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Association of Diabetes Mellitus and Biochemical Knee Cartilage Composition Assessed by T2 Relaxation Time Measurements: Data from the Osteoarthritis Initiative

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Abstract

Purpose—To investigate the association of presence and severity of diabetes mellitus (DM) with articular cartilage composition, using MRI-based T2 relaxation time measurements, and structural knee abnormalities.

Materials and Methods—In the Osteoarthritis Initiative 208 participants with DM (age 63.0±8.9y; 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±9.1y; 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 T2, including texture and laminar analyses derived from the patella, medial and lateral femur and tibia and for structural abnormalities using the modified WORMS. Clustered linear regression analyses were used to assess associations of DM with MRI findings.

Results—DM subjects had significantly higher cartilage T2 in the patella (mean difference 0.92ms [95% confidence interval (CI) 0.79, 1.06]; $P=0.001$) and medial femur (mean difference 0.36ms [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 T2 in the medial tibial

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deep and superficial layers ($P=0.011$ and $P=0.041$) compared to controls. No significant differences in cartilage, meniscus and overall WOMBS were found between the groups ($P>0.05$).

Conclusion—In comparison to non-diabetic controls, cartilage in DM subjects showed a higher and more heterogeneous cartilage T2 values, indicating increased articular cartilage degeneration. This affected even more compartments in subjects with severe DM.

Keywords

Knee osteoarthritis; diabetes; cartilage imaging; magnetic resonance imaging

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with an increasing prevalence in the last decade (1). The National Diabetes Statistics Report has estimated that approximately 29 million people in the US population have DM (2). Osteoarthritis (OA) causes a breakdown of cartilage and is associated with changes in adjacent knee joint structures such as soft tissue and subchondral bone that lead to structural knee joint abnormalities and consequently to clinical symptoms, such as pain and disability (3). 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 (4). Previous studies have suggested that DM or hyperglycemia is a probable risk factor and prognostic predictor for OA (5–9). 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 (10), 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) (11). 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 (12), as well as adverse structural changes of knee joints with increased rates of tibial cartilage loss and incident bone marrow lesions (12,13). 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 (14). Even though studies investigating the association of DM and OA have been performed (4), the exact pathogenic role of DM in OA remains unclear.

Cartilage T2 relaxation time measurements reflect change of hydration and organization of anisotropic arrangement of collagen fibrils in the extracellular cartilage matrix (15). Knee cartilage T2 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 with risk for OA, before radiographic evidence for OA is present by providing additional data on the T2 value distribution of neighboring pixels (16,17). Laminar analysis, in which cartilage is separated

into a deep bone and superficial articular layer, may also visualize early laminar disruption within cartilage when overall T2 does not yet reveal changes of cartilage composition (18).

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.

METHODS

Subjects

The Osteoarthritis Initiative is a longitudinal, multi-center 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 entire cohort group (0.E.1) were used.

We excluded subjects with moderate to advanced knee OA (Kellgren-Lawrence (KL) score 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 (19), T2 values may be limited for the evaluation of cartilage degradation (20). Moreover, subjects with a possible history of rheumatoid arthritis ($n=206$) and with missing clinical MR imaging or missing T2 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. (21), 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 (21) as subjects with presence of diabetes-related renal or ophthalmological complications or insulin treatment (22) as assessed at baseline ($n = 50$). The severe diabetes group is a subset of the diabetes group. The subject selection process is shown in Figure 1 and subject characteristics are presented in Table 1.

MR imaging

MR images of the right knee were obtained using four identical 3.0T scanners (Siemens Magnetom Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites.

A sagittal 2D multi-slice multi-echo (MSME) spin-echo sequence with seven echo times (TEs 10ms, 20ms, 30ms, 40ms, 50ms, 60ms, 70ms; TR=2700 ms; field of view (FOV) = 12cm, slice thickness = 3mm; gap = 0.5mm; in-plane spatial resolution = $0.31 \times 0.54 \text{mm}^2$) was used to obtain cartilage T2 relaxation times. The following four sequences were used

for the morphological analysis of the cartilage: (i) a 2D intermediate-weighted (IW) turbo spin echo (TSE) sequence in the coronal plane (3700ms/29ms, repetition time (TR)/ echo time (TE)); (ii) a 2D IW TSE sequences with fat suppression (FS) in the sagittal plane (3200ms/30ms, TR/TE); (iii) 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 (iv) a 3D T1-weighted fast low-angle shot (FLASH) 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 (23).

MR Image analysis

For T2 analysis, MR images of all subjects were analyzed by using an in-house, spline-based algorithm written in MATLAB (the Mathworks, Natick, Massachusetts), which was used for segmentation, as previously described (24,25). The cartilage of five compartments (patella (PAT), medial femoral condyle (MF), lateral femoral condyle (LF), medial tibia (MT), and lateral tibia (LT)) was semi-automatically segmented by two trained researchers using the first echo of the sagittal 2D MSME sequence (Figure 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. T2 values of each compartment were calculated by using a mono-exponential decay model as fitting function for the signal intensity using 6 echoes (TE 20–70 ms) 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 multi-echo Carr-Purcell-Meiboom-Gill Sequence (24,26) and using 3 parameter fittings accounting for noise (26,27). Mean T2 values were computed for each cartilage compartment, and the global T2 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 (18). In addition, cartilage GLCM texture analysis was performed to evaluate the spatial distribution of cartilage T2 values within each cartilage compartment, reflecting heterogeneity of T2 values throughout the cartilage matrix, as a measure for cartilage degeneration (16,17,28–30). Based on our previous work, three GLCM texture parameters were included in the analysis: contrast (contrast group), entropy (orderliness group) and variance (statistics group) (16,30). These additional analyses were performed and interpreted as described previously (30).

Morphological MR sequences from both groups were reviewed on a picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA) by two radiologists (N.C. and A.S.G. with 6 and 5 years of experience, respectively), blinded to patient information, using the semi-quantitative modified WORMS grading system, as previously described (31,32). 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 =

non-displaced tear, 3 = displaced or complex tear, and 4 = complete destruction or maceration of the meniscus).

Cartilage lesions were evaluated in 6 regions (PAT, TRO, MF, LF, MT and LT) with an 8-point scale: 0 = normal, 1 = 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 (< 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 (> 75% of the region) full-thickness loss.

Bone marrow edema pattern (BMEP) lesions were identified as poorly margined areas of increased signal intensity in the normally fatty marrow on T2-weighted TSE images with FS and were graded in the subchondral zone of the same 6 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 (31). 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 inter-reader 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 (33). Inter-reader 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 inter-reader reproducibility for image segmentation for T2 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 intra-reader reproducibility, both readers repeated the image segmentation for T2 evaluation in the same 10 randomly selected subjects with at least 14 days separating the readings. The intra-reader reproducibility for image segmentation over all compartments for T2 evaluation was 1.12% and 2.06%, respectively. Intra-reader 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, respectively.

In order to calculate the intra- and inter-reader reproducibility of the WORMS grading, each of the two radiologists performed WORMS grading twice independently for 10 randomly selected subjects, the two readings of each reader were at least 14 days apart. Intra-class correlation coefficients (ICCs) were calculated in order to compare the WORMS overall and to compare each WORMS subscore (meniscus and cartilage) separately. The intra-reader

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 inter-reader 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 intra-reader and inter-reader agreements of WORMS gradings by our group have been published in previous studies (25,34).

Statistical Analysis

The statistical analysis was performed with Stata Version 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), respectively, between subjects with DM and controls without DM.

The differences between outcome variables (mean T2, 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 (16,28,35,36): primary outcomes (compartments: overall compartments, MT, PAT; imaging parameter: mean T2, deep layer T2 (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 ± 8.9 years) were matched to 208 subjects from the control group without DM (mean age, 63.3 ± 9.1 years). Mean baseline BMI (mean \pm SD) of DM subjects and subjects without DM was similar (31.0 ± 4.4 kg/m² and 31.2 ± 4.5 kg/m², 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 into the regression analyses. Mean age of the severe DM subjects in this study (n = 50) was 57.71 ± 8.95 years and BMI was 30.95 ± 4.26 kg/m².

T2 measurements

Mean T2 values in subjects with and without DM are shown in Table 2. In the primary analyses, cartilage T2 measurements of the patella (mean difference 0.92ms [95% confidence interval (CI) 0.79, 1.06]; $P=0.001$; Figure 3) and in the medial femur condyle (mean difference 0.36ms [95% confidence interval (CI) 0.27, 0.81]; $P=0.006$) were significantly elevated in subjects with DM compared to those without DM. In the laminar subanalyses, T2 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 $P<0.001$; Table 3), in the patella and medial tibia (for each, $P<0.01$; Figure 4).

Mean T2 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 T2 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 T2 of the deep layer in the patella (mean difference 1.44ms [95% CI 1.02, 1.85], $P<0.001$). Subjects with more severe DM also showed significantly elevated T2 values in the deep and superficial layer of medial tibia ($P=0.011$ and $P=0.041$).

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 T2 relaxation time mapping. Subjects with DM showed significantly increased cartilage T2 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 cartilage T2 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.

The associations found between DM and elevated cartilage T2 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 repair of articular cartilage through different pathways. Previous studies have demonstrated that DM may favor the development or progression of OA (5–9). For example, when chondrocytes are exposed to high glucose levels over a longer period of time, they are unable to down regulate GLUT-1 protein, and therefore accumulate glucose and produce more reactive oxygen species (ROS) (37). An intracellular increase of glucose and ROS are major mediators for cartilage destruction which can promote cartilage degeneration (38). High glucose levels in vitro can impair the synthesis of type II collagen due to a diminished transportation of dehydroascorbate into chondrocytes, which overtime could reduce collagen quality (39). Also, the signal transmitted through the receptors for advanced glycation endproducts on chondrocytes leads to an overexpression of pro-inflammatory and pro-degradative 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 (40). Furthermore, insulin-like growth factor-1 (IGF-1) and inflammation may have a role for DM and OA acceleration (41).

In order to investigate potential cartilage impairment and its association with DM, 3T MRI-based T2 relaxation time mapping was used. Cartilage T2 mapping detects an increase in water content and disruption of the organization of the anisotropic arrangement of collagen fibrils in the extracellular cartilage matrix (15), visualized as cartilage T2 relaxation time increase (42) 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 to both occurrence and progression of knee OA (43), a previous study found that certain metabolic risk factors (high abdominal circumference, hypertension, high fat consumption and diabetes) were associated with elevated baseline T2 values (35). 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 T2 pixel values (16).

Moreover, there have been associations reported between hand OA and metabolic syndrome components, showing a strong correlation of OA with DM (44). The findings of our secondary analysis that focused on patients with severe DM revealed significantly elevated cartilage T2 in the deep layer of the cartilage of the patella and additionally in the medial tibia compared to non-diabetic controls, suggesting that there may be an association between not only presence, but also severity of DM and cartilage degeneration.

Cartilage T2 has been shown to correlate with the severity of morphological degenerative change in the cartilage and meniscus (24). 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, neither regarding cartilage lesions nor regarding any other morphological abnormality assessed. Therefore, cartilage T2 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. Firstly, 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 T2 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 T2 relaxation times (45–48). Biochemical analyses of the cartilage compositional changes were not able to be performed in this study. Based on previous studies, T2 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 T2 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 T2 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.

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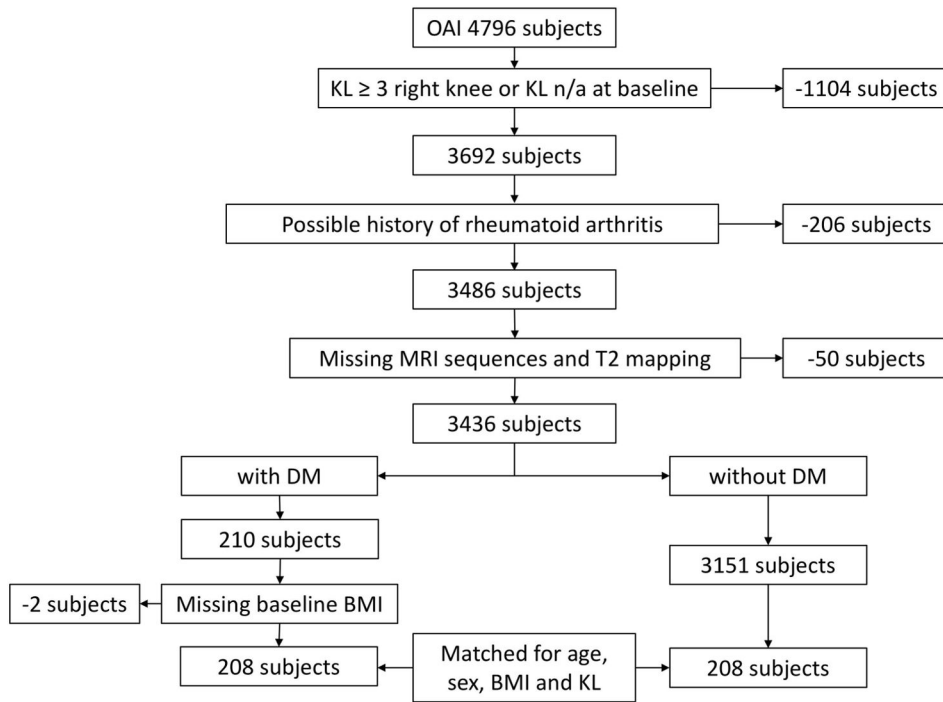


Figure 1. Flowchart illustrating subject selection from OAI database

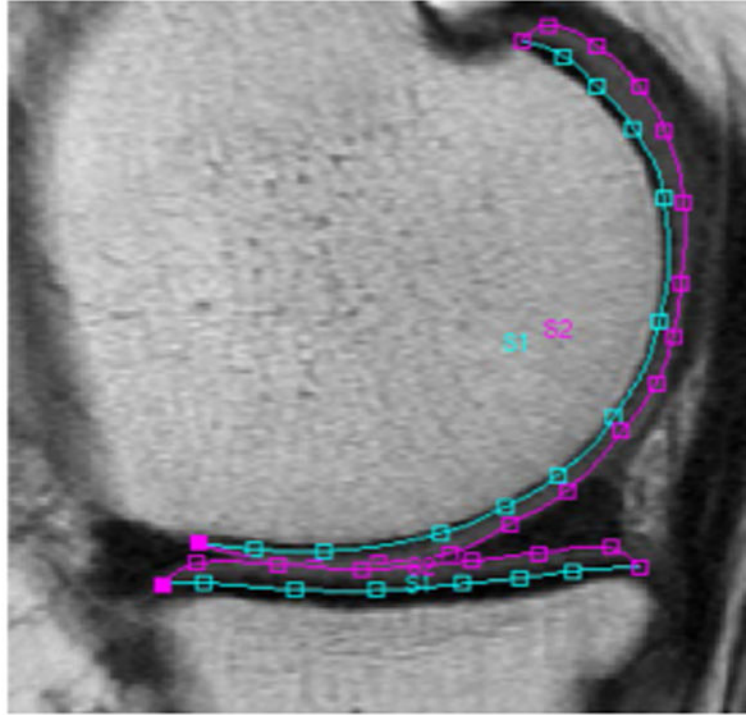


Figure 2. Example of T2 segmentation splines of the medial compartment (medial femur and medial tibia) of the right knee of a study subject.

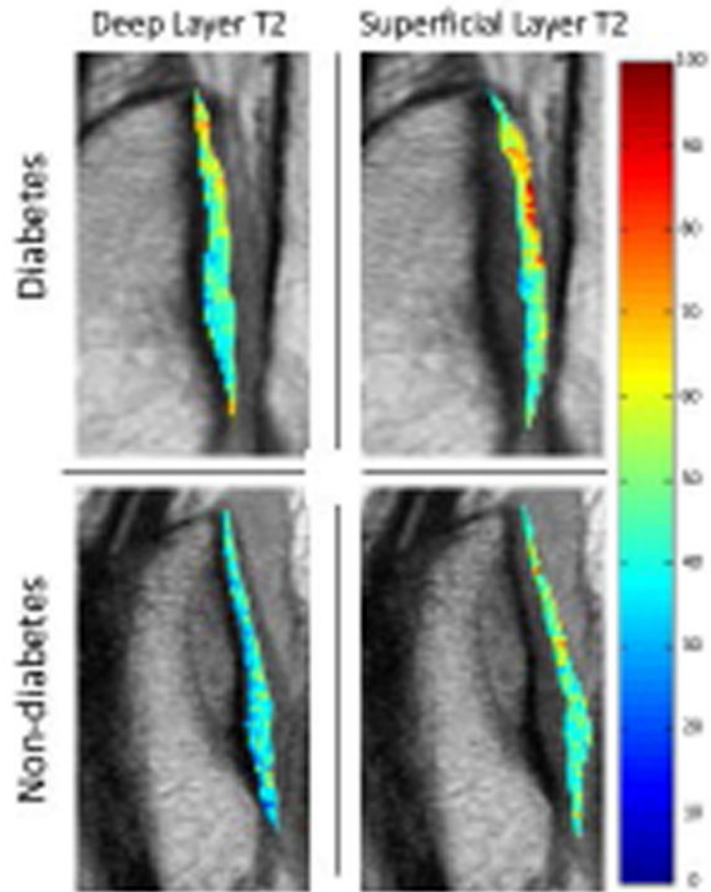


Figure 3. Sagittal T2 color maps of the patella of the deep and superficial layer of the right knee of a subject with diabetes mellitus and a matched subject without diabetes mellitus. Blue color indicates low, while red color high cartilage T2 values. Cartilage of diabetic subject showed elevated T2 relaxation time (red) compared to the subject without diabetes mellitus, compatible with severer cartilage matrix degeneration of the subject with diabetes mellitus compared to the subjects without diabetes mellitus.

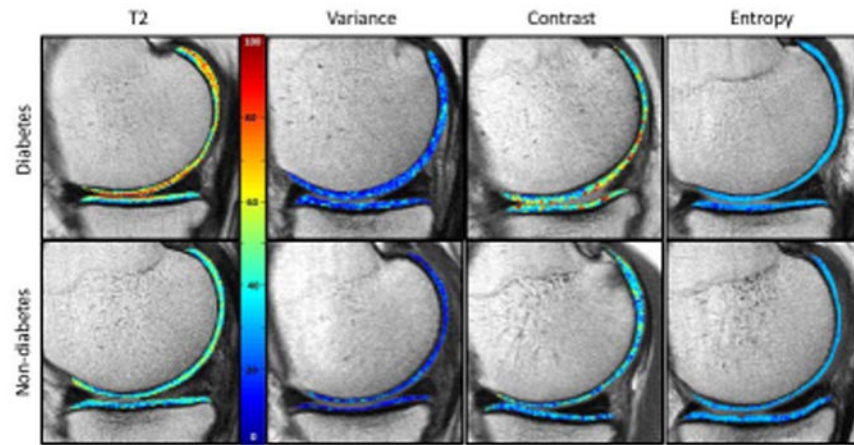


Figure 4.

Sagittal T2 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 diabetes mellitus and a matched subject without diabetes mellitus. On the T2 maps, blue color indicates low, while red color high cartilage T2 values. Cartilage of diabetic subject showed elevated T2 relaxation time compared to the subject without diabetes mellitus. 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 diabetes mellitus compared to the subjects without diabetes mellitus.

Table 1

Subject characteristics

| | Non-diabetics (n=208) ¹ | Diabetics (n=208) ¹ | P-value |
|---|------------------------------------|--------------------------------|------------------------------|
| Demographics | | | |
| Age (years) | 63.27 ± 9.13 | 63.00 ± 8.89 | 0.76 ² |
| Body mass index (kg/m ²) | 31.01 ± 4.44 | 31.18 ± 4.54 | 0.70 ² |
| Height (m) | 1.68 ± 0.09 | 1.69 ± .09 | 0.69 ² |
| Females [n (%)] | 111 (53.4%) | 111 (53.4%) | 1.00 ³ |
| Males [n (%)] | 97 (46.6%) | 97 (46.6%) | 1.00 ³ |
| Physical Activity Score for the Elderly | 154.97 ± 85.46 | 146.34 ± 79.26 | 0.29 ² |
| Right knee Kellgren-Lawrence | | | 0.93 ³ |
| 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 | | | <0.001³ |
| Caucasian [n (%)] | 82.7% | 59.6% | |
| African American [n (%)] | 14.9% | 35.6% | |
| Asian [n (%)] | 0.5% | 1.9% | |
| Other Non-white [n (%)] | 1.9% | 2.9% | |
| Health status | | | |
| Heart attack [n (%)] | 9 (4.3%) | 10 (5.0%) | 0.77 ³ |
| Stroke, cerebrovascular accident, blood clot or bleeding in brain, or transient ischemic attack [n (%)] | 6 (2.9%) | 11 (5.3%) | 0.21 ³ |
| Osteoarthritis risk factors | | | |
| History of knee injury [n (%)] | 75 (36.4%) | 81 (39.1%) | 0.57 ³ |
| History of knee surgery [n (%)] | 32 (15.4%) | 37 (17.8%) | 0.51 ³ |
| Family history of knee replacement surgery [n (%)] | 28 (13.5%) | 20 (9.8%) | 0.23 ³ |

¹Subjects 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.

²T test

³Chi-squared test

Table 2

Comparison of global, deep and superficial layer T2 relaxation times of the cartilage compartments of the knees between the non-diabetes, diabetes and severe diabetes groups.

| Parameter | Non-diabetes (n = 208) | Diabetes(n = 208) | P-value ¹ diabetes vs non-diabetes | Severe diabetes (n = 50) | P-value ¹ severe diabetes vs non-diabetes |
|-----------------------------|------------------------|---------------------|--|--------------------------|---|
| 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] | 0.001 | 33.07 [32.30,33.85] | 0.002 |
| 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] | 0.006 | 38.86 [38.39,39.32] | 0.012 |
| 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] | 0.000 | 30.04 [29.34,30.74] | 0.000 |
| MT deep layer T2 | 26.95 [26.62,27.28] | 27.39 [27.07,27.72] | 0.05 | 27.90 [27.25,28.54] | 0.011 |
| 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] | 0.005 | 36.31 [35.32,37.29] | 0.015 |
| MT superficial T2 | 32.78 [32.19,33.37] | 33.48 [33.07,33.90] | 0.07 | 34.09 [33.11,35.08] | 0.041 |

¹Multivariable linear regression adjusting for race and cluster pair; Numbers are given as predicted mean values [95% confidence intervals] (ms); PAT, patella; MT, medial tibia; LT, lateral tibia; MF, medial femur; LF, lateral femur. Significant results (P-value <0.05) are in bold.

Table 3

Comparison of T2 texture parameters between subjects with and without diabetes mellitus.

| Parameter | Non-diabetes (n = 208) | Diabetes (n = 208) | <i>P</i> -value ¹ diabetes vs. non-diabetes |
|----------------------|-------------------------|-------------------------|---|
| Variance | | | |
| Global knee Variance | 213.93 [207.42, 220.45] | 229.35 [222.40, 236.30] | 0.001 |
| PAT Variance | 198.68 [188.92, 208.45] | 220.36 [210.31, 230.42] | 0.002 |
| MT Variance | 219.69 [211.01, 228.37] | 249.64 [238.76, 260.51] | 0.000 |
| Contrast | | | |
| Global knee Contrast | 296.77 [286.87, 306.67] | 316.79 [306.17, 327.40] | 0.002 |
| PAT Contrast | 263.70 [250.35, 277.05] | 291.71 [278.16, 305.25] | 0.002 |
| MT Contrast | 319.60 [306.55, 332.66] | 366.06 [348.51, 383.61] | 0.000 |
| Entropy | | | |
| Global knee Entropy | 6.17 [6.12, 6.21] | 6.30 [6.27, 6.34] | 0.000 |
| PAT Entropy | 5.96 [5.90, 6.01] | 6.09 [6.03, 6.15] | 0.001 |
| MT Entropy | 5.85 [5.79, 5.91] | 6.04 [5.99, 6.09] | 0.000 |

¹Multivariable linear regression adjusting for race and cluster pair; Numbers are given as predicted mean values [95% confidence intervals] (ms); PAT, patella; MT, medial tibia; Significant result (*P*-values <0.05) are in bold.

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) | <i>P</i>-value^I |
|--------------------------|-------------------------------|---------------------------|-----------------------------------|
| 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 |

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

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