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Early T2 Changes predict Onset of Radiographic Knee Osteoarthritis – Data from the Osteoarthritis Initiative

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Abstract

Objective—To evaluate whether T2 relaxation time measurements obtained at 3 Tesla Magnetic Resonance Imaging (MRI) predict the onset of radiographic knee osteoarthritis (OA).

Methods and Materials—We performed a nested case-control study of incident radiographic knee OA in the Osteoarthritis Initiative (OAI) cohort. Cases were 50 knees with baseline KL grade of 0 that developed KL grade of 2 or more over a 4-year period. Controls were 80 knees with KL grade of 0 after four years of follow-up. Baseline T2 relaxation time measurements and laminar analysis of T2 in deep and superficial layers were performed in all knee compartments. The association of T2 values with incident OA was assessed with logistic regression and differences in T2 values by case-control status with linear regression, adjusting for age, sex, body mass index (BMI) and other covariates.

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MN, TL, NL, JL and HL designed the study. HL wrote the analysis plan, coordinated and conducted data acquisition and drafted the manuscript. He is the guarantor. JL provided data, analysis tools and coordinated data analysis. NS performed data analysis, acquisition and assisted with the manuscript draft. SK provided tailored software solutions for the data collection, performed post processing with GJ, as well as data acquisition and analysis. SK and GL drafted methodological sections of the manuscript. CM and GJ wrote the statistical analysis plan, analyzed the data with JL and HL, and drafted the statistical analysis part of the manuscript. TL, MN, JL and NL monitored data acquisition and revised the draft paper by HL. PJ and UH performed data acquisition, post processing, data analysis, drafted sections of the paper and revised the draft paper. MN, NL, CM, TL, SK, JL, GJ, UH, PJ and NS internally revised the manuscript draft by HL. BW externally revised the manuscript. All authors revised the final version of the manuscript draft after external review.

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Results—Baseline T2 values in all compartments except the medial tibia were significantly higher in knees that developed OA compared to controls, and were particularly elevated in the superficial cartilage layers in all compartments. There was an increased likelihood of incident knee OA associated with higher baseline T2 values particularly in the patella, adjusted odds ratio (OR) per 1 SD increase in T2: 3.37 (95% CI: 1.72; 6.62), but also in the medial femur: 1.90 (1.07; 3.39), lateral femur: 2.17 (1.11; 4.25) and lateral tibia: 2.23 (1.16; 4.31).

Conclusions—These findings suggest that T2 values assessed when radiographic changes are not yet apparent may be useful in predicting the development of radiological tibiofemoral OA.

Keywords

Osteoarthritis; Cartilage; MRI; Quantitative Imaging

Introduction

Osteoarthritis (OA) is the most common joint disease and the leading cause of long-term disability, placing tremendous financial burdens at the individual and societal level.[1] Plain film radiography is the currently accepted, low-cost method for monitoring OA progression.[2] A major limitation of conventional radiography is the inability to identify early cartilage changes. Indeed, the onset of biochemical changes leading to irreversible cartilage loss and the corresponding clinical and radiographic signs may lag behind several years.[3] Accordingly, candidate Magnetic Resonance Imaging (MRI) parameters are being investigated aiming to detect and monitor OA at the earliest time possible, as cartilage degenerates irreversibly and treatment options are limited.

T2 relaxation time measurements in the knee have been shown to be sensitive to initial cartilage degeneration and to reflect the histological changes of the cartilage matrix, in particular affecting water and collagen content as well as tissue anisotropy.[4-7] In addition, T2 values are associated with risk factors for OA, including meniscal damage and malalignment;[8-12] and predict pain worsening and progression of morphologica lesions.[13, 14] However, their predictive value for the onset of radiographically apparent OA has not been studied. To analyze the predictive capabilities of T2 measurements for incident radiographic tibiofemoral OA (TFOA), we used the publicly accessible dataset of the Osteoarthritis Initiative (http://www.oai.ucsf.edu/). This database contains clinical data, biological samples, radiographs, and MRI including T2 mapping sequences.[15]

The purpose of our study was to evaluate whether baseline T2 measurements can predict incident radiographic TFOA over 48 months. Furthermore we studied the role of spatial T2 distribution throughout each compartment. This included laminar analysis, separating a superficial articular cartilage layer from deeper cartilage layers adjacent to the subchondral bone, as well as gray level co-occurrence matrix (GLCM) texture analysis.

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Materials and Methods

Study design

This study analyzed T2 measurements in a nested case-control study of incident radiographic knee OA among subjects from the Osteoarthritis Initiative (OAI), a longitudinal, observational multicenter study launched by the National Institutes of Health that enrolled 4796 participants with, or at risk of developing, knee OA, to better understand the natural history of OA. Specific datasets used were baseline clinical dataset 0.2.2, baseline MRI dataset 0.E.1 and central radiograph reading datasets kXR_SQ_BU 0.5, 1.5, 3.4, 5.4 and 6.2. The study protocol, amendments and informed consent documentation were approved by the local institutional review boards.

Participants had bilateral PA fixed flexion knee radiographs at baseline and annually[16], which were assessed centrally for Kellgren-Lawrence (KL) grade by an academically based musculoskeletal radiologist and two rheumatologists, with disagreements resolved by adjudication.[17, 18] Incident TFOA was defined as a knee with a KL grade of 0 at baseline that developed and maintained a KL grade ≥2 by the 48-month follow-up visit, including knees that developed only a definite osteophyte without joint space narrowing (JSN) or knees with both JSN and osteophytes.[18] Controls were knees that remained a KL grade of 0 through the 48-month follow-up.

Incident TFOA cases and controls were selected as shown in the subject flow diagram (Figure 1). To increase the likelihood that elevated T2 values represent early, pre-radiographic abnormalities, participants were required to have a right knee with a baseline KL grade of 0 and a T2 map scan, a baseline BMI <35 to avoid phase wrap in large knees and a central reading of the 48-month radiograph to ensure that control/case status was maintained throughout follow-up. Of the 1205 participants meeting all criteria, there were 58 incident TFOA cases in right knees. T2 analyses could not be performed on 8 knees due to arterial flow artifacts, leaving 50 case knees for analysis. From the 1,147 remaining eligible knees (with KL=0 at follow-up), we randomly selected 80 control knees with analyzable T2 maps frequency matched to the extent possible with cases within baseline age (45-49, 50-59, 60-69, 70-79) and BMI strata (<20, ≥20-25, ≥25-30, ≥30-35).

Magnetic resonance imaging

MRI sequences for T2 mapping were acquired in right knees at 4 clinical sites using 3T MRI scanners (Siemens Magnetom Trio; Siemens, Erlangen, Germany) and standard transmit-receive knee coils (USA Instruments, Aurora, OH). Details of the acquisition protocol have been published.[15]

T2 relaxation time measurements

Two trained researchers (N.S. and H.L.) performed semi-automated spline-based segmentation with in-house developed software implemented in MATLAB (The Mathworks Inc., Natick, MA). Five cartilage compartments were analyzed in consensus (patella, medial and lateral femur, medial and lateral tibia) under supervision of an experienced radiologist (T.L.). The entire artifact-free knee cartilage plates were segmented on the first echo images,

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where tissue contrast and image quality are excellent delineation of cartilage. The trochlea was excluded because of interfering flow artifacts from the popliteal artery.

T2 maps were created using a monoexponential decay model as fitting function to calculate the signal intensity at each echo time. Thresholded T2 calculations were measured from the second (20 ms) to the last (70 ms) echo images dropping the first echo as suggested by recent studies to optimize signal-to-noise ratio.[19-21]

Laminar and GLCM texture analysis

To account for the focal nature of cartilage degeneration, particularly at early stages of OA, laminar analysis was performed separating cartilage into a deep layer adjacent to the subchondral bone and a superficial articular layer.[22] Furthermore, the subcompartmental spatial distribution of cartilage T2 values was evaluated by Gray-Level Co-Occurrence Matrix (GLCM) texture analysis. The frequency of similar neighboring grey-level values occurring in an image were measured as described by Haralick et al.[23, 24] Three GLCM parameters were chosen as published by Carballido-Gamio et al.:[25] Contrast, with high T2 contrast signifying high differences in neighboring pixel values; Entropy, representing a measure of T2 value co-occurrence; and Variance, with elevated values representing disorder in an image. Recent studies suggests that GLCM texture parameters may detect heterogeneity within the cartilage matrix more efficiently than compartmental T2 measurements by providing information on a pixel level.[10, 26, 27]

Reproducibility

Inter-observer agreement for T2 measurements across all compartments calculated on a percentage basis as the root mean square average of the single coefficients of variation for each compartment was 1.57 %, (0.53 ms) while mean intra-observer reproducibility was 1.66 % (0.55 ms).[28]

Statistical analysis

The 50 incident TFOA cases were frequency matched with 80 controls (1 to 1.6). A power analysis using a sample size of 130 showed a power of 0.8 to find statistically significant differences between low and high baseline T2 subjects if an odds ratio of roughly 3 was achieved. Mean baseline T2 values, deep and superficial layer T2 values and GLCM texture parameters (contrast, variance, and entropy) and their standard deviations were calculated for each compartment in each knee. Linear regression was used to estimate adjusted mean differences in baseline T2 values between cases and controls. Logistic regression models were used to analyze the association of baseline T2 values with incident TFOA during follow-up. Odds ratios were calculated for each group and compartment based on a one standard deviation difference in the predictor. Due to small numbers in each age by BMI strata, some imbalances between cases and controls remained after frequency matching, so all analyses were adjusted for age, gender and BMI. We also adjusted for other potentially important baseline covariates: race/ethnicity (Caucasian vs. African American), physical activity assessed with the Physical Activity in the Elderly Scale (PASE)[29], any knee pain or stiffness in the past 12 months, a history of knee injury resulting in activity limitation for at least 2 days, a history of knee surgery, and the OAI MR scanner. None of these additional

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adjustments materially changed our results (change in coefficients of less than 5%). We repeated the main analysis restricting incident cases to knees that developed both JSN and osteophytes with baseline compartmental T2 values as the predictor. Associations with P <0.05 were considered statistically significant. Statistical analysis was performed with STATA11 software (StataCorp LP, College Station, TX).

Results

Baseline T2 in relation to incident radiographic OA

Subjects with incident TFOA were slightly older, had higher BMIs and were more likely to be male than controls (Table 1). Of the 50 incident TFOA cases, 31 developed both JSN and osteophytes and 19 developed just osteophytes. Of the 31 incident cases with JSN, 22 showed predominantly medial and 8 predominantly lateral JSN (1 was narrowed equally in both compartments). Fifteen out of 50 incident TFOA cases were identified at the 12-month follow-up, 7 at 24 months, 17 at 36 months, and 11 at the 48-month visit.

Knees with incident TFOA had higher mean T2 values in each compartment compared to controls (Table 2). Adjusted differences between cases and controls in mean T2 were significant for all compartments combined and for each individual compartment except the medial tibia (MT). The largest differences were observed at the patella (PAT): adjusted difference in mean: 2.26 ms; 95%CI 1.14; 3.38. Higher baseline compartment T2 values (with the exception of the MT) were associated with an increased risk of incident TFOA (Table 3), with adjusted odds ratios ranging from 1.90 (95%CI: 1.07; 3.39) for the medial femur (MF) to 3.37 (1.72; 6.62) for the patella. When restricting incident cases to knees that developed both JSN and osteophytes, odds ratios and p-values were nearly identical except for the lateral tibia, which had an odds ratio of 1.77 (0.87, 3.62), with P =0.118.

Laminar cartilage analysis

Superficial cartilage layer T2 values were higher than T2 values in the deep cartilage layer adjacent to the bone in each compartment (Table 2). Furthermore cases showed significantly higher superficial cartilage layer T2 compared to controls. Table 3 shows the association of superficial layer T2 with incident TFOA with adjusted odds ratios up to 3.09 (1.73; 5.52) at the patella for a one SD difference in baseline T2. Deep T2 values did not differ significantly by case-control status (Table 2).

GLCM texture analysis

GLCM texture parameters demonstrated less homogenous spatial distribution of T2 values in the cases compared to controls. All three parameters, contrast, variance and entropy showed higher baseline values in all five compartments of the TFOA incidence group (Table 2), although not all differences were significant. For the patella compartment higher baseline values of all three GLCM parameters showed an association with incident TFOA as shown in Table 3 (contrast: OR 3.91; 95%CI 1.87; 8.18; variance: OR 4.42; 95%CI 2.29; 8.53; entropy: OR 5.07 95%CI 2.24; 11.46). Furthermore higher baseline contrast and variance in the lateral tibia were each associated with incident TFOA while in the lateral femur greater variance was associated with incident TFOA (Table 3).

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Discussion

This study examined the ability of baseline T2 relaxation time measurements obtained at 3T MRI to predict the development of incident radiographic TFOA over a period of 4 years. Knees that developed radiographic TFOA in the follow-up had significantly higher baseline T2 values in all compartments except for the medial tibia compared to the control group. The superficial cartilage layer showed particularly elevated T2 values and significant associations with the onset of TFOA in all five compartments studied, with the highest odds ratios for T2 values at the patella.

At present plain radiographs are still considered standard of care to diagnose and monitor knee OA. However, quantitative MRI parameters, such as T2 relaxation time measurements, allow for the evaluation of structural disruption in the cartilage matrix depicting early biochemical changes at initial stages of cartilage degeneration that occur before OA changes are seen on radiographs.[30] Associations between T2 measurements and cartilage degeneration have been demonstrated in numerous in-vivo studies [31-33], as well as in animal studies [34, 35] and with histology in specimen studies in vitro.[36-38] Previous studies have found elevated T2 values in knees with diagnosed OA and in knees of individuals with risk factors for OA.[32, 39-42]

This is the first study to demonstrate that T2 relaxation time measurements in the articular cartilage of radiographically normal tibiofemoral compartments predict the later onset of radiographic TFOA. Our results suggest that changes in biochemical cartilage composition detectable by changes in T2 measurements precede radiological manifestations of disease, as detectable by KL grading. Only knees with a radiographically normal joint space and no osteophytes were included (KL=0). Implications of elevated T2 values for prevention and treatment are presently uncertain since treatment options for OA are limited, but early indication of pre-radiographic knee OA using MRI could prove valuable once disease-modifying interventions are available, since by the time even mild radiographic changes are apparent destruction of joint tissues may already be irreversible.[43, 44].

Previous studies of T2 measurements in samples of knees that include those with mild to moderate OA are consistent with our results in showing that higher baseline T2 values are associated with subsequent worsening of morphological tissue damage in the knee assessed by MRI.[41, 45, 4613, 47] However, other studies have not found T2 values to predict progression of cartilage loss assessed by quantitative methods in knees with KL grade of 2 or 3.[48] It is possible that in knees with more advanced OA, cartilage T2 values are more uniformly elevated and therefore do not discriminate well for further cartilage loss. In addition as large areas of degenerated cartilage are lost, mean T2 values may decrease in the remaining intact cartilage. Other quantitative MRI techniques such as delayed gadolinium-enhanced MRI (dGEMRIC) and T1rho of cartilage also provide promising approaches and have been shown to be associated with the biomechanical properties of cartilage in vivo.[49-51]

The KL grading is based on tibiofemoral osteophytes and joint space narrowing, but does not reflect radiographic findings in the patellofemoral compartment. Interestingly, for an

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increase of baseline patella T2 by one SD, our study reports a more than 3-fold higher likelihood for incident TFOA, a larger odds ratio than any TF compartment. Previous studies found that early signal inhomogeneities and morphologic lesions in the natural history of knee OA frequently occur at the patella, where the cartilage is thickest and therefore may be most vulnerable and sensitive to early degradation.[8, 47, 52-54] Duncan et al. studied early radiographic findings in the patellofemoral joint and proposed that the onset of knee OA follows a common sequence initiating at the patellofemoral joint.[55] Our results lend support to the hypothesis that early biochemical changes in the patella cartilage may precede TFOA.

Because compartmental T2 values do not account for the distribution of T2 values within the compartments, our study also investigated laminar and spatial distribution. Consistent with previous studies, T2 values in the superficial articular cartilage layer were higher compared to the deep layer, in part due to collagen fibril orientation.[56-59] When comparing TFOA incidence cases and controls, the T2 values of the superficial layer in all 5 compartments were associated with incident OA, whereas the deep layer showed no association. Deep layer cartilage may be less prone to early degeneration or its analysis more limited due to chemical shift artifacts. Our data suggests that inhomogeneous deep layer measurements may limit the utility of overall compartmental T2 values. Tibial T2 measurements may be most susceptible to this effect, due to thin cartilage at the tibia plateau, as reflected in the lack of association of incident TFOA with global T2 values at the medial tibia despite an association with superficial layer T2 values in this compartment. The GLCM parameters, which reflect heterogeneity of T2 values throughout the cartilage matrix,[10, 25, 27, 60] further support the findings observed for the laminar analysis. Interestingly, as with compartmental and superficial layer T2 values, the associations of elevated contrast, variance and entropy values with incident TFOA were particularly strong at the patella.

Our study has several important strengths. Both incident case and control knees had KL grades of 0 at baseline so our findings for T2 values are likely to represent early cartilage degeneration prior to detectable early TFOA radiographic findings. Our outcome was incident radiographic TFOA, since plain radiographs are still considered the gold standard in evaluating OA with a KL grade of 2 being a widely accepted threshold for radiographic disease with known clinical and epidemiologic relevance. Our results were nearly identical when we restricted the analysis to cases with incident JSN and not just new osteophytes, further strengthening their clinical relevance. Future studies are needed to determine whether baseline T2 values in knees without any detectable morphologic cartilage damage predict the onset of morphologic cartilage lesions.

Our study also has several limitations. Our results may not apply to knees with existing OA (KL≥1) and subjects with a BMI>35. To minimize the potential for selection bias, both cases and controls were drawn from the same pool of eligible knees. In addition, we adjusted for multiple important covariates. However, our results may still be influenced by uncontrolled covariates that differ between cases and controls, including any that resulted from the selection process. Elevated T2 values may serve as an indicator for various causes of cartilage degeneration and whether it predicts incident TFOA independently of other baseline imaging biomarkers, such as meniscal damage or bone marrow lesions (which we did not assess), or is casually linked to the subsequent development of OA remains to be

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determined. Longitudinal studies measuring T2 at multiple time-points are needed to establish its role in the sequence of pathological events in cartilage and other tissues leading to onset of OA. Radiographic patellofemoral OA was not assessed, so our findings are limited to incident TFOA. T2 maps were available for right knees only, but we have no reason to expect different results for left knees.

Conclusion

The results of this study indicate that elevated baseline T2 values predict the later onset of radiographic TFOA in knees that appear to have normal and healthy tibiofemoral compartments by radiograph. Given the irreversible nature of cartilage degeneration, earliest possible diagnosis represents a key factor to maximize the effect of potentially available disease modifying interventions and to monitor treatment efficacy. Our findings underscore that T2 measurements are sensitive to the earliest changes in the biochemical cartilage composition that are precursors to the development of radiographic disease and through early diagnosis may play a role in efforts to support a paradigm shift from palliation of late OA towards prevention of disease.

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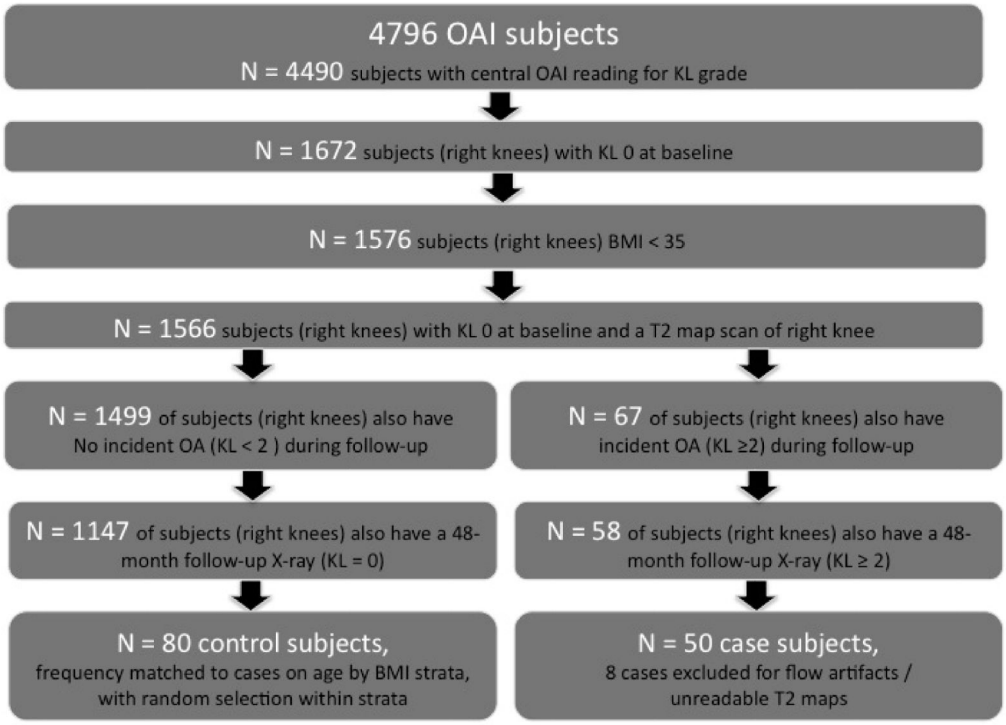

Figure 1.
Flow chart diagram illustrating selection of study subjects from the OAI dataset

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Table 1
Subject characteristics and differences by case and control status

Right knee OA status	Incident tibiofemoral OA cases	Controls	All subjects	Differences by case/control status
n	50	80	130	-
Age (in years) mean ± SD	59.88 ± 8.23	58.44 ± 7.71	25.31 ± 3.37	p = 0.314
BMI (kg/m^2) mean ± SD	27.24 ± 3.54	25.31 ± 3.37	26.05 ± 3.55	**p = 0.005**
Gender (females)	28 (56%)	50 (63%)	78 (60%)	p = 0.379
PASE	183.42 ± 90.18	168.28 ± 72.08	174.10 ± 79.53	p = 0.186
Previous injury reported	10 (20%)	16 (20%)	26 (20%)	p = 0.884
Previous surgery reported	2 (4%)	2 (2.5%)	4 (3%)	p = 0.609

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Table 2

Cartilage T2 values (in ms)* and mean Gray Level Co-occurrence Matrix (GLCM) parameters in knees with incident radiographic OA and controls

Parameter		Lateral Femur (LF)	Lateral Tibia (LT)	Medial Femur (MF)	Medial Tibia (MT)	Patella (PAT)
Compartment T2	OA Incidence	36.02 ± 2.70	30.43 ± 3.12	40.38 ± 3.23	32.34 ± 2.39	35.03 ± 4.57
	Controls	34.96 ± 2.37	28.91 ± 2.39	38.88 ± 2.93	31.4 ± 3.16	33.45 ± 2.65
	Adjusted Difference **	1.12	1.27	1.30	0.43	2.26
	95% Confidence Interval	0.16; 2.08	0.27; 2.26	0.18; 2.42	−0.57: 1.45	1.14; 3.38
Superficial Layer T2	Incidence Group	38.74 ± 3.56	34.37 ± 4.04	42.37 ± 3.79	34.26 ± 3.82	40.04 ± 4.49
	Controls	37.29 ± 2.62	32.51 ± 2.95	40.65 ± 3.44	32.71 ± 3.49	36.67 ± 3.22
	Adjusted Difference **	1.51	1.55	1.36	1.42	3.13
	95% Confidence Interval	0.38; 2.63	0.30; 2.82	0.05; 2.66	0.07; 2.77	1.73; 4.53
Deep Layer T2	Incidence Group	32.42 ± 2.89	26.14 ± 2.81	37.35 ± 3.37	30.15 ± 3.13	31.31 ± 2.71
	Controls	32.61 ± 2.40	25.20 ± 2.34	37.14 ± 2.91	30.22 ± 4.67	30.34 ± 2.60
	Adjusted Difference **	−0.14	0.74	0.13	−0.94	0.83
	95% Confidence Interval	−1.11; 0.83	−0.20; 1.68	−1.01; 1.28	−2.3;0.49	−0.15; 1.82
Contrast	Incidence Group	256.57 ± 49.61	237.2 ± 133.54	439.45 ± 122.09	450.13 ± 181.43	357.09 ± 145.42
	Controls	237.01 ± 59.46	179.49 ± 82.20	377.67 ± 134.81	426.44 ± 232.02	244.89 ± 99.98
	Adjusted Difference **	15.96	48.00	37.96	−18.06	101.11
	95% Confidence Interval	−4.56; 36.47	9.21; 86.78	−7.21; 83.12	−91.83; 55.72	57.31; 144.90
Variance	Incidence Group	195.87 ± 37.35	200.29 ± 113.21	300.35 ± 79.60	316.29 ± 130.36	309.30 ± 123.41
	Controls	174.20 ± 41.28	149.46 ± 56.73	261.83 ± 91.74	298.51 ± 160.27	201.78 ± 76.24
	Adjusted Difference **	18.77	44.23	23.94	−10.60	100.55
	95% Confidence Interval	4.42; 33.11	13.46; 75.00	−0.57; 54.45	−62.29; 41.10	64.68; 136.43
Entropy	Incidence Group	6.67 ± 0.25	5.75 ± 0.33	6.73 ± 0.24	5.82 ± 0.30	6.093 ± 0.27
	Controls	6.59 ± 0.25	5.63 ± 0.36	6.72 ± 0.23	5.72 ± 0.32	5.84 ± 0.32
	Adjusted Difference **	0.08	0.10	−0.02	0.10	0.24
	95% Confidence Interval	−0.01; 0.17	−0.03; 0.22	−0.11; 0.07	−0.02; 0.21	0.13; 0.35

* T2 values in table are mean ± SD unless otherwise indicated

** Adjusted for age, gender and BMI

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Table 3

Odds ratios (95% confidence intervals) for the association of global cartilage compartment T2 values, superficial cartilage T2 values and patella GLCM parameters in knees with incident radiographic OA and controls

Parameter	Compartment	p value	Adjusted Odds Ratio*	95% Confidence Interval
Compartment T2 (in ms)	LF	**p = 0.024**	2.17	1.11; 4.25
	LT	**p = 0.017**	2.23	1.16; 4.31
	MF	**p = 0.029**	1.90	1.07; 3.39
	MT	p = 0.405	1.30	0.70; 2.41
	PAT	**p < 0.0001**	3.37	1.72; 6.62
Superficial Layer T2 (in ms)	LF	**p = 0.011**	2.23	1.20; 4.13
	LT	**p = 0.02**	1.92	1.11; 3.32
	MF	**p = 0.045**	1.71	1.01; 2.88
	MT	**p = 0.042**	1.71	1.02; 2.85
	PAT	**p < 0.0001**	3.09	1.73; 5.52
Deep Layer T2 (in ms)	LF	p = 0.786	0.91	0.46; 1.81
	LT	p = 0.121	1.76	0.86; 3.61
	MF	p = 0.839	1.06	0.59; 1.90
	MT	p = 0.188	0.72	0.44; 1.17
	PAT	p = 0.091	1.81	0.91; 3.59
Contrast	LF	p = 0.126	2.39	0.78; 7.32
	LT	**p = 0.029**	2.08	1.08; 4.01
	MF	p = 0.115	1.50	0.90; 2.50
	MT	p = 0.614	0.92	0.68; 1.26
	PAT	**p < 0.0001**	3.91	1.87; 8.18
Variance	LF	**p = 0.013**	4.16	1.35; 12.83
	LT	**p = 0.018**	2.32	1.16; 4.64
	MF	p = 0.138	1.48	0.88; 2.50
	MT	p = 0.675	0.94	0.69; 1.27
	PAT	**p < 0.0001**	4.42	2.29; 8.53
Entropy	LF	p = 0.074	2.12	0.93; 4.85
	LT	p = 0.144	1.55	0.86; 2.79
	MF	p = 0.607	0.80	0.33; 1.90
	MT	p = 0.097	1.76	0.90; 3.45
	PAT	**p < 0.0001**	5.07	2.24; 11.46

* Odds ratios are calculated per one standard deviation difference in the predictor and are adjusted for age, gender and BMI