent than disease in the lateral compartment (28). Therefore, not to be biased by anatomical and gender differences, we restricted our study to female subjects with medial OA and 40 years old. Informed consent was obtained from all subjects after the nature of the study had been fully explained. The study was approved by and performed in accordance with the rules and regulations of the Committee for Human Research at our institution.

Joint Loading and MR Image Acquisition

MR imaging was performed on a 3 Tesla (T) scanner (Signa HDx, General Electric, Milwaukee, WI), using an eight-channel phased array transmit-receive knee coil (Invivo, Gainesville, FL), and a custom-made MR-compatible loading apparatus mounted on the scanner table (Fig. 1). Two sets of MR images of one knee (dominant knee for controls and selected study knee for OA patients) were acquired under both unloaded and loaded conditions. One half hour before imaging, the subjects were seated in a wheelchair and asked to remain seated until after the MRI to avoid placing loads on their knee. Following

this period of unloading, subjects were positioned supine on top of the loading apparatus, with 20° of knee flexion and 10° of foot external rotation (placed on a footplate and supported in place), with no load applied. An imaging protocol (see below for details) was acquired taking approximately 45 minutes. The next set of images was acquired in the same position while applying a load of 50% of the subject's weight at the bottom of subjects' foot by means of a footplate and a pulley system (Fig. 1), intended to simulate static standing conditions. Padding was used to ensure there was no movement, and there was a consistent and comfortable knee positioning during scanning. The MR imaging protocol included five sequences: coronal three-dimensional (3D) water excitation high-resolution spoiled gradient-echo (SPGR) images, sagittal fat-saturated T_2-weighted fast spin-echo (FSE) images, coronal fat-saturated T_2-weighted FSE images, 3D coronal

$T_{1\rho}$-weighted images based on SPGR acquisition that was previously developed in our lab (Magnetization-prepared Angle-modulated Partitioned-k-space Spoiled Gradient-Echo Snapshots (MAPSS), and 3D T_2-weighted images covering the same region as the $T_{1\rho}$ sequence. The acquisition parameters are given in Table 1.

MRI: Semiquantitative Analysis

MR images were evaluated and scored by two radiologists independently. In instances of conflicting scoring, consensus readings by both radiologists were performed. Cartilage subscores of modified whole-organ MRI score (mWORMS) grading were used to semiquantitatively assess the meniscal cartilage in all subjects as previously described (32). Meniscus lesions were scored using a 5-point score; 0 = no lesion; 1 = intrasubstance abnormalities; 2 = nondisplaced tear; 3 = displaced or complex tear without deformity; 4 = maceration of the meniscus. Ligamentous abnormalities were also semiquantitatively assessed as they are associated with joint degeneration (0, none; 1, signal abnormalities around tendon/ligament; 2, signal abnormalities within the tendon/ligament; 3, partial tear; 4, complete tear).

MRI: Quantitative Analysis

MR images were transferred to a HP workstation (Hewlett-Packard, Palo Alto, CA) for off-line quantification of MR relaxation times ($T_{1\rho}$ and T_2). The regions of interest (ROIs) for quantifying $T_{1\rho}$ and T_2 values in the meniscus body were defined on the coronal SPGR images using a software program developed in-house based on a spline-based semiautomated (automated edge detection and manual correction) segmentation algorithm in MATLAB (Mathworks Inc, El Segundo, CA) and superimposed over relaxation time maps. Anterior and posterior horns were not evaluated due to substantial partial volume effects in the coronal images. Medial and lateral meniscus bodies were divided into three different zones (outer, middle, and inner) from the outer periphery in radial direction. The meniscus was divided on the basis of vascularization into the "outer zone" (outer one-third of the meniscus, which receives a full blood supply), the "inner zone" (inner one-third of the meniscus, which includes mainly fibrocartilage and is completely avascular), and the "middle zone" (transition zone between the outer vascular and inner avascular regions) (33). These zones were defined by dividing the meniscus ROIs into three different parts with each part occupying one-third the width of the meniscus as shown in Figure 2.

Quantification of T$_{1\rho}$ and T$_2$ Relaxation Times—The T$_{1\rho}$- and T$_2$ maps were reconstructed by fitting the image intensity (pixel-by-pixel) to the equation below using a Levenberg-Marquardt mono-exponential fitting algorithm developed in-house: $S(TSL) = S_0 exp(-TSL/T_{1\rho})$ for T$_{1\rho}$ fitting, where S_0 is the signal intensity of shortest spin-lock time (TSL) images; $S(TE) = S_0 exp(-TE/T_2)$ for T$_2$ fitting, where S_0 is signal intensity of the shortest echo time (TE) images. Only the first three T$_{1\rho}$- or T$_2$-weighted images were used to reconstruct the meniscus maps. Our preliminary data suggest that the T$_{1\rho}$-weighted images with TSL = 80 ms and T$_2$-weighted images with TE = 54.8 ms will have a very low SNR (<5) for meniscus due to short T$_{1\rho}$ and T$_2$ in meniscus, respectively, and, therefore, were not be used during map reconstruction (15). To minimize the error due to knee motion between the scans, T$_{1\rho}$- and T$_2$-weighted images with the shortest TSL or TE (therefore with highest SNR) was rigidly registered to high-resolution SPGR images acquired in the same examination using the VTK CISG Registration Toolkit (Kitware Inc., Clifton Park, NY). The transformation matrix was applied to the reconstructed T$_{1\rho}$ and T$_2$ maps. The original splines of segmented cartilage contours from the high-resolution SPGR images were superimposed on the corresponding reconstructed T$_{1\rho}$ and T$_2$ maps to define the ROIs for T$_{1\rho}$ and T$_2$ assessment. To reduce artifacts caused by partial volume effects with synovial fluid, regions were corrected to exclude fluid pixels on the relaxation-time map before quantification.

Reproducibility—To measure the reproducibility of measurements made in this study, we rescanned five subjects within 2 weeks after the initial image acquisition. The same imaging and loading protocol was followed. The reproducibility of T$_{1\rho}$ and T$_2$ values before and after loading was measured in these subjects using the coefficient of variation.

Statistical Analysis

The subjects were stratified based on two separate criteria. For radiographic OA comparison, subjects with the KL score of 0 and 1 were included in controls group and subjects with the KL score of 2 were included in OA group. Second, subjects were stratified based on clinical MRI scoring by our radiologists. The distributions of all variables were plotted and examined. Mean, standard deviation, and median T$_{1\rho}$ and T$_2$ values were calculated for different zones of the meniscus. After adjusting for potential confounders (age and BMI) in the general linear regression model, repeated-measures analysis of variance (ANOVA) was used to determine the main effects of loading on the changes in MR relaxation times of meniscus between the medial and lateral compartments in osteoarthritic knees and age-matched healthy controls. All statistical analysis was performed using JMP 7.0 (SAS Institute, Cary, NC), and the significance level was set to $P = 0.05$.

RESULTS

Scan-Rescan Reproducibility

Coefficient of variation (CV) values for measuring reproducibility of relaxation time measurement for scan–rescan reproducibility ranged from 4.2% to 8.9% for T$_{1\rho}$ and 3.8% to 9.7% for T$_2$. The reproducibility of T$_{1\rho}$ and T$_2$ measurements in subregions of the meniscus was as follows: for T$_{1\rho}$ (range 4.6–10.2%), outer = 4.6%; middle = 6.3%; inner = 10.2% and

for T_2 (range = 4.5–10.5%), outer = 4.5%; middle = 7.1%; inner = 10.5%. The overall CV for $T_{1\rho}$ and T_2 with loading for scan–rescan reproducibility was 12.8% and 15.1%.

$T_{1\rho}$ and T_2 Times in the Meniscus Body of Controls and OA Patients

One control subject (KL score 1) and 14 OA subjects (KL score 2) had at least one meniscus lesion. In terms of lesion prevalence, 6 subjects had nondisplaced tears (mWORMS 2) and 9 subjects had displaced or complex tears (mWORMS 3 and 4).

The $T_{1\rho}$ and T_2 times in the three zones (outer, middle, and inner) of the menisci of the controls and OA subjects in unloaded condition are shown in Table 2. Overall, the $T_{1\rho}$ and T_2 times in these zones were elevated in OA subjects compared with the controls, but only reached significance in the outer and middle zones of the medial meniscus.

Effect of Acute Loading on $T_{1\rho}$ and T_2 Times in the Meniscus of Controls and OA Patients

When compared with the unloaded condition, the average $T_{1\rho}$ and T_2 values in the outer zone of the medial meniscus during the loaded condition was significantly higher in both controls and OA patients (Fig. 3). The same trend was observed in the middle zone of the medial meniscus as well, but it reaches significance only in healthy subjects. $T_{1\rho}$ and T_2 in the inner zones of the both medial and lateral meniscus showed almost no change with loading in both the groups.

With regard to the changes in relaxation times between the loaded and unloaded conditions, $T_{1\rho}$ and T_2 in the outer zone of the medial meniscus in controls was significantly higher compared with the OA subjects (15.7% versus 6.6%; $P = 0.046$ for $T_{1\rho}$, and 14.3% versus 5.8%; $P = 0.027$ for T_2). In other zones (middle and inner), the same trend was observed but it did not reach significance.

Effect of Loading on $T_{1\rho}$ and T_2 Times in the Meniscus of Subjects With and Without Meniscus Lesions

When subjects were stratified by the presence (n = 15) or absence (n = 15) of a meniscus lesions (meniscus mWORMS score greater than 1), the average $T_{1\rho}$ and T_2 times in the meniscus of subjects with lesions was higher compared with those with no lesions. In line with the results of KL score based subjects' categorization, $T_{1\rho}$ and T_2 in the outer zone of the medial meniscus in subjects with no lesions was significantly higher than in the subjects with meniscus lesions (15.1% versus 8.3%, $P = 0.039$ for $T_{1\rho}$, and 11.5% versus 6.9%, $P = 0.049$ for T_2) (Fig. 4). The same trend was observed in the outer zone of the lateral meniscal body, but it did not reach significance (8.3% versus 5.7%, $P = 0.315$ for $T_{1\rho}$, and 7.9% versus 5.9%, $P = 0.271$ for T_2).

DISCUSSION

Regional changes in quantitative MR relaxation times ($T_{1\rho}$ and T_2) in the body of the menisci with acute loading in osteoarthritic knees and age-matched healthy subjects were investigated. Our results showed that (a) $T_{1\rho}$ and T_2 times in all zones were elevated in subjects with OA compared with controls, but only reached significance in outer and middle

zones of the medial meniscus, (b) significantly elevated $T_{1\rho}$ and T_2 times in the outer zone of medial meniscus were observed under acute loading conditions, and (c) the change in relaxation times between the unloaded and loaded conditions ($\Delta T_{1\rho}$ and ΔT_2) in the outer zone of the medial meniscus in OA subjects were significantly higher than in the controls. These findings suggest that while the OA process appears to affect the relaxation times of all regions within the meniscus, it may affect some regions sooner or to a greater degree. Furthermore, the differences in change scores between unloaded and loaded conditions may reveal evidence about load transmission failure of the outer zone of the medial meniscus in persons with knee OA. It is possible that these metrics ($\Delta T_{1\rho}$ and ΔT_2) may be valuable as an early biomechanical biomarker which could be used to predict load transmission to the underlying articular cartilage.

Longer meniscus relaxation times ($T_{1\rho}$ and T_2) were observed in OA subjects when compared with the healthy subjects. The reported $T_{1\rho}$ and T_2 values in this study are in the expected range compared with previously reported $T_{1\rho}$ (6,7,15,17,25) and T_2 (15,17,25) relaxation times of normal menisci at 3T. In addition, our findings of elevated relaxation times in persons with OA is in agreement with, Rauscher et al (15) who reported longer $T_{1\rho}$ and T_2 relaxation times in subjects with mild OA compared with subjects with healthy cartilage. However, they analyzed the entire meniscus as a single region of interest and did not perform any regional analysis. Jungmann et al (7) showed elevated $T_{1\rho}$ values in subjects with meniscal damage and Bolbos et al (6) reported that meniscus regions, adjacent to a damaged cartilage, had longer $T_{1\rho}$ values when compared with undamaged regions in the same subjects. Sun et al (18) reported much higher aggrecan content in OA menisci when compared with normal menisci. It has been demonstrated that in articular cartilage $T_{1\rho}$ values are related to tissue proteoglycan content. While this phenomenon has not been evaluated specifically for meniscus cartilage, it is possible that this metric is similarly evaluating proton–proteoglycan interaction in the fibrocartilage. In healthy menisci, proteoglycan molecules are responsible for hydration within the meniscus body, restricting water molecules movement, thus providing compressive stiffness. Elevated $T_{1\rho}$ and T_2 values observed in our participants with OA likely reflect the degenerative process in the meniscus, and this difference between OA and control subjects may suggests that the mechanical properties of the menisci are altered in knee OA.

Regional variations in $T_{1\rho}$ and T_2 values from outer to inner zones of the meniscus body were observed in this study. Chiang et al (11) and Tsai et al (16) showed in a study on regional variations in T_2 values in different zones of the posterior horn of the menisci and also reported that the medial menisci had longer T_2 times than the lateral meniscus. The meniscus is not a homogeneous tissue, and inner and outer areas of the meniscus differ in composition and biomechanical properties. The peripheral portion of the menisci is vascularized while inner portion is avascular (4). The meniscus has the intrinsic ability to heal itself; unfortunately, this property is limited only to the vascular portions of the tissue (1). Depending on the vascular structure, the healing properties of the menisci and structural properties of the menisci also vary (13,33–35). It has been observed that the $T_{1\rho}$ distribution in articular cartilage is inversely correlated with the PG content (20,36). Significant regional variations in GAG content (higher in the inner zones and lower in the outer regions) have been demonstrated in porcine and bovine menisci (35). Thus, the $T_{1\rho}$ and T_2 values of the

outer zone are likely dominated by the abundant blood vessels within this vascular zone. Anatomic studies have shown that the degree of vascular penetration is 10 to 30% of the width of the medial meniscus and 10 to 25% of the width of the lateral meniscus (13). The perimeniscal tissue of the medial and lateral meniscus is not only very vascular, but also well innervated (13,34). Difference in biochemical composition and structure of medial and lateral meniscus may be a reason for the observed variations in $T_{1\rho}$ and T_2 values of medial and lateral meniscus.

To the best of our knowledge, this study is the first to evaluate the effects of acute loading on $T_{1\rho}$ and T_2 relaxation times of meniscus body. Our results revealed larger change scores (between loaded and unloaded conditions) in $T_{1\rho}$ and T_2 of the medial meniscus when compared with the lateral side. These observations supported by reports from the literature that demonstrates that loads transferred through the medial compartment of the knee are greater than the lateral compartment (37). It is likely that the greater load-response was the result of greater load across the medial compartment with loading. Unlike hyaline articular cartilage, where several studies have reported reductions in relaxation times with acute loading (25,38,39), we observed increased $T_{1\rho}$ and T_2 of the meniscal body with loading. While the authors are uncertain about the cause of this difference in behavior between articular and fibrocartilage, potential explanations include difference in matrix composition, fluid dynamics, and biochemical exchange with surroundings tissues (2,13,33–35,40,41). However, these results do reveal that the biophysical basis of the $T_{1\rho}$ and T_2 in meniscus thus is different than the articular cartilage. It is known that one of the major differences between fibrocartilage and hyaline cartilage is the predominance of type I collagen in menisci compared with type II collagen in articular cartilage (2,4,42,43). Also, Sun et al (18) reported that meniscal degeneration and cartilage degeneration in OA follow different pathways. They have observed that in OA *cartilage* both severe collagen loss and PG loss, indicating that both collagen-degrading enzymes and PG-degrading enzymes are actively involved in the degenerative process. While in *OA menisci* only severe collagen loss was observed but not PG content loss, indicating that collagen-degrading enzymes are much more actively involved in the degenerative process than PG-degrading enzymes. Studies have reported that the mobility of proteoglycans in the outer zone is higher than the other zones, which may explain the observation that the outer zone showed the highest changes with loading. Also, it is important to note that unlike the articular cartilage, the menisci are mobile and it has been demonstrated that the loading significantly increase meniscus extrusion in subjects with osteoarthritis (44). This extrusion may actually position the outer zone outside of the joint and reduce the load transmitted through this tissue.

The $T_{1\rho}$ and T_2 values, from unloaded to loaded condition, were observed to be higher in OA subjects when compared with healthy controls. The overall absolute change in relaxation times in response to loading was greater in the outer zones of the medial menisci compared with the lateral menisci in both groups. This result suggests that the degenerated or damaged menisci lose their biomechanical and biochemical properties substantially, so the effect of acute loading on $T_{1\rho}$ and T_2 values in OA subjects is relatively minimal compared with the healthy subjects. Type I collagen fibers, the major organic matter in the meniscus composition, provide the primary meniscal structural scaffolding. Studies have

shown that degeneration in OA meniscus leads to loss of collagen fibers and disorganized collagen network that affect its load transmission capability (convert compressive loads into circumferential or "hoop" stress) (2,13). This is in agreement with the elevated $T_{1\rho}$ and T_2 values in OA subjects in unloaded condition that reflect increased PG/water ratio and disorganized collagen network of the menisci compared with healthy meniscus (15,17,21,45,46). Meniscal shock absorption property is time dependent due to the exudation of water out of the ECM (2). This may reflect that $T_{1\rho}$ and T_2 values of the meniscus are sensitive to measure structural degradation of meniscus in OA subjects.

The limitations of our study have to be considered while interpreting the findings. The number of subjects recruited to our study is relatively low (10 healthy subjects and 20 OA patients), which may have led to statistical power issues for some of the variables studied. A larger database of quantitative MR images under loading and unloading conditions would be valuable in improving our understanding of the phenomenon observed in this study. $T_{1\rho}$ and T_2 relaxation times were assessed only in the meniscus body using coronal MR images, and anterior and posterior horn regions were not evaluated due to substantial partial volume effects. Previous studies have shown that the meniscal body experiences the second highest incidence of tears after the posterior horn (47–49). Although, sagittal MR images are most commonly used in evaluating meniscal pathology and $T_{1\rho}$ and T_2 quantification; however, studies have shown that the coronal MR images improve the detection and characterization of injuries to the meniscal body (50). The relatively large static loads that needed to be supported by participants used in the current study likely resulted in small movement artifacts which may be responsible for relatively large standard deviations observed in $T_{1\rho}$ and T_2 relaxation times. Fixating the femur and tibia with more rigid immobilization braces might improve homogeneity of results. Also, all subjects with radiographic signs of OA had medial joint space narrowing which limits the generalization of the results obtained in this study to subjects with lateral knee OA or bilateral knee OA. Finally, much of our understanding of the relationship between MRI relaxation times and biochemical composition comes from literature on articular cartilage and while extrapolating these associations to fibrocartilage is reasonable, it might not be entirely accurate. Future studies should investigate the biochemical contributors to $T_{1\rho}$ and T_2 relaxation times in meniscal cartilage.

In conclusion, our study demonstrated, similarly to findings in articular cartilage, that subjects with radiographic knee OA have elevated $T_{1\rho}$ and T_2 relaxation times in outer and middle zones of the medial meniscus. However, in contrast to articular cartilage, acute loading was observed to result in increased relaxation times in these same areas. While the cause of this inverse behavior remains unknown, the authors speculate that differences in matrix composition, fluid dynamics, and biochemical exchange with surroundings tissues may be responsible for this observation. Finally, change scores (difference between loaded and unloaded conditions) in $T_{1\rho}$ and T_2 values with loading was greater in healthy subjects than in subjects with OA. It is possible that these metrics ($T_{1\rho}$ and T_2) may be valuable as an early biomechanical bio-marker which could be used to predict load transmission to the underlying articular cartilage.

Acknowledgments

REFERENCES

1. Henning CE. Semilunar cartilage of the knee: function and pathology. Exerc Sport Sci Rev. 1988; 16:205–213. [PubMed: 3292257]

2. Mow, VC.; Gu, WY.; Chen, FH. Structure and function of articular cartilage and meniscus. In: Mow, VC.; Huiskes, R., editors. Basic orthopedic biomechanics and mechanobiology. Lip-pincott Williams & Wilkins; Philadelphia: 2005. p. 181-237.

3. Englund M. The role of the meniscus in osteoarthritis genesis. Med Clin North Am. 2009; 93:37–43. x. [PubMed: 19059020]

4. Ghadially FN, Lalonde JM, Wedge JH. Ultrastructure of normal and torn menisci of the human knee joint. J Anat. 1983; 136(Pt 4):773–791. [PubMed: 6688412]

5. Bennett LD, Buckland-Wright JC. Meniscal and articular cartilage changes in knee osteoarthritis: a cross-sectional double-contrast macroradiographic study. Rheumatology (Oxford). 2002; 41:917–923. [PubMed: 12154209]

6. Bolbos RI, Link TM, Ma CB, Majumdar S, Li X. T1rho relaxation time of the meniscus and its relationship with T1rho of adjacent cartilage in knees with acute ACL injuries at 3 T. Osteoarthritis Cartilage. 2009; 17:12–18. [PubMed: 18602280]

7. Jungmann PM, Li X, Nardo L, et al. Do cartilage repair procedures prevent degenerative meniscus changes?: longitudinal t1rho and morphological evaluation with 3.0-T MRI. Am J Sports Med. 2012; 40:2700–2708. [PubMed: 23104606]

8. Englund M, Felson DT, Guermazi A, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. Ann Rheum Dis. 2011; 70:1733–1739. [PubMed: 21646417]

9. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum. 2003; 48:2178–2187. [PubMed: 12905471]

10. Guermazi A, Hayashi D, Jarraya M, et al. Medial posterior meniscal root tears are associated with development or worsening of medial tibiofemoral cartilage damage: The Multicenter Osteoarthritis Study. Radiology. 2013; 268:814–821. [PubMed: 23696679]

11. Chiang SW, Tsai PH, Chang YC, et al. T2 values of posterior horns of knee menisci in asymptomatic subjects. PLoS One. 2013; 8:e59769. [PubMed: 23555775]

12. Kurz B, Lemke AK, Fay J, Pufe T, Grodzinsky AJ, Schunke M. Pathomechanisms of cartilage destruction by mechanical injury. Ann Anat. 2005; 187:473–485. [PubMed: 16320827]

13. Kawamura S, Lotito K, Rodeo SA. Biomechanics and healing response of the meniscus. Oper Techn Sport Med. 2003; 11:68–76.

14. Bursac P, York A, Kuznia P, Brown LM, Arnoczky SP. Influence of donor age on the biomechanical and biochemical properties of human meniscal allografts. Am J Sports Med. 2009; 37:884–889. [PubMed: 19336615]

15. Rauscher I, Stahl R, Cheng J, et al. Meniscal measurements of T1rho and T2 at MR imaging in healthy subjects and patients with osteoarthritis. Radiology. 2008; 249:591–600. [PubMed: 18936315]

16. Tsai PH, Chou MC, Lee HS, et al. MR T2 values of the knee menisci in the healthy young population: zonal and sex differences. Osteoarthritis Cartilage. 2009; 17:988–994. [PubMed: 19332176]

17. Zarins ZA, Bolbos RI, Pialat JB, et al. Cartilage and meniscus assessment using T1rho and T2 measurements in healthy subjects and patients with osteoarthritis. Osteoarthritis Cartilage. 2010; 18:1408–1416. [PubMed: 20696262]

18. Sun Y, Mauerhan DR, Kneisl JS, et al. Histological examination of collagen and proteoglycan changes in osteoarthritic menisci. Open Rheumatol J. 2012; 6:24–32. [PubMed: 22550551]

19. Li X, Kuo D, Theologis A, et al. Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2-initial experience with 1-year follow-up. Radiology. 2011; 258:505–514. [PubMed: 21177392]

20. Duvvuri U, Goldberg AD, Kranz JK, et al. Water magnetic relaxation dispersion in biological systems: the contribution of proton exchange and implications for the noninvasive detection of cartilage degradation. Proc Natl Acad Sci USA. 2001; 98:12479–12484. [PubMed: 11606754]

21. Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: overview and applications. Semin Musculoskelet Radiol. 2004; 8:355–368. [PubMed: 15643574]

22. Menezes NM, Gray ML, Hartke JR, Burstein D. T2 and T1rho MRI in articular cartilage systems. Magn Reson Med. 2004; 51:503–509. [PubMed: 15004791]

23. Souza RB, Fang C, Luke A, Wu S, Li X, Majumdar S. Relationship between knee kinetics during jumping tasks and knee articular cartilage MRI T1rho and T2 relaxation times. Clin Biomech (Bristol, Avon). 2012; 27:403–408.

24. Souza RB, Baum T, Wu S, et al. Effects of unloading on knee articular cartilage T1rho and T2 MRI relaxation times. J Orthop Sports Phys Ther. 2012; 42:511–520. [PubMed: 22402583]

25. Subburaj K, Kumar D, Souza RB, et al. The acute effect of running on knee articular cartilage and meniscus magnetic resonance relaxation times in young healthy adults. Am J Sports Med. 2012; 40:2134–2141. [PubMed: 22729505]

26. Subburaj K, Souza RB, Stehling C, et al. Association of MR relaxation and cartilage deformation in knee osteoarthritis. J Orthopaed Res. 2012; 30:919–926.

27. Mosher TJ, Liu Y, Torok CM. Functional cartilage MRI T2 mapping: evaluating the effect of age and training on knee cartilage response to running. Osteoarthritis Cartilage. 2010; 18:358–364. [PubMed: 19948266]

28. Felson DT, Nevitt MC, Zhang Y, et al. High prevalence of lateral knee osteoarthritis in Beijing Chinese compared with Framing-ham Caucasian subjects. Arthritis Rheum. 2002; 46:1217–1222. [PubMed: 12115226]

29. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008; 58:26–35. [PubMed: 18163497]

30. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am. 2013; 39:1–19. [PubMed: 23312408]

31. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage. 2005; 13:769–781. [PubMed: 15978850]

32. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004; 12:177–190. [PubMed: 14972335]

33. Hauger O, Frank LR, Boutin RD, et al. Characterization of the "red zone" of knee meniscus: MR imaging and histologic correlation. Radiology. 2000; 217:193–200. [PubMed: 11012444]

34. Day B, Mackenzie WG, Shim SS, Leung G. The vascular and nerve supply of the human meniscus. Arthroscopy. 1985; 1:58–62. [PubMed: 4091911]

35. Gold GE, Pauly JM, Macovski A, Herfkens RJ. MR spectroscopic imaging of collagen - tendons and knee menisci. Magn Reson Med. 1995; 34:647–654. [PubMed: 8544684]

36. Keenan KE, Besier TF, Pauly JM, et al. Prediction of glycosaminoglycan content in human cartilage by age, T1rho and T2 MRI. Osteoarthritis Cartilage. 2011; 19:171–179. [PubMed: 21112409]

37. Stewart TD, Hall RM. Basic biomechanics of human joints: hips, knees and the spine. Curr Orthopaed. 2006; 20:23–31.

38. Subburaj K, Souza RB, Stehling C, et al. Association of MR relaxation and cartilage deformation in knee osteoarthritis. J Orthop Res. 2012; 30:919–926. [PubMed: 22161783]

39. Souza RB, Stehling C, Wyman BT, et al. The effects of acute loading on T1rho and T2 relaxation times of tibiofemoral articular cartilage. Osteoarthritis Cartilage. 2010; 18:1557–1563. [PubMed: 20950693]

40. Englund M. The role of the meniscus in osteoarthritis genesis. Rheum Dis Clin North Am. 2008; 34:573–579. [PubMed: 18687273]

41. Mcnicol D, Mcqueen C. Localization of proteoglycan in the meniscus of the human knee-joint. J Bone Joint Surg Br. 1983; 65:100–100.

42. Roughley PJ, Mcnicol D, Santer V, Buckwalter J. The presence of a cartilage-like proteoglycan in the adult human meniscus. Biochem J. 1981; 197:77–83. [PubMed: 6895594]

43. Mcnicol D, Roughley P. Extraction of a cartilage-like proteoglycan from human meniscus. Connect Tissue Res. 1981; 8:139–140.

44. Stehling C, Souza RB, Le Graverand MP, et al. Loading of the knee during 3.0T MRI is associated with significantly increased medial meniscus extrusion in mild and moderate osteoarthritis. Eur J Radiol. 2012; 81:1839–1845. [PubMed: 21684704]

45. Regatte RR, Akella SV, Lonner JH, Kneeland JB, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. J Magn Reson Imaging. 2006; 23:547–553. [PubMed: 16523468]

46. Li X, Pai A, Blumenkrantz G, et al. Spatial distribution and relationship of T1rho and T2 relaxation times in knee cartilage with osteoarthritis. Magn Reson Med. 2009; 61:1310–1318. [PubMed: 19319904]

47. Ding C, Martel-Pelletier J, Raynauld JP, et al. Osteoarthritis risk factors: a cross-sectional study of associations between meniscal tear and knee structure, radiographic changes and symptoms in an undiagnosed OA cohort. Arthritis Rheum. 2006; 54:S135.

48. Ding CH, Martel-Pelletier J, Pelletier JP, et al. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J Rheumatol. 2007; 34:776–784. [PubMed: 17361984]

49. Englund M, Guermazi A, Gale D, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med. 2008; 359:1108–1115. [PubMed: 18784100]

50. Magee T, Williams D. Detection of meniscal tears and marrow lesions using coronal MRI. AJR Am J Roentgenol. 2004; 183:1469–1473. [PubMed: 15505322]
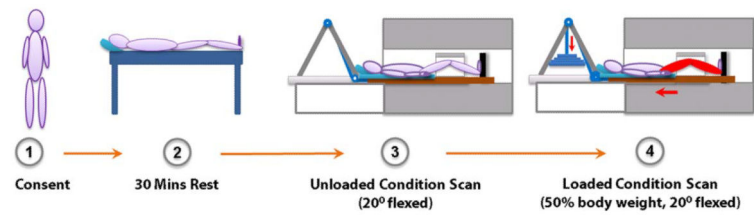
Figure 1.
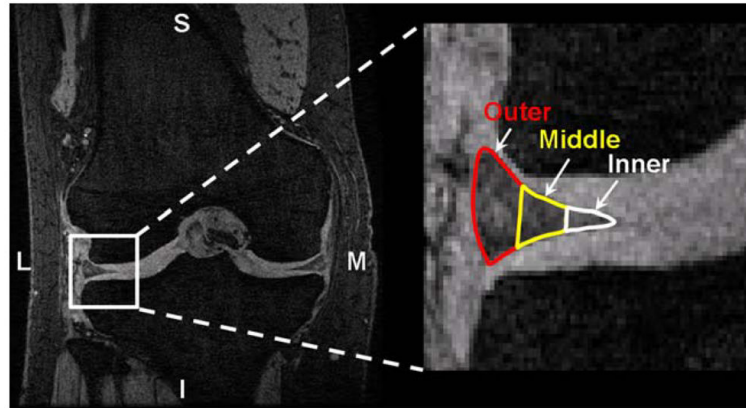Schematic representation of sequence of data acquisition.

Figure 2.
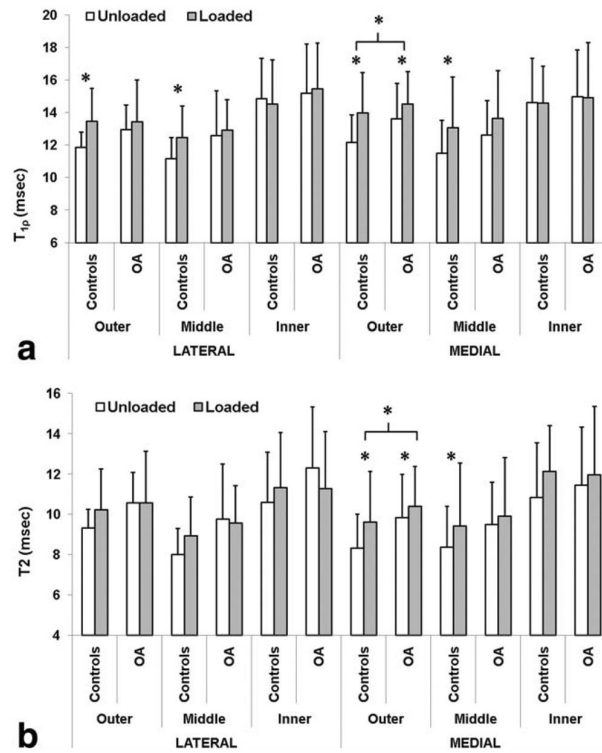Representative SPGR image showing different zones of meniscus.

Figure 3.
The bar chart of T1ρ **(a)** and T2 **(b)** values within each meniscus subregions for control and OA subjects grouped based on Kellgren-Lawrence (KL) grading score. Error bars represent the standard deviations (SD). Asterisks indicate significant differences.
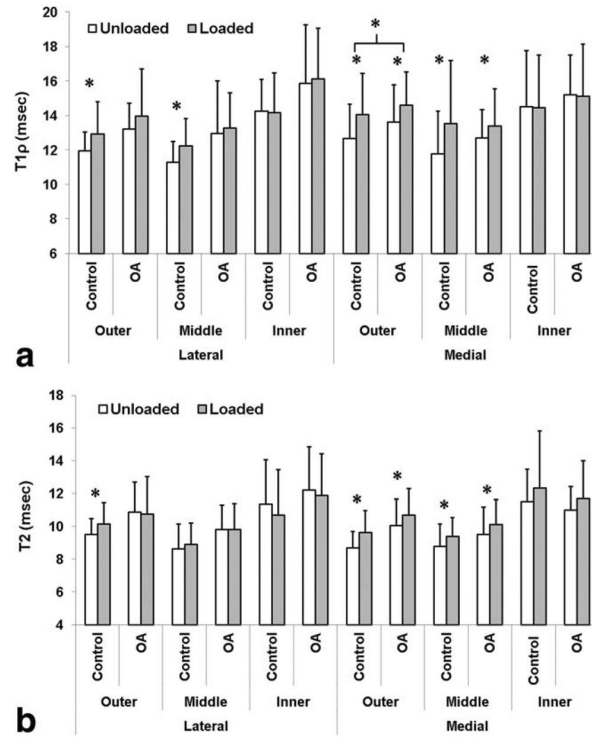
Figure 4.
The bar chart of T1ρ **(a)** and T2 **(b)** values within each meniscus subregions for control and OA subjects grouped based on meniscus WORMS grading score. Subjects with the WORMS score of 0 and 1 are considered as controls and >1 are considered as OA patients. Error bars represent the standard deviations (SD). Asterisks indicate significant differences.

Table 1

MR Image Acquisition Parameters

Parameters	SPGR (Coronal)	FSE (Coronal)	FSE (Sagittal)	$T_{1\rho}$ (Coronal)	T_2 (Coronal)
TR/TE (ms)	22/7.0	3000/10	4000/48	9.3/3.7	9.3/3.7 Preparation TE = 4.1,14.5,25,54.6
FOV (cm)	14	14	14	14	14
Matrix	512×512	384×192	384×192	256×128	256×128
Slice thickness (mm)	1.5	2.0	2.0	3.0	3.0
Bandwidth (kHz)	31.25	23.44	23.44	31.25	31.25
Pixel size (mm × mm)	0.3125×0.3125	0.3125×0.3125	0.3125×0.3125	0.5469×0.5469	0.5469×0.5469
No. of slices	44	38	52	22	22
No. of excitations	1	2	2	–	–
Echo train length	–	10	9	–	–
Flip angle	18	–	–	–	–
Spin-lock time (ms)	–	–	–	0,10,40,80	–
Recovery time (s)	–	–	–	1.5	1.5
Views/segment	–	–	–	64	64
Freq. of spin-lock (Hz)	–	–	–	500	–

Table 2

$T_{1\rho}$ and T_2 Values Within Each Meniscus Subregions for Control and OA Subjects in Unloaded Condition

Zones		$T_{1\rho}$ (ms)			T_2 (ms)		
		Control	OA	p-Value	Control	OA	p-Value
Medial	Outer	12.1 (1.8)	13.7 (2.0)	0.041*	8.2 (0.9)	10.0 (1.4)	0.001*
	Middle	11.1 (1.9)	12.8 (1.9)	0.035*	8.2 (0.9)	9.7 (1.6)	0.010*
	Inner	14.1 (2.8)	15.3 (2.8)	0.283	10.5 (1.9)	11.7 (1.5)	0.076
Lateral	Outer	12.1 (1.3)	12.9 (1.5)	0.173	9.5 (1.0)	10.6 (1.7)	0.086
	Middle	12.0 (3.5)	12.2 (1.7)	0.880	8.6 (2.3)	9.6 (1.0)	0.129
	Inner	15.3 (3.3)	14.9 (2.6)	0.766	11.4 (3.1)	11.9 (2.5)	0.611

Asterisks indicate significant value.