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Assessment of meniscus with adiabatic $T_{1\rho}$ and $T_{2\rho}$ relaxation time in asymptomatic subjects and patients with mild osteoarthritis: a feasibility study

A.W. Kajabi † ‡ *, V. Casula † ‡, M.J. Nissi §, A. Peuna † ||, J. Podlipská † ¶, E. Lammentausta † ||, S. Saarakkala † ‡ ||, A. Guermazi #, M.T. Nieminen † ‡ ||

† *Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland*
‡ *Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland*
§ *Department of Applied Physics, University of Eastern Finland, Kuopio, Finland*
|| *Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland*
¶ *Infotech Oulu, University of Oulu, Oulu, Finland*
# *Department of Radiology, Boston University School of Medicine, Boston, MA, USA*

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SUMMARY

Objective: To investigate the ability of magnetic resonance imaging (MRI) adiabatic relaxation times in the rotating frame (adiabatic $T_{1\rho}$ and $T_{2\rho}$) to detect structural alterations in meniscus tissue of mild OA patients and asymptomatic volunteers.

Method: MR images of 24 subjects (age range: 50–67 years, 12 male), including 12 patients with mild osteoarthritis (OA) (Kellgren–Lawrence (KL) = 1, 2) and 12 asymptomatic volunteers, were acquired using a 3 T clinical MRI system. Morphological assessment was performed using semiquantitative MRI OA Knee Score (MOAKS). Adiabatic $T_{1\rho}$ and $T_{2\rho}$ ($AdT_{1\rho}$, $AdT_{2\rho}$) relaxation time maps were calculated in regions of interest (ROIs) containing medial and lateral horns of menisci. The median relaxation time values of the ROIs were compared between subjects classified based on radiographic findings and MOAKS evaluations.

Results: MOAKS assessment of patients and volunteers indicated the presence of meniscal and cartilage lesions in both groups. For the combined cohort group, prolonged $AdT_{1\rho}$ was observed in the posterior horn of the medial meniscus (PHMED) in subjects with MOAKS meniscal tear ($P < 0.05$). $AdT_{2\rho}$ was statistically significantly longer in PHMED of subjects with MOAKS full-thickness cartilage loss ($P < 0.05$). After adjusting for multiple comparisons, differences in medians of observed $AdT_{1\rho}$ and $AdT_{2\rho}$ values between mild OA patients and asymptomatic volunteers did not reach statistical significance.

Conclusion: $AdT_{1\rho}$ and $AdT_{2\rho}$ measurements have the potential to identify changes in structural composition of meniscus tissue associated with meniscal tear and cartilage loss in a cohort group of mild OA patients and asymptomatic volunteers.

Introduction

Degeneration or destruction of the knee meniscus disrupts normal weight-bearing capacity of the joint; leading to increased contact stresses in the articular cartilage (AC) and progression of osteoarthritis (OA)[1–3]. Meniscal tear and extrusion are known to be strongly associated with the progression of symptomatic OA and considered to be a potent risk factor for the development of radiographic OA[4–7]. Early detection of compositional changes indicative of meniscal tissue disintegration is critical in therapeutic

* Address correspondence and reprint requests to: A.W. Kajabi, Research Unit of Medical Imaging, Physics and Technology, Oulu University Hospital, P.O. Box 50, FI-90029 Oulu, Finland. Tel/Fax: 358-50-3037425.
E-mail addresses: abdul.kajabi@oulu.fi (A.W. Kajabi), victor.casula@oulu.fi (V. Casula), mikko.nissi@uef.fi (M.J. Nissi), arttu.peuna@ppshp.fi (A. Peuna), jana.podlipska@oulu.fi (J. Podlipská), eveliina.lammentausta@ppshp.fi (E. Lammentausta), simo.saarakkala@oulu.fi (S. Saarakkala), ali.guermazi@bmc.org (A. Guermazi), miika.nieminen@oulu.fi (M.T. Nieminen).

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efforts to preserve the tissue and avoid the onset or progression of OA. Hence, a noninvasive and standardized method to objectively diagnose and quantify early structural alterations in the tissue is needed.

Magnetic Resonance imaging (MRI) can demonstrate essential anatomic details of the meniscus with sensitivity and specificity of 85–95%[8–11]. Previous studies have shown that MRI can be used to identify meniscal lesions[12,13], and the meniscal tear signals are associated with meniscal extrusion[13].

Various quantitative MRI (qMRI) sequences have been used to evaluate meniscal tissue biochemical changes quantitatively[14–18]. Continuous-wave (CW) rotating frame of reference (RFR) relaxation time ($T_{1\rho}$), in which a CW spin-lock pulse is applied on- or off-resonance, and T_2 have been used in assessing meniscal degeneration[15–18]. The studies have concluded that CW-$T_{1\rho}$ and T_2 can be used to quantify meniscal degeneration and differentiate healthy subjects from OA patients. However, both CW-$T_{1\rho}$ and T_2 have been reported to be affected by magic angle artifact[19–22]. Shao *et al.* concluded that changes in CW-$T_{1\rho}$ and T_2 values due to magic angle effect can be several times more than that caused by degeneration[19]. Furthermore, clinical application of CW-$T_{1\rho}$ has remained a challenge due to its susceptibility to magnetic field inhomogeneity and relatively high specific absorption rate (SAR)[23].

Recently, adiabatic RFR relaxation time parameters, namely adiabatic $T_{1\rho}$ and $T_{2\rho}$, have been utilized, e.g., to study macromolecular alteration of tissue constituents in AC during early OA[24,25]. Compared to CW-$T_{1\rho}$, adiabatic RFR methods are less prone to the magnetic field nonuniformity, and their adiabatic nature provides flexibility in pulse design, thus helps reducing SAR[26–28]. Adiabatic $T_{1\rho}$ and $T_{2\rho}$, as CW-$T_{1\rho}$, are inherently sensitive to slow molecular motions[29,30]. Moreover, a wide range of effective frequencies ($\omega_{eff}(t)$) created during adiabatic pulse extends the sensitivity of relaxation to many frequencies of molecular fluctuations as compared with CW spin-lock sequences, in which the ω_{eff} is constant. It has also been demonstrated that adiabatic $T_{1\rho}$ and $T_{2\rho}$ relaxation times are at least equivalent in detecting early degenerative changes in AC compared to numerous other qMRI techniques[31,32]. To our knowledge, neither *in vivo* nor ex vivo study has been previously tested the association of adiabatic $T_{1\rho}$ ($AdT_{1\rho}$) or adiabatic $T_{2\rho}$ ($AdT_{2\rho}$) relaxation times with meniscal structural changes.

In this *in vivo* study, $AdT_{1\rho}$ and $AdT_{2\rho}$ sequences[33,34] were used to assess compositional changes in meniscus tissue obtained from MRI of patients with mild OA and asymptomatic volunteers. The findings of the relaxation parameters were compared against semiquantitative MRI OA Knee Score (MOAKS)[35]. Since both cartilage and meniscus are composed of a macromolecular framework of collagen fibers and proteoglycans, the hypothesis of this study was that $AdT_{1\rho}$ and $AdT_{2\rho}$ are sensitive to structural changes in meniscus tissue and can differentiate meniscal tissue alterations between mild OA patients and asymptomatic volunteers.

Method

Subjects

Our cross-sectional study was approved by the local institutional ethical board. The subjects included in the study had no contraindications to MR imaging. All the subjects signed an informed consent prior to participation in our study.

A subcohort of the Oulu Knee OA (OKOA)[36,37] study was investigated; a total of 34 subjects (16 men and 18 women) aged 50–70 (mean 60.0 ± 6.1 [standard deviation]) years with a mean body mass index (BMI) of 27.4 ± 5.4 kg/m^2 were recruited between February and November 2014. The participants were from Oulu University Hospital referrals and general public recruited via newspaper advertisement.

The inclusion criteria for the asymptomatic volunteers were no history of diagnosed OA, no previous knee surgery or traumatic knee injuries (fractures, sprains, or torsion in the past 15 years), and no functional impairment or moderate to severe physical symptoms in the past 6 months in either knee joint. The inclusion criteria for mild OA patients were radiographic osteoarthritis with pre or mild radiographic OA signs without joint space narrowing (Kellgren–Lawrence (KL) score[38] = 1, 2), knee pain, and fulfilling the American College of Rheumatology (ACR) criteria for classification of idiopathic OA[39]. Of all participants, 24 subjects (12 females, mean age 59.5 years, year range: 50–67; 12 males, mean age 58.7, year range: 50–65) met the inclusion criteria and were included in the final analysis. Of the 24 eligible subjects, 12 were asymptomatic volunteers (mean age 59.8 ± 5.6 years, mean BMI 24.4 ± 2.6 kg/m^2) and 12 were mild OA patients (mean age 59.1 ± 5.9 years, mean BMI 30.3 ± 6.3 kg/m^2). Both males and females in the cohorts were matched for age with a maximum of 2 year difference.

MRI protocol

MRI of all subjects was performed on a 3 T clinical system (Skyra, Siemens Healthcare, Erlangen, Germany) in combination with a 15-channel local transmit knee coil (QED, Mayfield Village, OH, USA). In asymptomatic volunteers the knee was chosen randomly while in the patients the knee with clinical signs of OA was selected for imaging. The protocol included proton density (PD) turbo spin echo (TSE), PD 3D-TSE (SPACE) fat-suppressed (FS), T_1 TSE, $AdT_{1\rho}$ and $AdT_{2\rho}$ mapping sequences. The imaging parameters of the sequences are listed in Table I.

For $AdT_{1\rho}$ mapping, as previously described[40], two single slice sagittal MR images were acquired in the medial and lateral tibiofemoral compartments from each participant. The slices were positioned at the center of each femoral condyle by using the scanner auto-align feature. The acquisition was performed using a preparation block consisting of a train of 0, 4, 8, 12 and 16 adiabatic fast passages (AFP) hyperbolic secant pulses (pulse duration (T_p) = 6 ms, resulting in spin-lock times (T_{SL}) = 0, 24, 48, 72, 96 ms) of the HSn family, here HS4; followed by a segmented gradient recalled echo (2D FLASH) readout (Table I). For $AdT_{2\rho}$, the AFP pulses were placed between two adiabatic half passage pulses (AHP) followed by FLASH readout. The peak radio frequency (RF) amplitude for both $AdT_{1\rho}$ and $AdT_{2\rho}$ was γB_{1max} = 600 Hz.

Table I
Sequence parameters for MRI protocols

Parameters	FLASH*	PD TSE	PD 3D FS	T_1 TSE
TR [ms]	4000	2800	1200	650
TE [ms]	3.36	33	26	18
Flip angle [deg]	15	150	120	150
Matrix	256 × 256	384 × 384	256 × 256	320 × 320
FOV [mm^2]	180 × 180	140 × 140	160 × 160	130 × 130
Slice TH [mm]	3	3	0.6	0.6
Slices [n]	2	35	176	25
ETL/# of segments	23†	7	49	2
Plane	Sagittal	Sagittal	Sagittal	Coronal
Acquisition time [min:s]	4:42‡	4:09	8:48	1:56

PD = proton density; TSE = Turbo Spin Echo; FS = fat suppressed; TR = time to repetition; TE = time to echo; FOV = field of view; ETL = echo train length; TH = thickness; FS = fat-suppressed; TSE = turbo spin echo.
* Readout for the adiabatic $T_{1\rho}$ and $T_{2\rho}$ sequences.
† Number of segments per preparation.
‡ Total acquisition time for adiabatic $T_{1\rho}$ or $T_{2\rho}$.

Quantitative assessment of menisci

MR images of all the subjects were assessed by an experienced musculoskeletal radiologist (AG, 17 years of experience with semi-quantitative MRI analysis of knee OA) and scored using MOAKS. PD-TSE weighted coronal, PD 3D-TSE FS (SPACE) weighted sagittal, and T_1 TSE weighted coronal images were used to obtain MOAKS for meniscal tear and full-thickness cartilage loss (Table II).

$AdT_{1\rho}$ and $AdT_{2\rho}$ maps were obtained by mono-exponential fitting of the signal intensity decays on a pixel-by-pixel basis (Fig. 1). Manual segmentation was carried out independently by an evaluator blinded for MOAKS grades, using an in-house developed application for MATLAB (Mathworks R2014, Natick, MA). No gross movements were observed during the scans for any subject. In each medial meniscus and lateral meniscus, distinct regions were defined, based on the signal intensity change of the meniscus compared with the signal intensity of the adjacent sections, and segmentation was performed on the sagittal $AdT_{1\rho}$ and $AdT_{2\rho}$ weighted images.

The regions of interest (ROIs) defined for segmentation included the following meniscus compartments: anterior horn medial (AHMED), posterior horn medial (PHMED), anterior horn lateral (AHLAT), and posterior horn lateral (PHLAT) (Fig. 2). Since a single slice was acquired at the center of each femoral condyle, meniscal body was hardly detectable on the sagittal $AdT_{1\rho}$ and $AdT_{2\rho}$ weighted images and was hence excluded from the ROI analysis. $AdT_{1\rho}$ and $AdT_{2\rho}$ maps were calculated in the ROIs by mono-exponential fitting of the signal intensity decay on a pixel-by-pixel basis.

Median meniscal horn $AdT_{1\rho}$ and $AdT_{2\rho}$ values of the ROIs were compared between patient with mild OA group vs asymptomatic volunteer group, and presence vs absence of MOAKS meniscal tear, and tibiofemoral full-thickness cartilage loss groups. Classification of subjects based on MOAKS was carried out, independent of their radiographic OA and clinical status, according to (1) presence of meniscal tear, complex tear or partial maceration in medial and lateral, body, anterior or posterior horn (tear group, MOAKS grade for meniscal morphology > 1) and absence of any tears (no tear group, MOAKS grade for meniscal morphology ≤ 1); (2) presence of full-thickness cartilage lesions in tibiofemoral compartments (full-thickness AC lesion group, MOAKS grade for full-thickness cartilage loss > 0) and absence of full-thickness cartilage lesions (no full-thickness AC lesion group, MOAKS grade for full-thickness cartilage loss $= 0$).

Reproducibility measurements

Root-mean-square coefficients of variation (CVs) were calculated to determine the reproducibility of $AdT_{1\rho}$ and $AdT_{2\rho}$ measurements in the meniscal horns. Four additional subjects aged 20–29, who did not have any clinical OA symptoms, were recruited from general public between October and November 2015. MRI of the subjects was performed utilizing the same system and protocols used for the other subjects. $AdT_{1\rho}$ and $AdT_{2\rho}$ measurements were repeated three times for each subject to acquire a new set of scans (scan–rescan), after repositioning the knee before each measurement, and the meniscal horn of each of the subjects was segmented from each scan to test the variability error in repeated measurements.

To test the intra- and inter-observer reproducibility, manual segmentation was performed on the four additional subjects, two volunteers and two patients randomly selected from the study participants. For intra-reader variability, one slice per subject was

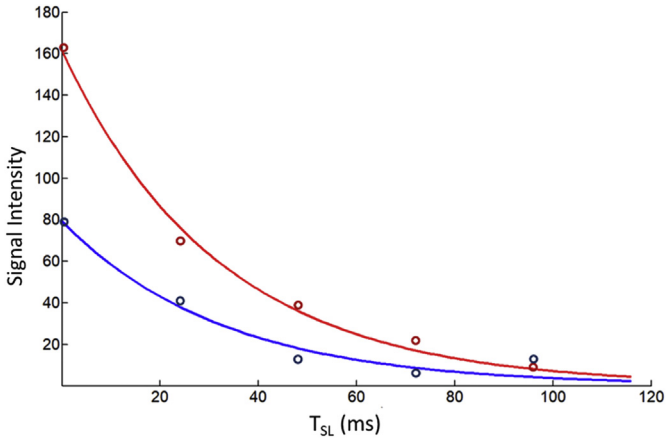

Fig. 1. A representative pixel-based fitting curve of adiabatic $T_{1\rho}$ (red, norm of residuals: 8.72) and adiabatic $T_{2\rho}$ (blue, norm of residuals: 11.02) relaxation.

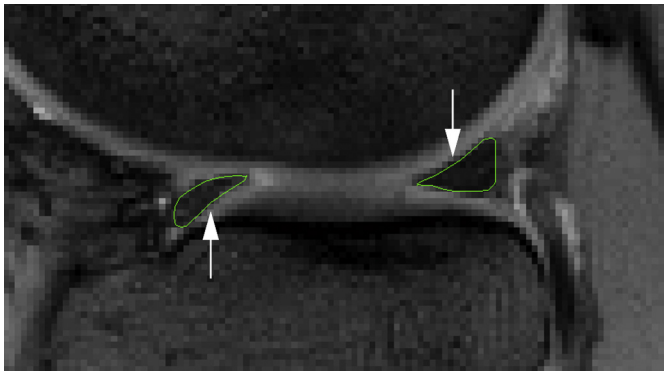

Fig. 2. Representative sagittal adiabatic $T_{1\rho}$ weighted image shows segmented anterior (arrow pointing upward) and posterior (arrow pointing downward) horns of the lateral meniscus.

Table II
Total number of subjects with meniscus signal, meniscus tear, meniscus partial maceration and full-thickness tibiofemoral AC lesions (in brackets, number of patients)

	Medial compartment			Lateral compartment		
	AHMED	Body	PHMED	AHLAT	Body	PHLAT
Meniscus signal (MOAKS = 1)	0	1 (0)	1 (1)	1 (1)	2 (1)	0
Meniscus tear (MOAKS = 2–5)	0	5 (3)	7 (5)	3 (3)	2 (1)	3 (2)
Meniscus maceration (MOAKS = 6)	0	5 (4)	2 (1)	0	0	0
	Medial compartment			Lateral compartment		
	Anterior	Central	Posterior	Anterior	Central	Posterior
Femur full-thickness AC lesions (MOAKS > 0)	0	4 (1)	1 (1)	1 (1)	1 (0)	0
Tibia full-thickness AC lesions (MOAKS > 0)	1 (1)	2 (2)	1 (1)	0	0	0

MOAKS = MRI OA knee score; AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus; AHLAT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus; AC = articular cartilage.

selected and segmentation was repeated three times by a single evaluator (AWK, 3 years of experience). For inter-reader variability, a second evaluator (VC, 5 years of experience), blinded from the first evaluator's segmentation process, segmented the same slices. Finally, CVs were calculated to test the intra- and inter-reader errors.

Statistical analysis

All statistical analyses were conducted using SPSS software (Version 23.0, IBM SPSS Statistics, New York, USA). Since no previous studies assessing meniscus tissue with $AdT_{1\rho}$ and $AdT_{2\rho}$ could be found, the real effect size could not be estimated using previously published data. Thus, we calculated a deductive sample size on the basis of the average CW-$T_{1\rho}$ values of the meniscus reported by Bolbos *et al.*[16]. The minimal required number of subjects for each group for Mann–Whitney *U* test was estimated (power = 0.80, *P* value < 0.05 indicated significance), which indicated a minimal sample size of 10 subjects per group. Thus, a sample size of 12 subjects per group was sufficient to detect significant differences.

After assessing the median $AdT_{1\rho}$ and $AdT_{2\rho}$ values (with interquartile range (IQR)) for the segmented meniscal horns, descriptive statistical evaluation was performed to test the normality of data distribution. Since our data were visually skewed and not distributed normally, differences in $AdT_{1\rho}$ and $AdT_{2\rho}$ relaxation times between the patients and volunteers, MOAKS meniscal tear and no tear, and MOAKS cartilage with and without tibiofemoral full-thickness defects were compared using nonparametric two-tailed Mann–Whitney *U* test. Furthermore, this approach was warranted given that the morphological changes were observed in both patients and volunteers. Differences were considered to be significant at *P* value of less than 0.05. Benjamini–Hochberg procedure was used with a false discovery rate of 5% to adjust the *P*-values for the multiple comparisons of $AdT_{1\rho}$ and $AdT_{2\rho}$. The correlations between $AdT_{1\rho}$ and $AdT_{2\rho}$ measurements were calculated using Pearson correlation. Effect sizes were calculated between the compared groups using *d*[41].

$$d = \frac{z}{\sqrt{N}},$$

where *z* and *N* represent normal approximation distribution and total sample size, respectively.

Results

MOAKS findings

After morphological assessment, not only patients but also asymptomatic volunteers were discovered to have meniscal and full-thickness cartilage findings. Medial meniscus body and posterior horn had the highest incidence of MOAKS tear and maceration as compared to the body in lateral compartment and other horn regions (Table II). Tibiofemoral full-thickness cartilage loss was detected in central and posterior regions of the medial compartment (Table II).

Comparing $AdT_{1\rho}$ and $AdT_{2\rho}$ in menisci of patients with mild OA and asymptomatic volunteers

The differences in the median values of $AdT_{1\rho}$ and $AdT_{2\rho}$ in the medial and lateral meniscal horns of the patients were not statistically significant as compared to the corresponding ROIs in the asymptomatic volunteers. Moderate effect sizes (d = 0.40–0.46) were observed between the two cohort groups (Table III). However, none of these differences reached statistical significance after Benjamini–Hochberg correction for multiple comparisons. The relaxation time maps from a representative patient with mild OA and asymptomatic volunteer show the spatial variation of the relaxation times in the meniscal lateral horns (Fig. 3).

Association of $AT_{1\rho}$ and $AdT_{2\rho}$ with meniscal tear and cartilage loss based on MOAKS

Median $AdT_{1\rho}$ values in PHMED of subjects with MOAKS meniscal tear were significantly longer than in the corresponding ROIs of subjects with no tear ($P < 0.05$, $d = 0.57$) (Table IV). Finally, a significantly longer $AdT_{2\rho}$ was found in PHMED of subjects with MOAKS full-thickness cartilage loss ($P < 0.05$, $d = 0.60$) (Table V).

Reproducibility measurement

Percentage CVs obtained from repeated measurements for $AdT_{1\rho}$ were always smaller as compared to $AdT_{2\rho}$ (Table VI). For both $AdT_{1\rho}$ and $AdT_{2\rho}$, the smallest reproducibility values were found in PHMED (1.73% and 4.51%, respectively), and the highest in AHMED (4.21% and 8.85%, respectively).

Overall CVs obtained for intra-observer image analysis repeatability were smaller than the CVs for repeated data acquisition (Table VI). The smallest intra-observer CVs for both $AdT_{1\rho}$ and $AdT_{2\rho}$ were found in PHMED (1.22% and 1.07%, respectively). The largest CVs for $AdT_{1\rho}$ were found in PHLAT (2.00%) and for $AdT_{2\rho}$ in AHMED (3.19%).

The inter-observer image analysis CVs were higher for $AdT_{2\rho}$ than for $AdT_{1\rho}$ for all the ROIs, as compared to the intra-observer CVs (Table VI). The smallest CVs for $AdT_{1\rho}$ were found in PHMED (2.76%) and for $AdT_{2\rho}$ in PHLAT (3.22%). The highest CVs for $AdT_{1\rho}$ were found in AHLAT (4.60%) and for $AdT_{2\rho}$ in AHMED (10.52%).

Table III
Median relaxation times and interquartile range (IQR) for adiabatic $T_{1\rho}$ ($AdT_{1\rho}$) and adiabatic $T_{2\rho}$ ($AdT_{2\rho}$) in asymptomatic volunteers and mild OA patients

ROI	Volunteers (n = 12)	Patients (n = 12)	*P*-value	Corrected *P*-value	Effect size
$AdT_{1\rho}$ (ms)					
AHMED	34.0 (36.2–32.2)	35.5 (37.0–33.8)	0.600	0.720	0.112
PHMED	37.3 (39.5–34.3)	41.0 (51.2–38.0)	0.037*	0.148	0.424
AHLAT	40.4 (44.4–35.1)	43.5 (50.4–38.6)	0.242	0.414	0.247
PHLAT	32.3 (35.7–29.1)	39.2 (42.7–36.2)	0.024*	0.144	0.460
$AdT_{2\rho}$ (ms)					
AHMED	31.8 (35.9–30.0)	35.9 (40.2–31.8)	0.114	0.228	0.330
PHMED	25.5 (27.9–23.8)	30.6 (38.8–26.6)	0.033*	0.132	0.436
AHLAT	35.0 (40.7–30.1)	42.4 (47.1–35.9)	0.047*	0.141	0.407
PHLAT	34.8 (38.5–31.5)	33.5 (39.5–30.1)	0.977	0.977	0.012

AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus.
AHLAT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus.
*$P < 0.05$.

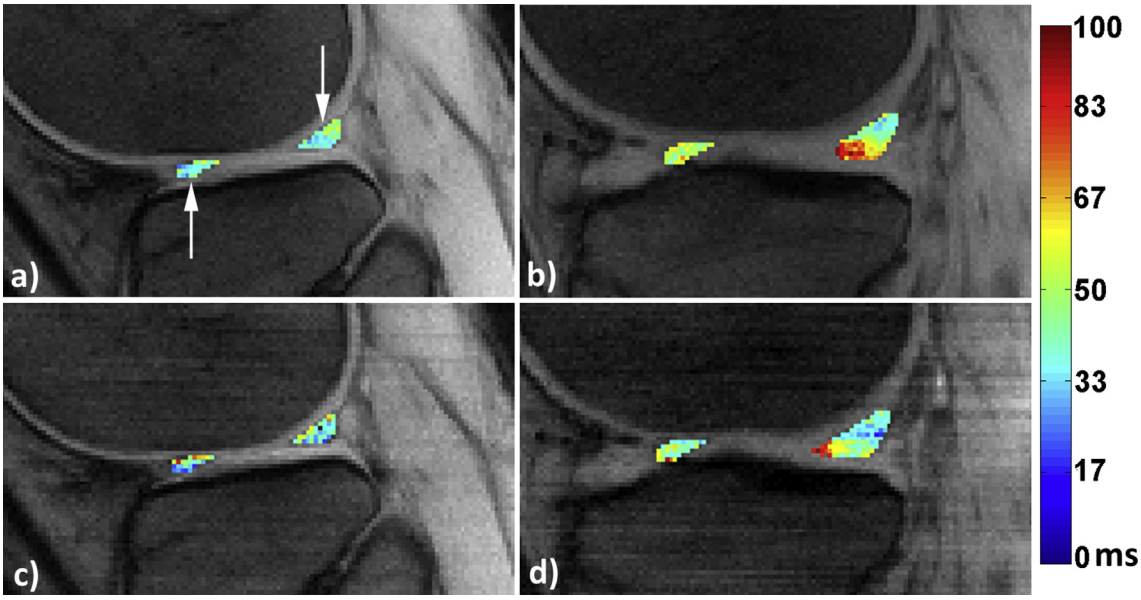

Fig. 3. Representative sagittal MR images showing adiabatic $T_{1\rho}$ (a, b) and adiabatic $T_{2\rho}$ (c, d) relaxation time map of the lateral menisci in asymptomatic subjects (a, c) (age 52, female), and patient with mild OA (b, d) (age 50, male, KL = 2). AHLAT (arrow pointing upward) and PHLAT (arrow pointing downward) correspond to anterior horn and posterior horn of the lateral meniscus respectively. Prolonged relaxation times in the patient's PHLAT ROIs as shown by the colormaps can clearly differentiate the meniscal matrix of the patient from the asymptomatic subject.

Table IV
Median relaxation times and interquartile range (IQR) for adiabatic $T_{1\rho}$ ($AdT_{1\rho}$) and adiabatic $T_{2\rho}$ ($AdT_{2\rho}$) in subjects with no meniscal tear (No tear, MOAKS $\leq$ 1) and with meniscal tear (Tear, MOAKS > 1)

ROI	No tear (n = 11)	Tear (n = 13)	*P*-value	Corrected *P*-value	Effect size
$AdT_{1\rho}$ (ms)					
AHMED	35.5 (36.3–33.0)	35.1 (36.1–32.2)	0.660	0.660	0.095
PHMED	37.4 (37.9–34.2)	41.2 (55.4–38.9)	0.004*	0.048*	0.574
AHLAT	39.0 (44.2–35.4)	45.2 (49.3–38.9)	0.119	0.238	0.325
PHLAT	36.2 (39.7–28.2)	34.7 (39.6–32.1)	0.649	0.708	0.100
$AdT_{2\rho}$ (ms)					
AHMED	33.8 (38.0–31.1)	34.8 (38.6–30.4)	0.776	>0.999	0.065
PHMED	25.5 (28.2–23.7)	29.8 (38.1–24.9)	0.082	0.197	0.360
AHLAT	35.6 (43.3–34.2)	40.7 (45.8–34.1)	0.598	0.897	0.112
PHLAT	37.4 (42.9–32.9)	31.9 (35.7–29.0)	0.026*	0.156	0.455

MOAKS = MRI OA knee score; AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus; AHLAT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus.
*$P < 0.05$.

Table V
Median relaxation times and interquartile range (IQR) for adiabatic $T_{1\rho}$ ($AdT_{1\rho}$) and adiabatic $T_{2\rho}$ ($AdT_{2\rho}$) in subjects with absence of full-thickness cartilage lesions (No full-thickness AC lesions, MOAKS = 0) and presence of full-thickness cartilage lesions (Full-thickness AC lesions, MOAKS > 0)

ROI	No full-thickness AC lesions (n = 15)	Full-thickness AC lesions (n = 9)	*P*-value	Corrected *P*-value	Effect size
$AdT_{1\rho}$ (ms)					
AHMED	34.7 (36.0–32.2)	37.8 (38.9–33.3)	0.062	0.186	0.384
PHMED	37.9 (40.9–35.4)	39.6 (55.9–37.4)	0.340	0.510	0.201
AHLAT	39.0 (49.1–37.3)	41.8 (45.2–39.1)	0.558	0.744	0.128
PHLAT	33.2 (39.0–28.9)	39.4 (39.8–36.2)	0.064	0.153	0.383
$AdT_{2\rho}$ (ms)					
AHMED	33.8 (38.6–30.4)	34.9 (38.0–31.2)	0.519	0.889	0.140
PHMED	25.5 (28.8–23.7)	35.0 (39.5–29.9)	0.002*	0.024*	0.602
AHLAT	40.7 (44.5–34.1)	38.1 (43.3–35.6)	0.804	0.964	0.055
PHLAT	33.9 (39.6–29.9)	34.1 (37.5–31.9)	0.953	>0.999	0.018

MOAKS = MRI OA knee score; AC = articular cartilage: AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus; AHLAT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus.
*$P < 0.05$.

Correlation between $AdT_{1\rho}$ and $AdT_{2\rho}$

There were statistically significant correlations between $AdT_{1\rho}$ and $AdT_{2\rho}$ parameters in PHMED and AHLAT ($r = 0.696$, $P < 0.01$; $r = 0.499$, $P = 0.013$; respectively).

Discussion

The findings of this study indicated that prolonged $AdT_{1\rho}$ and $AdT_{2\rho}$ relaxation times in menisci were associated with subjects having meniscal tear and full-thickness cartilage loss as assessed

Table VI
CVs for repeated measurements, intra- and inter-observer reproducibility of adiabatic $T_{1\rho}$ ($AdT_{1\rho}$) and adiabatic $T_{2\rho}$ ($AdT_{2\rho}$)

	CVs (%) for $AdT_{1\rho}$				CVs (%) for AdT2ρ			
	AHMED	PHMED	AHLAT	PHLAT	AHMED	PHMED	AHLAT	PHLAT
Repeated measurements (n = 4)	4.21	1.73	2.33	3.53	8.85	4.51	5.77	6.30
Intra-observer (n = 8)	1.33	1.22	1.43	2.00	3.19	1.06	1.79	1.22
Inter-observer (n = 8)	4.60	2.76	7.58	4.42	10.52	3.51	7.49	3.22

AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus.
AHLAT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus.

semiquantitatively using MOAKS. Differences in the relaxation parameters between patients and asymptomatic volunteers did not reach statistical significance after correction for multiple comparisons.

PHMED was the region that had statistically significantly longer $AdT_{1\rho}$ for meniscal tear, and $AdT_{2\rho}$ for full-thickness cartilage loss. Medial meniscus was the region, which presented most of the tears based on MOAKS assessment (Table II). The presence of prolonged relaxation time values in the same region associated with meniscal tear and cartilage loss most likely reflects early degenerative structural changes in the menisci matrix. Histological studies have indicated that lesions in meniscal tissue cause alterations in the collagen network matrices, decline in proteoglycan content and infiltration of synovial fluid into the damaged area, which could explain the elevation in the relaxation time values[18,42].

Previous studies have demonstrated that meniscal relaxation parameters such as dGEMRIC, CW-$T_{1\rho}$, and T_2 can be used to differentiate OA patients from healthy subjects[2,14–17]. In the present study, longer $AdT_{1\rho}$ and $AdT_{2\rho}$ values in multiple ROIs were observed in patients with symptoms and radiographic signs of OA (Table III). However, no significance was found after the multiple comparison correction, probably due to the small sample size. Therefore, the ability of $AdT_{1\rho}$ and $AdT_{2\rho}$ measurements in menisci to distinguish mild OA patients against asymptomatic volunteers needs to be confirmed in larger studies.

In $AdT_{1\rho}$ spin-locking is achieved with a different approach than conventional CW-$T_{1\rho}$ experiments. While in CW-$T_{1\rho}$ an RF pulse with constant spin-lock frequency is applied either on- or off-resonance, in $AdT_{1\rho}$ the spin-lock frequency sweeps from off-resonance toward on-resonance. During an adiabatic RF pulse, both amplitude and frequency of the pulse are modulated over time creating a wide range of effective frequencies[30]. These effective frequencies extend the sensitivity of the adiabatic RF pulse to many frequencies of molecular fluctuations[27,43]. Another significant advantage of $AdT_{1\rho}$ is its smaller dependence on orientation[22,44], indicating less sensitivity to the magic angle effect and reducing major sources of uncertainty that can confound the readings of CW-$T_{1\rho}$ and conventional T_2[19,20]. Reducing the magic angle effect in CW-$T_{1\rho}$ is possible only by using very high spin-lock frequencies (about 2 kHz)[45], which dramatically increases SAR beyond the limit for clinical application. The associations of meniscus $AdT_{1\rho}$ and $AdT_{2\rho}$ with radiographic signs of OA or semiquantitative grading scores have not been studied before. In this study, elevations of $AdT_{1\rho}$ and $AdT_{2\rho}$ were statistically associated with MOAKS findings.

It has been shown that $AdT_{1\rho}$ and $AdT_{2\rho}$ are differentially affected by different relaxation mechanisms[46], and therefore may be able to supply complementary information[25]. The results of this study, particularly the lack of complete correlation between the two parameters, seem to confirm this view. A positive moderate-to-strong correlation was found between $AdT_{1\rho}$ and $AdT_{2\rho}$ in AHLAT and PHMED. Nonetheless, they were associated with different findings in the region with the strongest correlation: in PHMED prolonged $AdT_{1\rho}$ values were associated with meniscal tear while prolonged $AdT_{2\rho}$ values were associated with full-thickness cartilage loss. Therefore, the two parameters can be seen as complementary to each other in revealing compositional changes associated with different morphological alterations in individuals aged 50 or above with no symptoms or mild signs of OA (i.e., no evidence of joint space narrowing).

Comparing the repeated measurement reproducibility of the two relaxation time parameters, the CVs were higher for $AdT_{2\rho}$ indicating that it may be less reproducible than $AdT_{1\rho}$. Comparing the intra-observer image analysis reproducibility of the two relaxation times, the CVs were similar to each other in all the meniscal compartments. Some small variations (ranging from 1.07% to 3.19%) were seen in multiple segmentations of the images by the same observer. Similar intra-observer reproducibility analysis performed by Rauscher *et al.* produced relatively higher CV values (ranging from 3.88% to 7.43%) for CW-$T_{1\rho}$ analyzing medial and lateral meniscal horns[15]. The inter-observer CVs were consistently higher than intra-observer CVs in all meniscal compartments and fluctuated between the compartments. The differences in inter-rater errors, by definition, depend on the subjectivity of the assessment; and suggest a need for more automated segmentation technique which would improve the inter-reader precision. The highest CVs for the relaxation times for repeated measurement, intra-observer and inter-observer image analysis reproducibility were mainly found in anterior horn of the medial meniscus (AHMED). The ROIs in this region were the smallest, making the segmentation difficult and increasing the chances of partial volume effects.

While the results were promising, there are certain limitations in our study. One source of inaccuracy was that we compared asymptomatic subjects and patients based on their symptoms confirmed by radiographic findings. It has been reported in numerous studies that the prevalence of meniscal tear is common in both asymptomatic subjects and patients, and tears have been observed in knees of subjects without knee pain or stiffness[2,47–50]. Consistent with these studies, we also noticed meniscal tears in the asymptomatic volunteer group but their prevalence and severity were lower comparing to our patient group (Table II). Therefore, to validate the exact association between the adiabatic relaxation parameters and meniscus constituents, a reference standard is needed in which arthroscopic or histologic data are available.

In our study, MOAKS assessment was performed on MR images covering whole knee joint, however, quantitative meniscal horn analysis was performed on single slice images. The main reason for choosing a single slice per compartment was to keep total acquisition time within an acceptable range. Therefore, we analyzed meniscus in the horn regions on a single 3 mm thick slice in the sagittal plane, which could lead to underestimation of meniscal lesions, especially at the body of the meniscus. Multislice imaging is a task designed for future sequence development. Other limitations of this study include a relatively small sample size consisting only of 24 subjects, and the cross-sectional nature of the study.

In conclusion, the results of this study demonstrate that $AdT_{1\rho}$ and $AdT_{2\rho}$ relaxation time measurements in menisci are able to detect tissue changes in the presence of structural lesions. Elevated $AdT_{1\rho}$ and $AdT_{2\rho}$ values were associated with meniscal tear and cartilage loss, respectively, in a population of individuals with mild signs or no symptoms of OA. Therefore, they may serve as potential clinical tools for confirming the presence of meniscal alterations in pre- and early clinical stages.

Author contributions

AWK: Conception and design of the study, analysis and interpretation of the data, drafting the article, final approval of the article and responsibility of the integrity of the whole study.

VC: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

MJN: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

AP: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

SS: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

EL: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

JP: the conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

AG: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

MTN: Conception and design of the study, analysis and interpretation of the data, drafting the article, and final approval of the article.

Conflict of interest

Ali Guermazi is the President of Boston Imaging Core Lab, LLC, and is a Research Consultant for Merck KgaA, Sanofi-Aventis, TissueGene Inc, OrthoTrophix and AstraZeneca PLC.

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