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T_2 relaxation time measurements are limited in monitoring progression, once advanced cartilage defects at the knee occur:

Longitudinal data from the Osteoarthritis Initiative

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Abstract

Purpose—To study the natural evolution of cartilage T_2 relaxation times in knees with various extents of morphological cartilage abnormalities, assessed with 3T MRI from the Osteoarthritis Initiative.

Materials and Methods—Right knee MRIs of 245, 45–60 year old individuals without radiographic OA were included. Cartilage was segmented and T_2 maps were generated in five compartments (patella, medial and lateral femoral condyle, medial and lateral tibia) at baseline and two-year follow-up. We examined the association of T_2 values and two-year change of T_2 values with various Whole-Organ MR Imaging Scores (WORMS). Statistical analysis was performed with ANOVA and Students t-tests.

Results—Higher baseline T_2 was associated with more severe cartilage defects at baseline and subsequent cartilage loss ($P<0.001$). However, longitudinal T_2 change was inversely associated with both baseline ($P=0.038$) and follow-up ($P=0.002$) severity of cartilage defects. Knees that developed new cartilage defects had smaller increases in T_2 than subjects without defects ($P=0.045$). Individuals with higher baseline T_2 showed smaller T_2 increases over time ($P<0.001$).

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Conclusion—An inverse correlation of longitudinal T_2 changes versus baseline T_2 values and morphological cartilage abnormalities suggests that once morphological cartilage defects occur, T_2 values may be limited for evaluating further cartilage degradation.

Keywords

Osteoarthritis; cartilage; WORMS; T_2 progression; MRI; longitudinal analysis

INTRODUCTION

Osteoarthritis (OA) is characterized by the progressive loss of hyaline articular cartilage (1). Conventional radiography and morphological MRI analysis are used to diagnose and monitor the disease. However, both detect degenerative disease at a stage when irreversible morphological cartilage loss has already occurred and may already be clinically apparent (2), (3). New molecular imaging techniques have therefore been developed as biomarkers to non-invasively detect early cartilage degeneration quantitatively prior to morphological changes (4). Among these, cartilage T_2 relaxation time measurements have been found to be promising as they are related to early biochemical changes in the cartilage matrix (5), (6) including deterioration of the collagen network and increased intra cartilage water content.

A correlation of higher T_2 relaxation time values with presence and severity of osteoarthritis has previously been described (7). Longitudinal data analysis has been performed either by assessing the absolute T_2 increase (8) or the percentage of T_2 increase (9). Previous studies suggested a non-linear correlation between disease severity and T_2 relaxation time (10). Natural longitudinal development of T_2 relaxation time in relation to baseline T_2 and morphological abnormalities has not yet been thoroughly studied in a larger cohort. Since the highest T_2 values were found in the superficial layer (9), the question is, what happens with T_2 values when this layer gets lost with further morphological cartilage degeneration.

The Osteoarthritis Initiative (OAI) is a longitudinal, prospective observational multi-center cohort study, focusing primarily on knee OA, initiated by the NIH to study the natural evolution of OA and identify potential prevention strategies. The study population consists of 4796 subjects between 45 and 79 years old (11). Sequences for T_2 relaxation time measurements are included in the OAI MR acquisition protocol, representing the largest population to date ever examined using this MR technique.

The purpose of our study was to determine, if the natural evolution of knee cartilage T_2 relaxation times over two years is different among knees with various extents of morphological cartilage abnormalities, assessed in 3 Tesla MRI images in a large sample of subjects from the OAI. We hypothesized that the longitudinal T_2 progression is dependent on the corresponding baseline T_2 values as well as the severity and progression of focal morphological cartilage degeneration.

MATERIALS AND METHODS

Subjects

A subset of 245 subjects (122 male, 123 female) of the 4976 participants in the Osteoarthritis Initiative (OAI) cohort was included in the present study. The study protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by the local institutional review boards. Data used in the preparation of this article were obtained from the Osteoarthritis Initiative (OAI) database, which is available for public access at http://www.oai.ucsf.edu/. Specific datasets used were dataset 0.2.2, 0.E.1. and 3.E.1.

In order to focus on mild degenerative changes in a middle-aged cohort, subjects were recruited from the OAI incidence and control cohorts. Subjects from the Incidence cohort did not have symptomatic OA but did have OA risk factors, which included (i) overweight, (ii) knee symptoms without radiographic OA, (iii) a history of knee surgery or injury without deformity of the knee, (iv) family history of total knee replacement, (v) Heberden's nodes or hand OA and (vi) physical activities with frequent knee bending. Of 300 randomly selected asymptomatic right knees (Western Ontario and McMaster University (WOMAC) pain score of 0 at the right knee at baseline)) with baseline Kellgren/Lawrence (KL) grades of 0 or 1 of subjects aged 45 to 60 at baseline, 55 were excluded due to incomplete MRI sequences at baseline or follow-up or poor image quality in either morphological MR sequences or T_2 relaxation time sequences. Finally, 245 subjects were analyzed in this study.

Imaging

Bilateral knee radiographs—Bilateral standing posterior anterior (PA) “fixed flexion” plain radiographs of the knee were obtained at a focus-to-film distance of 72 inches. Knee radiographs were obtained in a plexiglass positioning frame (SynaFlexerTM; CCBR-Synarc, San Francisco, California) with 20–30° flexion and 10° internal rotation of bilateral feet. Kellgren-Lawrence (KL) scores of the resulting plain radiographs were assessed in our institution (XXX, 22 years of experience).

Magnetic resonance (MR) imaging—MRI knee examinations were obtained with four identical 3T MRI systems using identical standard knee coils (Siemens, Erlangen, Germany). The following three sequences were used for morphological analysis of the right knee (11): (i) coronal 2D intermediate-weighted (IW) fast spin-echo (FSE) sequence (repetition time (TR)/echo time (TE) = 3850/29 ms, field of view (FOV) = 14 cm, slice thickness = 3 mm, in-plane spatial resolution = 0.365 × 0.456 mm^2, bandwidth = 352 Hz/pixel), (ii) sagittal 3D dual-echo steady-state (DESS) sequence with water excitation (WE) and coronal and axial reformations (TR/TE = 16.3/4.7 ms, FOV = 14 cm, slice thickness = 0.7 mm, in-plane spatial resolution = 0.365 × 0.456 mm^2, flip angle = 25^0, bandwidth = 185 Hz/pixel) and (iii) sagittal 2D IW fat-suppressed (fs) FSE sequence (TR/TE = 3200/30 ms, FOV = 16 cm, slice thickness = 3 mm, in-plane spatial resolution = 0.357 × 0.511 mm^2, bandwidth = 248 Hz/pixel).

For quantitative T_2 relaxation time measurements a sagittal 2D multislice multiecho (MSME) spin echo (SE) sequence (TR = 2700 ms, seven TEs = 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, 70 ms, FOV = 12 cm, slice thickness = 3 mm with 0.5mm gap, in-plane spatial resolution = 0.313 × 0.446 mm^2, bandwidth = 250 Hz/pixel) was used at the right knee.

MR Image analysis

Semi-quantitative morphological analyses—MRIs were evaluated by two radiologists separately (XX and XXX, 6 and 4 years of experience); if scores were not identical consensus readings by both radiologists and an additional experienced musculoskeletal radiologist were performed (XXX, 22 years of experience). MR images of the right knee were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ). The whole-organ magnetic resonance imaging score (WORMS) system was used to assess OA-related morphological abnormalities of the cartilage (11). The analysis protocol was modified concerning the anatomical compartments as previously described (8), (12), (13). Cartilage was evaluated and graded for each of five compartments separately: patella, medial and lateral tibia plateau, as well as medial and lateral femoral condyle. The trochlea was not included because relaxation time measurements were limited in this compartment due to pulsation artifacts from the popliteal artery. Briefly, WORMS grade 0 is defined as normal cartilage, grade 1 as increased signal in T2 weighted images or cartilage swelling, grade 2 as a partial thickness focal defect <1 cm, grade 2.5 as a full thickness focal defect <1 cm, grade 3 as multiple areas of grade 2 lesions or a partial thickness lesion ≤75 % width of the region, grade 4 as a grade 3 score with >75 % of the region involved in the lesion, grade 5 as multiple areas of grade 2.5 lesions or a full thickness lesion ≤75 % width of the region, and grade 6 as a grade 5 score with >75 % of the region involved in the lesion. The WORMS maximum cartilage score (WORMS max) was based on the most severe lesion within all regions analyzed in each knee (14). Since subject numbers in each WORMS category would have been relatively small and different in number, the classification was collapsed down to three categories: WORMS max grades 0 and 1 were defined as “No cartilage defect”. Grades 2 to 4 were defined as “mild-moderate cartilage defects”. This group included WORMS scores 2.5 and 4, since the mean T_2 increases in these individuals differed the less from individuals with WORMS scores 2 and 3. Grade 5 and 6 were defined as “severe cartilage defects”.

T_2 relaxation time measurements—The MSME spin echo sequences were transferred to a remote workstation (SPARC; Sun Microsystems, Mountain View, California). Images were analyzed by using software developed in house in an interactive display language (IDL; Research Systems, Boulder, Colorado) environment. Segmentation of artifact free cartilage areas of the patella, medial and lateral femoral condyle and medial and lateral tibia in every section was performed by one observer and supervised by two radiologists. Due to flow artifacts from the popliteal artery the trochlea was excluded from the analysis. Mean T_2 values of the baseline and two-year follow-up time point were calculated individually for each compartment and globally (average of all compartments) from the segmented regions of interest, skipping the first echo and using a noise-corrected exponential fitting as previously described (15). To calculate variations over time, the individual longitudinal

change over time was calculated as percentage increase (($T_{2\ follow\text{-}up}$ / $T_{2\ baseline}$)*100-100) and as the absolute difference (delta T_2; $T_{2\ Follow\text{-}up}$ - $T_{2\ baseline}$).

Reproducibility measurements

Reproducibility was calculated in a randomly selected sample of 10 OAI image data sets for each compartment. For WORMS measurements, each subregion of the images was graded twice by two radiologists on two separate occasions with a minimum time-span of two weeks in-between those two readings. For cartilage defects, linear weighted Cohens Kappa's values were calculated for inter- and intra-observer agreement to compare the exact WORMS score in each compartment by treating the data as an ordinal variable. Inter-observer kappa was 0.89 for cartilage defects. Intra-observer kappa was 0.91 and 0.95 for cartilage defects, respectively. Reproducibilities for T_2 measurements in our group were described previously with an inter-reader reproducibility error for mean T_2 of 1.57 %, respectively 0.53 ms (15) and a mean intra-reader reproducibility of 1.76 % respective 0.56 ms (16).

Statistical analysis

Statistical data analysis was performed with JMP software Version 7 (SAS Institute, Cary, NC, USA). Initially descriptive statistics were obtained. Demographic data was reported using means ±standard deviation (SD) and two-sided Student's t-test. Histograms of T_2 values were visually inspected and a normal distribution with a mean of 33.2 ±1.9 ms for global T_2 values was confirmed. For analysis of the correlation of T_2 values between the different knee compartments, a multiple regression model was used. To compare baseline T_2 measurements and change in T_2 measurements by categories of collapsed baseline WORMS cartilage lesion severity scores (No, mild-moderate, severe) and by categories of cartilage defect progression (No to mild-moderate; mild-moderate to severe), one-way analysis of variance (ANOVA; level of significance of $P<0.05$), including overall P-values and Student's t-tests comparing different categories, was used. Results are presented for global values. Pearson coefficients were used for the correlation between baseline T_2 and follow-up T_2 measurements. Two-tailed p-values using Fisher transformation were calculated.

RESULTS

Demographic data

Subjects characteristics are summarized in Table 1. Mean age of the subjects (N=245) was 51.6 ±4.0 years. The cohort included 122 male and 123 female subjects, with a mean body mass index (BMI) of 27.7 ±0.3 kg / m^2. There was no significant difference between male and female subjects regarding age (51.6 ±0.4 years versus 52.1 ±0.4 years; P=0.393) or BMI (28.2 ±0.4 kg / m^2 versus 27.2 ±0.4 kg / m^2; P= 0.091). Physical Activity Scale for the Elderly (PASE) was significantly different between male (mean PASE score: 209 ±78) and female subjects (188 ±78; P=0.029). PASE scores were not significantly different between the analyzed groups with “No” (194 ±80), “Mild-moderate” (200 ±81) and “Severe” cartilage defects (208 ±55; P>0.05). Individuals with increasing cartilage defects over time were less physically active (179 ±44) than individuals that remained in the same analysis group at follow-up (199 ±82), but this difference was not significant (P=0.397). Three

individuals had received steroid injections within 6 months prior to the MR examination at both time-points; one of them had received hyaluronic acid injections additionally. All three subjects were in the group with “Severe cartilage defects” at the follow-up time-point, one of them increased from “Mild-moderate” to “Severe” defects over time.

T_2 relaxation time measurements

T_2 measurements were significantly different between all individual compartments (multiple regression, for each predictor in the model: $P<0.001$; Table 2) except for patella compared to medial tibia ($P=0.722$). T_2 values were higher in both femoral condyles than in the other compartments (medial femoral condyle: 37.7 ±2.5 ms; lateral femoral condyle: 34.6 ±2.3 ms). T_2 values of the lateral tibia were the lowest (30.4 ±3.3 ms), while patella (31.7 ±2.5 ms) and medial tibia (31.7 ±3.0 ms) were slightly higher. The same rank ordering of mean T_2 values by compartment was found after 2 years.

T_2 relaxation time showed a significant increase over time during the two-year follow-up for global T_2 values from 33.2 ±1.9 ms at baseline to 34.5 ±1.9 ms at follow-up ($P<0.001$). The mean absolute difference was 1.3 ±1.4 ms (described as delta T_2) while the percentage increase amounted to 4.0 ±4.5 %. Medial and lateral tibial compartments showed the highest increase over time (Medial tibia: delta T_2 = 1.8 ±2.7 ms, percentage change = 6.2 ±8.9 %; Lateral tibia: delta T_2 = 1.9 ±2.1 ms, percentage change = 6.4 ±7.2 %).

Morphological cartilage abnormalities

At baseline, average maximum cartilage WORMS score (WORMS max) for the whole knee was 2.0 ±1.4, considering WORMS scores as continuous variables. The highest scores were found at the patella (mean WORMS 1.6 ±1.5) followed by the lateral tibia plateau (1.0 ±1.0). At baseline 82/245 (37.1 %) subjects had no cartilage defects (WORMS 0 and 1), of which 10/82 (12.2 %) increased over time to “Mild-moderate cartilage defects” (WORMS 2 – 4). In 141/245 (57.6 %) subjects “Mild-moderate cartilage defects” were found at baseline, of which 6/141 (4.3 %) increased to “Severe cartilage defects” over time. “Severe cartilage defects” (WORMS 5 and 6) at baseline were found in 22/245 (9.0 %) subjects.

Analysis according to WORMS gradings

Baseline analysis: Mean baseline T_2 of subjects with a WORMS max of 0, 1 or 3 were the lowest. Baseline T_2 values were higher in subjects with a WORMS max of 2, 2.5 and 4. In subjects with a WORMS max of 5 or 6, T_2 values were lower again. For individual compartments, a similar tendency for a certain ceiling effect was found; T_2 values increased with increasing WORMS scores in case of lower WORMS scores, but for high WORMS scores no further increase of T_2 values was observed. At the patella, T_2 values showed no further increase for WORMS scores 5 and 6; for other compartments T_2 values already showed no further increase at lower WORMS scores.

Longitudinal analysis: Delta T_2 showed a significant decrease in subjects with WORMS max scores of 5, compared to subjects with lower WORMS max scores. For the individual compartments, similar tendencies were found. At the patella, delta T_2 decreased at a

WORMS score of 4; for other compartments delta T_2 already decreased at lower WORMS scores.

T_2 baseline measurements in relation to morphological abnormalities

Subjects with more severe cartilage defects in any compartment of the knee presented higher baseline global T_2 values ($P<0.05$; Table 3). For subjects included in the WORMS scoring range "No cartilage defects" the mean global T_2 value was the lowest with 32.6 ±1.8 ms, for "Mild-moderate cartilage defects" it was 33.3 ±1.8 ms (versus "No cartilage defects", P=0.003) and for "Severe cartilage defects" it was 34.2 ±1.8 ms (versus "Mild-moderate defects", P=0.039; Figure 1). Individuals (n=10) with an increase from "No" to "Mild-moderate cartilage defects" had a baseline T_2 of 34.5 ±1.7 ms (versus "No cartilage defects" at both time-points, P=0.007) and individuals (n=6) with an increase from "Mild-moderate" to "Severe cartilage defects" had a baseline T_2 of 35.5 ±1.8 ms (versus "Mild-moderate defects" at both time-points; P=0.004; Table 3).

Additionally, subjects with any increases in WORMS max (n=38) over time were compared to subjects without increases (n=207). Baseline T_2 values were higher in subjects with an increase in WORMS (34.0 ±0.3 ms) than in subjects without change of WORMS max over time (33.1 ±0.1; P=0.003). Detailed analysis of each change is presented in Figure 2.

Longitudinal T_2 changes in relation to morphological abnormalities

More severe cartilage defects were associated with smaller increases of global T_2 values over time (Figure 3). Global delta T_2 was slightly higher in individuals with "No cartilage defects" (1.5 ±1.3 ms) than in those with "Mild-moderate cartilage defects" (1.3 ±1.5 ms; P=0.226) and significantly higher than in those with "Severe cartilage defects" (0.6 ±1.0 ms; P=0.012; overall test, P=0.038). A similar trend was found in the femoral and tibial compartments for delta T_2, with the exception that at the medial tibia no severe cartilage defects were detected, but the results were not significant ($P>0.05$). For femoral compartments there was actually a decrease in T_2 found for severe cartilage defects (Medial femoral condyle: −0.9 ±2.9 ms; overall test, P=0.231; Lateral femoral condyle: −1.2 ±1.7 ms; overall test, P=0.150).

Similar results were found for the two-year time point with lower delta T_2 values found in individuals with more severe degenerative changes. Global delta T_2 was higher in individuals with "No cartilage defects" (1.6 ±1.3 ms) than in those with "Mild-moderate cartilage defects" (1.2 ±1.6 ms; P=0.049) or "Severe cartilage defects" (0.5 ±1.1 ms; $P<0.001$).

Subjects with progression of cartilage defects (n=16) demonstrated also lower delta T_2 values compared to those that did not progress (P=0.037; Table 3). Additionally, subjects with any increases in WORMS max (n=38) over time were compared to subjects without increases (n=207) and tended to have a lower change in delta T_2 than the latter (0.9 ±0.3 ms versus 1.4 ±0.1 ms, P=0.085; Figure 2).

Longitudinal T_2 changes in relation to baseline T_2

Change of T_2 relaxation time presented an inverse correlation with the corresponding baseline T_2 relaxation time for global T_2 values, as well as for each individual compartment ($P<0.001$; Table 2). Subjects with higher T_2 values at baseline showed a lower T_2 increase over 2 years. The regression coefficient (R) was higher for the correlation of baseline T_2 values versus percentage increase than versus absolute delta T_2. R was highest for the medial tibia ($R=-0.59$; Mean of Response, 1.8; Root Mean Square Error, ±2.2) and lowest at the lateral tibia ($R=-0.37$; 1.8 ±2.0). Fisher transformation revealed a significant difference ($P=0.002$). At the femur, R was higher at the lateral femoral condyle ($R=-0.50$; 1.0 ±1.7) than at the medial femoral condyle ($R=-0.42$; 0.4 ±1.9), however not significantly ($P=0.263$). Fisher transformation further showed significant differences between the R-values of the medial tibia and medial femoral condyle ($P=0.011$), as well as medial tibia and patella ($P=0.024$). The difference between the lateral tibia and the lateral femoral condyle showed a statistical trend ($P=0.077$). As presented in Figure 4, bivariate linear fits of delta T_2 by baseline T_2 showed a negative correlation. High baseline T_2 values were associated with small delta T_2. The steepest slope of the curve, corresponding to the greatest decrease of delta T_2 in relation to baseline T_2, was found at the medial tibia. The shallowest slope, corresponding to the smallest decrease of delta T_2 was found at the medial femoral condyle.

DISCUSSION

Our study confirmed a longitudinal increase of T_2 relaxation time in a two-year follow-up, which was previously demonstrated (17); it also showed that high T_2 values were associated with severity of morphological cartilage defects and with an increase of morphological cartilage defects over time (Table 4). However, our study revealed that worsening of morphological cartilage degeneration does not necessarily imply greater T_2 progression over time. In fact, we identified a negative correlation of longitudinal T_2 changes (delta T_2) with the severity of morphological cartilage abnormalities (WORMS at baseline and follow-up) and also a negative correlation of longitudinal T_2 changes (delta T_2) with appearance of new cartilage defects over time (WORMS progression). This observation is supported by an inverse correlation of longitudinal T_2 progression with baseline T_2 values. Correlations varied between different compartments. Overall these findings indicate that subjects with more advanced cartilage degeneration at baseline, consistent with higher T_2 values, show a lower T_2 increase over 2 years, suggesting that T_2 measurements may be less suited for more advanced cartilage lesions due to a limited dynamic range of T_2 values.

Cartilage T_2 relaxation time measurements are able to detect early cartilage degeneration, by determining indirectly its biochemical cartilage composition, mainly the collagen integrity and water content (18). Since these intrasubstance abnormalities precede radiological OA, T_2 measurements have been used in studies focusing on subjects with early degenerative disease, such as those with knee radiographs classified as KL 0 or 1 (12), (14), (19). However, the natural development of T_2 values over time has not been sufficiently described in a larger cohort study yet, and longitudinal T_2 analysis remains challenging. There is increasing evidence that a linear relationship between T_2 values and severity of OA grade may not exist (10), (20), e.g. Koff et al could not identify a correlation of severity of

patellofemoral OA with T_2 values (20). While in that study, only radiological OA severity based on KL scores was analyzed, our study looked precisely at morphological cartilage defects detected by 3T MRI. Our study evaluated T_2 value progression over time in a longitudinal study, in addition to cross-sectional analyses.

There are several possible explanations for our findings that a smaller longitudinal T_2 increase in subjects is associated with higher baseline T_2 values. First, T_2 relaxation times may be subject to ceiling effects. Cartilage may reach a saturation point where a maximum T_2 relaxation time is reached before complete cartilage deterioration. This would indicate that the measure has a limited clinically-relevant dynamic range. Our results are in line with previous findings of cartilage T_2 values in pigs at different ages: Shinar et al reported increasing T_2 values up to the age of 18 month, followed by a steady state to decrease of T_2 values with further aging (21). For other scoring methods on radiological images, such as plain radiographs, a ceiling effect was also described (22). Second, the superficial cartilage layer is characterized by higher T_2 values than the deep layer (9) and once the superficial layer is lost during morphological cartilage degeneration (23), these high values are not included in the segmented region of interest anymore. Although the remaining cartilage T_2 relaxation time in the deep layer might also increase with further degeneration (higher T_2 for a WORMS score of 4 than for a score of 3), the mean value T_2 is likely to decrease with cartilage loss. This observation is illustrated in Figure 5, and explains, why subjects with a WORMS score of 3 show lower T_2 relaxation times than subjects with a WORMS score of 2 or 2.5. This theory is supported by our observation, that subjects with cartilage that remained free of morphological defects over time showed a significantly higher T_2 progression than subjects with a morphological cartilage loss (P=0.045). Third, a statistical artifact is involved in all T_2 progression analysis due to regression to the mean: Delta T_2 is identical with ($T_{2\ \text{follow-up}} - T_{2\ \text{baseline}}$). Therefore, the correlation of delta T_2 with $T_{2\ \text{baseline}}$ is equivalent to the correlation of ($T_{2\ \text{follow-up}} - T_{2\ \text{baseline}}$) with $T_{2\ \text{baseline}}$. The presence of the negative of the $T_{2\ \text{baseline}}$ in delta T_2 tends to make the correlation of T_2 with its progression smaller or even negative, as visualized in Figure 4.

The previously mentioned study of Koff et al analyzed the correlation of the severity of OA with T_2 values only at the patellofemoral compartment, whose cartilage composition is known to differ slightly from other compartments (20), (23). Different effects in this region have also been demonstrated in our study, i.e. at the patella, a decrease of delta T_2 was only detected for “severe cartilage defects”. This may be related to its particularly thick cartilage (24). Consequently, superficial cartilage loss in a small area, especially on the lateral facet (25), had not such an impact on the T_2 increase as in other compartments with less volume, less surface and fewer MR slices. This observation is supported by the fact that the thick cartilage at the lateral tibia (24) also showed a small difference of T_2 progression between “No” and “Mild-moderate cartilage defects”. Therefore a conclusion cannot be drawn from this compartment to others. Low numbers of subjects with cartilage defects in the individual compartments may be responsible for missing significance in the individual compartments. In subjects with extensive cartilage loss, cartilage segmentation was not possible and subjects were excluded from this study. However, differences can still be detected. Thicker cartilage at the tibia corresponds to a higher increase of T_2 values in the tibial compartments.

Thinner cartilage at the femoral condyles (24) may play an important role for the negative progression of their T_2 values for “severe cartilage defects”.

In previous studies, progression has been determined either by analyzing the increase in percentage or by analyzing the absolute T_2 increase (delta) (8), (9). Both depend on baseline T_2 values. Our study did not reveal substantial differences between both methods, however, in most cases P-values were even smaller for the negative association of the percentage increase of T_2 values with morphological cartilage defects than for delta T_2. This observation seems logical, since for example an increase of 1 ms in case of a baseline T_2 of 30 ms corresponds to a percentage increase of 3.3 %, while the same increase of 1 ms in case of a baseline T_2 of 40 ms corresponds to a percentage increase of 2.5 %, making the observed negative correlation even more profound. Interestingly, T_2 progression was also even stronger correlated with WORMS cartilage scores at the two-year time-point than with WORMS scores at baseline.

Important conclusions for future investigations and clinical applications with respect to detection and monitoring of early OA can be drawn: (i) in longitudinal studies of T_2 relaxation time, differences in T_2 baseline measurements between the analyzed groups need to be taken into account when evaluating and interpreting T_2 progression; (ii) stratifying cohorts by KL scores is not sufficient as correlations of these gradings with cartilage loss are limited (4,26); (iii) T_2 measurements should always be considered in the context of presence or absence of morphological cartilage defects. The authors recommend only prudent application of T_2 measurements for advanced OA; and finally (iv) whether percentage or absolute T_2 progression values are used for analysis in general does not impact results.

There are several limitations of our study. Firstly, despite the inclusion criteria of “no knee pain” and “no radiographic OA”, three subjects had received steroid injections. Since the injections were prior to the MRI at both time-points, no major influence on the results is expected. Secondly, only a small number of subjects without radiographic OA presented cartilage defects WORMS grade 5 or 6, which could still be segmented adequately. Thirdly, based on the results of the analysis of the individual WORMS scores, WORMS scores 5 and 6, were collapsed into one group and WORMS scores 0 and 1 were collapsed into one group, to increase the number of subjects in each group for statistical analysis. The rationale for collapsing these two groups was as follows: both group 0 and 1 do not show any morphological cartilage lesions; group 5 and 6 both show large full thickness cartilage lesions. These were compared to subjects with intermediate scores, who presented mild to moderate cartilage defects, but no extended denuded areas. Fourthly, the interrelationship with cartilage volume loss at the superficial layer is speculative and needs investigation in future studies. Fifthly, a relatively short follow-up interval of two years was evaluated. However, this observation period has been shown to be adequate to obtain significant changes of T_2 during OA progression analysis (27). Lastly, co-registering the data sets of the different time-points would be desirable. To date, no large cohort study using quantitative cartilage mapping co-registered the data sets. This should be subject of future investigations to further increase accuracy and explanatory power.

In conclusion, our study demonstrated that natural longitudinal evolution of cartilage T_2 relaxation time values in a two-year follow-up is dependent on the presence of morphological cartilage defects and is inversely correlated with baseline T_2 values, assessed on 3T MRIs. The findings of this study will have very important implications for cartilage T_2 progression analyses at the knee in longitudinal research studies and for potential clinical applications of T_2 relaxation times.

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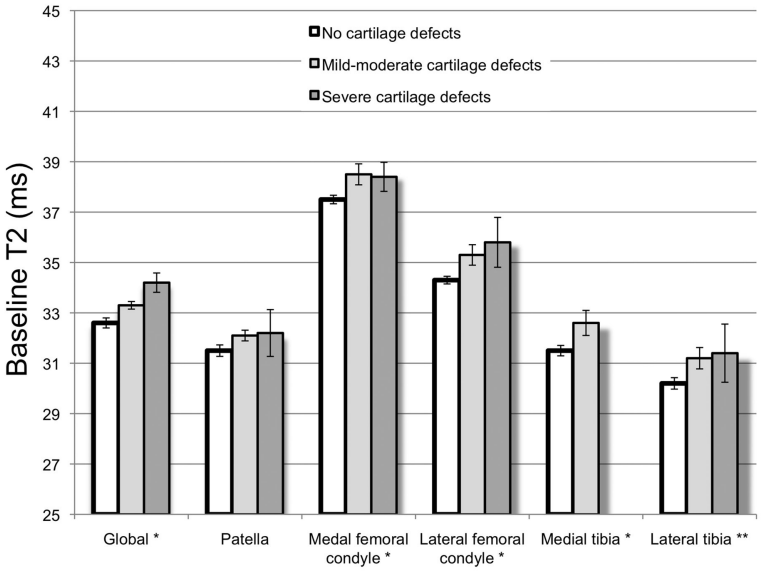

Figure 1.

Mean baseline T_2 relaxation times ± SEM of groups with different severity of cartilage defects. *P<0.05, **P<0.1.

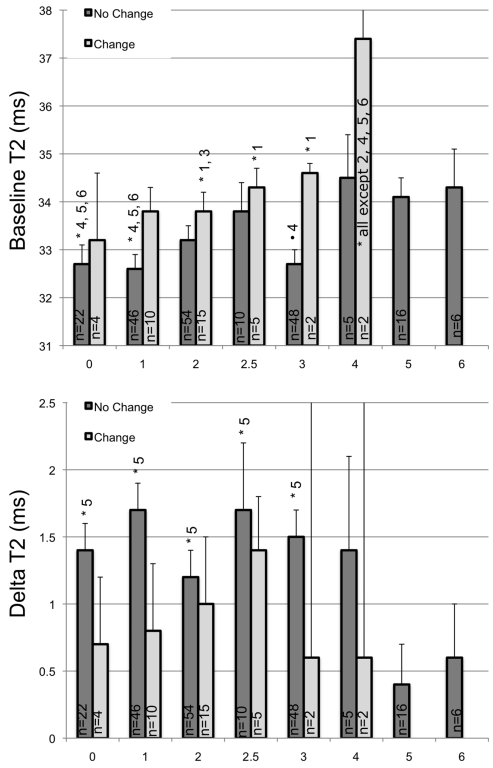

Figure 2.

Mean baseline T_2 relaxation times ± Standard error of the mean (SEM) and mean delta T_2 values ± SEM of groups with different WORMS max (Maximum WORMS cartilage score out of all knee compartments in each individual; 0 to 6). Subjects with the same WORMS max scores at baseline and follow-up are presented in dark grey; subjects that demonstrated longitudinal increase in WORMS scores are presented in light grey. (* indicates statistical significance compared to the indicated (above the error bars) WORMS max groups without increase, $P<0.05$).

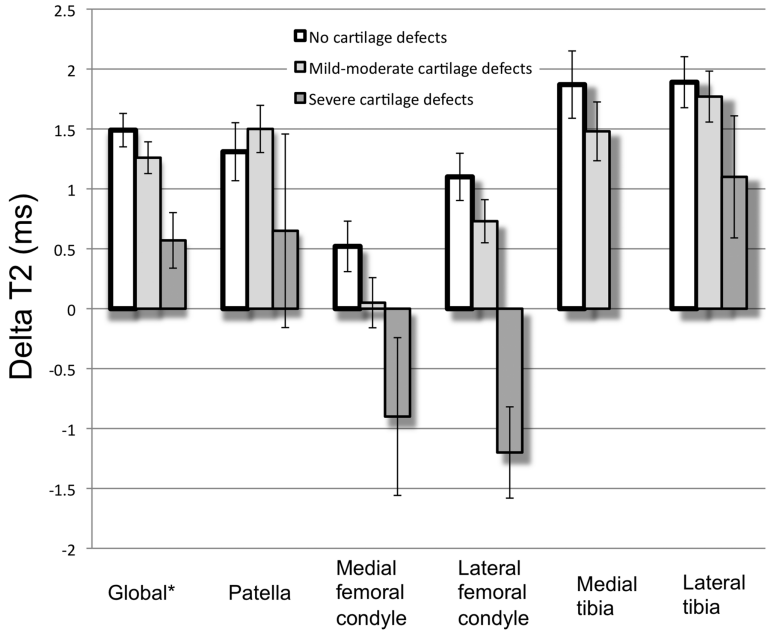

Figure 3.

T_2 value progression (delta T_2) ± SEM for different severity of cartilage defects at baseline. Global delta T_2 changes were significantly dependent on presence of “No” (n=82), “Mild-moderate” (n=141) or “Severe cartilage defects” (n=22; P=0.038*).

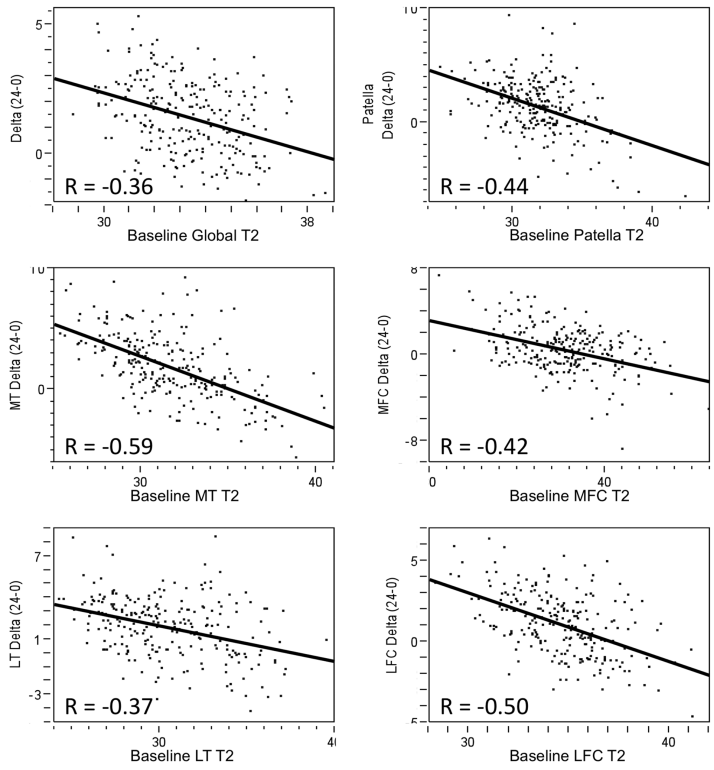

Figure 4.

Bivariate linear fit of delta T_2 by baseline T_2 relaxation time values (global and for each compartment). A significantly negative correlation was found for every compartment ($P<0.001$*). MT, medial tibia; LT, lateral tibia; MFC, medial femoral condyle; LFC, lateral femoral condyle.

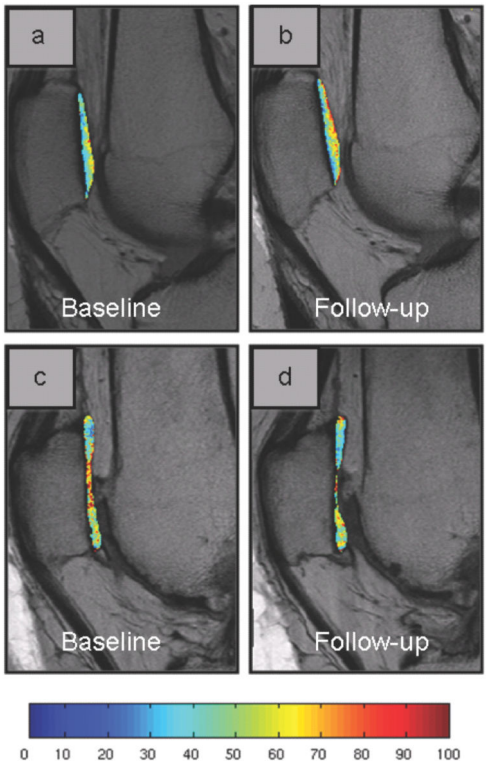

Figure 5.

T_2 color maps of the patellar cartilage overlaid on the first-echo images of the MSME sequence at baseline and follow-up. Blue color indicates low, red color high cartilage T_2 values. Subjects without cartilage defect at (a) baseline and (b) follow-up showed a higher T_2 progression (increase from 31.7 ms to 34.0 ms = 2.3 ms) than subjects with advanced cartilage defects at (c) baseline and (d) follow-up with progressing OA (increase from 37.8 ms to 38.0 ms = 0.2 ms). During follow-up (d) superficial cartilage with high T_2 values is lost leaving only the areas with lower T_2 values.

Table 1

Subject characteristics.

Parameter	Mean
Number of subjects	N=245
Gender	122 male : 123 female
Age	51.8 ± 4.0 years
Body mass index	27.7 ± 4.7 kg/m2
Mean T2 at baseline	33.2 ± 1.9 ms
Mean T2 change (absolute)	1.3 ± 1.4 ms
Mean T2 change (relative)	4 ± 4 %
Mean WORMS at baseline	2.0 ± 1.4

Table 2

T_2 relaxation time values at baseline and their correlation with T_2 progression (delta T_2 and T_2 increase in percentage, respectively).

	Baseline T_2 ±SD (ms)		T_2 change ±SD		Correlation Baseline T_2 vs T_2 change	
Compartment	**Baseline**	**Follow-up**	**Delta (ms)**	**Percentage (%)**	**R Delta (Lower 95% CI; Upper 95% CI)**	**R Percentage (Lower 95% CI; Upper 95% CI)**
Global joint	33.2 ±1.9	34.5 ±1.9	1.3 ±1.4	4.0 ±4.5	−0.36 * (−0.48; −0.25)	−0.41 * (−0.52; −0.29)
Patella	31.7 ±2.5	33.1 ±2.6	1.3 ±2.4	4.5 ±7.5	−0.44 * (−0.55; −0.32)	−0.46 * (−0.57; −0.37)
Medial femoral condyle	37.7 ±2.5	38.1 ±2.5	0.4 ±2.1	1.3 ±5.7	−0.42* (−0.54; −0.31)	−0.43 * (−0.55; −0.32)
Lateral femoral condyle	34.6 ±2.3	35.6 ±2.1	1.0 ±1.9	3.2 ±5.7	−0.50* (−0.61;-0.39)	−0.53 * (−0.64; −0.43)
Medial tibia	31.7 ±3.0	33.5 ±2.6	1.8 ±2.7	6.2 ±8.9	−0.59 * (−0.69; −0.49)	−0.62 * (−0.72; −0.52)
Lateral tibia	30.4 ±3.1	32.4 ±3.0	1.9 ±2.1	6.4 ±7.2	−0.37 * (−0.49; −0.28)	−0.45 * (−0.56; −0.33)

* P<0.001; CI, confidence interval.

Table 3

Mean T_2 values at baseline ± SEM and mean delta T_2 for subjects in the different WORMS scoring ranges.

Group		**Baseline cartilage defects according to WORMS**				
		None		***Mild-moderate***		***Severe***
Change from baseline to year 2[a]		**A. No**	***B. Yes***	**C. No**	***D. Yes***	**E. No**
n		72	*10*	135	*6*	22
WORMS scoring	Baseline	0 – 1	*0 – 1*	*2 – 4*	*2 – 4*	*5 – 6*
	Follow-up	0 – 1	*2 – 4*	*2 – 4*	*5 – 6*	*5 – 6*
Global T2 value	Baseline T2	32.6 ± 1.8 ms	*34.5 ± 1.7 ms*	33.3 ± 1.8 ms	*35.5 ± 1.8 ms*	34.2 ± 1.8 ms
	Delta T2	1.6 ± 1.3 ms	*0.5 ± 1.7 ms*	1.3 ± 1.6 ms	*0.6 ± 1.6 ms*	0.6 ± 1.0 ms
Statistics		A vs E	*A vs B*	A vs C	*C vs D*	C vs E
	P (Baseline T2)	<0.001*	*0.007* *	0.003*	*0.004* *	0.039*
	P (Delta T2)	0.004*	*0.045* *	0.081**	*0.287*	0.046*

Scoring ranges included subjects with “No” (A), “Mild-moderate” (C), “Severe” (E) cartilage defects at baseline and follow-up time-point. Further groups included subjects, which increased from “No” to “Mild-moderate” (B) and from “Mild-moderate” to “Severe” (D) over time (change from baseline to year 2; italic).

* P<0.05;

** P<0.1.

[a] Change of cartilage abnormalities to more severe defects over time (“cartilage Max WORMS values”).

Table 4

Summary of tendencies of interactions between different parameters.

Parameter	Trend of Parameter	Effect	
		Baseline T2	T2 Progression [a]
Baseline T2	High	-	Low
	Low	-	High
Baseline Morphological Defects (WORMS scores)	Severe	High	Low [b]
	Mild-moderate	Intermediate	Intermediate [b]
	None	Low	High [b]
Progression of Morphological Defects (Increase of WORMS scores)	No	Low	High
	Yes	High	Low

[a] Effects on T_2 progression were more pronounced for percentage increases than for delta T_2.

[b] Effects on T_2 progression were more pronounced for presence of morphological defects at follow-up than for presence of morphological defects at baseline.