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### Permalink

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### Journal

Journal of Magnetic Resonance Imaging, 47(2)

### ISSN

1053-1807

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### Publication Date

2018-02-01

### DOI

10.1002/jmri.25766

Peer reviewed

# Association of Diabetes Mellitus and Biochemical Knee Cartilage Composition Assessed by T<sub>2</sub> Relaxation Time Measurements: Data From the Osteoarthritis Initiative

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**Purpose:** To investigate the association of the presence and severity of diabetes mellitus (DM) with articular cartilage composition, using magnetic resonance imaging (MRI)-based T<sub>2</sub> relaxation time measurements, and structural knee abnormalities.

**Materials and Methods:** In the Osteoarthritis Initiative 208, participants with DM (age 63.0 ± 8.9 years; 111 females) and risk factors for osteoarthritis (OA) or mild radiographic tibiofemoral OA (Kellgren–Lawrence [KL] grade ≤2) were identified and group-matched with 208 controls without DM (age 63.3 ± 9.1 years; 111 females). Subjects with diabetes-related renal or ophthalmological complications or insulin treatment at baseline (*n* = 50) were defined as severe DM. 3T MR images of the right knee were assessed for articular cartilage T<sub>2</sub>, including texture and laminar analyses derived from the patella, medial, and lateral femur and tibia and for structural abnormalities using the modified whole-organ magnetic resonance imaging score (WORMS). Clustered linear regression analyses were used to assess associations of DM with MRI findings.

**Results:** DM subjects had significantly higher cartilage T<sub>2</sub> in the patella (mean difference 0.92 msec [95% confidence interval (CI) 0.79, 1.06]; *P* = 0.001) and medial femur (mean difference 0.36 msec [95% CI 0.27, 0.81]; *P* = 0.006) compared to controls. Averaged over all compartments, DM subjects showed significantly higher texture parameters (variance, *P* = 0.001; contrast, *P* = 0.002; entropy, *P* < 0.001). Subjects with severe DM additionally showed higher T<sub>2</sub> in the medial tibial deep and superficial layers (*P* = 0.011 and *P* = 0.041) compared to controls. No significant differences in cartilage, meniscus, and overall WORMS were found between the groups (*P* > 0.05).

**Conclusion:** In comparison to nondiabetic controls, cartilage in DM subjects showed higher and more heterogeneous cartilage T<sub>2</sub> values, indicating increased articular cartilage degeneration. This affected even more compartments in subjects with severe DM.

**Level of Evidence:** 2

**Technical Efficacy:** 5

J. MAGN. RESON. IMAGING 2018;47:380–390.

Diabetes mellitus (DM) is a metabolic disorder with an increasing prevalence in the last decade.<sup>1</sup> The National Diabetes Statistics Report has estimated that approximately 29 million people in the US have DM.<sup>2</sup> Osteoarthritis (OA) causes a breakdown of cartilage and is associated with changes in adjacent knee joint structures such as soft tissue

View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com). DOI: 10.1002/jmri.25766

Received Feb 28, 2017, Accepted for publication May 5, 2017.

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and subchondral bone that lead to structural knee joint abnormalities and consequently to clinical symptoms, such as pain and disability.<sup>3</sup> OA and DM are frequently associated diseases, which may indicate that DM adversely affects articular cartilage and knee joint health and therefore may result in knee OA. On a cellular level, Type 2 DM typically demonstrates an insulin resistance. Consequently, insulin activity is reduced, resulting in prolonged hyperglycemia, which leads to osmotic and oxidative stress and results in damage to the kidneys, eyes, and other tissues.<sup>4</sup> Previous studies have suggested that DM or hyperglycemia is a probable risk factor and prognostic predictor for OA.<sup>5–9</sup> The Third National Health and Nutrition Examination Survey (NHANES III) has demonstrated that 11% of the patients with OA had DM, which was a significantly higher prevalence compared to the prevalence of 6% in the general population,<sup>10</sup> suggesting DM is a risk factor for OA. Previous studies have also reported that hyperglycemia is significantly more prevalent in the population with OA versus the population without OA (30.7% vs. 11.2%, respectively).<sup>11</sup> High concentrations of fasting serum glucose, an indicator for hyperglycemia and therefore for DM, were also found to be associated with symptomatic OA in an epidemiological study,<sup>12</sup> as well as adverse structural changes of knee joints with increased rates of tibial cartilage loss and incident bone marrow lesions.<sup>12,13</sup> DM and OA share many risk factors including aging, obesity, unhealthy dietary patterns, and physical inactivity. Moreover, the co-occurrence of DM and OA causes significantly more disability and significantly more pain in patients with OA compared to patients without OA.<sup>14</sup> Even though studies investigating the association of DM and OA have been performed,<sup>4</sup> the exact pathogenic role of DM in OA remains unclear.

Cartilage  $T_2$  relaxation time measurements reflect a change of hydration and organization of anisotropic arrangement of collagen fibrils in the extracellular cartilage matrix.<sup>15</sup> Knee cartilage  $T_2$  measurements have been used to assess cartilage degradation previously. Texture analysis using gray-level co-occurrence matrices (GLCM) has shown to allow early detection of compositional changes of cartilage in subjects at risk for OA, before radiographic evidence for OA is present, by providing additional data on the  $T_2$  value distribution of neighboring pixels.<sup>16,17</sup> Lamina analysis, in which cartilage is separated into a deep bone and superficial articular layer, may also visualize early lamina disruption within cartilage when overall  $T_2$  does not yet reveal changes of cartilage composition.<sup>18</sup>

The purpose of this study was to investigate the relationship between DM and cartilage composition to determine if an imaging biomarker could identify biochemical cartilage abnormalities in DM patients.

## Materials and Methods

### Subjects

The Osteoarthritis Initiative is a longitudinal, multicenter cohort study that recruited 4796 participants prospectively from which subjects for this analysis were selected. Baseline age of the subjects included in this study ranged from 45 to 79 years and only subjects with symptomatic knee OA (progression cohort) or at risk for symptomatic knee OA (incidence cohort) were included. In this study, the re-release of the baseline clinical datasets (0.2.2) as well as the first release of the baseline imaging dataset of the entire cohort group (0.E.1) were used.

We excluded subjects with moderate to advanced knee OA (Kellgren–Lawrence [KL] score  $\geq 3$ ) or missing KL score ( $n = 1104$ ), since previous studies have shown that once advanced cartilage loss occurs, as found in individuals with higher KL score,<sup>19</sup>  $T_2$  values may be limited for the evaluation of cartilage degradation.<sup>20</sup> Moreover, subjects with a possible history of rheumatoid arthritis ( $n = 206$ ) and with missing clinical magnetic resonance imaging (MRI) or missing  $T_2$  mapping of the right knee at baseline were excluded from the analyses ( $n = 50$ ). Using data from the Charlson comorbidity questionnaire developed by Katz et al,<sup>21</sup> self-reported DM treated with either oral antidiabetic medication or insulin was present in 210 of the remaining subjects. Baseline body mass index (BMI) was not available in two of the DM subjects. Complete datasets were therefore available for 208 DM subjects. Subjects without DM were defined as subjects without self-reported DM and without oral antidiabetic medication or insulin treatment ( $n = 3151$ ). Of the subjects without DM, 208 subjects were randomly selected and group-matched to the previously selected subjects with DM. For a secondary analysis, DM subjects with severe disease were defined based on the Charlson comorbidity questionnaire data<sup>21</sup> as subjects with presence of diabetes-related renal or ophthalmological complications or insulin treatment<sup>22</sup> as assessed at baseline ( $n = 50$ ). The severe diabetes group is a subset of the diabetes group. The subject selection process is shown in Fig. 1 and subject characteristics are presented in Table 1.

### MRI

MR images of the right knee were obtained using four identical 3T scanners (Siemens Magnetom Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH) at four sites.

A sagittal 2D multislice multiecho (MSME) spin-echo sequence with seven echo times (TEs 10 msec, 20 msec, 30 msec, 40 msec, 50 msec, 60 msec, 70 msec; repetition time [TR] = 2700 msec; field of view [FOV] = 12 cm, slice thickness = 3 mm; gap = 0.5 mm; in-plane spatial resolution =  $0.31 \times 0.54$  mm<sup>2</sup>) was used to obtain cartilage  $T_2$  relaxation times. The following four sequences were used for the morphological analysis of the cartilage: 1) a 2D intermediate-weighted (IW) turbo spin echo (TSE) sequence in the coronal plane (3700/29 msec, TR / echo time [TE]); 2) a 2D IW TSE sequences with fat suppression (FS) in the sagittal plane (3200/30 msec, TR/TE); 3) a 3D dual echo steady-state (DESS) gradient-echo with water excitation (WE) sequence obtained in the sagittal plane (16.3/4.7/25°, TR/TE/flip angle); and 4) a 3D  $T_1$ -weighted fast low-angle shot (FLASH)

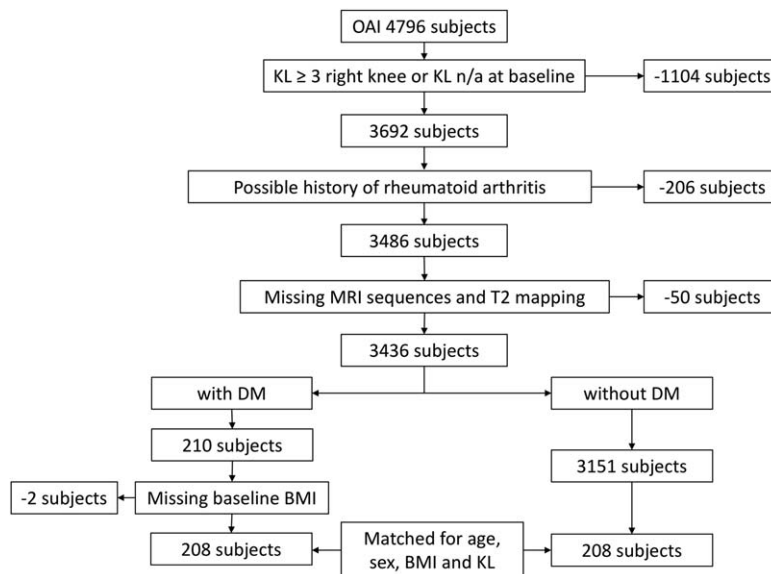


FIGURE 1: Flowchart illustrating subject selection from OAI database.

gradient-echo with WE sequence in a coronal plane (20/7.57/12°, TR/TE/flip angle). Further details regarding the MRI sequences analyzed can be found in the OAI protocol.<sup>23</sup>

### MR Image Analysis

For  $T_2$  analysis, MR images of all subjects were analyzed by using an in-house, spline-based algorithm written in MatLab (MathWorks, Natick, MA), which was used for segmentation, as previously described.<sup>24,25</sup> The cartilage of five compartments (patella [PAT], medial femoral condyle [MF], lateral femoral condyle [LF], medial tibia [MT], and lateral tibia [LT]) was semiautomatically segmented by two trained researchers using the first echo of the sagittal 2D MSME sequence (Fig. 2) and manually correcting the position of the points, in consensus and under supervision of an experienced radiologist. The trochlea (TRO) was not segmented due to flow artifacts caused by the popliteal artery.  $T_2$  values of each compartment were calculated by using a monoexponential decay model as fitting function for the signal intensity using six echoes (TE 20–70 msec) after excluding the first echo in order to prevent possible errors due to the contribution of stimulated echoes to the overall MR signal in a multiecho Carr–Purcell–Meiboom–Gill sequence<sup>24,26</sup> and using three parameter fittings accounting for noise.<sup>26,27</sup> Mean  $T_2$  values were computed for each cartilage compartment, and the global  $T_2$  value for the overall knee joint was calculated from the mean of all compartments.

Laminar analysis algorithms automatically subdivided the cartilage of each compartment into a superficial layer (articular surface) and a deep layer (bone interface) of equal thickness.<sup>18</sup> In addition, cartilage GLCM texture analysis was performed to evaluate the spatial distribution of cartilage  $T_2$  values within each cartilage compartment, reflecting heterogeneity of  $T_2$  values throughout the cartilage matrix, as a measure for cartilage degeneration.<sup>16,17,28–30</sup> Based on our previous work, three GLCM texture parameters were included in the analysis: contrast (contrast group), entropy (orderliness group), and variance (statistics group).<sup>16,30</sup> These additional analyses were performed and interpreted as described previously.<sup>30</sup>

Morphological MR sequences from both groups were reviewed on a picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ) by two radiologists (N.C. and A.S.G. with 6 and 5 years of experience, respectively), blinded to patient information, using the semiquantitative modified whole-organ magnetic resonance imaging score (WORMS) grading system, as previously described.<sup>31,32</sup> In cases of disagreement, a consensus reading was performed with a third more experienced musculoskeletal radiologist (T.M.L. with 23 years of experience).

Meniscal lesions were assessed in six regions (anterior/body/posterior regions of the medial and lateral menisci) and graded from 0 to 4 (0 = normal, 1 = intrasubstance abnormality, 2 = nondisplaced tear, 3 = displaced or complex tear, and 4 = complete destruction or maceration of the meniscus).

Cartilage lesions were evaluated in six regions (PAT, TRO, MF, LF, MT, and LT) with an 8-point scale: 0 = normal thickness but increased or otherwise abnormal signal on fluid sensitive sequences, 2 = 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 defects (grade 2) intermixed with areas of normal thickness, or grade 2 defect wider than 1 cm but <75% of the entire region, 4 = diffuse ( $\geq 75\%$  of the region) partial-thickness loss, 5 = multiple areas of full-thickness defect (grade 2.5) but <75% of the region, and 6 = diffuse ( $\geq 75\%$  of the region) full-thickness loss.

Bone marrow edema pattern (BMEP) lesions were identified as poorly marginated areas of increased signal intensity in the normally fatty marrow on  $T_2$ -weighted TSE images with FS and were graded in the subchondral zone of the same six regions as described in the cartilage score, using a scale from 0 to 3 based on lesion size: 0 = none, 1 = minimal (<5 mm in diameter), 2 = moderate (5–20 mm in diameter), and 3 = severe (>20 mm in diameter).

Ligamentous abnormalities of the anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, lateral collateral ligament, patellar tendon, and popliteal tendon as well as other findings (subchondral cysts, effusion, loose bodies, and popliteal cysts) were graded according to WORMS as previously described.<sup>31</sup>

	<b>Nondiabetics (n = 208)<sup>a</sup></b>	<b>Diabetics (n = 208)<sup>a</sup></b>	<b>P-value</b>
<b>Demographics</b>			
Age (years)	63.27 ± 9.13	63.00 ± 8.89	0.76 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	31.01 ± 4.44	31.18 ± 4.54	0.70 <sup>b</sup>
Height (m)	1.68 ± 0.09	1.69 ± .09	0.69 <sup>b</sup>
Females [n (%)]	111 (53.4%)	111 (53.4%)	1.00 <sup>c</sup>
Males [n (%)]	97 (46.6%)	97 (46.6%)	1.00 <sup>c</sup>
Physical Activity Score for the Elderly	154.97 ± 85.46	146.34 ± 79.26	0.29 <sup>b</sup>
Right knee Kellgren-Lawrence			0.93 <sup>c</sup>
Grade 0 [n (%)]	86 (41.3%)	83 (39.9%)	
Grade 1 [n (%)]	49 (23.6%)	52 (25.0%)	
Grade 2 [n (%)]	73 (35.1%)	73 (35.1%)	
Race			<b>&lt;0.001<sup>c</sup></b>
Caucasian [n (%)]	82.7%	59.6%	
African American [n (%)]	14.9%	35.6%	
Asian [n (%)]	0.5%	1.9%	
Other nonwhite [n (%)]	1.9%	2.9%	
<b>Health status</b>			
Heart attack [n (%)]	9 (4.3%)	10 (5.0%)	0.77 <sup>c</sup>
Stroke, cerebrovascular accident, blood clot or bleeding in brain, or transient ischemic attack [n (%)]	6 (2.9%)	11 (5.3%)	0.21 <sup>c</sup>
<b>Osteoarthritis risk factors</b>			
History of knee injury [n (%)]	75 (36.4%)	81 (39.1%)	0.57 <sup>c</sup>
History of knee surgery [n (%)]	32 (15.4%)	37 (17.8%)	0.51 <sup>c</sup>
Family history of knee replacement surgery [n (%)]	28 (13.5%)	20 (9.8%)	0.23 <sup>c</sup>
<sup>a</sup> Subjects in the two groups are matched in terms of age, sex, baseline BMI, and KL score. Significant results (P-value < 0.05) are in bold.			
<sup>b</sup> T-test.			
<sup>c</sup> Chi-squared test.			

For each subscale a sum score was calculated by adding the lesions scores of all subregions of each knee and an overall WORMS score was estimated by adding all of these.

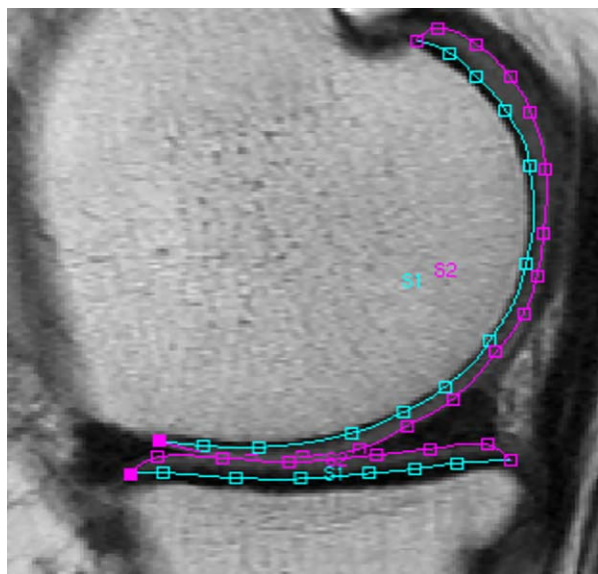
### **Reproducibility**

To calculate both the intra- and interreader reproducibility, the reproducibility error was assessed by calculating the root mean square average of the single coefficients of variation (CV) on a percentage basis, as previously reported.<sup>33</sup> Interreader reproducibility was assessed in 10 randomly selected subjects between the two readers overall and for each of the five compartments segmented (PAT, MF, LF, MT, and LT). Averaged over all compartments, the interreader reproducibility for image segmentation for T<sub>2</sub>

evaluation was 1.93%. The CVs for each compartment were 2.26% for PAT, 1.63% for MF, 1.59% for LF, 2.36% for MT, and 1.83% for LT. For intrareader reproducibility, both readers repeated the image segmentation for T<sub>2</sub> evaluation in the same 10 randomly selected subjects with at least 14 days separating the readings. The intrareader reproducibility for image segmentation over all compartments for T<sub>2</sub> evaluation was 1.12% and 2.06%, respectively. Intrareader CVs were calculated for each compartment: 1.12% and 1.78% for PAT, 0.75% and 1.00% for MF, 0.64% and 1.63% for LF, 1.92% and 2.85% for MT, 1.18% and 2.80% for LT.

In order to calculate the intra- and interreader reproducibility of the WORMS grading, each of the two radiologists performed





**FIGURE 2:** Example of  $T_2$  segmentation splines of the medial compartment (medial femur and medial tibia) of the right knee of a study subject.

WORMS grading twice independently for 10 randomly selected subjects; the two readings of each reader were at least 14 days apart. Intraclass correlation coefficients (ICCs) were calculated in order to compare the WORMS overall and to compare each WORMS subscore (meniscus and cartilage) separately. The intrareader agreement for overall WORMS grading were 0.85 (0.74–0.92) and 0.86 (0.76–0.95), 0.85 (0.79–0.93) and 0.87 (0.81–0.94) for meniscus WORMS, and 0.87 (0.81–0.92) and 0.84 (0.78–0.95) for cartilage WORMS, respectively. ICCs for interreader agreement were 0.83 (0.74–0.95) for overall WORMS, 0.83 (0.76–0.91) for meniscus WORMS, and 0.80 (0.74–0.87) for cartilage WORMS. Similar intrareader and interreader agreements of WORMS gradings by our group have been published in previous studies.<sup>25,34</sup>

### Statistical Analysis

The statistical analysis was performed with Stata v. 13 (StataCorp, College Station, TX) using a 2-sided 0.05 level of significance. *T*-tests and chi-square tests were used to assess the differences in continuous variables (age, BMI, height, and Physical Activity Score for the Elderly [PASE]) and categorical variables (gender, KL grade of the right knee at baseline, race, health status, risk factors for osteoarthritis) between subjects with DM and controls without DM.

The differences between outcome variables (mean  $T_2$ , laminar parameters, texture parameters, WORMS scores) between subjects with and without DM were assessed using clustered linear regression analyses adjusting for race and cluster pair. Similar analyses were performed to determine differences in outcome parameters between subjects with severe DM and controls without DM.

Due to a large number of outcome parameters, analyses were split into the following categories based on previously published analyses<sup>16,28,35,36</sup>: primary outcomes (compartments: overall compartments, MT, PAT; imaging parameter: mean  $T_2$ , deep layer  $T_2$  [laminar analysis], texture parameters contrast and variance); secondary outcomes (compartments: LF, LT, and MF; imaging

parameters: texture parameter entropy, overall WORMS, subscores cartilage and meniscus).

## Results

### Subject Characteristics

Subject characteristics are illustrated in Table 1. The subjects with DM ( $n = 208$ ; mean age,  $63.0 \pm 8.9$  years) were matched to 208 subjects from the control group without DM (mean age,  $63.3 \pm 9.1$  years). Mean baseline BMI (mean  $\pm$  SD) of DM subjects and subjects without DM was similar ( $31.0 \pm 4.4$  kg/m<sup>2</sup> and  $31.2 \pm 4.5$  kg/m<sup>2</sup>, respectively;  $P = 0.70$ ). The subjects in the two groups showed no significant differences in age, height, the distribution of sex and KL scores, risk factors for osteoarthritis, and health status ( $P > 0.05$ ). In both groups, 65% of the subjects had either no signs (KL = 0) or only doubtful signs of OA (KL = 1). There were significant differences between the groups regarding the distribution of race ( $P < 0.001$ ), therefore this variable was included in the regression analyses. Mean age of the severe DM subjects in this study ( $n = 50$ ) was  $57.71 \pm 8.95$  years and BMI was  $30.95 \pm 4.26$  kg/m<sup>2</sup>.

### $T_2$ Measurements

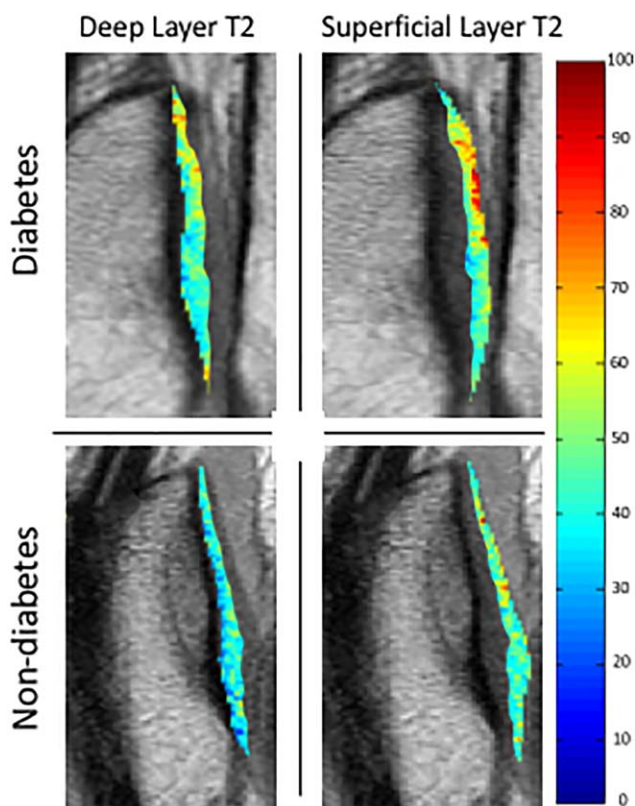
Mean  $T_2$  values in subjects with and without DM are shown in Table 2. In the primary analyses, cartilage  $T_2$  measurements of the patella (mean difference 0.92 msec, 95% confidence interval [CI] 0.79, 1.06;  $P = 0.001$ ; Fig. 3) and in the medial femur condyle (mean difference 0.36 msec, 95% CI 0.27, 0.81;  $P = 0.006$ ) were significantly elevated in subjects with DM compared to those without DM. In the laminar subanalyses,  $T_2$  of the deep layer was significantly elevated in the patella in the group with DM compared to the group without DM ( $P < 0.001$ ). Moreover, the texture parameters GLCM variance, contrast, and entropy showed significantly higher values in the global knee cartilage ( $P = 0.001$ ,  $P = 0.002$ , and  $P < 0.001$ , respectively; Table 3), in the patella and medial tibia (for each,  $P < 0.01$ ; Fig. 4).

Mean  $T_2$  values in each compartment as well as averaged over all compartments were elevated in the group of severe DM subjects compared to the controls without DM. The  $T_2$  values of the individuals with severe DM were significantly elevated compared to the control group without DM in the patella as well as the medial femur condyle ( $P = 0.002$  and  $P = 0.012$ , respectively; Table 2) and reached an even higher level of significance in the cartilage  $T_2$  of the deep layer in the patella (mean difference 1.44 msec, 95% CI 1.02, 1.85,  $P < 0.001$ ). Subjects with more severe DM also showed significantly elevated  $T_2$  values in the deep and superficial layer of medial tibia ( $P = 0.011$  and  $P = 0.041$ ).

**TABLE 2. Comparison of Global, Deep, and Superficial Layer T2 Relaxation Times of the Cartilage Compartments of the Knees Between the Nondiabetes, Diabetes, and Severe Diabetes Groups**

Parameter	Nondiabetes (n = 208)	Diabetes (n = 208)	P-value <sup>a</sup> diabetes vs. nondiabetes	Severe diabetes (n = 50)	P-value <sup>a</sup> severe diabetes vs. nondiabetes
Cartilage T2					
Global knee T2	32.58 [32.22,32.93]	32.61 [32.33,32.88]	0.89	32.89 [32.27,33.50]	0.46
PAT T2	31.69 [31.36,32.02]	32.61 [32.15,33.08]	<b>0.001</b>	33.07 [32.30,33.85]	<b>0.002</b>
MT T2	29.74 [29.27,30.21]	29.94 [29.61,30.27]	0.49	30.43 [29.67,31.20]	0.16
LT T2	27.60 [27.28,27.92]	27.78 [27.46,28.10]	0.46	28.16 [27.36,28.09]	0.19
MF T2	37.67 [36.85,38.52]	38.03 [37.66,38.04]	<b>0.006</b>	38.86 [38.39,39.32]	<b>0.012</b>
LF T2	35.30 [34.98,35.73]	34.77 [34.37,35.17]	0.07	35.30 [34.49,36.11]	0.91
Deep layer T2					
Global knee deep layer T2	29.67 [29.37,29.97]	29.80 [29.55,30.04]	0.50	30.04 [29.51,30.56]	0.25
PAT deep layer T2	28.60 [28.32,28.89]	29.53 [29.09,29.97]	<b>0.000</b>	30.04 [29.34,30.74]	<b>0.000</b>
MT deep layer T2	26.95 [26.62,27.28]	27.39 [27.07,27.72]	0.05	27.90 [27.25,28.54]	<b>0.011</b>
Superficial layer T2					
Global knee superficial T2	35.56 [35.15,35.97]	35.75 [35.41,36.08]	0.50	36.12 [35.38,36.86]	0.27
PAT superficial T2	34.87 [34.39,35.34]	35.89 [35.31,36.48]	<b>0.005</b>	36.31 [35.32,37.29]	<b>0.015</b>
MT superficial T2	32.78 [32.19,33.37]	33.48 [33.07,33.90]	0.07	34.09 [33.11,35.08]	<b>0.041</b>

<sup>a</sup>Multivariable linear regression adjusting for race and cluster pair. Numbers are given as predicted mean values [95% confidence intervals] (msec); PAT, patella; MT, medial tibia; LT, lateral tibia; MF, medial femur; LF, lateral femur. Significant results (P-value < 0.05) are in bold.



**FIGURE 3:** Sagittal T<sub>2</sub> color maps of the patella of the deep and superficial layer of the right knee of a subject with DM and a matched subject without DM. Blue color indicates low, while red color high cartilage T<sub>2</sub> values. Cartilage of diabetic subject showed elevated T<sub>2</sub> relaxation time (red) compared to the subject without DM, compatible with severer cartilage matrix degeneration of the subject with DM compared to the subjects without DM.

**Morphological Knee Abnormalities**

The prevalence of cartilage WORMS subscores of cartilage lesions was low in both groups in all compartments and did not differ significantly ( $P > 0.05$ ; Table 4), indicating a low degree of focal cartilage abnormalities and comparable morphological cartilage status between the subjects with and without DM. Moreover, there were no significant differences in the overall WORMS score and the meniscus WORMS subscores between the subjects with and without DM ( $P > 0.05$ ). For subgroup analyses, subjects with severe DM showed no significant differences in the WORMS subscores in comparison to subjects with DM ( $P > 0.05$ ).

**Discussion**

In this study, the association between DM and the biochemical composition and texture of cartilage was assessed in individuals with risk factors for OA and mild OA, using 3T MR-based cartilage T<sub>2</sub> relaxation time mapping. Subjects with DM showed significantly increased cartilage T<sub>2</sub> values in the patella and medial femur compared to controls, indicating more advanced biochemical cartilage degradation. These findings are supported by the texture parameters GLCM variance, entropy, and contrast in the patella and medial tibia as well as averaged over all compartments, showing significantly elevated texture parameters in individuals with DM compared to the controls without DM. Interestingly, significant differences were found in even more compartments when comparing severe DM subjects to the controls without DM, showing significantly elevated

**TABLE 3. Comparison of T2 Texture Parameters Between Subjects With and Without Diabetes Mellitus**

Parameter	Non-diabetes (n = 208)	Diabetes (n = 208)	P-value <sup>a</sup> diabetes vs. nondiabetes
Variance			
Global knee variance	213.93 [207.42, 220.45]	229.35 [222.40, 236.30]	<b>0.001</b>
PAT variance	198.68 [188.92, 208.45]	220.36 [210.31, 230.42]	<b>0.002</b>
MT variance	219.69 [211.01, 228.37]	249.64 [238.76, 260.51]	<b>0.000</b>
Contrast			
Global knee contrast	296.77 [286.87, 306.67]	316.79 [306.17, 327.40]	<b>0.002</b>
PAT contrast	263.70 [250.35, 277.05]	291.71 [278.16, 305.25]	<b>0.002</b>
MT contrast	319.60 [306.55, 332.66]	366.06 [348.51, 383.61]	<b>0.000</b>
Entropy			
Global knee entropy	6.17 [6.12, 6.21]	6.30 [6.27, 6.34]	<b>0.000</b>
PAT entropy	5.96 [5.90, 6.01]	6.09 [6.03, 6.15]	<b>0.001</b>
MT entropy	5.85 [5.79, 5.91]	6.04 [5.99, 6.09]	<b>0.000</b>

<sup>a</sup>Multivariable linear regression adjusting for race and cluster pair. Numbers are given as predicted mean values [95% confidence intervals] (msec); PAT, patella; MT, medial tibia. Significant results ( $P$ -values < 0.05) are in bold.



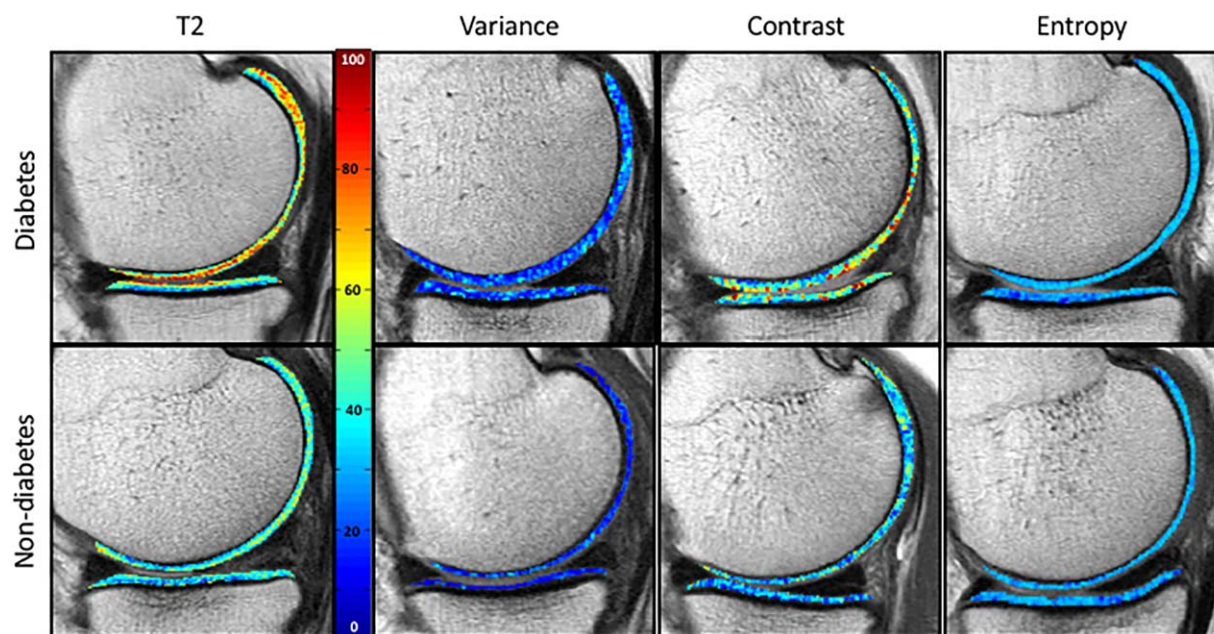


FIGURE 4: Sagittal T<sub>2</sub> color maps as well as the corresponding texture maps (variance, contrast, and entropy) of the medial compartment of the right knee of a subject with DM and a matched subject without DM. On the T<sub>2</sub> maps, blue color indicates low, while red color high cartilage T<sub>2</sub> values. Cartilage of diabetic subject showed elevated T<sub>2</sub> relaxation time compared to the subject without DM. The corresponding texture maps show a wider range of values, displayed through colors, in the subject with compared to the subject without diabetes. Again, these findings are compatible with severer cartilage matrix degeneration of the subject with DM compared to the subjects without DM.

cartilage T<sub>2</sub> additionally in the deep and superficial layer of the medial tibia in individuals with severe DM compared to those without DM. These findings may suggest even more extensive cartilage degeneration in subjects with severe DM.

Interestingly, however, we did not see significant differences in knee morphological abnormalities using the WORMS grading, suggesting that findings in DM patients predominantly affect the cartilage matrix.

**TABLE 4. Comparison of WORMS Subscores of the Knee Between Subjects With and Without Diabetes Mellitus**

WORMS scores	Non-diabetes (n = 208)	Diabetes (n = 208)	P-value <sup>a</sup>
Cartilage lesions			
Global knee joint	4.54 [4.02, 5.05]	4.11 [3.48, 4.74]	0.20
PAT	2.42 [2.08, 2.75]	2.34 [2.01, 2.67]	0.68
MT	0.21 [0.10, 0.32]	0.16 [0.07, 0.25]	0.51
LT	0.67 [0.53, 0.82]	0.52 [0.37, 0.68]	0.14
MF	0.76 [0.60, 0.92]	0.65 [0.49, 0.80]	0.32
LF	0.48 [0.33, 0.63]	0.45 [0.29, 0.61]	0.72
Cartilage max	2.81 [2.52, 3.09]	2.57 [2.26, 2.88]	0.17
Meniscus lesions			
Bilateral menisci	1.79 [1.48, 2.11]	1.84 [1.53, 2.14]	0.83
Medial meniscus	0.64 [0.50, 0.79]	0.85 [0.70, 0.99]	0.05
Lateral meniscus	0.61 [0.44, 0.78]	0.62 [0.48, 0.76]	0.96
WORMS overall	7.77 [6.94, 8.60]	7.12 [6.13, 8.11]	0.24

<sup>a</sup>Multivariable linear regression adjusting for race and cluster pair. Numbers are given as predicted mean values [95% confidence intervals] (msec); PAT, patella; MT, medial tibia; LT, lateral tibia; MF, medial femur; LF, lateral femur. Significant results (P-value < 0.05) are in bold.

The associations found between DM and elevated cartilage  $T_2$  values suggest that DM may have an effect on cartilage degeneration. DM is a modifiable metabolic disorder in which elevated blood sugar levels are present over a prolonged period of time. There are several studies revealing that DM may adversely affect the homeostasis and reparation of articular cartilage through different pathways. Previous studies have demonstrated that DM may favor the development or progression of OA.<sup>5-9</sup> For example, when chondrocytes are exposed to high glucose levels over a longer period of time, they are unable to downregulate GLUT-1 protein, and therefore accumulate glucose and produce more reactive oxygen species (ROS).<sup>37</sup> An intracellular increase of glucose and ROS are major mediators for cartilage destruction, which can promote cartilage degeneration.<sup>38</sup> High glucose levels in vitro can impair the synthesis of type II collagen due to a diminished transportation of dehydroascorbate into chondrocytes, which over time could reduce collagen quality.<sup>39</sup> Also, the signal transmitted through the receptors for advanced glycation end-products on chondrocytes leads to an overexpression of proinflammatory and prodegradative mediators and therefore can adversely affect chondrocytes. Moreover, increased glucose and sorbitol levels cause osmotic stress mechanisms, accelerating fibrocartilage matrix catabolism in the intervertebral discs of patients with DM.<sup>40</sup> Furthermore, insulin-like growth factor-1 (IGF-1) and inflammation may have a role for DM and OA acceleration.<sup>41</sup>

In order to investigate potential cartilage impairment and its association with DM, 3T MRI-based  $T_2$  relaxation time mapping was used. Cartilage  $T_2$  mapping detects an increase in water content and disruption of the organization of the anisotropic arrangement of collagen fibrils in the extracellular cartilage matrix,<sup>15</sup> visualized as cartilage  $T_2$  relaxation time increase<sup>42</sup> and is therefore a useful tool to estimate early cartilage degeneration before irreversible cartilage loss occurs. Since studies had suggested that metabolic risk factors, including obesity, DM, hypertension, and dyslipidemia are significantly associated with both occurrence and progression of knee OA,<sup>43</sup> a previous study found that certain metabolic risk factors (high abdominal circumference, hypertension, high fat consumption, and diabetes) were associated with elevated baseline  $T_2$  values.<sup>35</sup> In the latter study the only results remaining statistically significant after adjusting for baseline BMI were the associations with diabetes. Therefore, in this study we primarily focused on DM by using a larger cohort with DM and by isolating the effects of DM on OA through our statistical analyses, including cartilage texture analysis. In the texture analysis, cartilage GLCM texture values averaged over all compartments as well as in each assessed compartment was elevated in individuals with DM and with severe DM compared to those without DM, indicating more severe cartilage degeneration in patients with DM averaged over all compartments

compared to controls without DM. These findings are in line with those of previous studies showing that quantitative analysis of cartilage GLCM texture parameters variance, contrast, and entropy allows earlier detection of biochemical changes within the cartilage before morphological evidence for OA has occurred, by providing information on the spatial distribution of  $T_2$  pixel values.<sup>16</sup>

Moreover, there have been associations reported between hand OA and metabolic syndrome components, showing a strong correlation of OA with DM.<sup>44</sup> The findings of our secondary analysis that focused on patients with severe DM revealed significantly elevated cartilage  $T_2$  in the deep layer of the cartilage of the patella and additionally in the medial tibia compared to nondiabetic controls, suggesting that there may be an association between not only the presence, but also the severity of DM and cartilage degeneration.

Cartilage  $T_2$  has been shown to correlate with the severity of morphological degenerative change in the cartilage and meniscus.<sup>24</sup> It should be noted that for the selection process of our study cohort we were limited to the KL grade for the assessment of the OA status of the subjects. Yet, after performing an analysis of the degenerative morphological findings, the cartilage lesion score appeared to be very low over all subjects analyzed and there were no significant differences found between the group with and without DM, either regarding cartilage lesions or regarding any other morphological abnormality assessed. Therefore, cartilage  $T_2$  differences between the groups were not caused by differences of the severity of morphological degenerative abnormalities between the groups.

Nevertheless, this study has several limitations. First, this work is a cross-sectional observational study. Therefore, we cannot establish whether cartilage changes occurred before or after development of diabetes. And there are confounding factors, which may affect the association between diabetes status and  $T_2$  values. Although our matching system allowed us to control for certain OA-related confounders, we were not able to control for all factors linked to OA, for example smoking, treatment for OA, and other comorbidities. Previous studies have reported that the collagen content and its orientation is the major factor in changes of cartilage  $T_2$  relaxation times.<sup>45-48</sup> Biochemical analyses of the cartilage compositional changes were not able to be performed in this study. Based on previous studies,  $T_2$  relaxation time imaging in individuals with diabetes may suggest increased articular cartilage degeneration compared to individuals without diabetes, yet future studies with biochemical analyses are needed in order to confirm these assumptions histologically. Moreover, plasma glucose or hemoglobin A1c levels were not available to determine associations of biochemical cartilage composition with degree of glycemic control. Longitudinal studies may provide further insight on the effect of DM on OA progression.

In conclusion, elevated  $T_2$  values and texture parameters in DM subjects compared to controls may indicate altered biochemical composition, possibly associated with cartilage degeneration, while there were no significant differences found in morphological knee joint abnormalities. Associations of DM with elevated  $T_2$  values were observed in even more compartments when comparing subjects with severe DM and controls without DM, which may suggest an association of more advanced biochemical cartilage degradation with severe DM.

## Acknowledgments

The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer; Novartis Pharmaceuticals; Merck Research Laboratories; and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This article has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation. The analyses in this study were funded through the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grants R01AR064771 and P50-AR060752). This article has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

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