Title

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Journal

Skeletal Radiology, 47(1)

ISSN

0364-2348

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Publication Date

2018

DOI

10.1007/s00256-017-2759-6

Peer reviewed

Skeletal Radiol
DOI 10.1007/s00256-017-2759-6

SCIENTIFIC ARTICLE

Conservatively treated knee injury is associated with knee cartilage matrix degeneration measured with MRI-based T2 relaxation times: data from the osteoarthritis initiative

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Received: 25 March 2017 / Revised: 29 June 2017 / Accepted: 9 August 2017

Abstract
Objective To investigate the association of cartilage degeneration with previous knee injuries not undergoing surgery, determined by morphologic and quantitative 3-T magnetic resonance imaging (MRI).
Materials and methods We performed a nested cross-sectional study of right knee MRIs from participants in the Osteoarthritis Initiative (OAI) aged 45–79 with baseline Kellgren-Lawrence score of 0–2. Cases were 142 right knees of patients with self-reported history of injury limiting the ability to walk for at least 2 days. Controls were 426 right knees without history of injury, frequency-matched to cases on age, BMI, gender, KL scores and race (1:3 ratio). Cases and controls were compared using covariate-adjusted linear regression analysis, with the outcomes of region-specific T2 mean, laminar analysis and heterogeneity measured by texture analysis to investigate early cartilage matrix abnormalities and the Whole-Organ Magnetic Resonance Imaging Score (WORMS) to investigate morphologic knee lesions.
Results Compared to control subjects, we found significantly higher mean T2 values in the injury [lateral tibia (28.10 ms vs. 29.11 ms, $p = 0.001$), medial tibia (29.70 ms vs. 30.40 ms, $p = 0.014$) and global knee cartilage (32.73 ms vs. 33.29 ms, $p = 0.005$)]. Injury subjects also had more heterogeneous cartilage as measured by GLCM texture contrast, variance and entropy ($p < 0.05$ in 14 out of 18 texture parameters). WORMS gradings were not significantly different between the two groups ($p > 0.05$).
Conclusion A history of knee injury not treated surgically is associated with higher and more heterogeneous T2 values, but not with morphologic knee abnormalities. Our findings suggest that significant, conservatively treated knee injuries are associated with permanent cartilage matrix abnormalities.

Keywords Cartilage imaging · Knee injury · Magnetic resonance imaging · Osteoarthritis · Cartilage · Conservative treatment of knee injury

Introduction

Osteoarthritis (OA) is a slowly progressive joint disease manifested by morphologic, biomechanical, biochemical and molecular changes and is the most prevalent type of arthritis, which is expected to affect 18% of the US population by 2020 [1]. The prevalence of OA in different joints and clinical manifestation varies by gender, ethnic groups and age [2] with a broad range of risk factors impacting the course of OA. The systemic risk factors age, female gender, family history, overweight as well as local risk factors such as increased biomechanical loading on part of the joint, physical activity and previous knee surgery have already been established in the incidence, progression and disease burden of knee OA [3–6].

Knee injuries are a local biomechanical insult that may damage joint structures and have been recognized to increase the risk for clinically significant symptomatic knee OA

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Published online: 29 August 2017

involving pain and impaired quality of life [7–9]. However, it is not well known how knee injuries that are conservatively treated in patients who have never undergone knee surgery affect the knee internal structures and the cartilage matrix. Insights into cartilage matrix breakdown associated with this type of knee injury could provide relevant information to patients in preventing knee OA by instituting lifestyle changes and adhering to injury-prevention regimens.

Magnetic resonance imaging (MRI) is a well-established technique to measure knee OA structural tissue changes [10] and also allows quantitative assessment of early cartilage matrix abnormalities. In previous studies, T2 relaxation time measurements [11–13], laminar and T2 gray-level co-occurrence matrix analysis (GLCM texture analysis) [14–16] have been shown to be sensitive biomarkers that can identify patients at risk for knee OA by characterizing collagen integrity and water content [12, 13].

The purpose of this cross-sectional nested study was to determine whether individuals with a history of right knee injury that was not treated surgically but with limited function for at least 2 days show differences in their biochemical cartilage composition and joint structure compared with control subjects without previous injury history. We used 3-T MRI-based T2 relaxation time measurements as well as laminar analysis and texture parameters of the knee cartilage to investigate biochemical cartilage composition and the Whole-Organ Magnetic Resonance Imaging Score (WORMS) to investigate the morphologic joint structure. Our hypothesis was that subjects with a history of knee injury are more likely to show differences in their biochemical cartilage composition and joint structure as compared to control subjects without a history of knee injury and are therefore at greater risk to develop OA.

Methods

Subjects

Subjects included in this study were participants in the Osteoarthritis Initiative (OAI), a longitudinal, prospective multicenter cohort study (http://www.oai.ucsf.edu/). The OAI was launched to improve prevention, diagnosis and treatment of OA by evaluating new biomarkers for assessment of onset and progression of knee OA. The 4796 participants enrolled in the study were aged between 45 and 79 years and were recruited at four clinical sites across the US. All subjects from our initial pool had symptomatic knee OA at baseline, a high risk of developing OA in the following years (with risk factors such as previous knee surgery, overweight or family history of total knee replacement) or no risk factors for OA and no clinical symptoms. The OAI study is HIPAA compliant and approved by the institutional review boards at each clinical site. All study participants signed informed consent forms prior to enrollment.

We performed a nested cross-sectional study of right knees with and without a history of injury at baseline. We included right knees with a Kellgren-Lawrence (KL) grade of 0–2 at baseline. We excluded subjects with rheumatoid arthritis or inflammatory arthritis and with self-reported diabetes, since we have previously found this to be associated with early degenerative cartilage alterations [17]. We also excluded those with a self-reported history of surgery in the right knee based on yes/no questions asking about arthroscopy, replacement surgery, ligament repair surgery, meniscectomy or any other kind of surgery of the right knee. Of the remaining 2934 right knees, cartilage T2 measurements and WORMS data were available in 759 right knees from previous and current studies by our group. Of these, we identified 142 case knees with a history of one or more right knee injuries that limited the ability to walk for at least 2 days. The selection of injured subjects was performed using the variable "P01INJR" from the Screening Visit workbook of the OAI. The variable is based on a self-reported history of having a right knee injury serious enough to limit the ability to walk for at least 2 days. This variable is well validated and has been used in both the Framingham OA study and the "Multicenter Osteoarthritis Study" (MOST). Two recent studies have used this variable in their study selection [18, 19]. From the remaining knees that did not have a history of injury, we randomly selected 426 knees (3 for each case), frequency-matched on age, BMI, gender, KL scores and race. A larger number of controls was included as increases in the control-to-case ratio have been shown to improve statistical power [20]. This resulted in a final total of 568 subjects. KL scores lower than 3 were chosen to assure that enough knee cartilage remained to assess MRI-based T2 relaxation time measurements. Fig. 1 shows a flowchart of patient selection.

Imaging

All participants in this study had bilateral standing posterior-anterior fixed flexion radiographs of the right knee taken at baseline. One musculoskeletal radiologist and two rheumatologists graded the radiographs using KL scores [21] with disagreements settled by adjudication [22, 23]. More information concerning the grading is available at http://www.oai.epi.org.

Using the OAI MRI Imaging Protocol in each patient, a right knee MRI was obtained at baseline [24]. All sequences were obtained at the four OAI clinical sites (Memorial Hospital of Rhode Island, Pawtucket, RI; University of Pittsburgh, Pittsburgh, PA; The Ohio State University, Columbus, OH; University of Maryland, School of Medicine, Baltimore, MD) using identical 3-T MRI scanners (Siemens Magnetom Trio; Siemens, Erlangen, Germany) and quadrature transmit-receive knee coils (USA Instruments,

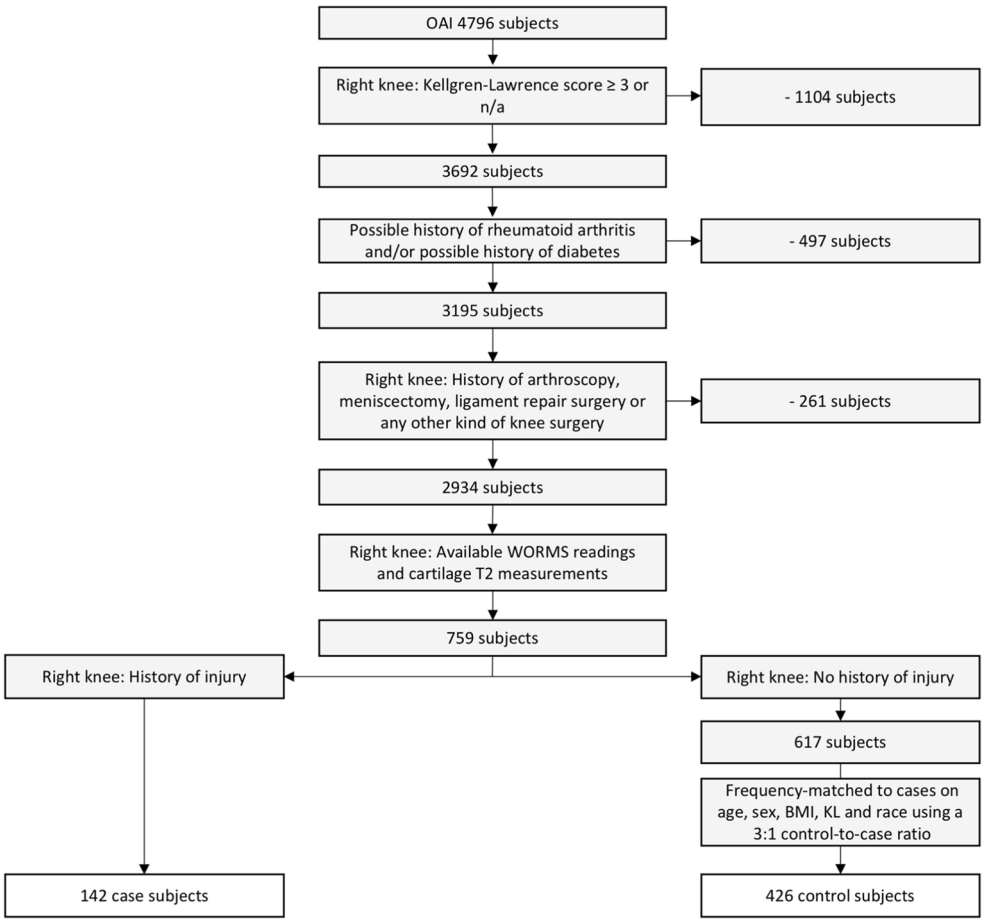

Fig. 1 Flowchart shows selected subjects from the OAI database

Aurora, OH). For the T2 measurements, the following sequence was used: a sagittal, 2D, multislice, multiecho (MSME) sequence [echo times (TE) = 10, 20, 30, 40, 50, 60 and 70 ms, spatial resolution = 0.313 × 0.446 × 3.0 mm and 0.5 mm gap, pulse repetition time (TR) = 2700 ms; field of view = 12 cm; bandwidth = 250 Hz/pixel]. For morphologic gradings, the following additional sequences were used: (1) coronal proton density-weighted fast spin-echo (FSE) (TE = 29 ms; TR = 3700 ms), (2) sagittal 3D dual-echo in steady state (DESS) with selective water excitation (TE = 4.7 ms; TR = 16.3 ms; flip angle = 25^0) and (3) sagittal intermediate-weighted FSE with fat suppression (FS) (TE = 30 ms; TR = 3200 ms). More information on the OAI MRI sequence parameters is available in Peterfy. et al. [24].

WORMS grading

Morphologic MR sequences were reviewed on a picture archiving communication system (PACS) workstation using the semiquantitative modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) grading system [25, 26]. The MR images were assessed for the location and severity of meniscal and cartilage lesions as well as bone marrow edema pattern (BMEP). Areas of elevated signal in the fatty bone marrow on fluid-sensitive, fat-suppressed FSE images with vague demarcation were considered BMEP lesions. They were graded in the subchondral zone of the lateral femur (LF), lateral tibia (LT), medial femur (MF), medial tibia (MT) and patella (PAT) with a scale ranging from 0 to 3 by lesion size (0 = none, 1 = smaller than 5 mm in diameter, 2 = 5–20 mm in diameter, 3 = larger than 20 mm in diameter).

Cartilage lesions were graded in the LF, LT, MF, MT and PAT using an 8-point scoring system, as detailed before [27]: 0 = normal, 1 = abnormal signal on fluid-sensitive sequences with and without swelling, 2 = focal defect smaller than 1 cm in width not reaching the subchondral bone, 2.5 = focal defect reaching the subchondral bone smaller than 1 cm in width, 3 = combination of normal thickness and multiple grade 2 lesions or grade 2 lesion wider than 1 cm but smaller than three quarters of the cartilage region, 4 = scattered cartilage loss of partial thickness covering ≥75% of the region, 5 = multiple areas of grade 2.5 lesions covering <75% of the region and 6 = diffuse full thickness cartilage loss in more than or at least three quarters of the region. Cartilage signal abnormalities are scored as WORMS grade 1 and are considered early degenerative changes, and a previous study by Schwaiger et al. [28] showed that signal abnormalities have a high probability to turn into focal cartilage defects.

For the evaluation of meniscal lesions, we defined the six separate regions that were reviewed: the anterior, body and posterior part of the medial and lateral meniscus, respectively. We used a score from 0 to 4 (0 = regular, 1 = abnormality within the substance, 2 = non-misplaced tear, 3 = displaced or complex tear and 4 = fully destructed/macerated meniscus).

A maximum BMEP (BMEP Max), cartilage (Cart Max) and meniscal (Men Max) value was computed for each knee for the respective greatest WORMS score in any compartment similar to previous studies [5, 29, 30]. A Max > 0 in any joint structure was interpreted as a lesion. Readers were blinded to the group status, risk profile and demographic characteristics of the corresponding patients.

MRI knee cartilage segmentation

For T2 cartilage segmentation, five cartilage compartments (LF, LT, MF, MT and PAT) were segmented by trained researchers under the supervision of a radiologist. Segmentations were performed creating regions of interest (ROIs) [31] that enclosed the entirety of the cartilage tissue of the compartment [27]. For this semiautomated, spline-based segmentation, the researchers used proprietary software designed as a MATLAB (The Mathworks Inc., Natick, MA) application [16, 32]. Segmentations were done on a slice-by-slice basis and spanned all slices that contained the cartilage tissue. Single slices were excluded if the quality of the image was poor because of artifacts in the MRI or if the image exhibited full thickness cartilage loss or severely damaged cartilage tissue or overlapping fluid, as described before [33] [34]. Segmentators were blinded to the group status, risk profile and demographic characteristics of the corresponding patients.

T2 relaxation time measurements

For all 568 subjects, T2 maps were computed on a pixel-by-pixel basis using three parameter fittings to account for noise. As it has been shown that sparing the first echo time (10 ms) maximizes the signal-to-noise ratio [35], T2 calculations were performed using the second (20 ms) to the last (70 ms) echo images (echo times = 20-70 ms) [35–37]. Averaging the mean T2 values of all five compartments provided a global T2 value for the entire joint. We did not use the trochlea compartment in our study because of pulsation artifacts originating from the popliteal artery, which limited segmentation and T2 measurement.

Laminar and GLCM texture analysis

To obtain more detailed information on the spatial distribution of T2 values within the respective knee cartilage compartment (LF, LT, MF, MT or PAT), we performed laminar and texture analysis, the latter with gray-level co-occurrence matrix (GLCM) algorithms [14, 15]. Laminar T2 analysis splits the cartilage into two layers of approximately the same width, a deep layer adjacent to the bone-cartilage interface (referred to as the bone layer) and a superficial layer along the articular surface (referred to as the articular layer) [38]. Furthermore, the spatial distribution of cartilage T2 relaxation times in the respective compartment was calculated by GLCM texture analysis. Occurrence of similarity in neighboring gray-level values in a specific compartment was calculated using the approach of Haralick et al. [15, 39]. GLCM parameters can be used as noninvasive imaging biomarkers for early cartilage matrix breakdown since they provide information on the extent of heterogeneity within the cartilage matrix going beyond information provided by regular T2 measurements. Three GLCM parameters were chosen in this study that have been used and validated in previous studies [14, 40]: (1) contrast, with elevated T2 contrast demonstrating higher differences in neighboring pixel values, (2) variance assessing the distribution of pixels about the mean and (3) 3ntropy measuring the disorder in an image with high entropy values signifying less uniform distribution of probabilities of T2 relaxation time co-occurrences. There is strong evidence that GLCM texture parameters, by measuring heterogeneity within the cartilage, provide additional information compared to regular T2 measurements in characterizing matrix collagen matrix breakdown [40, 41].

Reproducibility

Intra- and interreader reproducibility for the semiquantitative analyses of the WORMS score by our group has previously been described [26, 42]. For intraobserver agreement, the intraclass correlation coefficients were reported to be 0.86 (0.80–0.93) for cartilage WORMS and 0.87 (0.80–0.93) for meniscus WORMS [42]. For interobserver agreement, intraclass correlation coefficients were reported to be 0.79 (0.72–0.87) for cartilage WORMS and 0.84 (0.77–0.91) for meniscus WORMS [42]. Averaged over all compartments, mean inter- and intraobserver reproducibilities for T2 measurements in our group have been previously reported with a root mean square error of 1.57% for interobserver reproducibility [43] and of 1.17% for mean intrareader reproducibility [29].

Statistical analysis

The statistical analysis for this study was performed with both STATA version 13 (StataCorp, College Station, TX) and SPSS 23 (SPSS Inc., Chicago, IL, USA). A two-sided 0.05 level of significance was used. The differences in subject characteristics between injured and uninjured subjects were assessed using T-tests for continuous variables and chi-square tests

for categorical variables. Linear regression models were used to determine the differences in T2 parameters (mean, laminar and GLCM texture) and WORMS scores between injured and uninjured subjects in each cartilage region (LF, LT, MF, MT, PAT). Our main analyses were adjusted for the matching variables age, BMI, gender, KL scores and race as well as the potentially important covariate physical activity assessed with the Physical Activity in the Elderly Scale (PASE) to account for remaining imbalances. We decided to adjust and thereby control for matching variables in order to control for confounding by the residual covariate imbalances of the matching factors in our main analysis as previously described [44]. Furthermore, we performed sensitivity analysis adjusting for Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain, which we treated as an outcome variable in our main analyses. In our subanalysis comparing remote versus more recent injuries, we compared both patients with one injury less than or exactly 5 years ago versus patients with one injury more than 5 years ago and patients with one injury less than or exactly 20 years ago versus patients with one injury more than 20 years ago. We used these cutoff points to generate statistically meaningful analyses with sufficient power in the individual adjustments. A two-sided p-value smaller than 0.05 was considered statistically significant.

Results

Subject characteristics

Subject characteristics are shown in Table 1. The case and control groups were comparable in age (58.80 ± 9.26 years and 59.61 ± 9.50 years, respectively (p = 0.38)) and mean BMIs (mean ± SD) [29.40 ± 4.68 kg/m^2 and 28.75 ± 4.04 kg/m^2, respectively (p = 0.12)]. There were also no significant differences in gender, KL grade and race distributions between cases and controls ($p > 0.05$). However, WOMAC Pain, Stiffness, Disability and WOMAC Total Scores were significantly higher in the case subjects ($p < 0.001$). For the Physical Activity Scale for the Elderly (PASE), we approached but did not reach clinical significance ($p = 0.082$) with the case subjects demonstrating a higher level of activity.

T2 measurements

The 142 case subjects demonstrated higher T2 values (mean T2, bone layer, articular layer) in all compartments and globally compared to the 426 uninjured control subjects as shown in Table 2. Regarding mean T2 values, a significant difference was found for two compartments and globally (LT: $p = 0.001$; MT: $p = 0.014$; Global: $p = 0.005$). Figure 2 shows a lower T2 relaxation time in the LT in a control subject without previous injury compared to an injured case subject. Similar results were found separately for the bone (LT, MT, PAT and global values significantly higher in case subjects; $p < 0.05$) and articular layer (LF, LT and global values significantly higher in case subjects; $p < 0.05$).

Differences in GLCM texture measures were even greater as shown in Table 3; GLCM *contrast* and GLCM *variance* were significantly higher globally and in the LF, LT, MT and PAT ($p < 0.05$). GLCM entropy was significantly higher for LF, LT, MT and globally ($p < 0.05$). Figure 3 demonstrates lower GLCM contrast in the LF in a control subject without previous injury compared to an injured case subject.

Impact of multiple injuries on T2 measurements

While mean T2 values in subjects with two and more injuries (n = 37) were higher for LT, MF, MT and globally compared to subjects who reported only one injury (n = 105), differences were not significant ($P > 0.05$). GLCM texture parameters were also higher for LF, LT, MF, MT, Global (variance), LF, LT, MF, MT, PAT, Global (contrast), LF, LT, MF, MT, Global (entropy) compared to subjects who reported only one injury, but differences were not significant ($p > 0.05$). Comparison was performed both without adjustments and adjusting for age, BMI, gender, KL scores, race and PASE.

Impact of years since injury on T2 measurement

We also analyzed the association of years since injury and T2 measurements in case knees with only one previous injury (n = 105). In these patients with one previous injury, we did not find a statistically significant relationship between the years since injury and the T2 parameters (mean T2, superficial and deep layer T2, GLCM contrast, GLCM entropy and GLCM variance) for any compartment or globally.

Separating subjects into two groups with a previous trauma less than or exactly 20 years ago (n = 54) and more than 20 years ago (n = 51), we found higher T2 values for the LF, LT, MF, PAT and global joint in knees with injury more than 20 years ago compared to subjects with injury less than 20 years ago, but only the difference in mean T2 of the LF approached significance ($P = 0.069$) in our comparison without adjustments. Similarly, a number of texture measures were higher in the knees with injury than 20 years ago compared to subjects with injury less than or exactly 20 years ago, but differences were not significant ($p > 0.05$).

In a sensitivity analysis comparing two groups with a previous trauma less or exactly 5 years ago (n = 22) and more than 5 years ago (n = 83), we did not find significant differences in T2 parameters (mean T2, superficial and deep layer T2, GLCM contrast, GLCM entropy and GLCM variance) for

Table 1 Subject characteristics and differences by case (n = 142) and control (n = 426) status

	Controls (n = 426)	Injury cases (n = 142)	P-value injury vs. controls
Age (years)	59.61 ± 9.50	58.80 ± 9.26	0.376
Body mass index (kg/m^2)	28.75 ± 4.04	29.40 ± 4.68	0.115
Gender-male [n (%)]	168 (39.4%)	55 (38.7%)	0.882
PASE score	159.4 ± 85.6	173.9 ± 84.8	0.082
WOMAC Pain	2.29 ± 3.17	3.72 ± 3.57	**<0.001**
WOMAC Stiffness	1.37 ± 1.54	2.18 ± 1.77	**<0.001**
WOMAC Disability	6.81 ± 9.90	13.04 ± 12.71	**<0.001**
WOMAC total score	10.44 ± 13.78	18.90 ± 17.12	**<0.001**
Baseline KL grade			0.671
KL 0 [n (%)]	177 (40.8%)	54 (38.7%)	
KL 1 [n (%)]	69 (16.2%)	22 (15.5%)	
KL 2 [n (%)]	180 (43.0%)	66 (45.8%)	
Racial composition			0.775
Caucasian [n (%)]	337 (79.1%)	110 (76.8%)	
Other non-white [n (%)]	8 (1.9%)	4 (2.8%)	
African American [n (%)]	81 (19.0%)	28 (20.4%)	
OAI risk factors			**<0.001**
History of 1 knee injury [n (%)]	0 (0.0%)	105 (73.9%)	
History of 2 knee injuries [n (%)]	0 (0.0%)	24 (16.9%)	
History of 3 knee injuries [n (%)]	0 (0.0%)	13 (9.2%)	
Years since first injury			**<0.001**
0–5 years ago [n (%)]	–	24 (16.9%)	
6–10 years ago [n (%)]	–	17 (12.0%)	
11–20 years ago [n (%)]	–	23 (16.2%)	
21–30 years ago [n (%)]	–	24 (16.9%)	
31–40 years ago [n (%)]	–	28 (19.7%)	
More than 40 years ago [n (%)]	–	26 (18.3%)	

Subjects in the two groups are matched on age, BMI, gender, KL scores and race. Differences were assessed using independent t-tests or Pearson's chi-squared test as appropriate. Data are expressed as unadjusted means ± SD. Significant p-values ($p < 0.05$) are highlighted in bold

any compartment or globally. All comparisons were performed both without adjustments and adjusting for age, BMI, gender, KL scores, race and PASE.

WORMS grading

None of the WORMS subscores (BMEP, cartilage and meniscus lesions) showed significant differences between the injured and the uninjured groups ($P > 0.05$; Table 4) in the adjusted and unadjusted comparisons. The two groups showed a similar number and severity of morphologic cartilage, meniscus and subchondral bone marrow abnormalities. Moreover, we did not detect significant differences between the subgroups with multiple injuries compared to a single injury. WORMS scores of subjects with trauma more and less than 20 years ago and more and less than 5 years ago were comparable, and there was no significant difference for any parameter ($P > 0.05$).

Sensitivity analysis by KL grade

Finally, we evaluated if any observed cartilage abnormalities were associated with more severe radiologic evidence of OA, suggesting OA and not trauma as the source of abnormality. We separately compared injured versus non-injured subjects by KL score included in Tables 2, 3 and 4. We divided all study subjects into subjects with KL scores 0/1 (no OA) and subjects with a KL score of 2 (mild OA). Our analysis resulted in 246 case subjects versus 76 control subjects with KL0/1 and 180 case subjects versus 66 control subjects with KL 2. All significantly elevated T2 parameters from the main analysis were significant for the 76 injured versus 246 control subjects with KL0/1 as well except for MT entropy. Moreover, in this subanalysis we found significantly elevated mean T2 for the PAT ($p = 0.038$) and deep layer T2 for the MF ($p = 0.045$). Also, we found significantly higher grades of WORMS cartilage lesions in the LF ($p = 0.033$), WORMS

Table 2 Comparison of cartilage T2 values (95% confidence intervals) between case (n = 142) and control (n = 426) cohorts

Parameter	Non-injured (n = 426) Predicted mean values [95% CI] (ms)	Injured (n = 142)	Adjusted P-value	Non-injured KL 0 & 1 (n = 246) Predicted mean values [95% CI] (ms)	Injured KL0 & 1 (n = 76)	Adjusted P-value	Non-injured KL 2 (n = 180) Predicted mean values [95% CI] (ms)	Injured KL2 (n = 66)	Adjusted P-value
Cartilage T2									
Global knee T2	32.73 [32.54, 32.93]	33.29 [32.96, 33.63]	**0.005**	32.48 [32.23, 32.73]	33.25 [32.80, 33.70]	**0.004**	33.07 [32.77, 33.37]	33.40 [32.90, 33.90]	0.256
LF T2	35.57 [35.32, 35.81]	36.05 [35.62, 36.48]	0.058	35.16 [34.86, 35.46]	35.69 [35.14, 36.24]	0.098	36.09 [35.67, 36.50]	36.56 [35.86, 37.25]	0.257
LT T2	28.10 [27.82, 28.39]	29.11 [28.62, 29.61]	**0.001**	28.09 [27.72, 28.47]	29.48 [28.81, 30.14]	**<0.001**	28.11 [27.66, 28.56]	28.70 [27.95, 29.45]	0.188
MF T2	38.95 [38.69, 39.21]	39.07 [38.61, 39.53]	0.654	38.38 [38.04, 38.72]	38.98 [38.36, 39.60]	0.096	39.70 [39.30, 40.10]	39.27 [38.59, 39.94]	0.281
MT T2	29.70 [29.43, 29.98]	30.40 [29.92, 30.88]	**0.014**	29.45 [29.09, 29.80]	30.39 [29.76, 31.02]	**0.011**	30.04 [29.62, 30.46]	30.43 [29.70, 31.17]	0.365
PAT T2	31.57 [31.27, 31.86]	32.13 [31.61, 32.65]	0.065	31.50 [31.13, 31.86]	32.29 [31.64, 32.94]	**0.038**	31.68 [31.17, 32.18]	31.90 [31.03, 32.78]	0.661
Deep layer T2									
Global knee deep layer T2	30.24 [29.92, 30.56]	31.19 [30.64, 31.75]	**0.004**	29.85 [29.55, 30.16]	30.89 [30.34, 31.44]	**0.001**	30.74 [30.12, 31.37]	31.62 [30.59, 32.66]	0.153
LF deep layer T2	33.27 [32.90, 33.64]	33.93 [33.28, 34.57]	0.087	32.72 [32.37, 33.06]	33.10 [32.48, 33.73]	0.290	34.00 [33.26, 34.75]	35.00 [33.76, 36.25]	0.176
LT deep layer T2	24.87 [24.46, 25.28]	26.37 [25.65, 27.08]	**<0.001**	24.78 [24.29, 25.27]	26.62 [25.74, 27.50]	**<0.001**	24.98 [24.29, 25.68]	26.08 [24.90, 27.26]	0.118
MF deep layer T2	36.79 [36.39, 37.19]	37.47 [36.77, 38.16]	0.098	36.12 [35.73, 36.51]	36.93 [36.24, 37.63]	**0.045**	37.68 [36.91, 38.46]	38.23 [36.91, 39.55]	0.486
MT deep layer T2	27.52 [27.10, 27.94]	28.66 [27.91, 29.40]	**0.009**	27.32 [26.78, 27.85]	28.47 [27.53, 29.42]	**0.037**	27.78 [27.09, 28.47]	28.96 [27.75, 30.16]	0.098
PAT deep layer T2	29.02 [28.61, 29.43]	30.11 [29.38, 30.83]	**0.011**	28.57 [28.18, 28.96]	29.84 [29.15, 30.54]	**0.002**	29.70 [28.84, 30.55]	30.50 [29.05, 31.95]	0.349
Superficial layer T2									
Global knee superficial T2	35.69 [35.33, 36.05]	36.54 [35.91, 37.16]	**0.021**	35.69 [35.33, 36.05]	36.54 [35.91, 37.16]	**0.011**	36.20 [35.50, 36.90]	37.01 [35.84, 38.17]	0.248
LF superficial T2	38.06 [37.65, 38.48]	39.08 [38.35, 39.80]	**0.018**	37.55 [37.13, 37.96]	38.48 [37.73, 39.23]	**0.034**	38.73 [37.93, 39.53]	39.91 [38.57, 41.25]	0.141
LT superficial T2	31.77 [31.35, 32.19]	32.98 [32.25, 33.72]	**0.005**	31.66 [31.22, 32.11]	32.93 [32.13, 33.73]	**0.007**	31.91 [31.11, 32.70]	33.07 [31.73, 34.40]	0.144
MF superficial T2	41.41 [40.99, 41.84]	41.85 [41.10, 42.60]	0.326	40.65 [40.20, 41.09]	41.53 [40.73, 42.33]	0.060	42.42 [41.62, 43.23]	42.38 [41.00, 43.76]	0.959
MT superficial T2	32.79 [32.35, 33.23]	33.52 [32.74, 34.30]	0.109	32.33 [31.81, 32.85]	33.03 [32.10, 33.95]	0.201	33.38 [32.61, 34.15]	34.24 [32.90, 35.59]	0.275
PAT superficial T2	34.74 [34.22, 35.25]	35.57 [34.66, 36.47]	0.118	34.53 [34.02, 35.04]	35.45 [34.54, 36.36]	0.085	35.05 [34.01, 36.10]	35.74 [33.96, 37.52]	0.511

Differences were assessed using linear regression adjusting for age, BMI, gender, KL scores, race and PASE in the main analysis and adjusting for BMI, gender, race and PASE in the sensitivity analysis by KL score. Significant P-values ($p < 0.05$) are highlighted in bold

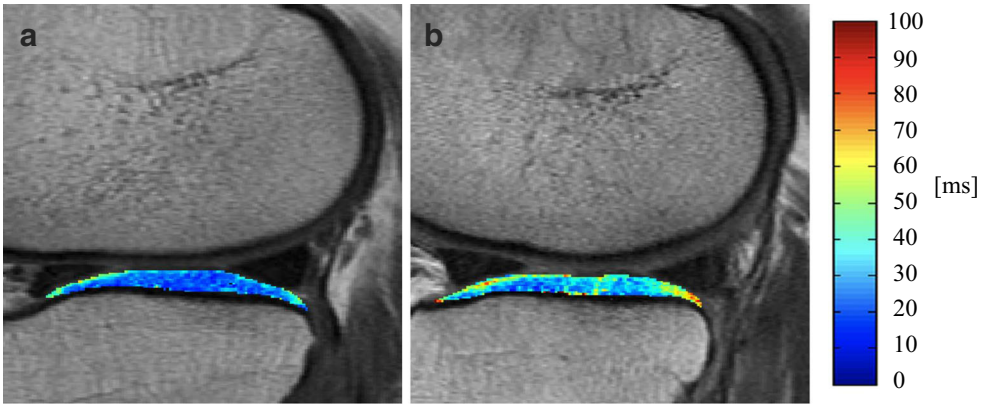

Fig. 2 Two representative sagittal T2 color maps of the lateral tibia cartilage of the right knee overlaid with the first-echo images of the MSME sequence. (A) A 61-year old female without injury (BMI 31.7, KL 1) from the control group and (B) 67-year old female with injury (BMI 31.5, KL 1) from the case group. Blue color demonstrates low, while red color demonstrates high cartilage T2 values. Lateral tibia cartilage of uninjured subject showed lower T2 relaxation time (22.18 ms) compared to the subject with injury (37.31 ms)

sum of lateral meniscus lesions ($p = 0.031$), WORMS maximal lateral meniscus lesions ($p = 0.024$), WORMS BME in the LF ($p = 0.050$) and WORMS BME in the LT ($p = 0.000$). When comparing the 66 injured subjects versus 180 control subjects with KL2, we did not find any significant differences for mean T2 measurements or laminar analysis. However, both mean T2 and laminar analysis still showed a slight but nonsignificant elevation for all parameters except MF mean T2 and MF superficial T2 in the injured subjects. However, in this subanalysis we found significantly elevated GLCM texture parameters in the injury group for LF contrast ($p = 0.028$), LT contrast ($p = 0.023$), LT entropy ($p = 0.037$), MT entropy ($p = 0.016$), LF variance ($p = 0.024$) and LT variance ($p = 0.010$). In this subanalysis, the injured subjects also showed significantly elevated WORMS cartilage lesions in the MT ($p = 0.048$).

Discussion

This study demonstrated a mild, but significant elevation of cartilage T2 mean and texture parameters (mean T2, superficial and deep layer T2, GLCM contrast, GLCM entropy and GLCM variance) in subjects with previous knee injury compared to uninjured controls. However, the prevalence of morphologic lesions such as cartilage lesions, meniscal abnormalities and BMEP assessed with WORMS was not associated with previous knee injury in this study population.

Cartilage 3-T MRI-based T2 relaxation time mapping detects increases in water content and disruption of the organization of the anisotropic arrangement of collagen fibrils in the extracellular cartilage matrix [45, 46]. Our findings suggest impairment of the cartilage matrix in subjects who have formerly experienced a knee injury that was not treated surgically; interestingly, at the same time there were no differences in morphologic cartilage abnormalities between injured and uninjured subjects with an overall mild degree of degeneration in both groups. The altered spatial distribution of T2 values found with the GLCM texture analysis is consistent with these findings and also suggests early cartilage matrix breakdown before irreversible cartilage loss occurs in these trauma subjects [40, 47, 48]. Especially local variance has been previously shown to serve as a sensitive biomarker for detection of early extracellular matrix changes in patients at risk for OA underlining that texture analysis is a promising tool to investigate early changes of the biochemical cartilage composition [49].

The relationship between surgically treated acute joint trauma and development of post-traumatic OA has been extensively studied [50]. Meniscal subluxation, meniscal tears, ACL tears and residual joint instability have been identified to elevate the risk for future OA [51–54]. T2 mapping has been used for postoperative evaluation of cartilage degeneration [49], and it has been proven to be a powerful tool to evaluate early changes of the cartilage matrix for example after acute ACL injury and reconstruction [55]. In our study, however, we focused on injuries that were not acute and did not require surgery (or at least the subjects did not undergo surgery of any kind) even though the injury limited function for 2 or more days. While T2 values were higher in the injury cohort, interestingly subjects did not show differences in WORMS scores, which would have reflected more severe focal morphologic damage. Accordingly, our findings suggest that the mild differences in the cartilage T2 matrix place an individual at increased risk for future cartilage damage. This hypothesis is supported by a previous study that showed that higher T2 values predict development of radiographic OA over 4 years [12]. This study indicates that it may take several years for these abnormalities to manifest themselves

Table 3 Comparison of mean gray level co-occurrence matrix (GLCM) parameters (95% confidence intervals) between case (n = 142) and control (n = 426) cohorts

Parameter	Non-injured (n = 426) Predicted mean values [95% CI]	Injured (n = 142)	Adjusted P-value	Non-injured KL 0 & 1 (n = 246) Predicted mean values [95% CI]	Injured KL 0 & 1 (n = 76)	Adjusted P-value	Non-injured KL 2 (n = 180) Predicted mean values [95% CI]	Injured KL2 (n = 66)	Adjusted P-value
Contrast									
Global knee contrast	276.16 [269.89, 282.43]	298.84 [287.97, 309.72]	**<0.001**	262.62 [255.10, 270.13]	288.87 [275.34, 302.40]	**0.001**	293.62 [282.87, 304.37]	312.97 [295.12, 330.81]	0.070
LF contrast	258.04 [252.97, 263.12]	275.47 [266.64, 284.31]	**<0.001**	245.27 [239.30, 251.25]	261.72 [250.95, 272.48]	**0.009**	274.77 [265.93, 283.61]	294.13 [279.37, 308.88]	**0.028**
LT contrast	174.44 [168.09, 180.80]	201.13 [190.04, 212.22]	**<0.001**	170.79 [162.58, 179.01]	201.34 [186.55, 216.12]	**0.000**	179.04 [168.93, 189.16]	202.06 [185.05, 219.07]	**0.023**
MF contrast	410.34 [400.14, 420.55]	426.49 [408.60, 444.39]	0.125	389.72 [376.65, 402.80]	415.60 [392.16, 439.04]	0.059	437.46 [421.08, 453.84]	443.71 [415.76, 471.67]	0.706
MT contrast	295.51 [284.78, 306.23]	322.95 [304.06, 341.85]	**0.014**	282.51 [268.66, 296.36]	316.67 [292.12, 341.23]	**0.018**	312.92 [295.78, 330.06]	331.94 [301.92, 361.96]	0.282
PAT contrast	243.30 [232.21, 254.39]	275.61 [256.16, 295.07]	**0.005**	227.78 [218.37, 237.20]	251.36 [234.49, 268.23]	**0.017**	266.12 [242.14, 290.10]	311.28 [270.45, 352.11]	0.062
Entropy									
Global knee entropy	6.08 [6.06, 6.11]	6.14 [6.11, 6.18]	**0.007**	6.07 [6.04, 6.10]	6.13 [6.08, 6.18]	**0.029**	6.10 [6.07, 6.14]	6.16 [6.10, 6.22]	0.095
LF entropy	6.58 [6.56, 6.60]	6.64 [6.60, 6.67]	**0.013**	6.55 [6.52, 6.57]	6.61 [6.56, 6.66]	**0.032**	6.62 [6.59, 6.66]	6.67 [6.61, 6.72]	0.196
LT entropy	5.56 [5.53, 5.60]	5.68 [5.61, 5.74]	**0.003**	5.56 [5.53, 5.60]	5.68 [5.61, 5.74]	**0.037**	5.57 [5.51, 5.63]	5.69 [5.59, 5.79]	**0.037**
MF entropy	6.78 [6.75, 6.80]	6.80 [6.76, 6.84]	0.325	6.74 [6.71, 6.77]	6.78 [6.73, 6.83]	0.195	6.82 [6.78, 6.86]	6.83 [6.76, 6.90]	0.810
MT entropy	5.69 [5.66, 5.72]	5.77 [5.71, 5.82]	**0.020**	5.66 [5.62, 5.71]	5.71 [5.63, 5.78]	0.336	5.73 [5.68, 5.78]	5.85 [5.77, 5.94]	**0.016**
PAT entropy	5.84 [5.80, 5.88]	5.83 [5.77, 5.90]	0.822	5.88 [5.83, 5.92]	5.94 [5.86, 6.02]	0.154	5.80 [5.72, 5.87]	5.68 [5.56, 5.81]	0.114
Variance									
Global knee variance	199.58 [195.37, 203.80]	215.71 [208.39, 223.03]	**<0.001**	190.14 [185.06, 195.23]	209.15 [200.00, 218.30]	**<0.001**	211.69 [204.52, 218.85]	225.28 [213.39, 237.18]	0.056
LF variance	191.10 [187.47, 194.72]	203.99 [197.68, 210.30]	**<0.001**	181.07 [176.69, 185.46]	193.80 [185.90, 201.70]	**0.006**	204.19 [198.03, 210.35]	218.05 [207.78, 228.33]	**0.024**
LT variance	140.84 [136.19, 145.48]	162.43 [154.32, 170.54]	**<0.001**	138.48 [132.13, 144.83]	164.19 [152.77, 175.61]	**<0.001**	143.74 [136.94, 150.54]	161.28 [149.84, 172.71]	**0.010**
MF variance	283.41 [277.13, 289.69]	291.05 [280.04, 302.06]	0.239	268.19 [260.13, 276.24]	283.39 [268.95, 297.83]	0.072	303.39 [293.37, 313.41]	303.43 [286.32, 320.53]	0.997
MT variance	200.57 [193.77, 207.37]	219.60 [207.61, 231.58]	**0.007**	191.74 [182.85, 200.63]	215.61 [199.84, 231.38]	**0.010**	212.35 [201.68, 223.02]	225.53 [206.85, 244.21]	0.231
PAT variance	183.97 [175.76, 192.18]	207.07 [192.67, 221.47]	**0.006**	174.25 [167.42, 181.08]	191.59 [179.36, 203.82]	**0.016**	198.29 [180.43, 216.16]	229.72 [199.30, 260.13]	0.081

Differences were assessed using linear regression models adjusting for age, BMI, gender, KL scores, race and PASE in the main analysis and adjusting for BMI, gender, race and PASE in the sensitivity analysis by KL score. Significant P-values ($p < 0.05$) are highlighted in bold

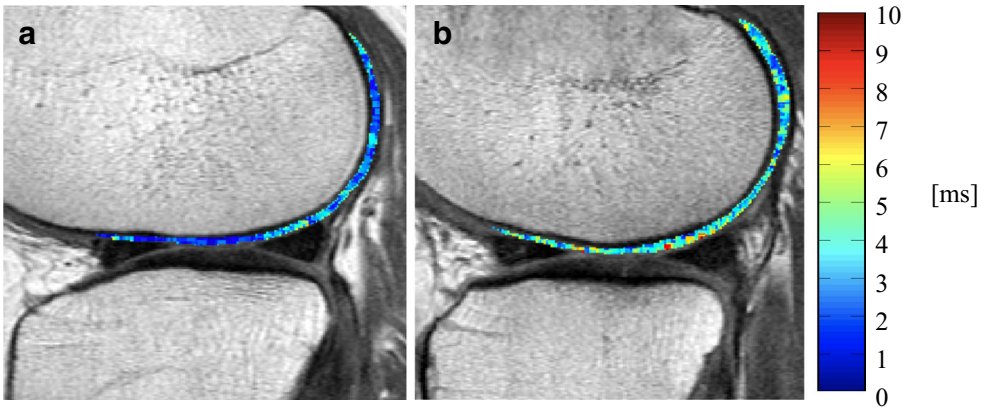

Fig. 3 Two representative sagittal T2 texture color maps of the lateral femur cartilage of the right knee overlaid with the first-echo images of the MSME sequence. (A) A 61-year old female without injury (BMI 31.7, KL 1) from the control group and (B) a 67-year old female with injury (BMI 31.5, KL 1) from the case group. Blue color demonstrates low, while red color demonstrates high differences in neighboring pixel values to visualize GLCM contrast texture measures. The calculated GLCM contrast of the lateral femur cartilage of the uninjured subject was lower (182.37) compared to the subject with injury (388.49)

morphologically. The mild elevations of T2 values we found may take a longer time or need potentially to be combined with other risk factors.

In addition to this, all of our superficial layer T2 times were higher than the corresponding deep layer T2 values, and in that sense our results are in line with existent literature on layer-specific cartilage T2 relaxation times in knees [56]. However, while the lateral femur demonstrated statistically more pronounced differences in the superficial layer, for the other compartments and globally we found statistically more distinct differences for the deep layer. The deep cartilage layer or tidemark (calcified) zone has previously been found to play a significant role in cartilage degeneration, especially in the evolution of cartilage delamination; therefore, we hypothesize that the deep layer may have been potentially more injured through trauma [51].

Interestingly, one study found that acute anterior cruciate ligament (ACL) disruption resulting in a chondral injury that is detectable at the time of injury using MRI may be associated with cartilage degradation in compartments unaffected by the initial trauma at follow-up MR-based assessment [57]. Considering that our results suggest altered T2 measurements for all compartments, our study supports these findings of global, post-traumatic degradation. It is important to note, however, that our study was not limited to ACL tears and may indicate that several kinds of knee trauma not requiring knee surgery trigger a whole joint response. These global, post-traumatic cartilage matrix abnormalities may be explained through damage of the cartilage homeostasis, which is associated with a stress response of chondrocytes and the subsequent release of cartilage matrix degeneration products [58]. In addition to this, recent data indicate an increased level of inflammatory mediators resulting from joint injury for a long-lasting period after trauma [59]. Inflammation affects both the quality and quantity of the extracellular matrix in cartilage, and inflammatory factors lead to an elevation of matrix-degrading proteins [60]. Cellular stress response and inflammation might both explain our findings of an abnormal cartilage matrix.

Another important finding of our study was that persons with a previous injury also had significantly more knee pain. While the injured subjects in this study reported significantly higher pain, the results for neither T2 measurements nor WORMS scores substantially changed when we adjusted for pain. On the other hand, a previous study showed that higher T2 values were associated with pain in subjects with risk factors for OA [26]. One may hypothesize that cartilage matrix changes related to injury and associated with higher T2 values may make the joint more susceptible to pain sensations. This could have a potentially protective effect on the knee joint and may explain why the subjects with previous injury have no increased morphologic damage compared to subjects without knee injury. Furthermore, the increased pain and an inflammatory reaction could make pharmacologic, analgesic treatment necessary. For this kind of injury without any abnormalities that require surgery, a broad range of treatments used in clinical practice is available [59]. Our results provide more insights into the potential need for anti-inflammatory pharmacologic treatment to avoid harmful side effects of the injury on the biochemical composition of cartilage as well as the consideration of therapeutic options that slow down or reverse matrix degeneration.

Finally, our study showed more pronounced differences in T2 measurements when comparing subjects in the two groups without OA (KL0/1). This may in part be due to the smaller number of KL grade 2 subjects. However, when focusing on KL2 we have to take confounding variables into account, which may have led to mild OA in these subjects. We hypothesize that in a cohort of KL2 subjects, confounders may act more strongly than an injury that did not require a surgical

Table 4 Comparison of WORMS grading for meniscal and cartilage lesions and bone marrow edema pattern (95% confidence intervals) between case (n = 142) and control (N = 426) cohorts

WORMS scores	Non-injured (n = 426) predicted mean [95% CI]	Injured (n = 142)	Adjusted P-value	Non-injured KL 0 & 1 (n = 246) predicted mean [95% CI]	Injured KL 0 & 1 (n = 76)	Adjusted P-value	Non-injured KL 2 (n = 180) predicted mean [95% CI]	Injured KL2 (n = 66)	Adjusted P-value
Cartilage lesions									
Sum Score	4.23 [3.92, 4.53]	4.12 [3.58, 4.65]	0.732	2.96 [2.61, 3.31]	2.92 [2.29, 3.55]	0.913	5.87 [5.32, 6.43]	5.71 [4.79, 6.63]	0.768
Max Score	2.58 [2.43, 2.74]	2.43 [2.16, 2.70]	0.330	1.94 [1.75, 2.13]	1.86 [1.52, 2.21]	0.717	3.42 [3.16, 3.68]	3.18 [2.75, 3.61]	0.357
LF	0.37 [0.28, 0.45]	0.45 [0.30, 0.60]	0.333	0.19 [0.09, 0.28]	0.40 [0.23, 0.58]	**0.033**	0.60 [0.45, 0.76]	0.54 [0.29, 0.80]	0.700
LT	0.65 [0.54, 0.76]	0.75 [0.56, 0.93]	0.393	0.49 [0.37, 0.61]	0.70 [0.48, 0.93]	0.101	0.86 [0.67, 1.05]	0.83 [0.51, 1.15]	0.881
MF	0.76 [0.65, 0.87]	0.64 [0.45, 0.83]	0.296	0.51 [0.38, 0.63]	0.37 [0.15, 0.60]	0.305	1.09 [0.89, 1.29]	0.99 [0.66, 1.32]	0.602
MT	0.23 [0.15, 0.30]	0.35 [0.22, 0.48]	0.122	0.15 [0.07, 0.23]	0.12 [−0.02, 0.26]	0.776	0.33 [0.19, 0.48]	0.62 [0.38, 0.87]	**0.048**
PAT	2.22 [2.05, 2.38]	1.93 [1.64, 2.21]	0.085	1.63 [1.44, 1.82]	1.32 [0.97, 1.66]	0.120	2.98 [2.69, 3.27]	2.72 [2.24, 3.20]	0.362
Meniscus lesions									
Sum Bilateral	1.62 [1.39, 1.85]	1.77 [1.37, 2.17]	0.536	1.26 [0.97, 1.54]	1.80 [1.28, 2.31]	0.072	0.91 [0.81, 1.01]	0.92 [0.75, 1.09]	0.926
Sum medial	0.88 [0.74, 1.02]	0.93 [0.68, 1.17]	0.750	0.69 [0.53, 0.86]	0.78 [0.48, 1.07]	0.635	1.12 [0.87, 1.37]	1.14 [0.73, 1.55]	0.937
Sum lateral	0.74 [0.58, 0.91]	0.84 [0.56, 1.13]	0.553	0.56 [0.36, 0.77]	1.02 [0.66, 1.38]	**0.031**	0.97 [0.69, 1.24]	0.68 [0.22, 1.14]	0.288
Max bilateral	0.91 [0.81, 1.01]	0.92 [0.75, 1.09]	0.926	0.73 [0.61, 0.85]	0.87 [0.66, 1.09]	0.275	1.14 [0.97, 1.30]	1.01 [0.75, 1.29]	0.461
Max medial	0.63 [0.55, 0.72]	0.66 [0.52, 0.81]	0.720	0.52 [0.42, 0.62]	0.52 [0.34, 0.70]	0.948	0.78 [0.64, 0.93]	0.85 [0.61, 1.09]	0.640
Max lateral	0.45 [0.37, 0.54]	0.49 [0.35, 0.64]	0.629	0.36 [0.25, 0.46]	0.60 [0.42, 0.79]	**0.024**	0.57 [0.43, 0.71]	0.39 [0.16, 0.62]	0.180
Bone marrow edema pattern									
Sum score	1.29 [1.14, 1.44]	1.26 [1.00, 1.52]	0.848	0.88 [0.72, 1.05]	0.93 [0.64, 1.22]	0.791	1.83 [1.55, 2.11]	1.72 [1.25, 2.18]	0.692
Max score	0.97 [0.88, 1.06]	0.84 [0.68, 0.99]	0.135	0.97 [0.88, 1.06]	0.84 [0.68, 0.99]	0.135	0.97 [0.88, 1.06]	0.84 [0.68, 0.99]	0.135
LF	0.08 [0.05, 0.12]	0.10 [0.03, 0.16]	0.734	0.04 [0.00, 0.08]	0.12 [0.05, 0.19]	**0.050**	0.15 [0.08, 0.21]	0.07 [−0.04, 0.18]	0.296
LT	0.14 [0.09, 0.18]	0.22 [0.14, 0.30]	0.083	0.06 [0.01, 0.10]	0.24 [0.15, 0.32]	**0.000**	0.24 [0.14, 0.33]	0.22 [0.06, 0.37]	0.858
MF	0.19 [0.14, 0.25]	0.15 [0.06, 0.23]	0.357	0.12 [0.07, 0.18]	0.08 [−0.02, 0.18]	0.463	0.29 [0.19, 0.38]	0.24 [0.07, 0.40]	0.600
MT	0.11 [0.07, 0.16]	0.17 [0.10, 0.25]	0.198	0.04 [0.00, 0.07]	0.07 [0.00, 0.14]	0.388	0.22 [0.13, 0.31]	0.30 [0.15, 0.45]	0.337
PAT	0.77 [0.68, 0.85]	0.63 [0.48, 0.78]	0.115	0.63 [0.53, 0.74]	0.42 [0.23, 0.61]	0.060	0.94 [0.80, 1.08]	0.88 [0.65, 1.12]	0.678
WORMS overall	8.96 [8.33, 9.58]	9.13 [8.04, 10.21]	0.794	6.14 [5.40, 6.88]	6.97 [5.65, 8.30]	0.283	12.63 [11.53, 13.73]	12.04 [10.22, 13.87]	0.590

Differences were assessed using linear regression models adjusting for age, BMI, gender, KL scores, race and PASE in the main analysis and adjusting for BMI, gender, race and PASE in the sensitivity analysis by KL score. None of the P-values was significant in the main analysis ($p > 0.05$). Significant P-Values in the sensitivity analysis by KL score are highlighted in bold

intervention. Furthermore, injuries that could have contributed to an observable difference in KL grade might already have progressed to KL3 and 4. This might explain that we did not find significant morphologic damage in our case cohort.

The prevalence of knee abnormalities has previously been shown to be associated with the level of physical activity measured using the PASE [5]. Our injured subjects demonstrated higher PASE scores with the differences between the two groups approaching statistical significance. However, our main analysis adjusting for the matching variables and PASE on the one hand and our analysis without adjustments on the other hand did not substantially differ, and we therefore do not believe that physical activity may have been a significant driver of our results.

Nevertheless, this study has several limitations. First, our definition of knee trauma may include a broad range of different injuries since the only criterion was the inability to walk for at least 2 days. However, we excluded all injuries that resulted in knee surgery, which means that our case knees were unlikely to have suffered a major knee injury; still we were able to demonstrate a strong link between knee trauma and alteration of the cartilage extracellular matrix. Second, there is a considerable potential for confounding in a cross-sectional study. Alterations in the cartilage matrix may have developed both before and after the injury. Furthermore, we did not include possible confounders such as medication, non-surgical treatment of the injury and other treatment for OA. Third, gait analysis was not included in our study as gait data were not provided by the OAI and beyond the scope of this study. Post-traumatic gait mechanics have been found to shift the loading patterns to cartilage regions that are not suited for this load [4]. Fourth, following the OAI MRI Procedure Manual for Examinations of the Knee, sagittal T2 maps are only acquired in the right knee. Only patients with a knee replacement or implants or foreign bodies identified on the right knee localizer had this sequence performed on the left knee. Therefore, we were not able to compare T2 measurements in the same patient. Fifth, our compartment-specific T2 analyses are suited to assessing cartilage matrix damage and identifying the affected compartment. However, we did not pinpoint the exact location of altered cartilage composition as correlation with the site of the injury is not possible retrospectively. Sixth, our retrospective design bears a higher risk of error because of confounding than a prospective study design, and we could not stratify our data according to a specific type of conservatively treated injury.

In conclusion, our study shows that elevated cartilage T2 average and texture measurements were associated with conservatively treated knee injuries. Our study suggests that cartilage T2 measurements are able to detect cartilage composition abnormalities in knees with a history of injury not treated with surgery before significant morphologic differences appear. Our findings both underline the need to treat post-traumatic cartilage matrix alterations and strongly encourage ongoing investigations on treatment that might help best protect the cartilage matrix after conservatively treated significant knee trauma.

Acknowledgements This study was performed with support by the OAI, which is a public-private partnership comprising five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, which constitutes a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. The private funding partners involved are Novartis Pharmaceuticals Corp.; Pfizer, Inc.; Merck Research Laboratories; and GlaxoSmithKline. The private sector funding for the OAI is administered by the Foundation for the National Institutes of Health. Analyses in this study were also funded through grants awarded by the NIH NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Diseases) grants R01AR064771 and P50-AR060752).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The OAI study is HIPAA compliant and approved by the institutional review boards at each clinical site. All study participants signed informed consent forms prior to enrollment.

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