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Medial Femur T_2 Z-scores Predict the Probability of Knee Structural Worsening Over 4–8 years: Data From the Osteoarthritis Initiative

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Objective: The purpose of this study was to determine the probability of structural worsening of knee cartilage and whole joint degeneration over 4–8 years based on cartilage T_2 Z-scores at baseline.
Design: Right knees with Kellgren-Lawrence (KL) grades of 0–2 in 587 participants from the Osteoarthritis Initiative were studied. 3T MR images were used to perform baseline cartilage T_2 quantification and assess 4-year changes in cartilage morphology (WORMS scoring) in 5 regions. Changes in joint space narrowing (JSN) and KL were assessed over 8 years. T_2 Z-scores were based on a reference database of knees without morphologic cartilage degeneration at baseline. Odds ratios for, and predicted probabilities of any worsening in WORMS cartilage, JSN and KL grade were obtained from logistic regression models.
Results: A one-unit increase in the baseline medial femur T_2 Z-score was associated with cartilage worsening in the same region (OR = 1.59; $P < 0.0001$) and in any region (OR = 1.37; $P < 0.0001$), and with worsening JSN (OR = 1.82; $P < 0.0001$) and KL grades (OR = 1.69; $P < 0.0001$). Predicted probabilities of worsening in knees with a medial femur T_2 Z-score from 2–4 were 38% for medial femur cartilage WORMS, 70% for any cartilage region, 28% for increasing JSN and 31% for increasing KL grade.
Conclusion: Knees with elevated cartilage T_2 (especially in the medial femur and those that are 2 to 4 SDs above the mean reference values) are significantly more likely to have structural worsening over 4 to 8 years. Knowing cartilage T_2 Z-scores may aid in targeting prevention efforts at early stages of osteoarthritis.
Level of Evidence: 2

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Implementing early preventative measures for knee osteoarthritis (OA), such as lifestyle modifications, relies on the early detection of OA, and such diagnostic markers are not yet available in the clinic. These diagnostic markers could potentially reduce the current rising rates of total knee replacement (TKR)[1] and may be especially beneficial to the 10–34% of individuals who have unfavorable long-term pain outcomes following TKR.[2]

Magnetic resonance imaging (MRI) is ideal for noninvasive assessment of early OA, as it can detect degeneration in various soft tissues such as the meniscus and cartilage. In particular, compositional MRI, such as T_2 mapping, identifies biochemical changes in cartilage including abnormalities of collagen fiber orientation[3] and increased water content,[4] which often occur prior to macroscopic cartilage defects and thinning. Subjects with OA have both elevated and more heterogeneous cartilage T_2 values compared to healthy knees,[5] demonstrating that cartilage T_2 holds promise as a biomarker for OA.[6,7] However, T_2 mapping is not currently standard clinical practice.

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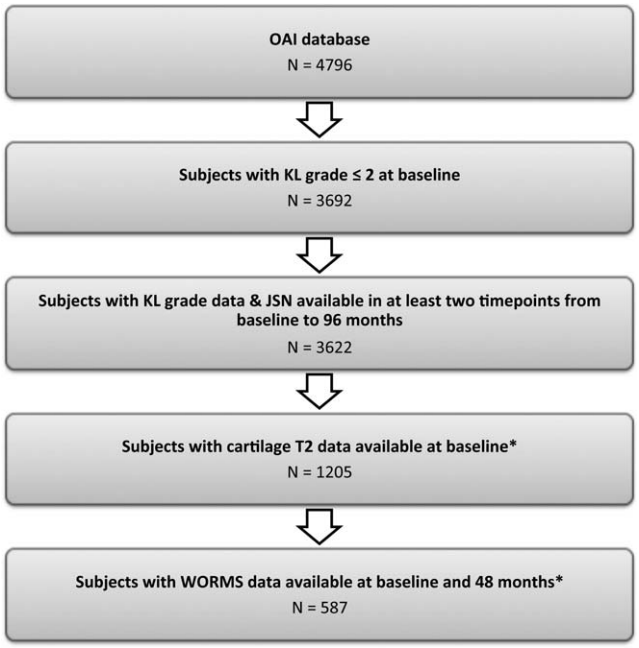


FIGURE 1: Subject selection flowchart. Subjects were selected based on measurements in the right knee. *The sample of knees was selected from previous analyses of T_2 measurements and WORMS scores.[11–15]

The first steps in developing cartilage T_2 mapping as a biomarker for OA are to standardize the technique for large-scale translation across clinics (for improved data interpretation) and then determine its efficacy in predicting OA progression. This study aims to address standardization issues with T_2 quantification using cartilage T_2 Z-scores and to determine the significance of an individual's T_2 value compared to a healthy population without OA.[8] Using these standardized values, an individual's risk for progressive degenerative changes in the knee may be predicted, similar to the role of T-scores for bone mineral density in osteoporosis.[9]

Thus, the purpose of this study was to determine the probability of cartilage degeneration (using MRI-based whole-organ MRI scores [WORMS]) after 4 years and structural worsening (using X-ray-based joint space narrowing [JSN] and Kellgren–Lawrence [KL] scores) after 8 years based on cartilage T_2 Z-scores at baseline, using data from the Osteoarthritis Initiative (OAI).

Materials and Methods

Sample Selection

This study utilized data from the OAI (http://www.oai.ucsf.edu/),[10] a multicenter, longitudinal study of persons aged 45–79 at enrollment aimed at assessing biomarkers in OA. The OAI dataset includes both MRI and radiographic images of subjects scanned over 8 years. This database can be used to longitudinally evaluate MRI biomarkers for the development and progression of OA. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local Institutional Review Boards of all participating centers.

Participants for the present study were selected from the OAI, which excluded individuals with inflammatory arthropathies (including rheumatoid arthritis and seronegative spondylarthropathies), MRI contraindications, and comorbid conditions that may affect the ability to participate in the study. The sample of knees was selected from previous analyses of T_2 measurements and WORMS scores.[11–15] Specific inclusion criteria for the present study was a radiographic KL score ≤ 2 in the right knee, having at least two timepoints of KL and JSN data (baseline to 8 years), and having WORMS and cartilage T_2 measurements at baseline and 4 years (Fig. 1). Exclusion criteria for the present study were baseline: 1) knee injury with deformity of the knee joint, 2) total joint replacement in the right knee, 3) MRI evidence of subchondral or stress fractures of the knee or abnormalities that did not fit into the spectrum of OA and indicated other severe disease, such as tumor or inflammation. Right knees from 587 participants were analyzed.

MRI

MR images were obtained using four identical 3.0T (Siemens Magnetom Trio, Erlangen, Germany) scanners and quadrature transmit-receive coils (USA Instruments, Aurora, OH) in Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania; and Pawtucket, Rhode Island. The following sequences were acquired and used for WORMS scoring: sagittal 2D intermediate-weighted fast spin-echo sequence (repetition time / echo time [TR/TE] = 3200/30 msec, spatial resolution = 0.357 × 0.511 mm, slice thickness = 3.0 mm), coronal 2D proton density fast spin-echo sequence (TR/TE = 3700/29 msec, spatial resolution = 0.365 × 0.456 mm, slice thickness = 3.0 mm), and sagittal 3D dual-echo in steady-state sequence (TR/TE = 16.3/4.7 msec, spatial resolution = 0.365 × 0.456 mm, slice thickness = 0.7 mm). A sagittal 2D multislice multiecho sequence (MSME, TR = 2700 msec, TE_1-TE_7 = 10–70 msec, spatial resolution = 0.313 × 0.446 mm, slice thickness = 3.0 mm, and 0.5 mm gap) was used for cartilage T_2 measurements.[16]

Image Analysis

WORMS SCORING. MR images of the right knee obtained at the baseline visit were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ), and were analyzed previously.[11–15] Three radiologists with 7, 5, and 5 years of experience, respectively, graded the cartilage lesions (M.K., A.S.G., B.J.S.); each study was read by two radiologists independently. In equivocal cases, a consensus reading was performed between the two radiologists and a musculoskeletal radiologist with 23 years of experience (T.M.L.). Initially, for standardization purposes, 20 cases were read simultaneously by all four readers together. Cartilage lesions were assessed in five regions (patella, medial femur, medial tibia, lateral femur, and lateral tibia) using a modified semiquantitative WORMS scores.[17] WORMS scoring was performed at baseline and at 4 years.

Worsening of cartilage lesions was defined as an increase in WORMS score at 4-year follow-up compared to baseline (not including signal abnormality changes [increases from WORMS = 0 at baseline to WORMS = 1 at 48 months]).[18,19] This outcome was defined on a region level and on a knee level (positive for

worsening if an increase occurred in at least one region). The WORMS reproducibility results have been described previously.[20,21] The interobserver reproducibility (weighted kappa) for WORMS scoring for (10 cases, 2 readers) was 0.91 for the patella, 0.91 for the medial femur, 0.86 for the lateral femur, 1.00 for the medial femur, and 0.85 for the lateral tibia.

JOINT SPACE AND KL SCORE. Radiographic changes were assessed over 8 years using JSN and KL grades,[22] from central readings. Worsening of a KL score was defined as having a baseline KL grade of 0 or 1 and having a KL grade greater than 1 at any subsequent timepoint (1 year, 2 years, 3 years, 4 years, 7 years, 8 years), or having a baseline KL grade of 2 with an increase of 1 or more grades at any subsequent timepoint. JSN grade was semi-quantitatively assessed using fixed flexion knee radiographs as previously described.[23] Test–retest reliability for JSN progression was good to excellent (medial JSN progression, $\kappa = 0.72$ [0.63–0.82]; lateral JSN progression, $\kappa = 0.83$ [0.70–0.96]). JSN was assessed at the same timepoints in the medial and lateral regions from PA radiographs. Worsening of JSN was defined as having a full or partial grade increase from baseline in either the medial or lateral compartment at any subsequent timepoint over 8 years. The KL grades and OARSI JSN scores are publicly available (file kXR-SQ_BU; versions 0.8, 1.8, 3.7, 5.7, 6.5, 8.2, and 10.2).[22]

T_2 MEASUREMENTS. All baseline images were analyzed using a Sun Workstation (Sun Microsystems, Palo Alto, CA). Semiautomatic cartilage segmentation of lateral femur, lateral tibia, medial femur, medial tibia, and patella regions was performed as previously described, using an in-house, spline-based software based on MatLab (MathWorks, Natick, MA).[21] We aimed to segment as many slices as possible to cover the entire cartilage but used rigorous criteria to exclude sections with compromised image quality. A slice was only segmented if the cartilage was clearly depicted and the slice did not have evidence of partial volume effects that would have blurred the border of the cartilage. Also, sections with artifacts limiting the segmentation of the cartilage were excluded. While the number of slices varied per knee (as this number may depend on knee size), in general we segmented 3–4 slices for the medial and lateral femur, 5–6 slices for the medial and lateral tibia, and 8–9 slices for the patella. In order to exclude potential chemical shift artifacts or fluid from the region of interest, the user simultaneously examined the T_2 map and the first echo of the MSME sequence (in neighboring image panels) with synchronized cursor/slice number/zoom. Areas with fluid or artifacts were not included in the region of interest.

T_2 maps were computed from the MSME images on a pixel-by-pixel basis using six echoes (TE = 20–70 msec) and three parameter fittings accounting for noise,[24,25] and averaged over all of the slices in each cartilage region. The first echo (TE = 10 msec) was not included in the T_2 fitting procedure in order to reduce potential errors resulting from stimulated echoes. A noise-corrected algorithm (which involves fitting the signal and noise to an exponential function) was implemented based on results from a recent study demonstrating increased accuracy and precision of T_2 relaxation time when using with a noise correction algorithm as compared to the traditional uncorrected exponential fit.[24,25] T_2 quantification was performed at the baseline timepoint. The cartilage T_2 reproducibility results have been described previously.[20,21]

TABLE 1. Participant Characteristics

	All participants
n	587
Age (years)	56.67 ± 7.56
BMI (kg/m^2)	27.50 ± 4.29
Gender (male)	209 (35.60%)
WOMAC* pain	1.50 ± 2.62
PASE^	172.55 ± 82.86
KL	
0	322 (54.86%)
1	130 (22.15%)
2	135 (23.00%)

*WOMAC: Western Ontario and McMaster Universities Arthritis Index; ^PASE: Physical Activity Scale for the Elderly.

The mean T_2 values had root mean square (RMS) coefficients of variation (CV) ranging from 0.83% in the medial femur to 3.21% in the patella (intrareader reproducibility). The cartilage T_2 inter-reader reproducibility ranged from 1.22% in the patella to 1.86% in the lateral tibia.

Statistical Analysis

Statistical analysis was performed using STATA v. 13 software (StataCorp, College Station, TX). Individualized cartilage T_2 Z-scores for each cartilage region were calculated using the following equation:

$$Z\ score = \frac{Measured\ cartilage\ T_2 - Reference\ cartilage\ T_2\ mean}{Reference\ cartilage\ T_2\ SD}$$

The reference values were obtained from 481 subjects without cartilage lesions (WORMS 0/1) in the study knee as previously published by Joseph et al.[8] The overlap between the two cohorts (the cohort in the present study, $n = 587$; and the reference cohort $n = 481$) was 239. We included the overlapping cases in the primary analysis to obtain a larger dataset yielding more power, and because there is no bias introduced as the reference cohort and target cohort were selected based on two independent inclusion criteria. In addition, we performed a sensitivity analysis to assess whether the results differed when excluding the $n = 239$ overlapping cases. Z-scores were calculated in the 1) overall database; 2) specific to BMI category (normal BMI = 18–24.9 kg/m^2; overweight BMI = 25–29.9 kg/m^2; obese BMI = 30–45 kg/m^2); and 3) specific to gender (male/female).

Logistic regression models were used to determine whether region-specific T_2 Z-scores were associated with worsening of 1) cartilage WORMS in *each* cartilage region over 4 years (ie, medial femur cartilage T_2 associated with medial femur WORMS change); 2) cartilage WORMS in *any* region over 4 years; 3) JSN over 8 years; and 4) KL grade over 8 years.

The predicted probabilities for each worsening outcome were calculated from the logistic regression models. We did not perform

TABLE 2. Cartilage T_2 Z-score

Outcome	Predictor: Region-specific cartilage T_2 Z-score	*N* (%) with outcome	OR (95% CI) per 1 unit increase in T_2 Z-score
Increase in region-specific WORMS over 4 years	LF	86 (14.65)	1.14 (0.94,1.39) $P = 0.17$
	LT	102 (17.38)	1.30 (0.98,1.71) $P = 0.07$
	MF	116 (19.76)	**1.59 (1.32,1.92) $P < 0.0001$**
	MT	60 (10.22)	1.19 (0.86,1.66) $P = 0.29$
	PAT	189 (32.30)	0.87 (0.73,1.03) $P = 0.11$
Increase in WORMS in any region over 4 years	LF	324 (55.20)	**1.21 (1.05,1.39) $P = 0.01$**
	LT		1.03 (0.83,1.28) $P = 0.76$
	MF		**1.37 (1.18,1.59) $P < 0.0001$**
	MT		0.92 (0.75,1.13) $P = 0.43$
	PAT		0.90 (0.77,1.06) $P = 0.21$
Increase in JSN score over 8 years	LF	68 (11.58)	**1.39 (1.12,1.72) $P = 0.003$**
	LT		**1.58 (1.14,2.20) $P = 0.007$**
	MF		**1.82 (1.44,2.30) $P < 0.0001$**
	MT		**1.71 (1.25,2.34) $P = 0.001$**
	PAT		1.08 (0.85,1.38) $P = 0.52$
Increase in KL score over 8 years	LF	82 (13.97)	**1.37 (1.12,1.67) $P = 0.002$**
	LT		**1.88 (1.38,2.57) $P < 0.0001$**
	MF		**1.69 (1.36,2.09) $P < 0.0001$**
	MT		**1.48 (1.11,1.97) $P = 0.008$**
	PAT		1.06 (0.84,1.34) $P = 0.61$

Association between baseline region-specific cartilage T_2 Z-score and 1) Region-specific worsening of cartilage lesion score over 4 years, 2) overall cartilage WORMS increase in any region over 4 years, 3) change in JSN over 8 years and 4) change in KL score over 8 years. Similar results (not shown) were found in a sensitivity analysis that only included participants with KL = 0 ($n = 322$). LF = lateral femur, LT = lateral tibia, MF = medial femur, MT = medial tibia, PAT = patella. A 1 unit increase in cartilage T_2 Z-score is equal to a 1 SD difference in cartilage T_2. Bold signifies that $P < 0.05$. OR = odds ratio; CI = confidence interval.

statistical adjustments for covariates to emphasize clinical translation of the technique (ie, in a clinical setting an individual would obtain T_2 quantification, be assigned a T_2 Z-score [without any statistical adjustments] and that Z-score would provide an estimate of the probability of OA worsening). In order to demonstrate sufficient sample size, we tested the stability of the calculations by taking a bootstrap sample and recalculating the predicted probability estimates. We found that the estimates were quite stable, showing minimal changes in the predicted probabilities and standard errors with bootstrapping. $P < 0.05$ was considered statistically significant.

Results

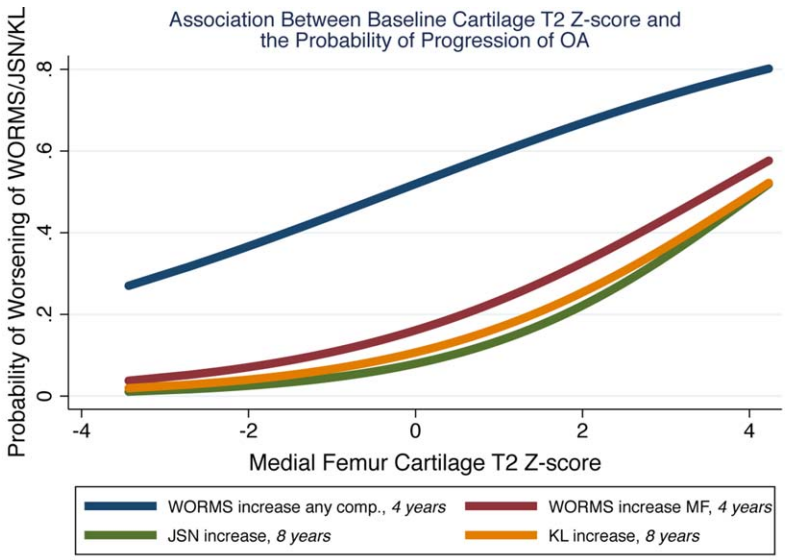
Subject Characteristics

The 587 participants in this study had a mean age of 56.67 ± 7.56 years and a mean BMI of $27.50 \pm 4.29\ kg/m^2$ at baseline. The distribution of KL grades as well as other participant characteristics are listed in Table 1.

Worsening of cartilage WORMS over 4 years ranged from 10% in the medial tibia region to 32% in the patella region, while cartilage worsening in any region occurred in 55% of knees (Table 2). The frequency of JSN and KL worsening over 8 years was 12% and 14%, respectively.

Increases in WORMS Scores Over 4 Years

For the regions-specific analysis of all cartilage regions, the baseline medial femur T_2 Z-score was most consistently associated with worsening of cartilage lesions in the medial femur (odds ration [OR] per 1 unit increase = 1.59, $P < 0.0001$, AUC = 0.65). Significant associations were also found between medial compartment T_2 Z-score and medial compartment WORMS worsening (OR per 1 unit increase = 1.73, $P < 0.0001$, AUC = 0.62); similar significant associations were found for the lateral compartment



Predicted Probabilities Of Progression of OA (Probability ± Standard Error)

MF Cartilage T2 Z-score	N#	Increase in Medial Femur WORMS score *over 4 years*	Increase in WORMS in any region *over 4 years*	Increase in JSN *over 8 years*	Increase in KL *over 8 years*
-4 to -2	7	0.06 ± 0.01	0.33 ± 0.03	0.02 ± 0.01	0.03 ± 0.01
-2 to -1	55	0.09 ± 0.01	0.41 ± 0.02	0.04 ± 0.01	0.06 ± 0.01
-1 to 1	347	0.17 ± 0.03	0.52 ± 0.04	0.08 ± 0.02	0.11 ± 0.03
1 to 2	119	0.27 ± 0.02^	0.63 ± 0.02*	0.17 ± 0.02*	0.20 ± 0.02
2 to 4	49	0.38 ± 0.05^	0.70 ± 0.03^	0.28 ± 0.06^	0.31 ± 0.05^

FIGURE 2: The predicted probability of worsening of KL score over 8 years (orange), joint space narrowing (JSN) change over 8 years (green), WORMS score in the medial femur over 4 years (MF, red), and WORMS change in any region over years (blue). Modeled values are based on logistic regression models with baseline cartilage T_2 Z-score in the medial femur as a predictor. For all outcomes, the probability of incidence/progression increases as a function of cartilage T_2 Z-score in the medial femur. The table shows the associated probabilities of incidence/progression based on categorical values of cartilage T_2 Z-scores in the medial femur. ^$P < 0.0001$ compared to the Z-score category –1 to 1; *$P < 0.05$ compared to the Z-score category –1 to 1; #note that 10 participants had missing T_2 values in the medial femur and were not included in the analysis.

(OR per 1 unit increase = 1.40, $P < 0.004$, AUC = 0.58). For the analysis of worsening in any cartilage region, cartilage T_2 Z scores in both the medial femur (OR = 1.37, $P < 0.0001$, AUC = 0.61) and the lateral femur (OR = 1.21, $P = 0.01$, AUC = 0.55) were associated with worsening (Table 2).

Increases in JSN Over 8 Years

Elevated baseline T_2 Z-scores were associated with worsening of JSN in the medial femur (OR per 1 unit increase = 1.82, $P < 0.0001$, AUC = 0.70), medial tibia (OR = 1.71, $P = 0.001$, AUC = 0.60), lateral femur (OR = 1.39, $P = 0.003$, AUC = 0.62), and lateral tibia (OR = 1.58, $P < 0.007$, AUC = 0.60; Table 2). In addition, medial compartment T_2 Z-score was significantly associated with medial compartment JSN (OR per 1 unit increase = 2.23, $P < 0.0001$, AUC = 0.68); similar significant associations were found for the lateral compartment (OR per 1 unit increase = 2.94, $P < 0.004$, AUC = 0.77).

Increases in KL Score Over 8 Years

Elevated baseline cartilage T_2 Z-score were associated with worsening of KL scores in the medial femur (OR per 1 unit increase = 1.69, $P < 0.0001$, AUC = 0.65), medial tibia (OR = 1.48, $P = 0.008$, AUC = 0.60), the lateral femur (OR = 1.37, $P = 0.002$, AUC = 0.61), and the lateral tibia (OR = 1.88, $P < 0.0001$, AUC = 0.64; Table 2).

BMI- and Gender-Specific Cartilage T_2 Z-Scores

The BMI- and gender-specific T_2 Z score results were similar for all outcomes to the overall T_2 Z-scores results discussed above. T_2 Z-scores in the medial femur region showed significant associations with worsening of cartilage lesions, JSN, and KL scores. The ORs for cartilage lesion worsening in the medial femur were 1.56 ($P < 0.0001$) for a 1-unit increase in BMI-specific T_2 Z-scores and 1.63 ($P < 0.0001$) for an increase gender-specific T_2 Z-scores.

In all of the analyses described above, the results did not change when adjusting for T_2 Z scores in other cartilage regions, or age, or gender. The results were also similar after excluding the $n = 239$ that overlap with the reference cohort.

Predicted Probability of OA Worsening

Figure 2 shows the predicted probability of worsening of 1) cartilage WORMS in the medial femur, 2) cartilage WORMS in any region, 3) JSN, and 4) KL score by category of baseline medial femur cartilage T_2 Z-score. We chose to focus on the medial femur T_2 specifically, as most of the significant associations occurred in this region, and because medial OA occurs more frequently than lateral OA.[26,27] Baseline medial femur cartilage T_2 Z-scores from 2 to 4 ($n = 49$) were associated with a 0.70 ± 0.03 (SE) predicted probability of worsening WORMS score in any region, a 0.38 ± 0.05 probability of worsening in the medial femur WORMS score, a 0.28 ± 0.06 probability of worsening JSN, and a 0.31 ± 0.05 probability of worsening KL score. These predicted probabilities were significantly greater compared to knees with a T_2 Z-score of –1 to 1 ($n = 347$ as shown in Fig. 2). In knees with an elevated baseline medial femur T_2 (Z-score 2–4), the predicted probability of WORMS cartilage worsening in any region was ~18% higher, the probability of worsening JSN was ~20% higher, and the probability of worsening KL score was ~20% higher compared to the reference group of knees with a Z-score of –1 to 1.

Discussion

This study showed that baseline cartilage T_2 Z-scores, and particularly those in the medial femur, are predictive of worsening of cartilage lesions over 4 years and radiographic OA measured by JSN/KL score change after 8 years. Having a medial femur cartilage Z-score that is 2–4 standard deviations above that of "reference" cartilage (defined as average cartilage T_2 in 45–65-year-old subjects without focal cartilage defects) is associated with an ~20% higher probability of worsening of JSN score over 8 years. Thus, subjects with substantial biochemical cartilage alterations measured with T_2 values are more likely to develop future joint degeneration than those with a normal cartilage extracellular matrix. The results of this study are part of the initial steps in establishing the cartilage T_2 Z-score as a prognostic biomarker for prediction for knee OA.

This study assessed the role of standardized cartilage T_2 Z-scores for the prediction of changes in MRI and radiographic measures of knee OA over 4 to 8 years in a large sample of subjects. The motivation for this work stems from the fact that interpretation of a "raw" cartilage T_2 value is ambiguous in the context of OA, and having a standardized value would aid in interpretation. A T_2 value can depend on many factors, including the type of MRI scanner,[28] MRI field strength,[28] radiofrequency coil,[29] MRI pulse sequence,[30] and T_2 fitting method[25] used. Even with standardized measuring procedures, cartilage T_2 values differ based on subject demographics, and understanding the meaning of a "raw" T_2 value in the context of OA hinges on comparisons to a reference group of healthy subjects, similar to the role of T-scores in osteoporosis. The cartilage T_2 Z-scores in this study are a first step in addressing standardization of T_2 values and developing their role as a potential imaging biomarker.

Knowing a T_2 Z-score may be beneficial for clinicians to identify patients at risk for OA progression; these patients would benefit most from modifiable lifestyle changes that slow OA progression. During early stages of biochemical cartilage degeneration (detected by elevated cartilage T_2 Z-scores) prior to irreversible cartilage defects, modification of certain risk factors for OA can delay or prevent morphologic degeneration.[31] Such modifiable risk factors include obesity, sedentary lifestyle, and vigorous exercise. Previous studies have shown that weight change[15,32] and various levels of exercise[14] impact OA changes in the knee joint as shown by MRI. Thus, implementing weight loss and moderate exercise, lifestyle interventions at the earliest stages of disease would be crucial for subjects to improve long-term symptoms and overall knee degeneration (especially those at high risk for progression).

The BMI- and gender-specific T_2 Z-scores yielded similar ORs for incidence/progression as the overall nonspecific Z-scores. While these results are somewhat unexpected, given that a cartilage T_2 value can vary with BMI,[8,32,33] these results suggest that demographic specific Z-scores are not essential for the prediction OA, thus yielding a technique that may be simpler for clinical translation and application.

In order for a measurement to become an established biomarker, it must fulfill any of the following biomarker criteria, which include providing a diagnosis of the disease, quantifying the disease burden, assessing prognosis, and assessing efficacy of intervention.[34] This classification, developed by Bauer et al,[34] is based on a previous article published by the Osteoarthritis Biomarkers Network, which is a consortium of five sites, funded by the National Institutes of Health / National Institute of Arthritis, Musculoskeletal, and Skin Disease (NIH/NIAMS) to develop and

characterize new biomarkers and refine existing OA biomarkers.[34,35] Cartilage T_2 quantification addresses these criteria: 1) it differentiates OA subjects and controls without OA[5,36]; 2) it allows quantification of disease *burden* through associations with clinical symptoms[5,37]; 3) it has *prognostic capabilities* through prediction of irreversible morphologic degeneration[38]; and 4) it allows assessment of the *efficacy of intervention* following surgical procedures.[39] The results from this study complement the consortium of data for *prognostic assessment of OA*, and help to establish cartilage T_2 as a biomarker for OA.

Of interest, the OR values from this study, which quantify the relationship between baseline T_2 Z score and incidence/progression of future OA, are similar in magnitude to relative risk (RR) values quantifying the relationship between bone mineral density and fracture risk. Sistrom and Garvan[40] describe that the OR and RR values are comparable when the probability of the outcome is low; a rule of thumb is that the OR should be corrected when incidence of the outcome being studied is greater than 10% if the OR is greater than 2.5 or the OR is less than 0.5.[41] Since the outcomes in this study are >10%, the ORs may slightly overestimate the RRs. For a direct comparison to fracture RR, we calculated RR values for the results in Table 2, which range from RR = 1.11 for lateral femur T_2 predicting any increase in WORMS, to 1.71 for lateral tibia T_2 predicting the increase in KL over 8 years (slightly lower than the OR values). For comparison, the Study of Osteoporotic Fractures reported relative risk values to predict hip fracture from 1.4 (from a one unit increase in spine BMD T-score) to 2.4 (from a one unit increase in hip BMD T-score).[42] Accordingly, the magnitudes of risk for prediction of fracture and odds for prediction of OA are approximately comparable.

Several limitations are pertinent to this study, including the generalizability of the results and focus on the assessment of only cartilage T_2. First, this method requires T_2 information from a reference cohort without OA: The Z-scores calculated in this study are based on a reference database derived from scanning parameters described in the OAI, as well as the fitting and quantification parameters described in this article. For Z-score implementation in the clinic, it is critical to use the same standardized scanning and quantification procedures for both patients and for the reference normal sample. Comparability between T_2 measurements obtained by different techniques has not been established, and the performance of T_2 derived by other methods in predicting knee OA outcomes is unknown. In addition, this study does not provide age-specific Z-scores, as the reference database only had data on a relatively small age range (45–65 years), and T_2 in all cartilage regions except the patella was not significantly associated with age. However, age matching may be a consideration for future studies, as others have found positive associations between age and T_2.[43] While males are underrepresented in this study (35.6%), the disproportionate gender distribution did not significantly impact the results. In addition, aside from cartilage T_2, it would be beneficial to study other quantification techniques such as cartilage T_1rho mapping and dGEMRIC (delayed gadolinium enhanced MR of cartilage) that are sensitive to proteoglycan in the extracellular matrix. We were only able to investigate cartilage T_2, as T_1rho and dGEMRIC were not available in the OAI. In addition, this study did not analyze joint topography or focal cartilage defects. Since cartilage is not a homogeneous structure (having a varied collagen network from the deep to superficial zone), calculating mean T_2 of the entire cartilage region may not capture laminar variations or detect focal cartilage lesions. Thus, for future studies, it would be important to investigate techniques that assess the heterogeneity of cartilage structure such as texture analysis and include laminar analysis.[12,44–46] Finally, not all subjects had X-ray (KL/JSN) data available at 8-year follow-up; there may have been participants with baseline and 4-year X-rays that showed no worsening, but indeed worsened over the next 4 years. In such a case, this study would count this participant as not having worsening of KL/JSN over 8 years, but this could only be confirmed over 4 years. Despite these limitations, we believe this study is valuable for understanding the feasibility of the use of cartilage T_2 Z-scores for predicting future OA.

Overall, this study showed that standardized cartilage T_2 values (especially in the medial femur) are associated with future cartilage and whole joint degeneration evidenced by worsening in WORMS cartilage scores over 4 years and worsening in JSN and KL scores over 8 years. The use of standardized cartilage T_2 Z-scores enables clinicians to understand the significance of a subject's T_2 value compared to a reference population without cartilage degeneration. The results suggest that participants with elevated cartilage T_2 (especially those that are 2–4 SDs above the reference values) are significantly more likely to have structural worsening of OA than participants with normal T_2 values. Since cartilage T_2 Z-score elevations are signs of early degenerative changes in the extracellular matrix, they may aid clinicians in identifying the earliest biochemical changes that may lead to morphologic, irreversible OA, and therefore implement preventative efforts such as lifestyle modifications (ie, weight loss and moderate exercise).

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