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Assessment Of Meniscus With Adiabatic T1p And T2p Relaxation Time In Asymptomatic Subjects And Patients With Mild Osteoarthritis: A Feasibility Study

Kajabi, AW

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Assessment of meniscus with adiabatic $T_1^r$ and $T_2^r$ 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

Objective: To investigate the ability of magnetic resonance imaging (MRI) adiabatic relaxation times in the rotating frame ($AdT_1^r$ and $AdT_2^r$) 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 $T_1^r$ and $T_2^r$ ($AdT_1^r$, $AdT_2^r$) 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 $AdT_1^r$ was observed in the posterior horn of the medial meniscus (PHMED) in subjects with MOAKS meniscal tear ($P < 0.05$). $AdT_2^r$ 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 $AdT_1^r$ and $AdT_2^r$ values between mild OA patients and asymptomatic volunteers did not reach statistical significance.

Conclusion: $AdT_1^r$ and $AdT_2^r$ 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). 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. Early detection of compositional changes indicative of meniscal tissue disintegration is critical in therapeutic...
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%19. Previous studies have shown that MRI can be used to identify meniscal lesions20,21, and the meniscal tear signals are associated with meniscal extrusion22.

Various quantitative MRI (qMRI) sequences have been used to evaluate meniscal tissue biochemical changes quantitatively14–18. Continuous-wave (CW) rotating frame of reference (RFR) relaxation time (T1) in a coil, where a CW spin-lock pulse is applied on- or off-resonance, and T2 have been used in assessing meniscal degeneration15–18. The studies have concluded that CW-T1, and T2 can be used to quantify meniscal degeneration and differentiate healthy subjects from OA patients. However, both CW-T1, and T2 have been reported to be affected by magic angle artifact18–22. Shao et al. concluded that changes in CW-T1, and T2 values due to magic angle effect can be several times more than that caused by degeneration15. Furthermore, clinical application of CW-T1, has remained a challenge due to its susceptibility to magnetic field inhomogeneity and relatively high specific absorption rate (SAR)19.

Recently, adiabatic RFR relaxation time parameters, namely adiabatic T1 and T2, have been utilized, e.g., to study macromolecular alteration of tissue constituents in AC during early OA24,25. Compared to CW-T1, adiabatic RFR methods are less prone to the magnetic field nonuniformity, and their adiabatic nature provides flexibility in pulse design, thus helps reducing SAR26–28. Adiabatic T1 and T2, as CW-T1, are inherently sensitive to slow molecular motions29,30. Moreover, a wide range of effective frequencies (\(\omega_{	ext{eff}}(t)\)) 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 \(\omega_{	ext{eff}}(t)\) is constant. It has also been demonstrated that adiabatic T1 and T2 relaxation times are at least equivalent in detecting early degenerative changes in AC compared to numerous other qMRI techniques31,32. To our knowledge, neither \(\text{in vivo}\) nor \(\text{ex vivo}\) study has been previously tested the association of adiabatic T1 (AdT1) or adiabatic T2 (AdT2) relaxation times with meniscal structural changes.

In this \(\text{in vivo}\) study, AdT1 and AdT2 sequences33,34 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 AdT1 and AdT2 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/m² 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 21 = 1, 2), knee pain, and fulfilling the American College of Rheumatology (ACR) criteria for classification of idiopathic OA38. 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/m²) and 12 were mild OA patients (mean age 59.1 ± 5.9 years, mean BMI 30.3 ± 6.3 kg/m²). 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), T1 TSE, AdT1, and AdT2 mapping sequences. The imaging parameters of the sequences are listed in Table 1.

For AdT1 mapping, as previously described40, 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 (TSL) = 0, 24, 48, 72, 96 ms) of the HSn family, here HS4; followed by a segmented gradient recalled echo (2D FLASH) readout (Table 1). For AdT2, the AFP pulses were placed between two adiabatic half passage pulses (AHP) followed by FLASH readout. The peak radio frequency (RF) amplitude for both AdT1 and AdT2 was \(\gamma B_{1\text{max}} = 600\) Hz.

### Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FLASH*</th>
<th>PD TSE</th>
<th>PD 3D FS</th>
<th>T1 TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR [ms]</td>
<td>4000</td>
<td>2800</td>
<td>1200</td>
<td>650</td>
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<tr>
<td>TE [ms]</td>
<td>3.36</td>
<td>33</td>
<td>26</td>
<td>18</td>
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<tr>
<td>Flip angle [deg]</td>
<td>15</td>
<td>150</td>
<td>120</td>
<td>150</td>
</tr>
<tr>
<td>Matrix</td>
<td>256 × 256</td>
<td>384 × 384</td>
<td>256 × 256</td>
<td>320 × 320</td>
</tr>
<tr>
<td>FOV [mm²]</td>
<td>180 × 180</td>
<td>140 × 140</td>
<td>160 × 160</td>
<td>130 × 130</td>
</tr>
<tr>
<td>Slice TH [mm]</td>
<td>3</td>
<td>3</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Slices [n]</td>
<td>2</td>
<td>35</td>
<td>176</td>
<td>25</td>
</tr>
<tr>
<td>ETL/# of segments</td>
<td>23</td>
<td>7</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Plane</td>
<td>Sagittal</td>
<td>Sagittal</td>
<td>Sagittal</td>
<td>Coronal</td>
</tr>
<tr>
<td>Acquisition time [min:s]</td>
<td>4:42</td>
<td>4:09</td>
<td>8:48</td>
<td>1:56</td>
</tr>
</tbody>
</table>

* 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.

1. Readout for the adiabatic T1 and T2 sequences.
2. Number of segments per preparation.
3. Total acquisition time for adiabatic T1 or T2.
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 T₁ TSE weighted coronal images were used to obtain MOAKS for meniscal tear and full-thickness cartilage loss (Table II).

AdT₁ₑ and AdT₂ₑ 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 AdT₁ₑ and AdT₂ₑ 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 AdT₁ₑ and AdT₂ₑ weighted images and was hence excluded from the ROI analysis. AdT₁ₑ and AdT₂ₑ maps were calculated in the ROIs by mono-exponential fitting of the signal intensity decay on a pixel-by-pixel basis.

Median meniscal horn AdT₁ₑ and AdT₂ₑ 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 = 0) and absence of any tears (no tear group, MOAKS grade for meniscal morphology = 0); (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 AdT₁ₑ and AdT₂ₑ 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. AdT₁ₑ and AdT₂ₑ 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

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)

<table>
<thead>
<tr>
<th></th>
<th>AHMED compartment</th>
<th>PHMED compartment</th>
<th>AHLAT compartment</th>
<th>PHLAT compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial compartment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meniscus signal (MOAKS = 1)</td>
<td>0</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Meniscus tear (MOAKS = 2–5)</td>
<td>0</td>
<td>5 (3)</td>
<td>7 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Meniscus maceration (MOAKS = 6)</td>
<td>0</td>
<td>5 (4)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meniscus signal (MOAKS = 1)</td>
<td>0</td>
<td></td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Meniscus tear (MOAKS = 2–5)</td>
<td>0</td>
<td></td>
<td>7 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Meniscus maceration (MOAKS = 6)</td>
<td>0</td>
<td></td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Femur full-thickness AC lesions (MOAKS &gt; 0)</td>
<td>0</td>
<td>4 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tibia full-thickness AC lesions (MOAKS ≥ 0)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

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 AdT1p and AdT2p 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-T1 values of the meniscus reported by Boblos et al.10. 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 AdT1p and AdT2p 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 AdT1p and AdT2p 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 correction for multiple comparisons. The change in the median values of AdT1p and AdT2p 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).

Table III

<table>
<thead>
<tr>
<th>ROI</th>
<th>Volunteers (n = 12)</th>
<th>Patients (n = 12)</th>
<th>P-value</th>
<th>Corrected P-value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdT1p (ms)</td>
<td>AHMED 34.0 (36.2–32.2)</td>
<td>35.5 (37.0–33.8)</td>
<td>0.600</td>
<td>0.720</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td>PHMED 37.3 (39.5–34.3)</td>
<td>41.0 (51.2–38.0)</td>
<td>0.037*</td>
<td>0.148</td>
<td>0.424</td>
</tr>
<tr>
<td></td>
<td>AHLAT 40.4 (44.4–35.1)</td>
<td>43.5 (50.4–38.6)</td>
<td>0.242</td>
<td>0.414</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td>PHLAT 32.3 (35.7–29.1)</td>
<td>39.2 (42.7–36.2)</td>
<td>0.024*</td>
<td>0.144</td>
<td>0.460</td>
</tr>
<tr>
<td>AdT2p (ms)</td>
<td>AHMED 31.8 (35.9–30.0)</td>
<td>35.9 (40.2–31.8)</td>
<td>0.114</td>
<td>0.228</td>
<td>0.330</td>
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<tr>
<td></td>
<td>PHMED 25.5 (27.9–23.8)</td>
<td>30.6 (38.8–26.6)</td>
<td>0.033*</td>
<td>0.132</td>
<td>0.436</td>
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<tr>
<td></td>
<td>AHLAT 35.0 (40.7–30.1)</td>
<td>42.4 (47.1–35.9)</td>
<td>0.047*</td>
<td>0.141</td>
<td>0.407</td>
</tr>
<tr>
<td></td>
<td>PHLAT 34.8 (38.5–31.5)</td>
<td>33.5 (39.5–30.1)</td>
<td>0.977</td>
<td>0.977</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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.

Comparison of AdT1p and AdT2p in menisci of patients with mild OA and asymptomatic volunteers

The differences in the median values of AdT1p and AdT2p 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 AT1p and AdT2p with meniscal tear and cartilage loss based on MOAKS

Median AdT1p 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 AdT2p 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 AdT1p were always smaller as compared to AdT2p (Table VI). For both AdT1p and AdT2p, 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 AdT1p and AdT2p were found in PHMED (1.22% and 1.07%, respectively). The largest CVs for AdT1p were found in PHLAT (2.00%) and for AdT2p in AHMED (3.19%).

The inter-observer image analysis CVs were higher for AdT2p than for AdT1p for all the ROIs, as compared to the intra-observer CVs (Table VI). The smallest CVs for AdT1p were found in PHMED (2.76%) and for AdT2p in PHLAT (3.22%). The highest CVs for AdT1p were found in AHMED (4.60%) and for AdT2p, in AHMED (10.52%).
Correlation between $\text{AdT}_{1r}$ and $\text{AdT}_{2r}$

There were statistically significant correlations between $\text{AdT}_{1r}$ and $\text{AdT}_{2r}$ 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 $\text{AdT}_{1r}$ and $\text{AdT}_{2r}$ relaxation times in menisci were associated with subjects having meniscal tear and full-thickness cartilage loss as assessed.
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 AdT1, for meniscal tear, and AdT2, 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.

Previous studies have demonstrated that meniscal relaxation parameters such as dGEMRIC, CW-T1r and T2 can be used to differentiate OA patients from healthy subjects. In the present study, longer AdT1r and AdT2r 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 AdT1r and AdT2r measurements in menisci to distinguish mild OA patients against asymptomatic volunteers needs to be confirmed in larger studies.

In AdT1r spin-locking is achieved with a different approach than conventional CW-T1r experiments. While in CW-T1r an RF pulse with constant spin-lock frequency is applied either on- or off-resonance, in AdT1r the spin-lock frequency sweeps 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. These effective frequencies extend the sensitivity of the adiabatic RF pulse to many frequencies of molecular fluctuations. An significant advantage of AdT1r is its smaller dependence on orientation indicating less sensitivity to the magic angle effect and reducing major sources of uncertainty that can confound the readings of CW-T1r and conventional T2. Reducing the magic angle effect in CW-T1r is possible only by using very high spin-lock frequencies (about 2 kHz), which dramatically increases SAR beyond the limit for clinical application. The associations of meniscus AdT1r and AdT2r with radiographic signs of OA or semi-quantitative grading scores have not been studied before. In this study, elevations of AdT1r and AdT2r were statistically associated with MOAKS findings.

It has been shown that AdT1r and AdT2r are differentially affected by different relaxation mechanisms, and therefore may be able to supply complementary information. 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 AdT1r and AdT2r in AHLT and PHMED. Nonetheless, they were associated with different findings in the region with the strongest correlation: in PHMED prolonged AdT1r values were associated with meniscal tear while prolonged AdT2r 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 AdT2r indicating that it may be less reproducible than AdT1r. 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-T1r, analyzing 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 (PHMED). 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. 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.

Table VI
CVs for repeated measurements, intra- and inter-observer reproducibility of adiabatic T1, (AdT1r) and adiabatic T2, (AdT2r)

<table>
<thead>
<tr>
<th>CVs (%) for AdT1r</th>
<th>AHMED</th>
<th>PHMED</th>
<th>AHLT</th>
<th>PHLAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated measurements (n = 4)</td>
<td>4.21</td>
<td>1.73</td>
<td>2.33</td>
<td>3.53</td>
</tr>
<tr>
<td>Intra-observer (n = 8)</td>
<td>1.33</td>
<td>1.02</td>
<td>1.43</td>
<td>2.00</td>
</tr>
<tr>
<td>Inter-observer (n = 8)</td>
<td>4.60</td>
<td>2.76</td>
<td>7.58</td>
<td>4.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CVs (%) for AdT2r</th>
<th>AHMED</th>
<th>PHMED</th>
<th>AHLT</th>
<th>PHLAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated measurements (n = 4)</td>
<td>8.85</td>
<td>4.51</td>
<td>5.77</td>
<td>6.30</td>
</tr>
<tr>
<td>Intra-observer (n = 8)</td>
<td>3.19</td>
<td>1.06</td>
<td>1.79</td>
<td>1.22</td>
</tr>
<tr>
<td>Inter-observer (n = 8)</td>
<td>10.52</td>
<td>3.51</td>
<td>7.49</td>
<td>3.22</td>
</tr>
</tbody>
</table>

AHMED = anterior horn of the medial meniscus; PHMED = posterior horn of the medial meniscus.
AHLT = anterior horn of the lateral meniscus; PHLAT = posterior horn of the lateral meniscus.
In conclusion, the results of this study demonstrate that AdT1ρ and AdT2ρ relaxation time measurements in menisci are able to detect tissue changes in the presence of structural lesions. Elevated AdT1ρ and AdT2ρ 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.

MKN: 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.

Conflicts 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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References


