T_2 mapping of the meniscus is a biomarker for early osteoarthritis

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In press, European Radiology (2019)

ABSTRACT

Objective: To evaluate *in vivo* T_2 mapping as quantitative, imaging-based biomarker for meniscal degeneration in humans, by studying the correlation between T_2 relaxation time and degree of histological degeneration as reference standard.

Methods: In this prospective validation study, conducted from April 2016 to July 2017, 13 menisci from seven patients with radiographic knee osteoarthritis (median age 67 year, three males) were included. Menisci were obtained during total knee replacement surgery. All patients underwent pre-operative magnetic resonance imaging using a 3-Tesla MR scanner which included a T_2 mapping pulse sequence with multiple echoes. Histological analysis of the collected menisci was performed using the Pauli score, involving surface integrity, cellularity, matrix organization, and staining intensity. Mean T_2 relaxation times were calculated in meniscal regions of interest corresponding with the areas scored histologically, using a multi-slice multi echo postprocessing algorithm. Correlation between T_2 mapping and histology was assessed using a Generalized Least Squares model fit by maximum likelihood.

Results: The mean T_2 relaxation time was 22.4 ± 2.7 ms (range 18.5-27). The median histological score was 10, IQR 7-11 (range 4-13). A strong correlation between T_2 relaxation time and histological score was found (r_s = 0.84, 95%CI [0.64-0.93]).

Conclusion: *In vivo* T_2 mapping of the human meniscus correlates strongly with histological degeneration. T_2 mapping enables the detection and quantification of compositional changes of the meniscus, providing a non-invasive imaging biomarker for early knee OA.

INTRODUCTION

The fascinating role of the meniscus in knee osteoarthritis (OA) has attracted considerable attention among researchers for decades. Not only is meniscal damage a radiological sign of OA -up to 91% of the patients with symptomatic knee OA have coexisting meniscal tears [1]-, a torn meniscus is also one of the strongest risk factors for the development and progression of knee OA [2-5]. Although the complex role of meniscal tissue composition in the etiology of meniscal tears and the subsequent development of knee OA is not entirely clear, it has become increasingly evident that the menisci play a critical role in the long-term health of the knee joint.

Hence, the ability to objectively assess meniscal tissue quality and composition is of key importance, particularly in patients at risk for developing knee OA [2]. In order to study the etiology of meniscal tears and meniscal degeneration in knee OA development and progression, and to allow early interventions and prevention of progression, changes in meniscal tissue composition need to be detected before gross morphological changes occur.

Using conventional magnetic resonance (MR) imaging, measuring such changes in meniscal tissue composition prior to surface breakdown, is challenging. Recent developments in quantitative MR imaging techniques have made great progress in addressing this challenge [6,7]. Among quantitative MR imaging techniques, T_2 mapping is the most commonly used in knee OA research [8,9]. Based on properties of biochemical tissue components, quantitative analysis of T_2 relaxation times can reveal the composition of extracellular matrix, without the need for contrast or special MR hardware [6,10]. Increased T_2 relaxation times indicate damage to the collagen network and a decrease in water content, both signals of tissue degeneration [11].

Recent studies have shown the potential of T_2 relaxation time as biomarker to quantify meniscal degeneration in patients with knee OA [6,12-14], yet validation studies of meniscal T_2 mapping are limited. Validation of T_2 mapping, using histological analysis; the gold standard for tissue changes, was performed in one previous study [7]. In that study, T_2 mapping was performed *ex vivo*, however it is unknown how well T_2 measurements, obtained *ex vivo*, reflect the actual in vivo situation. To our knowledge, validation of *in vivo* meniscal T_2 mapping, using histological analysis as reference test, has not been performed.

We aimed to validate *in vivo* meniscal T_2 mapping in patients with knee OA by evaluating the correlation between T_2 mapping and histological reference standards for meniscal degeneration.

METHODS

Study design and participants

Our prospective observational study was conducted between April 2016 and July 2017. Meniscal specimens were obtained from patients with primary end-stage knee OA undergoing elective total knee replacement surgery at our institution. Participants were selected consecutively. Study approval was granted by the institutional Medical Ethical Committee (MEC-2012-218), and written informed consent was obtained from all participants.

Assessment of radiographic knee OA

The assessment of radiographic knee OA is described in Supplementary Material 1.

MR image acquisition

MR imaging was performed on a 3 Tesla (T) MR unit (Discovery MR750, GE Healthcare, Milwaukee, USA), 1 day prior to surgery. The MR imaging protocol included routine morphological knee sequences (Proton Density weighted sequences in sagittal, coronal and axial plane, T_2 weighted sequences with Fat Saturation (Fat-Sat) in sagittal, coronal and axial plane) and a sagittal 3D Fat-Sat fast spin echo (FSE) T_2 mapping sequence with multiple echoes. A 8-channel Send&Receive rigid dedicated knee coil (GE Healthcare, Milwaukee, WI, United States) was used. Sequence parameters are displayed in Table 1.

Table 1. MR Imaging Sequence Parameters

Scanner type	Discovery MR750, GE Healthcare, Milwaukee, WI, United States
Scanner field strength	3 T
Sequence type	3D Fast Spin Echo Fat-suppression
Matrix (RO x PE)	288 x 192
Interpolated resolution (mm^2)	0.5 x 0.8
Slice thickness / spacing	3/0
Number of slices	36
Number of echoes	5
TE (ms)	3.1; 13.4; 27.0; 40.7; 68.1
TE used for map reconstruction (ms)	3.1; 13.4; 27.0
FOV (cm)	15
Coil	8-channel S&R rigid knee coil, GE Healthcare, Milwaukee, WI, United States
Scan time (mm:ss)	09:41

Abbreviations: T = Tesla, O = readout, PE = phase encoding, TE = echo time, TR = repetition time, FOV = field of view, S&R = send and receive.

Harvesting of meniscal tissue and histological analysis

Meniscal specimens were obtained intra-operatively, during total knee replacement surgery. If present, both medial and lateral menisci were harvested, meniscal samples were stored in formaldehyde. Within three days of harvesting, menisci were cut in a standardized way according to Pauli et al. [15] (Figure 1). For each meniscus, the anterior horn and the posterior horn were processed. The menisci were cut at 45° (for the anterior horn) and 135° (for the posterior horn) angles relative to the sagittal plane (Figure 1-A). Meniscal samples were cut along two different planes: the vertical plane and the horizontal plane. The vertical section provided an overview of the longitudinally oriented collagen bundles and the tibial and femoral surfaces of the meniscus (Figure 1-C). The horizontal section, cut from the inner rim to the vascular zone at a 30° angle relative to the tibial plateau, revealed the parallel organization of the collagen bundles and matrix morphology (Figure 1-B).

The samples were fixed, dehydrated in alcohol, and infiltrated with paraffin. Next, meniscal samples were paraffin-embedded and sectioned using a microtome (MR2235, Leica-Biosystems, Wetziar, Germany) into six-micrometer sections.

To provide an overview of the overall tissue organization, and to assess border integrity, cellularity, and cell morphology, sections were stained using Hematoxylin and Eosin. Safranin O-Fast Green and Alcian Blue stain were used to evaluate proteoglycan content and mucoid degeneration, respectively. To assess collagen fiber organization, Picrosirius Red stain was used. Stained sections were visualized using (polarized-) light microscopy (Olympus-BX50, Olympus-Optical, Shinjuku, Tokyo) [16]. To assess the histological degree of degeneration, the validated, semi-quantitative Pauli score [15] was performed by two investigators with four years of experience in musculoskeletal research (Table 2). Both investigators were blinded to patient information and imaging outcomes. They examined all meniscal samples individually; in case of discrepancies, sections were assessed in consensus.

Quantitative MR image analysis

On T_2 mapping images, meniscal regions of interest (ROIs) were manually segmented by a researcher with a medical degree and four years of experience in musculoskeletal research (Figure 2), who was blinded to patient information and histology outcomes. Meniscal segmentation was performed using an image collected with the echo time (TE) showing optimal contrast between menisci and surrounding tissues (TE 7.3 ms).

Great care was taken to match MR imaging ROIs and histological ROIs. As described earlier, histological tissue processing was performed using predefined anatomical regions; the most central part of the anterior horn and the most central part of the posterior horn. As histological samples were cut in a fixed and standardized way, MR imaging ROIs were matched to histological ROIs. To do so, we identified the most central slice through the medial and lateral meniscus (defined as the sagittal slice depicting the maximum width of the anterior horn and posterior horn as individual triangles) along with the neighboring slices medially and laterally.

Table 2. Histological scoring system for meniscal degeneration by Pauli et al.	
1. Surface integrity	
Femoral surface	**Score**
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
Tibial surface	
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
Inner rim	
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
2. Cellularity	
• Normal	0
• Hypercellularity	1
• Diffuse hypocellularity	2
• Acellular	3
3. Collagen organization/alignment and fiber organization	
• Collagen fibers organized	0
• Collagen fibers organized and foci of mucinous degeneration	1
• Collagen fibers unorganized and foci of mucinous degeneration	2
• Collagen fibers unorganized and fibrocartilaginous separation	3
4. Matrix staining (Safranin O-Fast Green)	
• None	0
• Slight	1
• Moderate	2
• Strong	3

Note: the range of possible total scores is 0 – 18. The total score can be converted to a grade as follows: grade 1 = 0-4 (normal), grade 2 = 5-9 (mild degeneration), grade 3 = 10-14 (moderate degeneration), grade 4 = 15-18 (severe degeneration). In the present study, the Pauli score was used as continuous measure; no conversion to grades was performed.

Four ROIs were defined per patient: the anterior and posterior horn of the medial and lateral meniscus. All ROIs consisted of three consecutive slices: the most central slice along with the adjacent slice medially and laterally. MR imaging scout views, using T_2 weighted images in the coronal and axial plane, were used to verify that the ROIs were correctly defined (i.e. that they matched histological ROIs).

For MR image post-processing, in-house developed registration and fitting algorithms in Matlab (R2011a; The MathWorks, Natick, Mass) were used [17]. Automated rigid registration in 3D was used for motion compensation [17]. Similar to previous studies [18,19], we excluded all images with TE above 30 ms because of the very low signal-to-noise-ratio in meniscal tissue (Table 1). To reduce effects of possible outliers within ROIs, T_2 relaxation times were weighted by the reciprocal of the uncertainty of the estimated T_2 relaxation time in each voxel. This

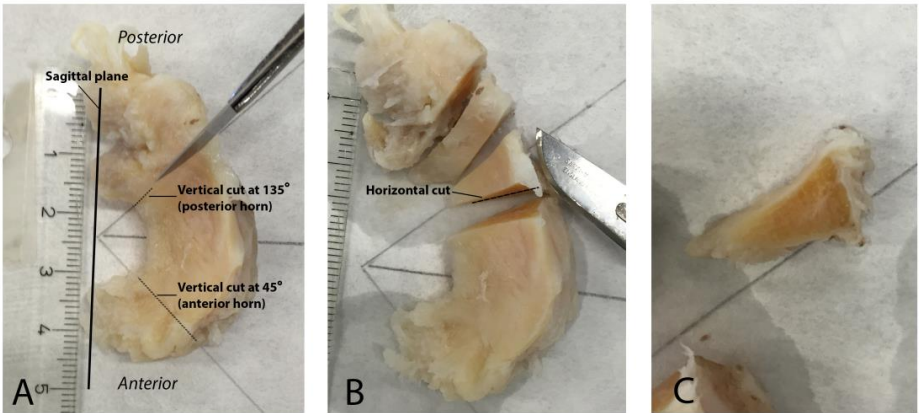

Figure 1. Preparation of meniscal samples. Example of a grossly intact lateral meniscus harvested during total knee arthroplasty in a left knee of a 59-year-old female with medial compartment knee OA (Kellgren and Lawrence grade 4). A) Cutting the meniscus according to the method of Pauli et al; vertical cut. B) Horizontal cut, from the inner rim to the vascular zone at a 30° angle relative to the tibial plateau. C) Detail view of vertical cut of the posterior horn.

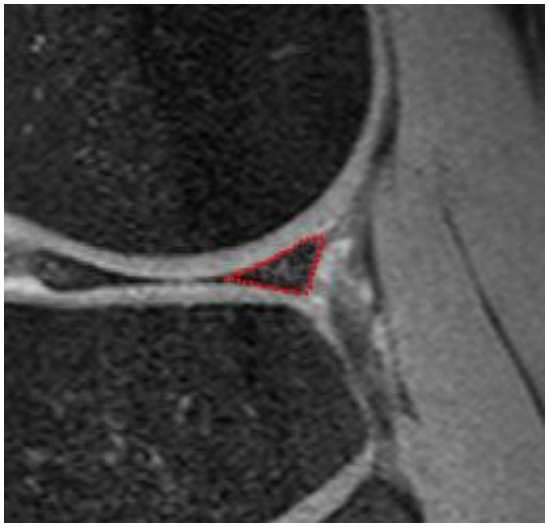

Figure 2. Segmentation of the meniscus. Representative example of sagittal T_2 mapping image with manually drawn region of interest (ROI) of the posterior horn of the lateral meniscus in a 67-year-old female with knee osteoarthritis.

uncertainty was measured with the square root of the Cramer-Rao lower bound, which gives a lower bound for the standard deviation of the estimated T_2 relaxation time [17]. The weighted T_2 mapping relaxation times for each ROI were averaged over the three consecutive MR imaging slices, further referred to as mean T_2 relaxation time [17].

Statistical analysis

Descriptive statistics for all available variables, including demographics, T_2 relaxation times per meniscal ROI, and histological scores, are reported. Normality was tested using Shapiro-Wilk tests. Normally distributed data were presented as mean with standard deviation; non-normally distributed data were presented as median with inter quartile range (IQR).

Inter-observer reliability of histological scoring was tested using two-way intraclass correlation coefficients (ICCs) of absolute agreement, taking single measurements.

We performed a linear mixed-effects model to assess the correlation between T_2 relaxation times and histological scores, where T_2 relaxation times were considered as dependent variable and histological score as independent variable. We employed Generalized Least Squares function in the "nlme"-library in the statistical software "R" [20] allowing to calculate the correlation in repeated measures data (i.e. in datasets that include multiple measures per patient). Age, BMI, and sex were tested as potential covariates since they might impact T_2 values. A backward variable selection and the likelihood ratio test were used for this purpose. Subgroup analyses were performed using a linear mixed-effects model, regarding regional differences.

Statistical analyses were performed using R version 3.4.2 (2017) [20].

RESULTS

Patient characteristics

In total, 13 menisci were collected from 7 patients with knee OA; six medial and seven lateral menisci. There was a slight overall female predominance of 57%, the median age of patients was 67 years (range 59-74). None of the menisci showed a macroscopic tear. Patient characteristics are shown in Table 3.

Radiographic knee OA

Patients had either moderate radiographic knee OA (KLG 3, n = 3) or severe radiographic knee OA (KLG 4, n = 4).

T_2 relaxation time in meniscal tissue

The mean meniscal T_2 relaxation time was 22.4 ± 2.7 ms (range 18.5-27). In addition to overall mean T_2 relaxation times (i.e. the mean of measurements from all ROIs), mean T_2 relaxation times were calculated for the four meniscal ROIs (medial anterior and posterior, lateral anterior and posterior) separately, reported in Table 4. Highest T_2 relaxation times were found in the medial anterior horn of the meniscus. Statistical significantly higher T_2 relaxation times were found in the medial menisci than in the lateral menisci ($P = 0.005$). No statistically significant differences between the anterior and posterior meniscal horns in T_2 relaxation time were found ($P = 0.14$). Representative T_2 mapping findings are displayed in Figure 3-I – 3-J.

Table 3. Characteristics of the Study Population		
No. of patients		7
No. of menisci		13
Age (y)*		67 (59-74)
Female patients		
	No. of patients	4
	Median age (y)	66
	Age range (y)	59-67
Male patients		
	No. of patients	3
	Median age (y)	73
	Age range (y)	66-74
Body Mass Index† (kg/m^2)		28 ± 4
Time interval between MR imaging and harvesting† (days)		1 ± 0
Radiographic OA grade		KL grade 3: n = 3 KL grade 4: n = 4
Most affected side of radiographic knee OA		Medial compartment: n = 6 Lateral compartment: n = 1
Patients with meniscal tear		0

* Data are median values (range)
† Data are mean values ± standard deviation
Abbreviations: OA = osteoarthritis, KL = Kellgren and Lawrence

Table 4. Meniscal T_2 Measurements and Histological Scores per ROI		
	T_2 (ms)*	Histological Score†
Medial meniscus, anterior	25.4 ± 1.5	12, 11-12
Medial meniscus, posterior	23.2 ± 2.6	10, 8.5-11.5
Lateral meniscus, anterior	20.8 ± 1.4	7, 6-8
Lateral meniscus, posterior	19.9 ± 1.2	8, 5-8

* Data are mean values ± standard deviations
† Data are median values, inter quartile range
Abbreviations: ROI = region of interest, ms = milliseconds

Histological findings in meniscal tissue

In two patients, all four meniscal regions (medial anterior, medial posterior, lateral anterior and lateral posterior) could be harvested. In the remaining five patients, as a result of partial maceration of the menisci due to end-stage knee osteoarthritis, not all four regions could be harvested (only three regions possible in four patients and a single region in one patient). In total, 21 meniscal regions were used for histological analysis.

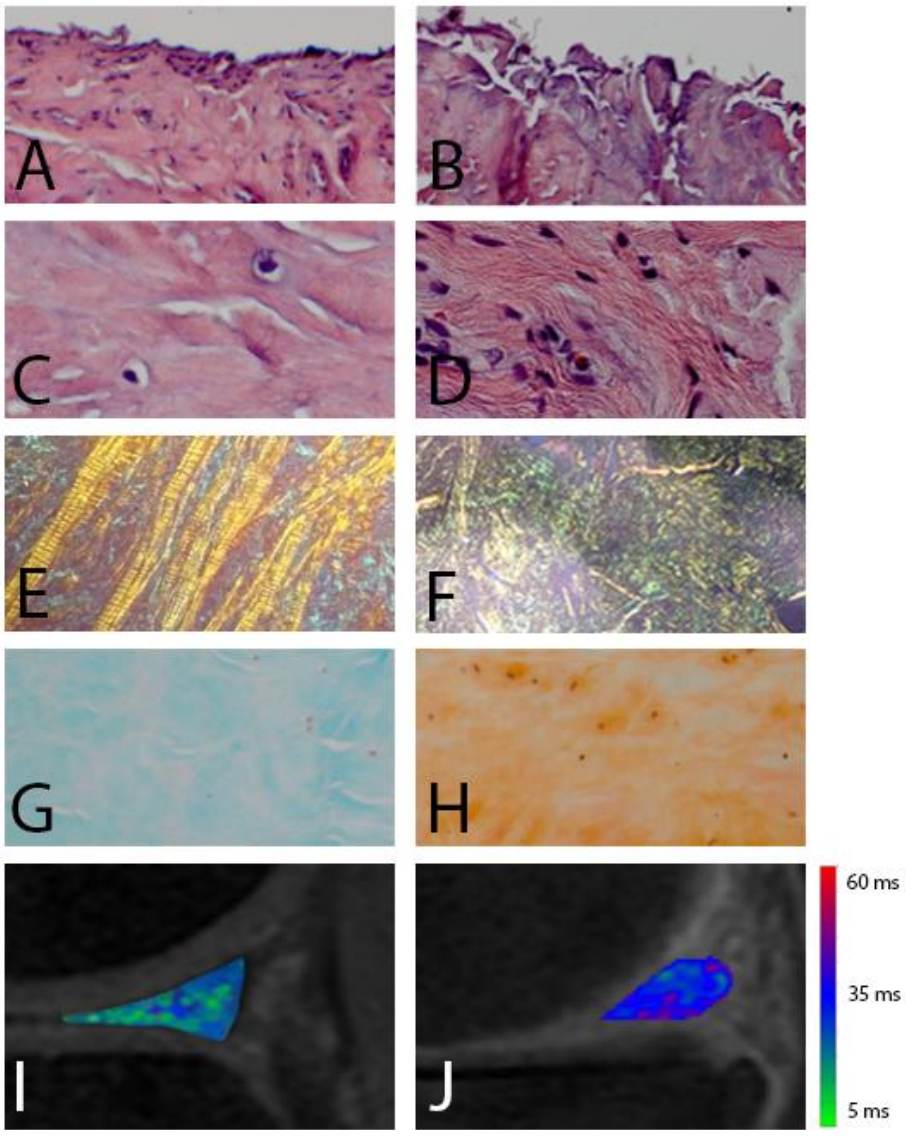

Figure 3. Representative images of histological findings and corresponding T_2 mapping images. A, C, E, G) Posterior horn of lateral meniscus of a 67-year-old female with knee OA (Kellgren and Lawrence grade 3), with a mean T_2 relaxation time of 18.6 ms and a histological score of 5. B, D, F, H) Posterior horn of medial meniscus of a 66-year-old female with knee OA (Kellgren and Lawrence grade 4) with a mean T_2 relaxation time of 26.9 ms and a histological score of 13. A, B) Surface integrity (HE staining, 10 x zoom). C, D) Cellularity (HE staining, 40 x zoom). E, F) Collagen organization (Picrosirius-Red staining, 5 x zoom). G, H) Collagen matrix staining intensity, a decreased intensity of green staining indicates disruption in collagen matrix (Saf-O-Green staining, 10 x zoom). I, J) Corresponding non-contrast sagittal T_2 mapping images with color map of the meniscus. The color bar on the right shows the range of T_2 values.

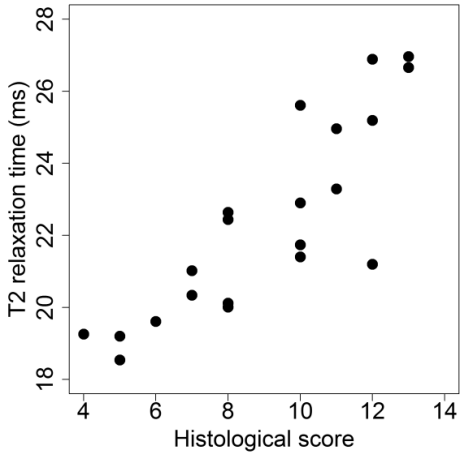

Figure 4. Scatterplot of histological scores versus T_2 relaxation times, in all patients and all measurements.

The inter-observer reliability of histological scoring between the two observers was excellent (ICC: 0.95, 95%CI [0.79-0.99]). We found an overall median histological score of 10, IQR 7-11 (range 4-13). Mean histological scores per meniscal ROI are shown in Table 4. As for T_2 relaxation times, the highest histological scores were found in the medial anterior horn of the meniscus and histological scores were found to be higher in the medial menisci than in the lateral menisci (P = 0.007). Also, no statistically significant differences between the anterior and posterior meniscal horns in histological score were found (P = 0.20). Representative histological findings are displayed in Figure 3-A - 3-H.

Correlation between T_2 mapping and histological scores

In the linear mixed-effects model, the variables age, sex and BMI were not statistically significant and were excluded from the model. To incorporate the potential effect of repeated measures (i.e. multiple measures per patient), the model has been statistically adjusted. A strong correlation between T_2 mapping and histology (correlation coefficient 0.85, 95%CI [0.68-0.93]) was found.

DISCUSSION

In this study, we assessed the correlation between *in vivo* meniscal T_2 mapping and histology in patients with radiographic knee OA. We demonstrated that meniscal T_2 relaxation times in patients with knee OA show a strong correlation with the degree of histological degeneration. These findings indicate the potential of T_2 relaxation times, obtained with *in vivo* T_2 mapping, as non-invasive imaging biomarker for meniscal degeneration.

The results of our study are in line with those of previous research on meniscal T_2 mapping where no histological analysis was performed. These studies showed that T_2 mapping can differentiate between healthy patients and those with knee OA. Zarins et al. found that meniscal T_2 mapping discriminated between healthy and severe OA, but not between healthy and mild OA, and only in the posterior meniscal horns [19]. Rauscher and colleagues reported that T_2 mapping discriminated between healthy, mild and severe OA in all meniscal regions [13]. In addition to OA patients, T_2 mapping has been investigated in patients with acute knee injury. Significantly higher T_2 relaxation times were reported in patients with an anterior cruciate ligament rupture, compared to healthy controls [12].

To our knowledge, this is the first study to investigate the validity of in vivo meniscal T_2 mapping in osteoarthritic patients, using histology as the reference test. Recently, Nebelung et al. performed a validation study of multiple quantitative MR imaging techniques, including T_2 mapping [7]. Histological analysis of meniscal samples from total knee replacement surgeries was used as the reference standard. In contrast to the present study, their T_2 mapping measurements were performed *ex vivo*. Whether T_2 measurements, obtained *ex vivo*, reflect the actual *in vivo* situation, could be questioned. Several factors in *ex vivo* experiments may affect T_2 relaxation times. First, storage of meniscal samples in medium and changes in tissue hydration may have potentially affected T_2 measurements [7,14]. Second, in *ex vivo* experiments, samples are typically scanned at room temperature and not at body temperature, potentially influencing T_2 relaxation times. Last, *ex vivo* quantitative MR imaging experiments usually have different acquisition parameters, such as the number and duration of echo times, field of view, and acquisition matrix, compared with *in vivo* [7,21]. These factors may have caused the lower correlation coefficient (*r*: 0.65) between T_2 mapping and histology in their study compared to ours.

In musculoskeletal imaging research, T_2 mapping was originally developed for the quantification of articular cartilage, yet T_2 relaxation times have been increasingly used to assess meniscal tissue composition [7,13,14,19]. It is suggested that meniscal T_2 mapping can be challenging due to the short T_2 components and the heterogeneity of meniscal tissue [22,23]. In previous studies, concerns have therefore been raised that standard spin echo based T_2 mapping is not suitable to quantitatively measure the menisci [24]. The results of the present study, however, suggest that in vivo spin echo based T_2 mapping can provide accurate T_2 measurements in menisci. An important advantage of T_2 mapping is that it has the potential to quantitatively assess a variety of knee tissues; as the range of echo times in T_2 mapping is usually wide [25,26]. Quantitative MR imaging techniques that obtain extremely short echo times, such as Ultrashort echo time-enhanced T_2* (UTE-T_2*) are less suitable for the assessment of, for example, superficial layers of articular cartilage, due to their higher T_2 signal [6,27]. Taking into account that knee OA is a complex multi-tissue disease, involving the whole joint, T_2 mapping has the best potential for quantifying knee OA [6,25].

The results of the present study suggest that T_2 relaxation times, obtained with *in vivo* T_2 mapping, can potentially be used as non-invasive biomarker to detect early changes in meniscal tissue that indicate degeneration. Given the important role of the menisci in the long-term health of the knee joint, such biomarkers for meniscal tissue quality and degeneration are of great value. The detection of early meniscal tissue changes, indicating degeneration, would allow a better understanding of the etiology and development of knee OA. Furthermore, it would allow the identification of patients at early OA stages, before irreversible damage occurs. Also, it would improve the monitoring of disease progression and treatment response. The long-term goal would be to allow the detection and monitoring of early meniscal tissue changes that indicate an increased risk for knee OA, potentially enabling early treatment strategies for knee OA.

In conclusion, *in vivo* T_2 mapping of the human meniscus provides accurate measurements of meniscal degeneration in patients with knee osteoarthritis. By quantifying subsurface meniscal changes, T_2 mapping potentially provides a non-invasive imaging biomarker for meniscal degeneration.

Acknowledgements

We would like to thank Nicole Kops (Erasmus MC University Medical Center, Rotterdam, The Netherlands) for technical assistance regarding histological experiments and Adam Weir (Erasmus MC University Medical Center, Rotterdam, The Netherlands) for his help regarding scientific writing. In addition, the authors would like to thank the department of Orthopedic Surgery of Erasmus MC University Medical Center for their cooperation in including patients and collecting meniscal tissue.

Disclosures of conflicts of interest:

E.H.G. Oei receives research support from GE Healthcare.

SUPPLEMENTARY MATERIAL 1: ASSESSMENT OF RADIOGRAPHIC KNEE OA

The degree of radiographic knee osteoarthritis was graded according to the Kellgren and Lawrence (KL) classification system ranging from 0 (no OA) to 4 (end stage OA). The KL classification includes the assessment of joint space narrowing, osteophytes, subchondral sclerosis, and deformity of bone contour. Grading was performed by a musculoskeletal radiologist with 12 years of experience, using weight bearing anteroposterior radiographs. Radiographs and MR imaging scans were acquired on the same day.

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