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## Baseline mean and heterogeneity of MR cartilage T<sub>2</sub> are associated with morphologic degeneration of cartilage, meniscus, and bone marrow over 3 years – data from the Osteoarthritis Initiative

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### SUMMARY

**Objective**—The purpose of this study is to determine whether the mean and heterogeneity of magnetic resonance (MR) knee cartilage T<sub>2</sub> relaxation time measurements at baseline are associated with morphologic degeneration of cartilage, meniscus, and bone marrow tissues over 3 years in subjects with risk factors for osteoarthritis (OA).

**Design**—Subjects with risk factors for OA ( $n = 289$ ) with an age range of 45–55 years were selected from the Osteoarthritis Initiative (OAI) database. 3.0 Tesla MR images were analyzed using morphological gradings of cartilage, bone marrow and menisci whole-organ magnetic resonance imaging scores (WORMS scoring). A T<sub>2</sub> mapping sequence was used to assess the mean and heterogeneity of cartilage T<sub>2</sub> (gray level co-occurrence matrix texture analysis). Regression models were used to assess the relationship between baseline T<sub>2</sub> parameters and changes in morphologic knee WORMS scores over 3 years.

**Results**—The prevalence of knee abnormalities in the cartilage ( $P < 0.0005$ ), meniscus ( $P < 0.00001$ ), and bone marrow significantly ( $P < 0.00001$ ) increased from baseline to 3 years in all compartments combined. The baseline mean and heterogeneity of cartilage T<sub>2</sub> were significantly

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#### Authors' contributions

GBJ assisted with the study design, performed T<sub>2</sub> assessment, performed statistical analysis, and drafted the manuscript. TB assisted in designing the study, supervised the cartilage segmentation, helped interpret the data, and helped perform the analysis. JCG developed the software for T<sub>2</sub> mapping quantification and texture analysis. LN performed WORMS grading and cartilage segmentations. WV performed WORMS grading. HA performed cartilage segmentation. JAL participated in the study design and patient selection. MCN assisted with data interpretation and manuscript revision. CM advised with and helped perform the statistical analysis. SM participated in the conceptual design of the study, data interpretation, and analysis. TML participated in the design of the study, interpretation of data, performing WORMS scoring, and manuscript revision. All authors have read and approved the manuscript.

#### Competing interests

The authors declare that they have no competing interests.

( $P < 0.05$ ) associated with morphologic joint degeneration in the cartilage, meniscus and bone marrow over 3 years.

**Conclusions**—The prevalence of knee abnormalities significantly increased over 3 years; increased cartilage  $T_2$  at baseline predicted longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA.

## Keywords

Osteoarthritis; Cartilage;  $T_2$  mapping; Magnetic Resonance Imaging; Osteoarthritis Initiative

## Introduction

Osteoarthritis (OA) is a heterogeneous disease characterized by joint degeneration including the progressive loss of hyaline articular cartilage, development of subchondral sclerosis, and degradation of the meniscus and bone marrow. While OA typically demonstrates gross morphologic changes in the joint, the initial degenerative changes occur on a cellular level, and can be quantified using novel Magnetic Resonance Imaging (MRI) techniques. The early stages of cartilage degeneration include proteoglycan loss, increased water content, and disorganization of the collagen network, which lead to morphologic degeneration. MRI  $T_2$  relaxation time is a technique sensitive to early biochemical changes in cartilage, including water content<sup>1</sup>, and collagen fiber orientation<sup>2</sup> and has been proposed as a marker for early OA. Previous studies have demonstrated that mean cartilage  $T_2$  relaxation time is significantly elevated in subjects with OA<sup>3,4</sup>, signifying degenerative changes in the collagen structure/content and mobility of water in the extracellular matrix (ECM)<sup>5</sup>. In addition to mean  $T_2$ , gray level co-occurrence matrix (GLCM) texture analysis, a method developed by Haralick *et al.*<sup>6</sup>, has been used to assess the spatial distribution of cartilage  $T_2$ . Preliminary studies have shown that subjects with OA have a more heterogeneous distribution of  $T_2$  values than controls<sup>7–9</sup>, demonstrating that the mean and heterogeneity of cartilage  $T_2$  pixels may be indicative of early cartilage matrix degeneration. The current study aims to further evaluate the potential of cartilage  $T_2$  as a marker for morphologic degenerative knee changes in OA, by studying the longitudinal evolution of OA in subjects with risk factors for the disease.

The Osteoarthritis Initiative (OAI; <http://www.oai.ucsf.edu/>) is a multi-center, longitudinal study aimed at assessing biomarkers in OA including those derived from MR imaging. The OAI is a cross-sectional and longitudinal dataset that includes both MRI and radiographic images of subjects scanned annually over 8 years, of which 3 years are currently available. This database provides a means to longitudinally evaluate MRI biomarkers including  $T_2$  relaxation time in the development and progression of OA, thus providing a wealth of information on OA development and progression.

The purpose of this study is to determine whether the mean and heterogeneity of MR knee cartilage  $T_2$  relaxation time measurements at baseline are associated with morphologic degeneration of cartilage, meniscus, and bone marrow tissues over 3 years in subjects with risk factors for OA.

## Methods

### Subjects

A subset of subjects ( $n = 289$ ) from the incidence cohort of the OAI was selected for this study, as described below. Subjects in the incidence subcohort did not have symptomatic knee OA, defined as frequent symptoms and radiographic OA in the same knee, in either knee at baseline. Frequent knee symptoms were defined as ‘pain, aching, or stiffness in or

around the knee on most days for at least 1 month during the past 12-months'. Radiographic knee OA was defined as definite tibiofemoral osteophytes (OARSI atlas grades 1–3, equivalent to Kellgren and Lawrence (KL) grade 2 on fixed flexion radiographs) in either knee at baseline<sup>10</sup>. However, participants in this cohort had risk factors for OA including knee symptoms without radiographic OA, overweight (ages 45–69 males > 205 lbs, females > 170 lbs), (knee injury, knee surgery, family history of total knee replacement, or Heberden's Nodes<sup>10</sup>). The exclusion criteria for the OAI included rheumatoid arthritis, bilateral total knee joint replacement, and a positive pregnancy test. For this study, we specifically included subjects with an age range of 45–55 years. Such individuals are of interest, as they may most benefit from treatment or behavioral interventions. Based on these criteria, 1055 subjects were eligible for the study. Of those, every third subject ( $n = 352$ ) was randomly selected to account for timing of cartilage segmentation and whole-organ magnetic resonance imaging scores (WORMS) readings. Next, subjects with KL grades > 2 and subjects with missing follow-up images were excluded, yielding a final sample size of  $n = 289$ . The following OAI datasets were assessed in this study: baseline clinical dataset 0.2.2, baseline imaging datasets 0.E.1 and 0.C.2, 36 month follow-up clinical dataset 5.2.1, and 36 month follow-up imaging datasets 5.E.1 and 5.C.1. All OAI study participants signed consent forms for participation in the study.

### Knee radiographs

Bilateral standing posterior–anterior fixed flexion knee radiographs were acquired at baseline. Knees were positioned in a Plexiglas frame (SynaFlexer, CCB-R-Synarc, Newark, CA, USA) with 20°–30° flexion and 10° internal rotation of the feet. Right knee radiographs were graded by two radiologists (LN with 4-years of experience and WV with 7-years of experience) in consensus by using the KL scoring system<sup>11</sup>.

### MR imaging

MR images were obtained using four identical 3.0 Tesla (Siemens Magnetom Trio, Erlangen, Germany) scanner and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) in Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania; Pawtucket, Rhode Island. The following sequences were acquired and used for image analysis: sagittal two dimensional (2D) intermediate-weighted fast spin-echo sequence (TR/TE = 3200/30 ms, spatial resolution = 0.357 mm × 0.511 mm, slice thickness = 3.0 mm), coronal 2D intermediate-weighted fast spin-echo sequence (TR/TE = 3700/29 ms, spatial resolution = 0.365 mm × 0.456 mm, slice thickness = 3.0 mm), sagittal three dimensional (3D) dual-echo in steady state sequence (TR/TE = 16.3/4.7 ms, spatial resolution = 0.365 mm × 0.456 mm, slice thickness = 0.7 mm) and a 3D fast low angle shot sequence with selective water excitation (TR/TE = 20/7.57 ms, spatial resolution = 0.313 mm × 0.313 mm, slice thickness = 1.5 mm). A sagittal 2D multi-slice multi-echo sequence (MSME, TR = 2700 ms, TE<sub>1</sub>–TE<sub>7</sub> = 10–70 ms, spatial resolution = 0.313 mm × 0.446 mm, slice thickness = 3.0 mm, and 0.5 mm gap) was used for T<sub>2</sub> measurements<sup>12</sup>.

### WORMS scoring

MR images of the right knee obtained at baseline and after 3-years were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgely, NJ, USA). MR images were read with baseline and follow-up paired and in known chronological order. A board certified radiologist (WV) with 7-years of experience and a 5th-year radiology resident (LN) with 4-years of experience read the images independently and graded meniscal and cartilage lesions as well as bone marrow edema pattern (BMEP). Cartilage lesions and BMEP were assessed in five compartments (patella, medial femur, medial tibia, lateral femur and lateral tibia) using a modified semi-quantitative WORMS<sup>13–15</sup>, with the highest grade of lesion recorded for each region. In case of disagreement, a consensus

reading was performed with a musculoskeletal radiologist with 22-years of experience (TML). For calibration purposes, the first 20 cases were read simultaneously by the three readers in consensus. Compared to the original WORMS grading system, only five compartments were analyzed as relatively mild lesions were expected. This could have potentially affected the number of grade 4 or grade 6 cartilage lesions as well as grade 3 BME lesions, all of which, however, are rare. The trochlea was not analyzed because T<sub>2</sub> measurements were not quantified in this compartment due to flow artifacts from the popliteal artery (that may have affected the accuracy of quantification). Cartilage signal and morphology were scored using an eight-point scale: 0 = normal thickness and signal; 1 = normal thickness but increased signal on T<sub>2</sub>-weighted images; 2.0 = partial-thickness focal defect <1 cm in greatest width; 2.5 = full-thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial-thickness (grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but <75% of the region; 4 = diffuse ( 75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6 = diffuse ( 75% of the region) full-thickness loss. Meniscal morphology was assessed in six regions using a modified WORMS score: the medial and lateral sides of the anterior, body, and posterior region; an additional grade was added to the meniscal classification “intrasubstance degeneration” to better assess early degenerative disease. The grading scale ranged from 1 to 4: 0 = normal, 1 = intrasubstance abnormalities, 2 = non-displaced tear, 3 = displaced or complex tear, and 4 = complete destruction. Sub-articular bone marrow abnormalities were defined as poorly margined areas of increased signal intensity in the normal subchondral and epiphyseal bone marrow on T<sub>2</sub>-weighted fast spin-echo fast-suppressed MR images. A four-point grading scale was employed to assess the size of the bone marrow abnormalities: 0 = none, 1 = minimal (<25% of region); 2 = moderate (25–50% of region); and 3 = severe (>50% of region)<sup>16</sup>.

## Image analysis

All images were analyzed using a Sun Workstation (Sun Microsystems, Palo Alto, CA, USA). Knee articular cartilage was segmented manually in five compartments: (patella, medial femur, medial tibia, lateral femur and lateral tibia) as previously reported<sup>16,17</sup>. An IDL software routine was implemented to manually segment the cartilage from the T<sub>2</sub> maps by one operator (HA). In order to exclude potential chemical shift artifacts or fluid from the region of interest, the user simultaneously examined the T<sub>2</sub> map and the first echo of the MSME sequence (in neighboring image panels) with synchronized cursor/slice number/zoom.

T<sub>2</sub> maps were computed based on equation 1 from the MSME images on a pixel-by-pixel basis using six echoes (TE = 20–70 ms) and three parameter fittings accounting for noise<sup>18,19</sup>.

$$S(TE)^2 = S_0^2 e^{-\frac{2TE}{T_2}} + B^2 \quad (1)$$

In equation 1,  $S$  is the signal intensity at a given echo time ( $TE$ ),  $S_0$  is the signal intensity at  $TE = 0$  ms, and  $B$  is the estimated noise at a given  $TE$ . The first echo ( $TE = 10$  ms) was not included in the T<sub>2</sub> fitting procedure in order to reduce potential errors resulting from stimulated echoes in a multi-echo Carr–Purcell–Meiboom–Gill sequence<sup>20,21</sup>. A noise-corrected algorithm was implemented based on results from a recent study demonstrating increased accuracy and precision of T<sub>2</sub> relaxation time when using with a noise correction algorithm as compared to the traditional uncorrected exponential fit<sup>18,19</sup>.

## Texture analysis

Texture analysis was performed on a slice-by-slice basis on the cartilage T<sub>2</sub> maps. This method is based on the GLCM as described by Haralick *et al.*<sup>6</sup>. The GLCM determines the frequency that neighboring gray-level values occur in an image. GLCM texture parameters including contrast, variance, and entropy were calculated in each cartilage region. Each texture parameter provides unique information on the spatial distribution of T<sub>2</sub> values in the cartilage. The equations for contrast, variance, and entropy are shown below (equations 2–4), respectively.

$$Entropy = \sum_{i=1}^N \sum_{j=1}^N P(i, j) (-\ln P(i, j)) \quad (2)$$

$$Variance = \sum_{i,j=0}^{N-1} P_{i,j} (i - \mu_{i,j})^2$$

where

$$\mu_{i,j} = \sum_{i,j=0}^{N-1} i(P_{i,j}) \quad (3)$$

$$Contrast = \sum_{i=1}^N \sum_{j=1}^N P(i, j) (i - j)^2 \quad (4)$$

$P$  represents the probability of the co-occurrence of pixel values  $i$  and  $j$  in an image.  $N$  represents the total number of pixel value co-occurrences in the image, and  $R$  is a normalizing constant. A pixel offset of 1-pixel was chosen based on the fact that approximately 3–4 pixels span the cartilage thickness. Analysis was performed using averaging the GLCM parameters across four orientations (0°-corresponding to the anterior–posterior axis, 45°, 90°-corresponding to the superior–inferior axis, and 135°).

## Statistical analysis

Statistical analysis was performed using STATA 11 software (StataCorp, College Station, TX, USA). Three GLCM texture parameters were analyzed (GLCM contrast, GLCM variance, and GLCM entropy), and were regarded as representative parameters from each of the three texture groups (contrast, statistics, and order, respectively)<sup>22</sup>. These texture parameters were selected based on results from previous studies demonstrating their elevation in subjects with OA<sup>8,9,23</sup>.

The prevalence of joint abnormalities was expressed as dichotomous variable. The changes in the prevalence of joint abnormalities from baseline to 3-year follow-up were assessed using McNemar's tests.

In addition to McNemar's tests, the prevalence of subjects with incident knee lesions [no lesions at baseline (WORMS = 0) and development of knee lesions at 3-year follow-up (WORMS > 0)] and with progression of knee lesions (knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up) were calculated.

The associations between baseline T<sub>2</sub> parameters and changes in joint morphology over 3 years were assessed in each compartment using logistic regression models with  $x$ -standardized coefficients, such that reported coefficients are per a one standard deviation (SD) change in the predictor. Logistic regression models were used for the prediction of a

dichotomous outcome variable. The outcome variable was: subjects with no changes in joint morphology over 3 years ( $\Delta$  WORMS = 0) vs subjects with increases in joint morphology over 3 years ( $\Delta$  WORMS > 0). The regression models were adjusted for baseline age, gender, body mass index (BMI), and KL score.

The analyses were subdivided into primary and exploratory compartmental predictors. The primary predictors focused on compartments with the highest prevalence of abnormalities to minimize errors due to multiple comparisons. Thus, the (1) patellar cartilage (2) posterior horn of the medial meniscus and (3) patellar BMEP were assessed. The remaining compartments were examined in an exploratory manner.

### Reproducibility measurements

The reproducibility of WORMS scoring for meniscus, cartilage and bone marrow lesion tissues was investigated in 15 subjects, read twice by two radiologists independently. An intra-class correlation coefficient (ICC) was calculated to determine the intra- and inter-reader reproducibility errors<sup>24</sup>. The reproducibility of mean  $T_2$  and texture analysis was determined by segmenting the cartilage in 15 subjects, three times by one operator (HA). The reproducibility error was calculated as the root mean square (RMS) coefficient of variation (CV) of the repeated measurements as described by Glüer *et al.*<sup>25</sup>.

## Results

### Baseline subject characteristics

The mean age of the subject cohort ( $n = 289$ ) was  $50.73 \pm 2.89$  years and the mean BMI was  $27.71 \pm 4.47$  kg/m<sup>2</sup>. Other subject characteristics are listed in Table I.

### Reproducibility

The reproducibility results are listed in Table II. In summary, the intra-observer reproducibility in all tissues (meniscus, cartilage, bone marrow) was 96%, while the inter-observer reproducibility was 97%. The mean  $T_2$  values had RMS CV ranging from 0.83% in the medial femur to 3.21% in the patella. GLCM entropy exhibited the lowest CVs (<3%), while contrast and variance had CVs <7.2%.

### Prevalence and progression of knee abnormalities

Of all tissues, cartilage lesions were the most prevalent: 238 subjects (82.35%) had at least one lesion at baseline and 250 subjects (86.50%) had at least one lesion at follow-up (Table III). Meniscus lesions were second-most in prevalence (191 subjects, 66.09% at baseline; and 212 subjects, 73.36% at follow-up; Table III) followed by BMEP (139 subjects, 48.43% at baseline; and 169 subjects, 58.48% at follow-up; Table III).

The patella demonstrated the highest rate of cartilage abnormalities (191 subjects, 66.08% at baseline; 206 subjects, 71.28% at 3-year follow-up; Table III). The highest prevalence of meniscus lesions was located in the medial posterior compartment (161 subjects, 55.70% at baseline; 177 subjects, 61.24% at 3-year follow-up; Table III). The patella also exhibited the highest rate of BMEP abnormalities (78 subjects, 26.98% at baseline; 102 subjects, 35.29% at 3-year follow-up; Table III).

The increase in prevalence of knee abnormalities over 3 years was statistically significant ( $P < 0.05$ ) for all meniscus compartments and most cartilage compartments (Table III). For BMEP, only the patella and medial femur compartments showed a significant increase in prevalence over 3 years (Table III).



Table IV reports the percentages of both incident lesions and progression of lesions; subjects with incident knee lesions have no lesions at baseline (WORMS = 0) and develop knee lesions at 3-year follow-up (WORMS > 0), subjects with progression of knee abnormalities have knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up. The medial posterior meniscus had the highest number of incident lesions (16 subjects, 5.53%) and the highest number of progressing lesions (20 subjects, 6.92%). Interestingly, the lateral posterior meniscus also had a high number of incident lesions (16 subjects, 5.53%) but a low number of progressive lesions (two subjects, 0.69%). The patella had the highest number of incident knee cartilage lesions (15 subjects, 5.19%) and progressing knee lesions (34 subjects, 11.76%) followed by the medial femur (incident lesions: eight subjects, 2.76%; progressing lesions: 10 subjects, 3.46%). Incident and progressing BMEP were most prevalent in the patella (incident lesions: 24 subjects, 8.30%; progressing lesions: 14 lesions, 4.84%).

### Association between baseline T<sub>2</sub> parameters and changes in knee morphology

Table V summarizes the results for cartilage, meniscus and bone marrow tissues. This table focuses on joint compartments with the highest prevalence of abnormalities (patellar cartilage, posterior horn of the medial meniscus, and patellar BMEP), and thus reports compartments with the highest statistical significance. The results demonstrate that elevated mean and heterogeneity of T<sub>2</sub> values at baseline predict cartilage, meniscus, and bone marrow degeneration after 3 years. Figure 1 shows representative images from a subject with elevated baseline cartilage T<sub>2</sub> parameters and both incidence and progression of morphologic joint degeneration in the medial femoral condyle.

#### Cartilage

Subjects with longitudinal increases in cartilage lesion scores ( $\Delta$  cartilage WORMS > 0 over 3-years) had greater baseline mean T<sub>2</sub> values than subjects with no longitudinal changes in cartilage lesion scores ( $\Delta$  cartilage WORMS = 0 over 3-years) in all compartments. The baseline mean T<sub>2</sub> in the patella was  $34.55 \pm 7.36$  ms in subjects with increasing WORMS scores ( $n = 49$ ) and was  $32.50 \pm 4.00$  ms in subjects with no change in WORMS scores ( $n = 240$ , odds ratio (OR) per SD change = 1.41,  $P = 0.025$ ). Similar trends were evident for GLCM contrast in the patella (OR per SD change = 1.27,  $P = 0.079$ ). The remaining baseline GLCM texture parameters were elevated in subjects with longitudinal progression of cartilage lesions, but these differences were not significant ( $P > 0.05$  for all compartments).

#### Meniscus

Baseline GLCM entropy of cartilage T<sub>2</sub> was elevated in subjects whose meniscus WORMS scores increased over 3 years ( $\Delta$  meniscus WORMS > 0) compared to subjects whose meniscus scores did not change ( $\Delta$  meniscus WORMS = 0), as listed in Table V. Subjects with longitudinal increases in their medial posterior meniscus WORMS scores ( $n = 36$ ) had greater cartilage GLCM entropy at baseline than subjects that had no changes in meniscal WORMS scores in the medial femur ( $7.02 \pm 0.21$  vs  $6.94 \pm 0.20$ , OR = 2.71,  $P = 0.057$ ) and the medial tibia ( $6.10 \pm 0.37$  vs  $5.91 \pm 0.30$ , OR per SD change = 2.75,  $P = 0.003$ ).

#### BMEP

Baseline cartilage T<sub>2</sub> parameters including mean T<sub>2</sub>, GLCM variance, and GLCM contrast were elevated in subjects with longitudinal increases in BMEP WORMS scores. The patellar compartment, in particular, demonstrated significant differences between groups in the mean T<sub>2</sub> ( $\Delta$  BMEP WORMS > 0:  $35.08 \pm 7.00$  ms;  $\Delta$  BMEP WORMS = 0:  $32.36 \pm 3.93$  ms, OR per SD change = 1.65,  $P = 0.003$ ), GLCM contrast ( $\Delta$  BMEP WORMS > 0:  $348.04 \pm$

208.04;  $\Delta$  BMEP WORMS = 0:  $282.16 \pm 139.13$ , OR per SD change = 1.57,  $P = 0.003$ ), and GLCM variance ( $\Delta$  BMEP WORMS > 0:  $271.43 \pm 173.41$ ;  $\Delta$  BMEP WORMS = 0:  $212.20 \pm 100.50$ , OR per SD change = 1.55,  $P = 0.001$ ), Table V.

## Discussion

This study evaluated cartilage biochemical composition and knee joint morphology in subjects with risk factors for OA. Our data show that increased cartilage  $T_2$  at baseline is associated with longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA. The GLCM contrast, entropy, and variance parameters each provide unique information on the spatial heterogeneity of the cartilage, and each was associated with morphologic joint degeneration. This study highlights the complex interactions between the various joint tissues involved in OA, and suggests that cartilage biochemical composition may play an integral role in the development and progression of morphologic disease.

Morphologic joint degeneration in cartilage is often preceded by biochemical alterations in the ECM. A theory of the potential mechanisms that link cartilage biochemical degeneration to future gross degradation in other joint tissues centers on mechanical loading. Initially, degenerative changes in the ECM disrupt the mechanical properties in cartilage tissue, thus reducing its ability to withstand load. The increasing number of large-diameter collagen fibrils in degenerative cartilage<sup>26</sup> cause the closely-knit collagen network to loosen, thus initiating a transformation from a highly structured entity to a random configuration. Changes to the cartilage matrix result in increased tissue stiffness and increased permeability<sup>27</sup>, consequently altering the mechanical loading environment in the joint and predisposing surrounding tissues to damage<sup>28</sup>. Bone tissue, for example, can be indirectly affected by changes in the mechanical properties of cartilage: biochemically compromised cartilage may develop micro-cracks that lead to BME, bleeding, and necrosis<sup>29</sup>. Such a relationship was detected in this study, revealing that disrupted cartilage biochemistry at baseline was predictive of the development and progression of BMEP. Thus, the initial degenerative changes in cartilage biochemical composition may disrupt the delicate equilibrium of joint mechanical loading and consequently lead to morphologic degeneration in the surrounding tissues, as seen in this study over 3-years.

In addition to mean cartilage  $T_2$ , this study assessed the spatial distribution of cartilage  $T_2$  pixels using GLCM texture analysis. GLCM contrast is a measure of the differences in neighboring pixel values; high contrast signifies that many pixels with different values are neighboring. GLCM entropy is a measure of disorder in an image; high entropy signifies that the probability of pixel co-occurrence is uniform throughout an image. GLCM variance is a measure of the distribution of pixels about the mean; high variance signifies a high dispersion of co-occurrences of relaxation times. Elevations in the mean and heterogeneity of cartilage  $T_2$  relaxation time are indicative of early cartilage biochemical degeneration, as previously reported<sup>3,8,23,30,31</sup>; Such biochemical changes to the ECM characterize the initial stages of OA, eventually leading to gross joint degeneration, as detected in this study.

Previous research has evaluated the potential of MRI markers in predicting the development of radiographic OA over 6-years<sup>32</sup> and cartilage loss over 2-years<sup>33</sup>. Eckstein *et al.* studied an array of clinical, radiographic, molecular, and MRI-based markers, and reported that cartilage thickness, varus malalignment, reduced joint space width, and joint space narrowing at baseline predicted longitudinal cartilage thinning<sup>33</sup>. In contrast to the results of the current study,  $T_2$  was not predictive of OA progression. While the results of the two studies differ, notable differences are also evident in the methodology and subject selection between the two studies. First, Eckstein *et al.* calculated cartilage  $T_2$  using two echo times,



while the current study acquired images with seven echo times; the number of echo times used for quantification may affect the accuracy of  $T_2$  quantification. Second, the subjects in Eckstein *et al.*'s study had KL grades of 2–3 while the majority of subjects in the current study had KL grades 0–1 ( $n = 271$ ); thus a marked difference in disease severity was evident between subject cohorts. Collectively, these studies suggest that the utility of  $T_2$  in predicting morphologic progression may be optimal at early stages of disease, in subjects without pronounced radiographic OA.

In addition to predicting morphologic cartilage degeneration over 3 years, abnormal cartilage biochemical composition at baseline was associated with longitudinal meniscus degradation. The meniscus provides joint stability, lubrication, and shock absorption to the joint<sup>34</sup> and lies adjacent to the articular cartilage; thus degeneration to the meniscus and cartilage tissues is often concomitant<sup>35–37</sup>. Studies have demonstrated a relationship between meniscus morphology and cartilage morphology<sup>35–37</sup> as well as cartilage biochemical composition<sup>38</sup>. Kai *et al.* established an association between meniscus signal-complex tears and increased MRI  $T_2$  values in the tibial articular cartilage<sup>38</sup>, and Zarins *et al.* reported an association between the presence of meniscal tears in the posterior horn of the medial meniscus and elevated  $T_2$  values in the medial tibial cartilage<sup>39</sup>. The results of the current study are consistent with those of other studies, highlighting an interaction between cartilage biochemical composition and meniscus degeneration.

The current research is novel, however, in its investigation of the heterogeneity of cartilage pixels in relation to joint morphology. Since the GLCM entropy of cartilage  $T_2$  was related to meniscus degeneration, this study suggests that a heterogeneous distribution of cartilage pixels may be predictive of future degenerative meniscus changes. In contrast to other studies, the mean  $T_2$  was not significantly predictive of meniscus degeneration. These findings may be related to the fact that this study focused on subjects with early or low-grade meniscus degeneration at baseline, while other studies recruited subjects with definite meniscus abnormalities: a majority of the subjects in this study had either no meniscus degeneration (WORMS = 0,  $n = 128$ ) or low-grade intrasubstance abnormalities (WORMS = 1,  $n = 93$ ) at baseline, compared to other studies that evaluated subjects with meniscal tears. As an additional exploratory analysis, the relationship between mean  $T_2$  and morphologic degeneration was assessed in only subjects with meniscal tears at baseline. When confining the analysis to subjects with meniscal tears (WORMS = 2) at baseline, the mean  $T_2$  was predictive of longitudinal meniscus degeneration, which is consistent with other studies<sup>38</sup>. Collectively, these results demonstrate that the spatial distribution and the mean of cartilage  $T_2$  values may be related to different stages of meniscus degeneration, and that these parameters may provide complementary information in the study of OA.

Several limitations are pertinent to this study. Other techniques such as dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) or T1 $\rho$  may have been useful in investigating the ECM during OA progression; however, this study did not assess these methods as they were not acquired in the OAI protocol. In addition, a comparison of texture parameters between subjects from the OAI incidence and normal control cohorts would have been of interest; however was not performed due to the time-consuming segmentation process. Finally, the WORMS score has inherent limitations due to its semi-quantitative nature; other quantitative scores such as the UCSF score<sup>40</sup> may be more sensitive in detecting longitudinal changes in joint morphology.

In conclusion, this study demonstrated that the prevalence of knee abnormalities significantly increased over 3 years, and that increased cartilage  $T_2$  at baseline is associated with longitudinal morphologic degeneration in the cartilage, meniscus, and bone marrow over 3 years in subjects with risk factors for OA.

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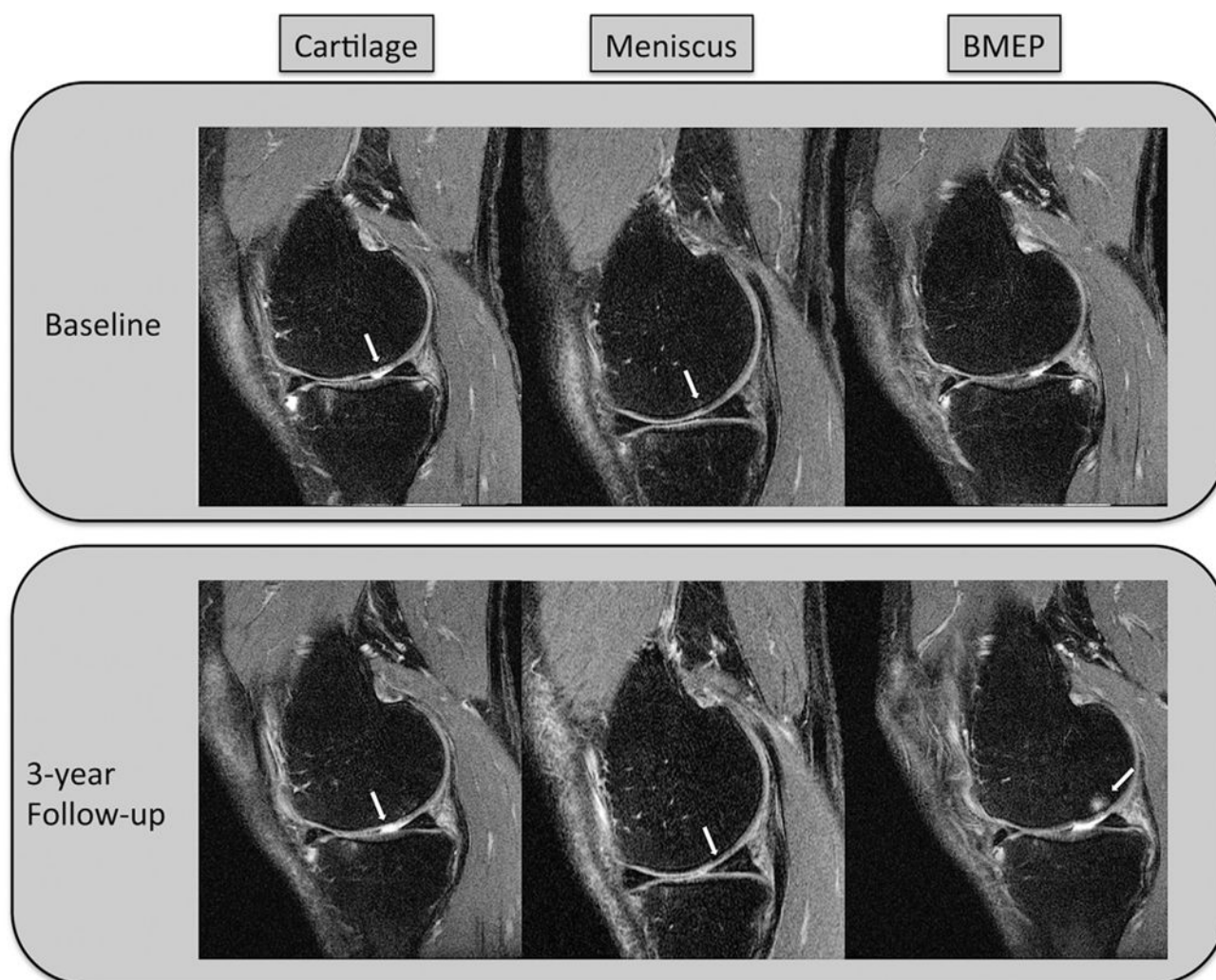
This manuscript has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

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**Fig. 1.**

Representative images (top row: baseline, bottom row: 3-year follow-up) from a subject with elevated baseline cartilage  $T_2$  parameters and both incidence and progression of morphologic joint degeneration in the medial femoral condyle.

*Cartilage morphology:* progression of cartilage defect (WORMS = 2.5 at baseline, WORMS = 5 at follow-up).

*Meniscus morphology:* progression from intrasubstance degeneration to a tear (WORMS = 1 at baseline, WORMS = 2 at follow-up).

*BMEP morphology:* absent at baseline and present at follow-up (WORMS = 0 at baseline, WORMS = 2 at follow-up).

**Table I**

## Subject characteristics

| Characteristic           | Incidence cohort |
|--------------------------|------------------|
| <i>n</i>                 | 289              |
| Age (years)              | 50.73 ± 2.89     |
| BMI (kg/m <sup>2</sup> ) | 27.71 ± 4.47     |
| <i>n</i> (females)       | 136 (47.0%)      |
| WOMAC pain score         | 0.98 ± 2.54      |
| <i>n</i> (KL score 0)    | 182 (62.9%)      |
| <i>n</i> (KL score 1)    | 89 (30.7%)       |
| <i>n</i> (KL score 2)    | 18 (6.2%)        |



Reproducibility measurements for WORMS and T<sub>2</sub> measurements. The reproducibility of WORMS scoring was investigated in 15 subjects, read out twice by two readers independently (ICC<sup>24</sup>). The reproducibility (CV%<sup>25</sup>) of T<sub>2</sub> measurements was determined in five subjects segmented three times each by one operator

Table II

| Tissue    | WORMS reproducibility |      | T <sub>2</sub> reproducibility |                    |                   |                  |                   |
|-----------|-----------------------|------|--------------------------------|--------------------|-------------------|------------------|-------------------|
|           | Reader                | ICC  | Compartment                    | T <sub>2</sub> [%] | GLCM contrast [%] | GLCM entropy [%] | GLCM variance [%] |
| Meniscus  | Reader 1              | 0.96 |                                |                    |                   |                  |                   |
|           | Reader 2              | 0.96 |                                |                    |                   |                  |                   |
|           | <i>Inter-reader</i>   | 0.97 |                                |                    |                   |                  |                   |
| Cartilage | Reader 1              | 0.98 |                                |                    |                   |                  |                   |
|           | Reader 2              | 0.95 |                                |                    |                   |                  |                   |
|           | <i>Inter-reader</i>   | 0.98 |                                |                    |                   |                  |                   |
|           |                       |      | Lateral femur                  | 1.23               | 3.20              | 1.16             | 4.06              |
|           |                       |      | Lateral tibia                  | 1.40               | 4.87              | 1.44             | 4.05              |
| BMEP      |                       |      | Medial femur                   | 0.83               | 2.72              | 1.59             | 2.04              |
|           |                       |      | Medial tibia                   | 2.44               | 3.84              | 2.59             | 4.40              |
|           |                       |      | Patella                        | 3.21               | 7.19              | 2.62             | 6.64              |
|           |                       |      | Mean                           | 1.82               | 4.36              | 1.88             | 4.24              |
|           | Reader 1              | 0.97 |                                |                    |                   |                  |                   |
|           | Reader 2              | 0.97 |                                |                    |                   |                  |                   |
|           | <i>Inter-reader</i>   | 0.97 |                                |                    |                   |                  |                   |

The reproducibility (CV%)<sup>25</sup> of T<sub>2</sub> measurements in five subjects segmented three times each by one operator.

**Table III**

The prevalence of knee abnormalities at baseline and 3-year follow-up. *P* values are based on McNemar's tests

|                       | Baseline             | 3-year follow-up     | <i>P</i> value |
|-----------------------|----------------------|----------------------|----------------|
|                       | <i>n</i> = 289 total | <i>n</i> = 289 total |                |
| Meniscus (WORMS > 0)  |                      |                      |                |
| Medial anterior       | 14 (4.84%)           | 19 (6.57%)           | <b>0.02</b>    |
| Medial body           | 63 (21.79%)          | 71 (24.56%)          | <b>0.01</b>    |
| Medial posterior      | 161 (55.70%)         | 177 (61.24%)         | <b>0.0001</b>  |
| Lateral anterior      | 31 (10.72%)          | 40 (13.84%)          | <b>0.002</b>   |
| Lateral body          | 46 (15.91%)          | 59 (20.41%)          | <b>0.0003</b>  |
| Lateral posterior     | 58 (20.06%)          | 74 (25.60%)          | <b>0.0001</b>  |
| All compartments *    | 191 (66.09%)         | 212 (73.36%)         | <b>0.00001</b> |
| Cartilage (WORMS > 0) |                      |                      |                |
| Patella               | 191 (66.08%)         | 206 (71.28%)         | <b>0.0001</b>  |
| Medial femur          | 69 (23.87%)          | 77 (26.64%)          | <b>0.0047</b>  |
| Medial tibia          | 27 (9.34%)           | 28 (9.68%)           | 0.317          |
| Lateral femur         | 52 (17.99%)          | 61 (21.10%)          | <b>0.0027</b>  |
| Lateral tibia         | 119 (41.17%)         | 128 (44.29%)         | <b>0.0027</b>  |
| All compartments *    | 238 (82.35%)         | 250 (86.5%)          | <b>0.0005</b>  |
| BMEP (WORMS > 0)      |                      |                      |                |
| Patella               | 78 (26.98%)          | 102 (35.29%)         | <b>0.0002</b>  |
| Medial femur          | 19 (6.57%)           | 29 (10.03%)          | <b>0.0124</b>  |
| Medial tibia          | 11 (3.80%)           | 13 (4.49%)           | 0.3173         |
| Lateral femur         | 17 (5.88%)           | 23 (7.95%)           | 0.0833         |
| Lateral tibia         | 27 (9.34%)           | 34 (11.76%)          | 0.0707         |
| All compartments *    | 139 (48.43%)         | 169 (58.48%)         | <b>0.00001</b> |

Bold values signify that  $P < 0.05$ .

\* All compartments: data points represent number of subjects with at least one lesion.

**Table IV**

The prevalence of subjects with (1) *incident knee lesions* (no lesions at baseline (WORMS = 0) and development of knee lesions at 3-year follow-up) (WORMS > 0), and (2) *progression of knee lesions* (knee lesions at baseline (WORMS > 0) that increase in severity at 3-year follow-up)

|                    | Number of subjects with incident lesions | Number of subjects with progression of lesions |
|--------------------|--|--|
| <b>Meniscus</b>    |  |  |
| Medial anterior    | 5 (1.73%)                                | 0 (0.00%)                                      |
| Medial body        | 9 (3.11%)                                | 10 (3.46%)                                     |
| Medial posterior   | 16 (5.53%)                               | 20 (6.92%)                                     |
| Lateral anterior   | 9 (3.11%)                                | 4 (1.38%)                                      |
| Lateral body       | 13 (4.49%)                               | 6 (2.07%)                                      |
| Lateral posterior  | 16 (5.53%)                               | 2 (0.69%)                                      |
| Total (knee level) | 21 (7.26%)*                              | 31 (10.72%) <sup>†</sup>                       |
| <b>Cartilage</b>   |  |  |
| Patella            | 15 (5.19%)                               | 34 (11.76%)                                    |
| Medial femur       | 8 (2.76%)                                | 10 (3.46%)                                     |
| Medial tibia       | 1 (0.34%)                                | 2 (0.69%)                                      |
| Lateral femur      | 9 (3.11%)                                | 11 (3.80%)                                     |
| Lateral tibia      | 9 (3.11%)                                | 10 (3.46%)                                     |
| Total (knee level) | 12 (4.11%)*                              | 40 (13.84%) <sup>†</sup>                       |
| <b>BMEP</b>        |  |  |
| Patella            | 33 (11.41%)                              | 14 (4.84%)                                     |
| Medial femur       | 13 (4.49%)                               | 2 (0.69%)                                      |
| Medial tibia       | 3 (1.03%)                                | 2 (0.69%)                                      |
| Lateral femur      | 9 (3.11%)                                | 2 (0.69%)                                      |
| Lateral tibia      | 11 (3.80%)                               | 7 (2.42%)                                      |
| Total (knee level) | 40 (13.8%)*                              | 25 (8.65%) <sup>†</sup>                        |

\* Defined as baseline WORMS Max = 0 and delta WORMS Max > 0.

<sup>†</sup> Defined as baseline WORMS Max > 0 and delta WORMS Max > 0.

Table V

The association between baseline cartilage T<sub>2</sub> parameters and changes in joint morphology over 3 years

| Joint tissue compartment* | Baseline cartilage T <sub>2</sub> parameter | Cartilage texture compartment | OR <sup>†</sup> | 95% confidence interval | P Value (adjusted) <sup>‡</sup> | P Values (unadjusted) |
|---------------------------|---|-------------------------------|-----------------|-------------------------|---------------------------------|-----------------------|
| Cartilage Patella         |   |                               |                 |                         |                                 |                       |
| Meniscus Medial posterior | Mean T <sub>2</sub> (ms)                    | Patella                       | 1.41            | 1.04                    | 1.91                            | <b>0.013</b>          |
|                           | Variance                                    | Patella                       | 1.23            | 0.96                    | 1.58                            | 0.068                 |
|                           | Entropy                                     | Patella                       | 0.71            | 0.42                    | 1.22                            | 0.110                 |
|                           | Contrast                                    | Patella                       | 1.27            | 0.97                    | 1.67                            | 0.570                 |
| BMEP Patella              | Mean T <sub>2</sub>                         | Medial tibia                  | 1.26            | 0.96                    | 1.65                            | 0.135                 |
|                           | Variance                                    | Medial tibia                  | 1.08            | 0.74                    | 1.57                            | 0.750                 |
|                           | Entropy                                     | Medial tibia                  | 2.75            | 1.41                    | 5.35                            | <b>0.002</b>          |
|                           | Contrast                                    | Medial tibia                  | 1.06            | 0.74                    | 1.53                            | 0.815                 |
|                           | Mean T <sub>2</sub>                         | Medial femur                  | 1.16            | 0.71                    | 1.90                            | 0.733                 |
|                           | Variance                                    | Medial femur                  | 1.08            | 0.63                    | 1.73                            | 0.928                 |
|                           | Entropy                                     | Medial femur                  | 2.71            | 0.97                    | 7.60                            | <b>0.039</b>          |
|                           | Contrast                                    | Medial femur                  | 0.84            | 0.49                    | 1.45                            | 0.587                 |
| BMEP Patella              | Mean T <sub>2</sub>                         | Patella                       | 1.65            | 1.19                    | 2.30                            | <b>0.003</b>          |
|                           | Variance                                    | Patella                       | 1.55            | 1.18                    | 2.02                            | <b>0.001</b>          |
|                           | Entropy                                     | Patella                       | 1.23            | 0.69                    | 2.17                            | 0.793                 |
|                           | Contrast                                    | Patella                       | 1.57            | 1.16                    | 2.13                            | <b>0.013</b>          |

\* The analyses were subdivided into primary and exploratory compartmental predictors. The primary predictors (listed in this table) focused on compartments with the highest prevalence of abnormalities to minimize errors due to multiple comparisons. Thus, (1) patellar cartilage (2) posterior horn of the medial meniscus and (3) patellar BMEP were assessed.

<sup>†</sup> The associations between baseline T<sub>2</sub> parameters and changes in joint morphology over 3 years were assessed using logistic regression models (adjusted for age, gender, BMI, and KL score) with x-standardized coefficients, such that reported ORs are per one SD change in the predictor. The outcome variable was dichotomous: subjects with no changes in joint morphology over 3 years ( $\Delta$  WORMS = 0) vs subjects with increases in joint morphology over 3 years ( $\Delta$  WORMS > 0). The SDs of cartilage T<sub>2</sub>, GLCM contrast, GLCM variance, and GLCM entropy among all subjects were: 5.12 ms, 146.70, 102.42, 0.54, respectively.

<sup>‡</sup> P-value adjusted for age, gender, BMI, and KL score. P-values < 0.05 are in bold.