Published in final edited form as:
Osteoarthritis Cartilage. 2013 October ; 21(10): 1474–1484. doi:10.1016/j.joca.2013.07.012.

Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures

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SUMMARY

Objective—The purpose of this work was to review the current literature on cartilage and meniscal T2 relaxation time.

Methods—Electronic searches in PubMed were performed to identify relevant studies about T2 relaxation time measurements as non-invasive biomarker for knee osteoarthritis (OA) and cartilage repair procedures.

Results—Initial osteoarthritic changes include proteoglycan loss, deterioration of the collagen network, and increased water content within the articular cartilage and menisci. T2 relaxation time measurements are affected by these pathophysiological processes.

It was demonstrated that cartilage and meniscal T2 relaxation time values were significantly increased in subjects with compared to those without radiographic OA and focal knee lesions, respectively. Subjects with OA risk factors such as overweight/obesity showed significantly greater cartilage T2 values than normal controls. Elevated cartilage and meniscal T2 relaxation times were found in subjects with vs without knee pain. Increased cartilage T2 at baseline predicted morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years. Furthermore, cartilage repair tissue could be non-invasively assessed by using T2 mapping. Reproducibility errors for T2 measurements were reported to be smaller than the T2 differences in healthy and diseased cartilage indicating that T2 relaxation time may be a reliable discriminatory biomarker.

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Authors' contributions

Conception and design: TB, TML, JSB; Analysis and interpretation of the available literature: TB, GBJ, DCK, PMJ, TML, JSB; Drafting of the article: TB; Critical revision of the article for important intellectual content: GBJ, DCK, PMJ, TML, JSB; Final approval of the article: TB, GBJ, DCK, PMJ, TML, JSB.

Competing interests

The authors declare that they have no competing interests.

Conclusions—Cartilage and meniscal T2 mapping may be suitable as non-invasive biomarker to diagnose early stages of knee OA and to monitor therapy of OA.

Keywords

Osteoarthritis; Knee; Magnetic resonance imaging; Cartilage and meniscal T2 relaxation time

Introduction

Osteoarthritis (OA) is the most common form of arthritis. The most affected joints are the knee, hip, and hands. Nearly 27 million individuals in the United States have clinically symptomatic OA, including about 9.2 million adults having symptomatic knee OA[1]. The predominant clinical symptoms of knee OA are pain and disability[2]. OA is characterized by progressive loss of articular cartilage, osteophyte formation, synovitis, and subchondral bone changes. Radiography and morphologic magnetic resonance imaging (MRI) of the knee joint are limited in their ability to detect early stages of OA and subtle changes due to therapy response, e.g., after cartilage repair procedures[3,4].

The initial osteoarthritic changes include proteoglycan loss and deterioration of the collagen network within the cartilage and menisci, which cause increased mobility of water and consequentially increased water content[5,6]. Quantitative MRI techniques including cartilage and meniscal T2 relaxation time measurements reflect these pathophysiological changes as outlined in previous review articles about OA imaging[7–11]. Due to promising results, cartilage T2 measurements were included in the National Institutes of Health (NIH) sponsored Osteoarthritis Initiative (OAI), a 9 year longitudinal, observational multicenter study with 4796 participants[12,13].

Thus, the purpose of this work was to review the current literature on cartilage and meniscal T2 relaxation time.

Cartilage and meniscal T2 relaxation time

Identification and selection of the literature

Electronic searches in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) were performed up to April 2013 to identify relevant studies for this review. No starting date was entered for the electronic searches to obtain the entire literature available in PubMed. Search terms used included “Osteoarthritis”, “Knee”, “Magnetic Resonance Imaging”, and “Cartilage T2”. The search was restricted to studies about humans. The reference lists of relevant articles were also screened.

Background on T2 measurements and comparison with other quantitative MRI techniques

Cartilage is composed by chondrocytes surrounded by the extracellular matrix, which consists primarily of water, proteoglycans (core protein with attached glycosaminoglycan (GAG) chains), and collagen fibers. These macromolecules restrict the motion of water in the extracellular matrix. Pathophysiological processes of early cartilage degeneration are characterized by GAG loss and deterioration of the collagen network causing increased mobility of water and consequentially increased water content within the cartilage[5,6]. These changes in the extracellular matrix can be detected by quantitative MRI techniques including sodium-23 (^{23}Na) MRI, glycosaminoglycan chemical exchange saturation transfer (gagCEST), delayed gadolinium enhanced MRI of the cartilage (dGEMRIC), diffusion-weighted and diffusion tensor imaging (DWI and DTI, respectively), T1rho and T2 relaxation time measurements.

GAG has a negative fixed-charge density resulting in the attraction of positive counterions such as sodium. Thus, a loss of GAG due to early cartilage degeneration results in the loss of sodium ions, which can be measured by ^{23}Na MRI[14]. Furthermore, Ling *et al.* demonstrated that the GAG concentration closely correlates with measures using gagCEST[15]. ^{23}Na MRI and gagCEST have shown promising results in the assessment of cartilage repair procedures[16–18]. However, ^{23}Na MRI and gagCEST are technically challenging and have been performed mostly on 7 T MRI systems to obtain a sufficient signal-to-noise ratio (SNR) and spatial resolution[19]. Therefore, these techniques are not available at the moment for broad clinical use.

The dGEMRIC technique requires an injection of the negatively charged contrast agent gadopentate dimeglumine (Gd-DTPA^{2-}). The contrast agent penetrates into the cartilage and distributes within the cartilage in an inverse relationship to the concentration of negatively charged GAG[20]. Thus, the GAG content of the articular cartilage can be estimated from measuring the T1 values after penetration of Gd-DTPA^{2-}. It has been demonstrated that dGEMRIC improves the differentiation of disease status and may predict the development of knee OA[21,22]. The drawbacks of the dGEMRIC technique are related to the need for the contrast agent injection and the relatively long examination time.

DWI, DTI, T1rho and T2 relaxation time measurements do not require a contrast agent injection and can be performed on most clinical 1.5 and 3.0 T MRI systems.

The increased mobility of water in early diseased cartilage can be assessed by DWI. Apparent diffusion coefficients (ADCs) were elevated in degenerated compared to healthy cartilage and provided additional information about cartilage repair tissue beyond morphological MRI[23–25]. DTI of the cartilage measures diffusion anisotropy (e.g., fractional anisotropy), which is an indirect measurement of the collagen architecture[26]. Raya *et al.* reported decreased fractional anisotropy in samples with cartilage degeneration, suggesting a good performance of DTI for detection of early cartilage degeneration[27].

In contrast to DWI and DTI, the performance of cartilage and meniscal T1rho and T2 relaxation time measurements as non-invasive biomarker for early stages of knee OA have been investigated in a considerable number of studies. In vitro studies observed correlations of T2 relaxation time measurements with the mechanical, histological and biochemical properties of cartilage[28,29]. In one of the early *in-vivo* studies, Dardzinski *et al.* performed cartilage T2 measurements in asymptomatic volunteers and observed a reproducible pattern of increasing T2 values that was proportional to the known spatial variation in cartilage water and inversely proportional to the GAG distribution[30]. In a subsequent study, Mosher *et al.* reported elevated T2 relaxation times in damaged compared to healthy articular cartilage[31]. While T2 measurements mostly characterize the deterioration of collagen network, T1rho relaxation time is a more specific indicator of the GAG content[32]. However, Li *et al.* found high correlations between T1rho and T2 relaxation times[33]. Although T1rho measurements have been developed over 20 years ago for *in-vivo* imaging and have been prototyped by many groups, this method remains work-in-progress.

Image acquisition

In-vivo knee cartilage T2 mapping is typically performed at clinical 1.5 and 3.0 T MRI systems. Several different sequences have been used for T2 quantification of articular cartilage including spin echo (SE), multi-echo SE, fast spin echo (FSE), and T2-prepared 3D spoiled gradient recalled (SPGR) acquisitions. Pai *et al.* compared these sequences and reported a considerable variability in scan time, SNR and reproducibility[34].

SE sequences are most commonly used and are provided by most manufactures of MRI systems. They can be applied with different numbers and values of echo times (TE). For example, a multi-slice multi-echo (MSME) SE sequence with seven echoes (TE = 10, 20, 30, 40, 50, 60, and 70 ms), repetition time (TR) of 2700 m, and total acquisition time of 10.6 min is performed in the OAI[13]. However, it is important to note that MSME SE sequences acquire multi-slice data using slice-selective refocusing pulses. In the presence of miscalibration or inhomogeneities of the transmit radiofrequency field, slice-selective refocusing pulses do not result in rectangular slice profiles, leading to imperfect refocusing throughout the slice and causing stimulated echo contributions to the measured signal[35,36]. The occurrence of the stimulated echoes causes therefore overestimation of T2 values in MSME sequences. Excluding the first echo from the later fitting process is one way to reduce the effects from stimulated echo signal contribution in the calculated T2 values[35,36]. Furthermore, off-resonance effects can be generated in multi-slice acquisitions by applying refocusing pulses for other slices. This introduces magnetization transfer contrast into the images, resulting in reduced signal intensity in cartilage and thus possibly in inaccuracy of the T2 measurements. To investigate the effect of magnetization transfer on multi-slice T2 measurements, Watanabe *et al.* measured T2 value with single-slice and multi-slice acquisition[37]. They reported a substantial drop in T2 values when obtained with the multi-slice compared to the single-slice acquisition. However, no apparent interslice variation in T2 values was observed when the multi-slice acquisition was used. They concluded that multi-slice acquisition of cartilage T2 measurements is clinically applicable when inaccuracies caused by multi-slice acquisition are taken into account.

T2 mapping based on 3D SPGR overcomes the error sources of an MSME SE sequence. The sequence consists of a nonselective T2 preparation and a 3D SPGR acquisition during the transient signal evolving towards steady state[34]. However, this sequence has been used only in a limited number of research studies and is not included in the image protocol of large trials, e.g., the OAI[38–41].

Cartilage T2 mapping has to be differentiated from cartilage T2* mapping. T2* and T2 values are related by the equation $\frac{1}{T2^*}=\frac{1}{T2}+\gamma\Delta B_0$, where γ is the gyromagnetic ratio of the observed nucleus and DB0 is the magnetic field inhomogeneity. Based on the assumption that the applied static magnetic field B0 is uniform, γΔB0 is only influenced by local magnetic susceptibility fields present at the cartilage—bone interface or within the cartilage microstruc-ture[42]. It has been hypothesized that T2* measurements may provide a greater sensitivity to cartilage degeneration, in particular close to the cartilage—bone interface. T2* mapping may be advantageous compared to T2 mapping, since it lacks radiofrequency refocusing pulses, thus avoiding errors resulting from simulated echoes and magnetization transfer. Significant association between T2 and T2* measurements have been reported in previous studies, indicating that both measurements reflect the microstructural composition of the cartilage[42–44]. However, T2* mapping has not shown clear advantages beyond T2 mapping so far.

Compared to hyaline articular cartilage, menisci have shorter T2 relaxation times (5–8 m). Therefore, T2 relaxation time measurements of the menisci have been performed using acquisitions with shorter TEs, e.g., TE = 4.1, 14.5, 25.0, and 45.9 ms, as reported by Rauscher *et al.*[40]. A promising alternative to quantitatively characterize the menisci is ultra-short echo time (UTE) imaging, in particular by using high-field MRI systems[45].

Image post-processing

The T2 relaxation time value for each pixel is computed by fitting the measured signal intensity S at each TE to a mono-exponential decay function $S(TEi) = S_0 \bullet e^{(-TE_i/T2)}$, where

S_0 is the signal intensity at zero TE. Different fitting methods such as linear least squares, weighted linear least squares or non-linear least squares algorithms have been used to solve the equation for T2 and S_0[46]. Since the accuracy and precision of T2 is substantially affected in images with low SNR, it was suggested to use noise-corrected fitting methods, which showed better accuracy and precision in phantom and *in-vivo* measurements with low SNR[47]. Finally, T2 maps displaying the computed T2 values of each pixel are generated.

Segmentation is required to extract T2 values from distinct cartilage compartments. Two different techniques have been used for cartilage segmentation: either direct segmentation on the T2 maps or segmentation on spoiled gradient echo (SPGR) or double-echo steady-state (DESS) images for cartilage volume measurements with later superimposition of these segmentations on the T2 maps.

Using the direct segmentation technique, regions of interest (ROIs) aremanually drawntodelineatecartilageareasontheT2maps.These ROIs are simultaneously defined on the T2 map and first echo of the MSME sequence in order to exclude fluid and chemical shift artifacts from the ROIs. This is done by opening separate image panels at the same time with synchronized cursor, slice number, and zoom as outlined by Stehling *et al.*[48]. The direct segmentation technique allows a fast and reliable, but manual segmentation of cartilage compartments for T2 quantifications. In contrast, (semi-) automatic segmentation software programs were developed for cartilage volume measurements using edge detection or graph-cuts algo-rithms[49,50]. In case of already existing segmentations for cartilage volume measurements, these can be superimposed on T2 maps to avoid a complete new segmentation for T2 quantifications. This requires software solutions to adjust for the different slice thickness of SPGR/DESS images and T2 maps, and registration of T2 maps on the SPGR/DESS images due to patient movement between DESS/SPGR and T2 mapping acquisitions[50,51]. After superimposition on the T2 maps, the segmented compartments often have to be manually corrected due to accidentally included fluid with elevated T2 relaxation time values.

Segmentation and T2 quantification of the articular cartilage of one knee is performed in about 60 min using the direct segmentation technique compared to a time effort up to 300 min using the segmentation superimposition techniques (including cartilage volume measurements)[48]. Therefore, the direct segmentation technique is recommended if only T2 quantifications are the research purpose of a study, since good agreement between the two segmentation techniques regarding T2 values have been reported[48].

Independent of the segmentation technique, the following compartments of articular cartilage are usually investigated: patella (PAT), trochlea (TRO), medial femur (MF), lateral femur (LF), medial tibia (MT), and lateral tibia (LT). The LF/MF compartment can be subdivided in a central and posterior sub-region, the TRO and PAT in a medial, central, and lateral sub-region. The medial and lateral sub-regions of the TRO are often added to the MF and LF compartment, respectively. Representative T2 maps with the segmented PAT, TRO, MF/LF/MT/LT compartments are displayed in Fig. 1. The medial/lateral meniscus is usually divided in anterior, posterior, and body compartment as shown in Fig. 2.

Mean T2 of all pixels included in the segmented compartment is the standard parameter of cartilage T2 mapping[40,41,52–54]. To account for the spatial distribution of T2 relaxation times[30,36], laminar (i.e., zonal) and texture analyses were introduced as more sophisticated parameters for T2 quantifications of the articular cartilage. Laminar analysis can be automatically performed and subdivides the segmented compartment, e.g., into a superficial and deeper cartilage layer[38,55,56]. The superficial layer is orientated to the articular surface, the deeper layer to the cartilage–bone interface. Carballido-Gamio *et al.* reported

significantly greater T2 relaxation times in the superficial compared to the deep cartilage layer and suggested that laminar analysis could lead to better and probably earlier identification of cartilage matrix degeneration[38,55]. Texture analysis was developed by Haralick *et al.*[57]. Based on grey level co-occurrence matrix (GLCM), information about the spatial distribution of T2 relaxation time values is extracted by analyzing their co-occurrences at a certain orientation and inter-pixel distance. Two texture parameters from the contrast group (contrast and homogeneity), three from the orderliness group (angular second moment, energy, and entropy) and three from the stats group (mean, variance, and correlation) were computed in previous studies[38,51,58–60]. To give some examples about the meaning of these texture parameter: contrast is a measure of the differences in neighboring pixel values. High T2 contrast signifies that many pixels with different T2 values are neighboring. Entropy is a measure of disorder in an image. Higher T2 entropy signifies less uniform distribution of probabilities of T2 relaxation time co-occurrences. Variance is a measure of the distribution of pixels about the mean. Higher T2 contrast, T2 entropy, and T2 variance were observed in subjects with OA risk factors compared to normal controls, thus providing additional information with respect to early cartilage degeneration[59].

Reproducibility of T2 measurements

T2 relaxation time is only a discriminatory biomarker if the reproducibility error for T2 values is lower than the T2 differences in healthy and diseased cartilage. In previous studies, normal controls had between 3% and 12% lower global T2 values than subjects with OA risk factors and OA, respectively[52,54,59]. Glaser *et al.* examined the reproducibility of mean T2 values in the PAT in replicate scans[56]. They reported reproducibility errors for patellar mean T2 values of 3–7%. Lower reproducibility errors of mean T2 values were observed in all articular cartilage compartments for repetitive segmentation in the same T2 maps (0.3–3.3%)[48]. Mosher *et al.* demonstrated moderate to excellent reproducibility in a clinical trial network (ACRIN-PA 4001 multicenter trial)[61]. Reproducibility measurements were performed in subjects without as well with mild and severe radiographic OA. In total, 50 subjects underwent cartilage T2 measurements multiple times. Reproducibility errors for cartilage T2 ranged from 4% to 14%.

T2 texture parameters showed greater reproducibility errors compared to mean T2 (between 1% and 7% for T2 entropy, contrast, and variance)[58,60]. Reproducibility errors of meniscal T2 mapping ranged from 4.55 to 13.71% as reported by Rauscher *et al.*[40].

The use of different radiofrequency coils and different MR scanners impact the reproducibility and comparison of T2 map-ping[62,63]. With higher SNR, significantly longer T2 values were measured in the deep cartilage layer of all compartments and in the whole cartilage of the MT and central MF compartments[63]. These error sources have to be taken into account when the clinical relevance of T2 mapping is discussed.

T2 and OA risk factors

Age, female gender, increased body mass index (BMI), and knee malalignment are well-known risk factors for knee OA[64–66]. Previous studies have found associations between these OA risk factors and T2 relaxation time measurements.

Elevated cartilage T2 values are associated with aging. Mosher *et al.* obtained patellar cartilage T2 relaxation time values from 30 asymptomatic women[67]. T2 values were significantly greater in the superficial 40% of cartilage in the 46–65 year old sub-group and over the entire cartilage in the 66–86 year old sub-group than in the 18–30 year old sub-group. These findings are consistent with the hypothesis that senescent changes of cartilage matrix begin near the articular surface and progress to the deeper cartilage with advancing

age[68]. Meniscal T2 values of the posterior horn (PH) of both menisci combined were significantly greater in women aged 50–70 (1.777 ms) and 35–49 (0.741 ms) compared to women aged 20–34 (0.088 ms) (study population: 30 women)[69]. However, corresponding differences in men were not significant (study population: 30 men). Furthermore, Rauscher *et al.* observed only a relatively low correlation of meniscal T2 values with age in 23 healthy subjects ($R^2 = 0.18$)[40]. Therefore, the association of meniscal T2 values and age may be considered as relatively weak.

The differences in cartilage T2 between genders have been investigated by Mosher *et al.*, who measured cartilage T2 relaxation times in young healthy males (n = 7) and females (n = 10)[70]. They observed no significant differences in meanT2 and spatial variation of T2 values between males and females. However, meniscal T2 values of the PH of both menisci combined were greater in asymptomatic women compared to men[69,71]. In the future, additional studies or the analysis of existing OAI data are needed comparing T2 measurements of older males and females to further our knowledge about the association of cartilage T2 relaxation times and the known fact that females are at increased risk for OA.

The effect of body mass on cartilage biochemical composition as assessed by T2 mapping has been investigated by Baum *et al.*[58]. They performed cartilage T2 measurements in 267 subjects aged 45–55 years consistingof 36 normal controls and 231 subjects with OA risk factors, including subjects with normal weight (n = 78), overweight (n = 84), and obesity (n = 69), respectively. They reported that obese subjects had the highest mean T2 values and the most heterogeneous cartilage as assessed by T2 texture analysis, while normal controls had the lowest meanT2 values and the most homogeneous cartilage at baseline. In addition, T2 entropy was constantly elevated over 36 months. These results indicate advanced cartilage matrix degeneration due to increased BMI and underline the importance of overweight and obesity as risk factor for knee OA (Fig. 3).

Knee malalignment has been identified as risk factor for the progression of knee OA, but controversial findings have been reported for the association between knee malalignment and incident knee OA[66]. Friedrich *et al.* observed greater T2 values in subjects with medial knee OA and varus compared to those with valgus malalignment in all compartments of the femoro-tibial joint, adding support to the hypothesis of an association between OA and knee malalignment (study population: n = 24)[72]. However, longitudinal studies are needed investigating the relation of knee malalignment and early cartilage matrix degeneration as assessed by T2 mapping.

T2 and physical activity

Acute loading of the knee during MR scanning resulted in a significant decrease in T2 relaxation times of the articular knee cartilage due to a loss of water content (study population: n = 30)[73]. Similarly, T2 values directly measured after running were decreased, while temporary non-weight bearing of the articular cartilage was associated with elevated T2 relaxation times[74–76].

Stehling *et al.* obtained meniscal T2 measurements of 13 marathon runners before, 48–72 h after, and 3 months after competition and compared them with those of 10 controls[77]. All marathon runners showed a significant increase in T2 values after competition in all meniscus compartments, which decreased after 3 months. Similar results were reported for articular cartilage T2 measurements by Luke *et al.*[78]. It remains to be investigated whether these changes are completely reversible or whether the biochemical composition of cartilage is partly irreversibly altered due to heavy loading conditions.

Regarding long-term loading, recent studies examined the association of physical activity and T2 measurements in subjects with risk factors for knee OA[79,80]. Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE). Subjects with high PASE scores perform greater amount of physical activity than subjects with low PASE scores. In addition to higher prevalence and severity of meniscal and cartilage lesions, significantly higher patellar T2 values were observed in subjects with high PASE scores compared to subjects with low PASE scores (study population: n = 120)[79]. Hovis *et al.* reported that light exercise was associated with low T2 values, whereas moderate/strenuous exercise in women with OA risk factors was associated with high T2 values (study population: n = 161)[80].

Future studies are needed to determine the causality of long-term loading and (pathophysiologic) adaptation processes of the cartilage.

T2 and morphologic findings of OA

Mean T2 and T2 texture parameters of the articular cartilage adequately differentiated subjects with radiographic OA and normal controls with AUC values up to 0.82[38,81]. Similar findings were reported for meniscal T2 measurements[40]. It is important to note that these studies had limitations. The studies by Rauscher *et al.* (study population: n = 60) and Carballido-Gamio *et al.* (study population: n = 36) investigating meniscal and cartilage T2 values had a cross-sectional study design[38,40]. In contrast, Blumenkrantz *et al.* assessed mean T2 and T2 texture parameter over 9 months[81]. However, the study population was relatively small (eight mild OA patients and 10 age-matched controls).

Interestingly, early cartilage matrix degeneration due to prevalent OA risk factors could be sensitively detected by T2 mapping, but not with radiography. Joseph *et al.* compared normal controls and subjects, who had diverse OA risk factors including history of knee injury or surgery, but no radiographic OA (Kellgren–Lawrence (KL) score of zero) (study population: n = 145)[59]. They found higher and more heterogeneous knee cartilage T2 in subjects with OA risk factors than in normal controls (mean T2 averaged over all compartments: 32.65 ± 1.55 ms vs 32.07 ± 1.38 ms). Baum *et al.* reported similar findings in a longitudinal study over 24 months[52]: subjects with OA risk factors, but no radiographic OA (n = 101) showed elevated T2 values compared to normal controls (n = 41) at baseline and 24 month follow-up (MF compartment at baseline: 37.9 ± 2.3 ms vs 36.9 ± 2.3 ms; MF compartment at 24 month follow-up: 38.2 ± 2.7 vs 36.8 ± 2.1). Both studies included only subjects with a BMI of 19–27 kg/m^2 to exclude obesity as an OA risk factor. Furthermore, differences in T2 values between subjects with and without OA risk factors were assessed by using multivariate linear regression models adjusting for age, gender, and BMI. Therefore, the elevated and more heterogeneous cartilage T2 in subjects with compared to those without OA risk factors are not associated with overweight/obesity, but with the other OA risk factors as defined by the OAI study protocol (history of knee injury, history of knee surgery, etc.)[12].

Furthermore, Baum *et al.* assessed in this study cartilage lesions by using the whole-organ magnetic resonance imaging score (WORMS) and observed significantly higher T2 values in subjects with compared to those without cartilage lesions (WORMS grade >0 vs WORMS grade of 0) at baseline and 24 month follow-up[52,82]. Similar findings were reported for meniscal lesions and alterations of the subchondral bone. The prevalence of meniscal lesions was associated with elevated meniscal T2 as well as increased T2 of the adjacent articular cartilage[41,83,84]. Bining *et al.* compared articular cartilage T2 values of 88 subjects with vs 60 subjects without bone marrow edema pattern (BMEP)[85]. They demonstrated that subjects with BMEP had significantly increased T2 values in the adjacent articular cartilage. Quantitative assessment of the subchondral bone microstructure revealed further insights in

the complex pathophysiology of knee OA. Bolbos *et al.* compared articular cartilage T2 values and microstructure parameters of the underlying trabecular bone of 16 healthy controls and 16 patients with early OA[86]. Early OA patients had significantly greater T2 and apparent trabecular separation values as well as lower apparent bone volume fraction than normal controls. In consistency, a recent study demonstrated that subjects with lesions in the PH of the medial meniscus had lower apparent bone volume fraction and greater apparent trabecular thickness in the subchondral bone as well as higher T2 relaxation times in the deep layer of the articular cartilage (study population: n = 59)[87]. These findings suggest that changes of bone, cartilage, and meniscus may be intimately related.

Furthermore, longitudinal studies demonstrated that cartilage T2 measurements at baseline predicted progression of focal knee lesions over 24 and 36 months, respectively[39,60]. Joseph *et al.* analyzed focal knee lesions as assessed by the WORMS, mean T2, and T2 texture parameters in 289 subjects with OA risk factors at baseline and 36 month follow-up[60,82]. They reported that elevated T2 and more heterogeneous T2 (based on T2 texture analysis) at baseline were associated with longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years. Prasad *et al.* made similar observations with increased T2 measurements at baseline as predictor of progression of cartilage abnormalities over a period of 2 years (study population: n = 55)[39]. These results demonstrate that T2 may be an early biomarker for future morphologic degeneration associated with OA.

T2 and OA associated knee pain

It was reported previously that focal knee lesions including meniscal tears, BMEP as well as synovitis and joint effusion were associated with pain severity in subjects with radiographic OA[88]. Baum *et al.* investigated the association between focal knee lesions and cartilage T2 with knee pain status in subjects without radiographic OA, but with OA risk factors[53]. They selected 42 subjects aged 45–55 years, right knee pain (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score >5), and no left knee pain (WOMAC pain score of 0). Two comparison groups consisting of 42 subjects with no knee pain (WOMAC pain score 0 in both knees) and 42 subjects with bilateral knee pain (WOMAC pain score >5 in both knees) were also recruited. The groups were frequency matched by sex, age, BMI, and KL score. Prevalence and severity of focal knee lesions as assessed by the WORMS grading and cartilage T2 values of the three groups were compared. Only cartilage lesions were significantly associated with knee pain status. However, elevated cartilage T2 values were observed in subjects with knee pain compared to asymptomatic subjects (mean cartilage T2 averaged over all compartments in the right knee: subjects with without knee pain: 32.4 ± 1.8 ms; subjects with right knee pain: 34.4 ± 1.8 ms; subjects with bilateral knee pain: 34.7 ± 4.7 ms). Similarly, Zarins *et al.* observed correlations of r = 0.55 for meniscal T2 values and pain score (study population: n = 63)[41].

Cartilage and meniscal T2 relaxation times reflect knee pain prevalence. However, cartilage itself cannot directly generate pain, since it does not contain nerve fibers[89]. Subchondral bone and synovium may be responsible for nociceptive stimuli in OA and not the cartilage itself. Therefore, the pathomechanism between cartilage matrix degeneration as assessed by T2 mapping and knee pain status remains unclear. In the future, the association of T2 mapping and knee pain has to be investigated in longitudinal studies.

T2 and cartilage repair tissue

Cartilage repair procedures are of interest due to their potential to provide pain relief and alter the progression of OA[90]. It was hypothesized that T2 measurements provide additional information about the outcome of cartilage repair procedures.

Healthy cartilage and cartilage repair tissue could be adequately differentiated by dGEMRIC, T2, and T2* mapping[43,44]. In particular, zonal T2 measurements revealed differences between healthy cartilage and cartilage repair tissue in subjects after matrix-associated autologous chondrocyte transplantation (MACT). While healthy cartilage showed a significant increase from deep to superficial cartilage zones, cartilage repair tissue did not show a significant stratification of T2 values.

T2 measurements were also able to detect compositional differences in cartilage repair tissue following different repair procedures. Welsch *et al.* compared cartilage T2 values after microfracture therapy (MFX) and MACT in two studies (study population: $n = 20$ and $n = 34$, respectively)[91,92]. Global T2 of control articular cartilage areas were similar in the MFX group (57.8 ± 8.7 ms) and MACT group (56.7 ± 6.0 ms)[91]. Compared to patients after MACT, global mean T2 in the cartilage repair area was significantly reduced in patients after MFX. The global T2 of cartilage repair tissue in patients after MFX amounted 47.3 ± 10.3 ms, whereas those in patients after MACT amounted of 56.4 ± 9.6. Furthermore, repair tissue after MACT showed a zonal variation in T2 values with a significant increase from deep to superficial zones. In contrast, no significant trend between different zones was observed for repair tissue after MFX. Previous histologic evaluation of repair tissue after MFX revealed disorganized fibrocartilage, whereas repair tissue after MACT was described as hyaline-like with a normal zonal collagen organization[90]. Thus, the T2 measurements of cartilage repair tissue performed by Welsch *et al.* were able to characterize these histologic differences with reduced global T2 values and less zonal T2 variation in subjects after MFX compared to those after MACT[91,92].

Subsequent studies confirmed the ability of T2 mapping to detect differences in cartilage repair tissue after different repair procedures. Salzmann *et al.* obtained T2 maps of 18 patients, who underwent MACT or osteochondral autograft transplantation (OCT), and reported significantly lower T2 values in cartilage repair tissue after MACT compared to OCT[93]. Welsch *et al.* obtained T2 measurements of cartilage repair tissue after MACT using either a hyaluronic-based or a collagen-based scaffold (study population: n = 20)[94]. They observed greater T2 values in the cartilage repair tissue using the collagen-based scaffold, indicating differences in the composition of the repair tissue even 2 years post-implantation.

Ideally, cartilage repair tissue develops over time a collagen network with a zonal organization similar to normal hyaline cartilage. It was demonstrated that zonal T2 measurements may be sensitive to characterize the maturation of cartilage repair tissue[95]. Welsch *et al.* obtained T2 measurements in 15 patients treated MACT 19.7 ± 12.1 months after surgery and 1 year later. Global T2 values showed no significant difference between sites of healthy cartilage and cartilage repair tissue. While healthy cartilage showed a significant T2 increase from the deep to superficial cartilage zone at both time points, a significant zonal T2 stratification in the repair tissue could be observed only in the later MRI exam. Similar findings were reported by Theologis *et al.*[96]. Thus, zonal T2 mapping may be able to visualize the maturation process of cartilage repair tissue.

In the lights of these results, Welsch *et al.* compared the Lysholm score (patient report on knee function) and the magnetic resonance observation of cartilage repair tissue (MOCART) score with T2 measurements in their ability to assess differences between cartilage repair tissue after MFX and MACT[25]. While no differences between MFX and MACT patients were observed by using the Lysholm and MOCART score, T2 measurements were lower in the cartilage repair tissue of patients after MFX compared to those after MACT. Therefore, T2 measurements may be a promising tool to assess non-invasively the different ultra-structural outcome and efficacy of cartilage repair techniques, which are currently incompletely evaluated with clinical and morphological information. However, it is

important to note that up to now clinical outcome and T2 values showed only a weak to moderate correlation (mean r = 0.53) according to a recent review article by de Windt *et al.*[97].

Limitations and future developments

Cartilage and meniscal T2 mapping have a number of limitations, which do not allow the routine clinical utilization of T2 values at the moment. The major limitations and future developments that could advance the use of T2 are discussed in this section.

T2 values obtained with different acquisition methods and at different MRI scanners showed substantial variations[34]. The MSME SE sequence has been most commonly used. Using this sequence, error sources including stimulated echoes and magnetization transfer have to be considered. Furthermore, more than two echoes are preferable for an acceptable SNR and accurate fitting process[46,47]. Thus, the same T2 acquisition method and calibration procedures are mandatory to assure a reliable comparison of T2 measurements longitudinally and across different MRI scanners. The quality assurance methods from the OAI are a step into this direction[98].

Practical issues have to be considered for T2 acquisition. Significant differences between cartilage T2 values obtained at the beginning and at the end of the MRI examination were reported by Apprich *et al.* resulting from the different states of unloading of the knee in the course of the MRI examination due to the supine position of the patient[99]. Therefore, the timepoint of T2 acquisition has to be considered in the MRI protocol. Apprich *et al.* recommended to measure T2 after unloading, i.e., at the end of the MRI examination.

Zonal T2 measurements, particularly important for the assessment of cartilage repair tissue, and T2 texture analysis may be affected by partial volume effects. Thus, the results concerning zonal T2 variation of cartilage repair tissue or cartilage T2 heterogeneity in general have to be interpreted carefully.

The reproducibility errors for T2 mapping (repetitive analyses as well as measurements) were all obtained in a research setting. Given the working conditions of a radiologist in clinical routine, T2 reproducibility errors are expected to increase when a radiologist performs the segmentation in a clinical setting. Therefore, a fully-automated segmentation algorithm for T2 maps seems to be the best way to implement T2 relaxation time measurements in clinical practice. Alternatively, T2 maps may be inspected visually to detect elevated cartilage T2 values. Kijowski *et al.* demonstrated that the addition of T2 mapping to the routine MRI protocol could improve the diagnostic performance in the detection of surgically confirmed cartilage lesions[100].

Lastly, T2 mapping has been used for the assessment of cartilage repair procedures, but has not been included in clinical trials with pharmaceutical intervention. Based on the published studies, it may be justified to adopt T2 relaxation time measurements in such a trial.

Conclusions

T2 relaxation time measurements showed promising results in multiple studies to assess non-invasively early cartilage degeneration reflecting changes of the biochemical composition of the articular cartilage and menisci. Most importantly, cartilage T2 mapping showed the potential to (1) predict longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow and (2) monitor subtle changes due to therapy response after cartilage repair procedures.

Acknowledgments

Role of the funding source

This work was in parts supported by NIH U01AR059507 (to TML), P50 (project 3, AR060752-01) (to TML) and F32AR059478-01 (to GBJ).

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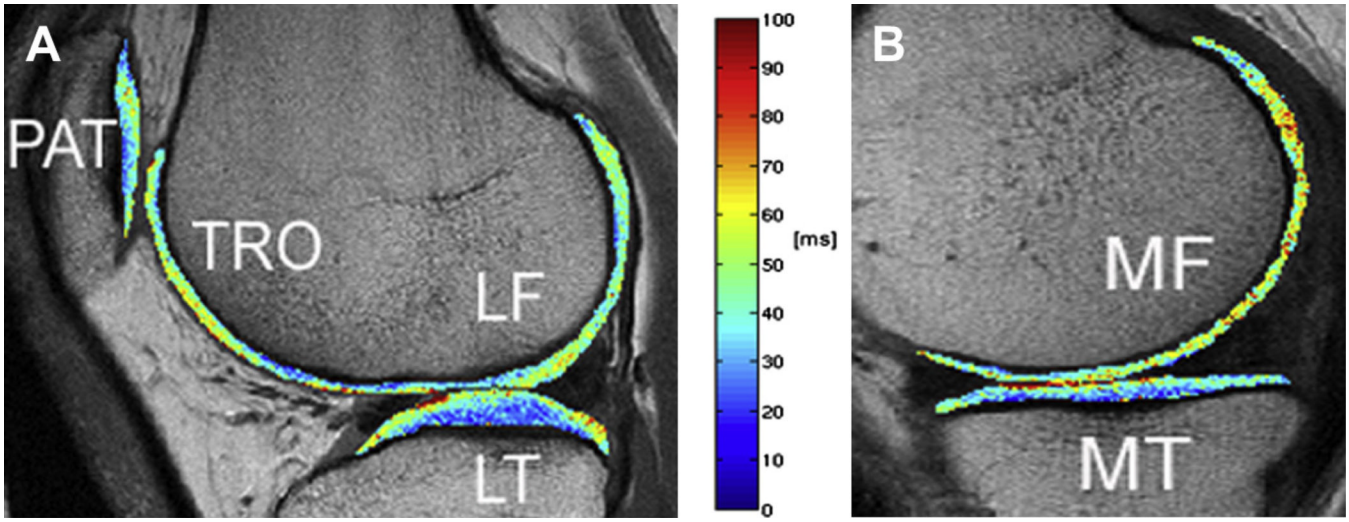

Fig. 1.

Representative color-coded, sagittal T2 maps with segmented PAT, TRO, LF, and LT compartments in A, and MF and MT compartments in B. A sagittal 2D MSME SE sequence was used for T2 mapping (TR of 2700 m; seven TEs of 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms; slice thickness of 3 mm with 0.5 mm gap, in-plane spatial resolution of $0.313 \times 0.446\ mm^2$, acquisition time of 10.6 min).

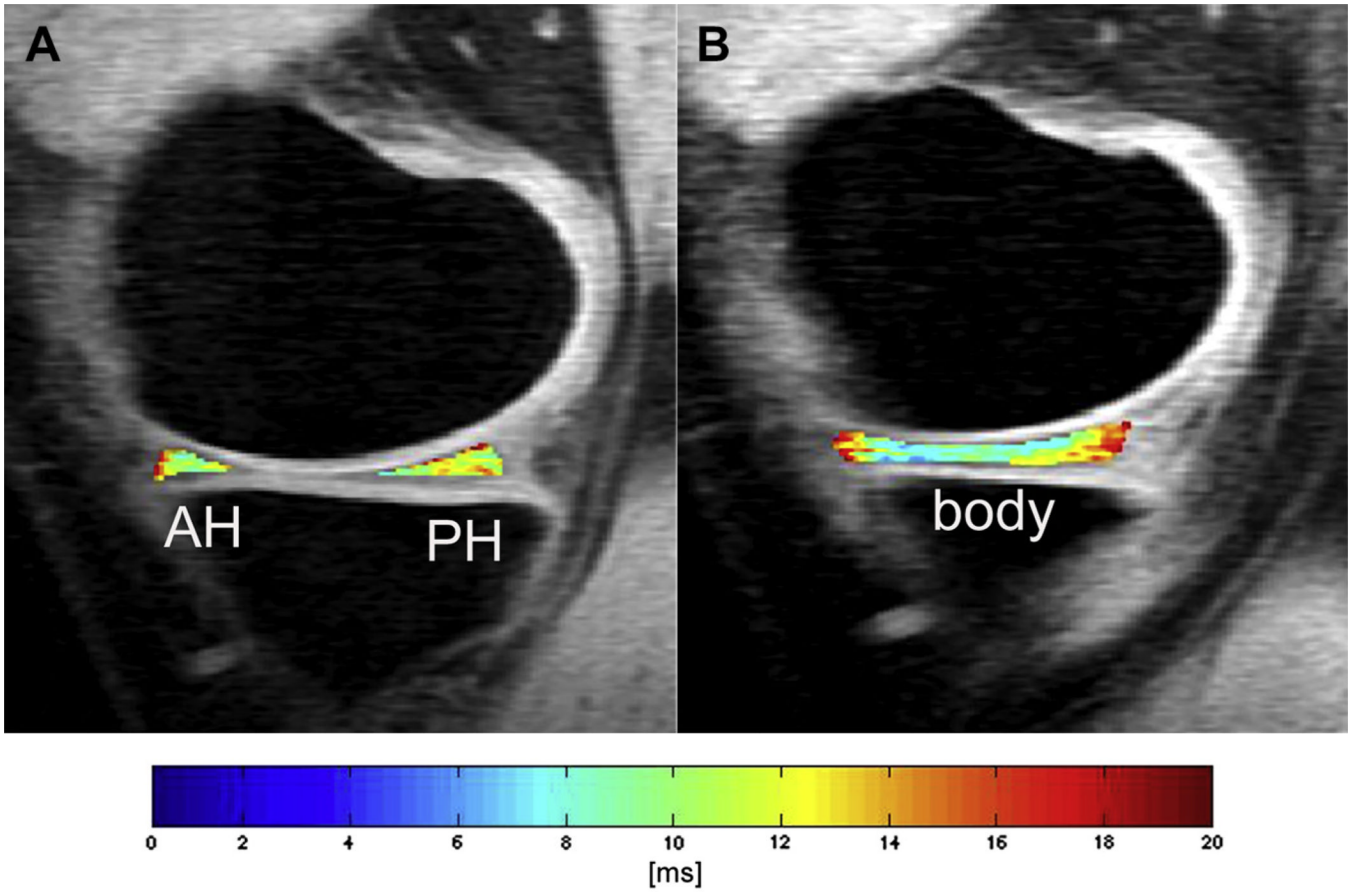

Fig. 2.

Representative color-coded, sagittal T2 maps with segmented anterior horn (AH) and posterior horn (PH) of the medial meniscus in A, and segmented body of medial meniscus in B. A nonselective T2 preparation and a 3D SPGR acquisition during the transient signal evolving towards steady state was used for T2 mapping (TR of 2000 ms; four TEs of 4.1 ms, 14.5 ms, 25.0 ms, and 45.9 ms; slice thickness of 3 mm; in-plane spatial resolution of 0.547 × 0.729 mm^2, acquisition time of 10.6 min).

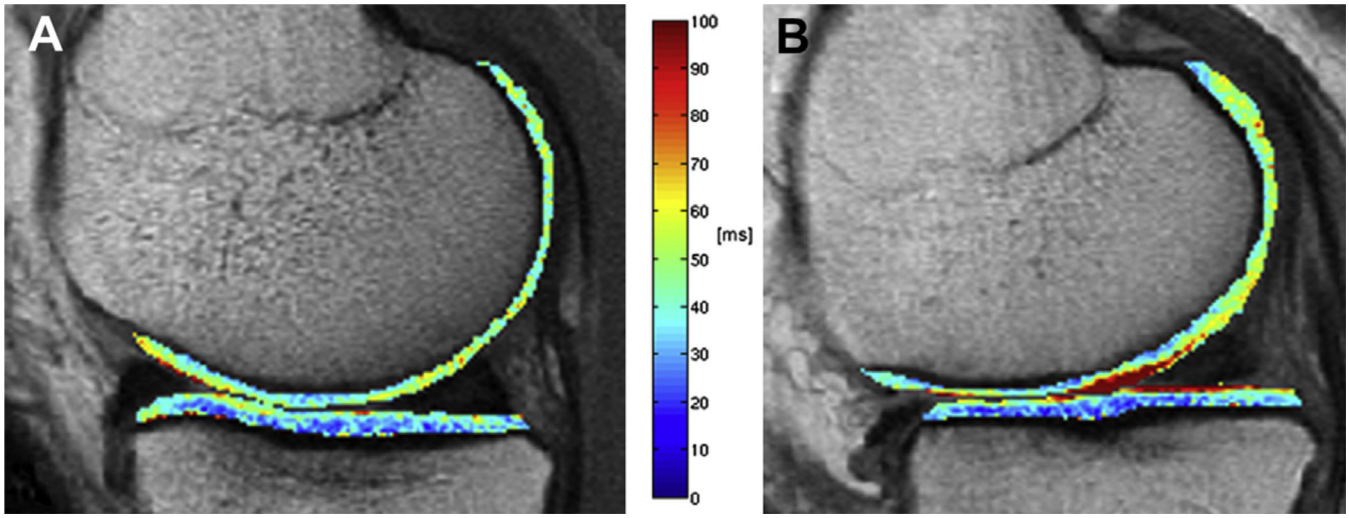

Fig. 3.

Representative color-coded, sagittal T2 maps with segmented MF and MT compartments of a normal control (A) and a subject with the OA risk factor obesity (B). Note the elevated cartilage T2 values in the obese subject compared to the normal control. A sagittal 2D multi-slice multi-echo (MSME) SE sequence was used for T2 mapping (TR of 2700 m; seven TEs of 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms; slice thickness of 3 mm with 0.5 mm gap, in-plane spatial resolution of 0.313 × 0.446 mm^2, acquisition time of 10.6 min).