Ahilan Arulanandan

ISP Description

1/30/13

Description of the project: This project studies normal weight, overweight, and obese subjects with risk factors for osteoarthritis (OA) and compares cartilage degeneration in their knees over a 36 month time period.

Rationale for the project: Osteoarthritis is a disease that affects about 27 million adults in the United States alone. Because of its prevalence, it's important to study the development and significance of the disease. Our project demonstrated that body weight impacted the severity of osteoarthritis, which was measured by the amount of cartilage lost.

How the project was done: We analyzed a total of 231 subjects from the Osteoarthritis Initiative database aged 45-55 with risk factors for knee OA but no radiographic evidence of OA. Of these patients, 78 were normal weight, 84 were overweight, and 69 were obese. The patients had MRIs of their right knee at the beginning of the study and a repeat MRI after 36 months. We traced markings around the meniscus and patellar cartilage and then compared the subjects before and after 36 months to determine our results.

What was achieved: We found that the prevalence and severity of cartilage lesions in the right knee were greatest in obese subjects and lowest in the normal subjects. An increase in body mass index was associated with an increased progression of cartilage lesions. This is important because we could directly associate increased body weight with increased development of osteoarthritis.

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Correlation of Magnetic Resonance Imaging–Based Knee Cartilage T2 Measurements and Focal Knee Lesions With Body Mass Index: Thirty-Six–Month Followup Data From a Longitudinal, Observational Multicenter Study

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Objective. **To compare magnetic resonance imaging (MRI)–based knee cartilage T2 measurements and focal knee lesions and 36-month changes in these parameters among knees of normal controls and knees of normal weight, overweight, and obese subjects with risk factors for knee osteoarthritis (OA).**

Methods. **A total of 267 subjects ages 45–55 years from the Osteoarthritis Initiative database were analyzed in this study. Two hundred thirty-one subjects had risk factors for knee OA, but no radiographic OA (Kellgren/Lawrence score ≤1) at baseline. Thirty-six subjects were normal controls. Subjects with OA risk factors were stratified in 3 groups: normal weight (n = 78), overweight (n = 84), and obese (n = 69). All subjects underwent 3T MRI of the right knee at baseline and after 36 months. Focal knee lesions were assessed and cartilage T2 measurements (mean T2 and T2 texture analysis) were performed.**

Results. **The baseline prevalence and severity of meniscal and cartilage lesions were highest in obese subjects and lowest in normal controls ($P < 0.05$). Obese subjects had the highest mean T2 values and the most heterogeneous cartilage (as assessed by T2 texture analysis), while normal controls had the lowest mean T2 values and the most homogeneous cartilage at baseline ($P < 0.05$). Increased body mass index (BMI) was significantly ($P < 0.05$) associated with greater progression of cartilage lesions and constantly elevated cartilage T2 entropy over 36 months.**

Conclusion. **In preclinical OA, increased BMI is associated with more severe cartilage degeneration as assessed by both morphologic and quantitative MRI measurements.**

INTRODUCTION

Nearly 27 million adults in the US have clinically symptomatic osteoarthritis (OA), most commonly affecting the knee joint (1). Risk factors for OA include female sex, previous knee injury, repetitive knee bending activities, and overweight/obesity (2). Being overweight or obese is considered an upcoming epidemic, and projections have suggested that 86.3% of adults in the US will be overweight or obese by 2030 (3,4). These conditions will have grave financial implications, not only for associated life-

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Significance & Innovations

- Increased body mass index is associated with more severely degenerated cartilage, as demonstrated by elevated mean and more heterogeneous cartilage T2, in subjects with risk factors for knee osteoarthritis (OA) but without knee pain and without radiographic knee OA.
- In preclinical OA, overweight and obese subjects showed a higher prevalence and severity of meniscal and cartilage lesions and a greater progression of cartilage lesions over 36 months.
- Cartilage T2 relaxation time measurements may be a sensitive biomarker for monitoring cartilage quality in subjects at risk for developing knee OA, since they offer interesting insights in the condition of cartilage matrix beyond morphologically detectable focal knee lesions.

threatening comorbidities such as diabetes mellitus and cardiovascular disease, but also for therapeutic management of overweight/obesity–associated OA (5).

Previous studies used magnetic resonance imaging (MRI) and observed that body mass index (BMI) was significantly associated with the prevalence of knee cartilage defects and bone marrow edema pattern (BMEP), and with reduced patellar cartilage volume (6–10). Furthermore, cartilage defects were associated with physical disability in obese adults (11). Therefore, it would be valuable to detect overweight and obese individuals in the early phase of OA, since they may benefit most from treatment or behavioral interventions prior to the occurrence of severe cartilage degeneration and clinical symptoms.

Quantitative MRI such as the T2 relaxation time measurement has emerged as a potential cartilage biomarker to assess early degenerative disease (12–15). The early phase of OA is characterized by biochemical changes of the cartilage, including proteoglycan loss, increased water content, and deterioration of the collagen network, which can be detected by T2 measurements (16,17). Furthermore, cartilage degeneration is associated with a more heterogeneous cartilage matrix, which can be analyzed using grey level co-occurrence matrix (GLCM)–based T2 texture analysis (18–22).

The National Institutes of Health launched the Osteoarthritis Initiative (OAI), a longitudinal, observational multicenter study with 4,796 participants, to better understand the natural evolution of OA (online at http://www.oai.ucsf.edu/). The OAI database contains clinical data, biologic samples, radiographs, and MRIs, including a T2 mapping sequence (23). The study population consists of subjects with symptomatic knee OA at baseline (progression cohort), those with no symptomatic knee OA but with risk factors for OA at baseline (incidence cohort), and normal controls. The OAI currently provides the largest longitudinally acquired database with T2 relaxation time measurements.

The purpose of this study was to compare MRI-based knee cartilage T2 measurements and focal knee lesions, and changes in these parameters over 36 months, among knees of normal controls without risk factors and normal weight, overweight, and obese subjects with risk factors for knee OA, but without knee pain and without radiographic knee OA. We hypothesized 1) that both focal knee lesions and cartilage T2 measurements would correlate with BMI and 2) that cartilage T2 measurements would be more sensitive than grading of focal knee lesions (by using a modified Whole-Organ MRI Score [WORMS]) cross-sectionally and longitudinally to observe differences in osteoarthritic changes between normal controls versus normal weight, overweight, and obese subjects with risk factors for knee OA.

MATERIALS AND METHODS

Subjects. The study was compliant with the Health Insurance Portability and Accountability Act. All subjects included in this study provided informed consent. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards.

Data used in the preparation of this article were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. Specific OAI data sets used were baseline clinical data set 0.2.2, baseline imaging data sets 0.E.1 and 0.C.2, 36-month followup clinical data set 5.2.1, and 36-month followup imaging data sets 5.E.1 and 5.C.1.

We studied the right knee of 267 subjects from the OAI incidence and normal control cohorts. Subjects in the OAI normal control cohort (n = 122) had no radiographic evidence of OA (defined as a definite tibiofemoral osteophyte) in either knee at baseline and had no OA risk factors at baseline. Subjects in the OAI incidence cohort (n = 3,284) did not have symptomatic knee OA (defined as frequent symptoms and radiographic OA in the same knee) in either knee at baseline, but had at least one of the following OA risk factors at baseline: overweight or obesity, knee symptoms (pain, aching, or stiffness in or around the knee in the past 12 months), history of knee injury, history of knee surgery, family history of total knee replacement, or Heberden's nodes.

Specific inclusion criteria for this study at baseline were age 45–55 years, Western Ontario and McMaster Universities Osteoarthritis Index pain score of 0 in both knees, and a Kellgren/Lawrence (K/L) score of ≤ 1 (based on an additional reading done for the present study) in the right knee. In addition, baseline and 36-month followup right knee MRIs had to be available and useable. These specific inclusion criteria were applied to focus on younger and relatively asymptomatic subjects. Based on these criteria, 36 normal controls (11 men, 25 women) and 231 subjects with OA risk factors (128 men, 103 women) were eligible and included in the study. The subjects with OA risk factors were stratified by BMI category: 78 subjects (33 men, 45 women) who had normal weight (baseline BMI <25.0 kg/m^2), 84 subjects (58 men, 26 women) who were overweight (baseline BMI 25.0–29.9 kg/m^2), and 69 sub-

jects (37 men, 32 women) who were obese (baseline BMI $\geq$30.0 kg/m^2). All included controls had normal weight (baseline BMI $<$25.0 kg/m^2). The individual subject groups were defined as group A (normal controls), group B (subjects with OA risk factors and normal weight), group C (subjects with OA risk factors and overweight), and group D (subjects with OA risk factors and obesity).

Imaging. Bilateral standing posteroanterior fixed flexion knee radiographs were acquired at baseline and 36-month followup. Knees were positioned in a Plexiglas frame (SynaFlexer, CCBR-Synarc) with 20–30° of flexion and 10° of internal rotation of the feet. Right knee radiographs were graded by 2 radiologists (LN with 4 years of experience and WV with 7 years of experience) in consensus by using the K/L scoring system (24).

All subjects underwent 3T MRI (Trio, Siemens) of the right knee at baseline and 36-month followup. MRIs were obtained as described in the OAI MRI protocol (23).

Grading of focal knee lesions. Baseline and 36-month followup MRIs of the right knee were transferred to picture archiving and communication system workstations (Agfa). The presence and grade of meniscal and cartilage lesions as well as the BMEP were assessed using a modified WORMS, as previously described (12,22,25–30). Meniscal lesions were graded separately in 6 regions (medial/lateral and anterior/body/posterior) using a 5-point scale. Cartilage lesions and BMEP were not assessed by using the original 15 regions, but 6 condensed regions (patella, trochlea, medial/lateral femur, and medial/lateral tibia). Cartilage lesions were graded using an 8-point scale and BMEP was graded using a 4-point scale. Three radiologists (LN with 4 years of experience, WV with 7 years of experience, and TML with 22 years of experience) analyzed 40 MRI studies in consensus to calibrate the thresholds for grading abnormalities. The remaining 227 MRI studies were read by 2 radiologists (LN and WV) independently. In case of disagreement, consensus reading was performed with the third, most experienced radiologist (TML). The radiologists were blinded to patient information while performing the WORMS grading. MRIs were read with baseline and followup paired and in known chronological order.

A WORMS maximum score (WORMS Max) was assigned to each knee by the greatest WORMS score in any compartment. The WORMS Max was used to express the severity of focal knee lesions. A WORMS Max $>$0 in any joint structure was defined as the presence of a lesion. A meniscal WORMS Max $>$1 indicated a nondisplaced tear or worse, while a cartilage WORMS Max $>$1 identified subjects with at least 1 partial thickness defect. A cartilage WORMS Max $>$1 was also used to exclude lesions characterized only by signal abnormalities, i.e., grade 1 lesions.

Incident focal knee lesions over 36 months were defined on a knee level basis as new lesions detected in the 36-month followup MRI studies that occurred in a knee with a WORMS score of 0 at baseline (i.e., a baseline WORMS Max of 0 and a 36-month followup WORMS Max $>$0). Possible remission of BMEP was defined as a baseline WORMS Max $>$0 and a 36-month followup WORMS Max of 0.

To determine the progression of focal knee lesions over 36 months, WORMS summation scores (WORMS Sum) were calculated for each joint structure on a knee level basis by summing the WORMS scores of all evaluated compartments. Progression of focal knee lesions over 36 months was defined as a baseline WORMS Sum $>$0 and ΔWORMS Sum $>$0 (36-month followup WORMS Sum $-$ baseline WORMS Sum). Possible regression of BMEP was defined as a baseline WORMS Sum $>$0, a 36-month followup WORMS Sum $>$0, and ΔWORMS Sum $<$0.

The incidence and progression of focal knee lesions over 36 months had partly low counts per group (e.g., normal controls). Therefore, we analyzed the incidence and progression combined as the total WORMS progression, which was defined as ΔWORMS Sum $>$0 (36-month followup WORMS Sum $-$ baseline WORMS Sum). Subjects with ΔWORMS Sum $<$0 for BMEP (i.e., BMEP regression or remission) were excluded for the statistical analysis of BMEP of total WORMS progression.

Cartilage T2 measurements. The multislice multiecho spin-echo sequences were transferred to a SUN workstation (Sun Microsystems) and T2 maps were calculated with custom-built software on a pixel-by-pixel basis, skipping the first echo and using a noise-corrected exponential fitting as outlined previously (31). Five distinct compartments (patella, medial/lateral femur, and medial/lateral tibia) were segmented with in-house software based on Interactive Data Language (Research Systems) directly in the T2 maps.

In order to exclude both fluid and chemical shift artifacts from the region of interest, a technique was used that allowed adjustment of the region of interest simultaneously in the T2 map and first echo of the multiecho sequence by opening separate image panels at the same time with a synchronized cursor, slice number, and zoom. This segmentation procedure has been used in previous studies (12,25,26,28,30,31). The patella compartment was segmented in the T2 maps of all subjects at baseline and 36-month followup by a single operator (HA). The remaining compartments were segmented by a second operator (AA). All segmentations were supervised by a radiologist (TB). Segmentation of the trochlea compartment was not performed due to flow artifacts from the popliteal artery.

Mean T2 values for each compartment were calculated after segmentation. T2 texture analysis of the segmented compartments was performed on a slice-by-slice basis using GLCM, as outlined by Haralick et al (32). GLCM extracts information related to the spatial distribution of pixel intensities in the T2 map. One texture parameter from the orderliness group (entropy), one from the contrast group (contrast), and one from the stats group (variance) were calculated as previously reported (18–22). A pixel offset of 1 pixel was chosen and texture parameters were calculated by averaging over the 4 computed directions (0°, corresponding to the anteroposterior axis; 45° and 90°, corresponding to the superior-inferior axis; and 135°). Contrast is a measure of the differences in neighboring

pixel values. High T2 contrast signifies that many pixels with different T2 values are neighboring. Entropy is a measure of disorder in an image. Higher T2 entropy signifies more uniform distribution of probabilities of T2 relaxation time co-occurrences, i.e., it is more likely to find any combination of T2 relaxation time co-occurrence. Variance is a measure of the distribution of pixels about the mean. Higher T2 contrast, T2 entropy, and T2 variance were found in subjects with OA risk factors compared to normal controls (22).

Changes in T2 measurements, including texture parameters over 36 months (Δmean T2, ΔT2 entropy, ΔT2 contrast, and ΔT2 variance), were computed by subtracting baseline T2 measurements from 36-month followup T2 measurements.

Statistical analysis. The statistical analyses were performed with SPSS statistical software, using a 2-sided level of significance of 0.05.

Cross-sectional analysis. Pearson's chi-square tests and analysis of variance were used to compare age, BMI, and frequencies of sex, OA risk factors, and K/L scores between the subject groups.

Multivariate linear regression models were used to compare T2 measurements between the 4 groups. The independent variable was the group and the normal control group was selected as the reference group. The dependent variable was the respective T2 measurement (mean T2, T2 contrast, T2 entropy, and T2 variance). Covariates sex, age, and OA risk factors other than BMI (i.e., knee symptoms, history of knee injury, history of knee surgery, family history of total knee replacement, and Heberden's nodes) were entered into the models to obtain adjusted effects. Similar to previous studies (12,22), T2 measurements were only analyzed in the medial femur compartment and for the average over all 5 compartments to avoid multiple testing. The medial femur was chosen because it is a predominant weight-bearing region and has a higher incidence of OA than the lateral side (33,34).

Logistic regression models were used to assess differences in the prevalence of focal knee lesions between the 4 groups. The independent variable was the group and the normal control group was selected as the reference group. The dependent variable was WORMS prevalence (a WORMS Max >0 or >1). Covariates sex, age, and OA risk factors other than BMI were entered into the models to obtain adjusted effects. Results were expressed as the odds ratio (OR) with the 95% confidence interval (95% CI) and the adjusted *P* value.

Differences in severity of focal knee lesions between the 4 groups were evaluated by using multivariate linear regression models. The independent variable was the group and the normal control group was selected as the reference group. The dependent variable was WORMS severity (WORMS Max). Covariates sex, age, and OA risk factors other than BMI were entered into the models to obtain adjusted effects.

Longitudinal analysis. Paired *t*-tests were used to determine differences between baseline and 36-month followup T2 measurements in each group. Multivariate linear regression models were used to compare changes in T2 measurements over 36 months between the 4 groups, similar to the cross-sectional analysis of T2 measurements.

Since the incidence and progression of focal knee lesions over 36 months had partly low counts per group, we analyzed the incidence and progression combined per group (total WORMS progression). Differences in the total WORMS progression of focal knee lesions between the 4 groups were assessed by using logistic regression models similar to the cross-sectional analysis of the prevalence of focal knee lesions.

Additional adjustment for change in BMI over 36 months in the regression models did not affect the *P* values of the longitudinal statistical analysis.

Reproducibility. Intrareader reproducibility for T2 measurements of each compartment was determined in baseline T2 maps of 20 randomly selected subjects. The patella compartment was segmented 3 times in the T2 maps of each subject by one operator (HA), and the remaining compartments were segmented as well 3 times by one operator (AA). Reproducibility errors for each compartment were calculated as the root mean square error coefficient of variation (35). Intrareader reproducibility for mean T2 ranged from 0.80–2.95% (mean 1.76%), for T2 contrast ranged from 2.84–6.99% (mean 4.66%), for T2 entropy ranged from 1.16–2.60% (mean 1.88%), and for T2 variance ranged from 2.14–6.32% (mean 4.29%). The highest reproducibility errors were observed in the patella and the lowest reproducibility errors were observed in the medial femur compartment. These results indicated good agreement for mean T2 and T2 entropy and moderate agreement for T2 contrast and T2 variance, similar to previous studies (12,22,25,31).

To assess the intra- and interreader reproducibility of the WORMS grading, 20 subjects were randomly selected and WORMS grading was performed 2 times by 2 readers (LN and WV) independently. Intraclass correlation coefficients were calculated to compare the exact WORMS score for meniscal and cartilage lesions and the BMEP in each compartment. Intrareader reproducibility was calculated for meniscal WORMS grading of 0.95 and 0.97 (interreader 0.97), for cartilage WORMS grading of 0.96 and 0.98 (interreader 0.98), and for BMEP WORMS grading of 0.98 and 0.98 (interreader 0.98). These results indicated good intra- and interreader agreement for WORMS grading.

RESULTS

Subject characteristics. Mean age and BMI, frequency of sex, K/L score, and OA risk factors of the 4 groups are listed in Table 1. Although the mean age of the 4 groups was not significantly different, the distribution of sex differed significantly between the 4 groups ($P < 0.05$). As defined by the inclusion criteria, all subjects had K/L scores ≤ 1 at baseline in the study knee. Six subjects with OA risk factors showed radiographic OA with K/L scores of 2 at 36-month followup. The frequency of K/L scores was not significantly different between the 3 BMI groups with OA risk factors at baseline and 36-month followup

Table 1. Characteristics of normal controls (group A), subjects with OA risk factors and normal weight (group B), subjects with OA risk factors and overweight (group C), and subjects with OA risk factors and obesity (group D)*

	Group A (n = 36)	Group B (n = 78)	Group C (n = 84)	Group D (n = 69)
Baseline age, mean ± SD years	50.4 ± 3.1	51.0 ± 2.7	50.3 ± 3.0	51.5 ± 2.6
Baseline BMI, mean ± SD kg/m^2	22.7 ± 1.5	22.9 ± 1.4	27.2 ± 1.5	32.9 ± 2.3
36-month followup BMI, mean ± SD kg/m^2	23.4 ± 2.1	23.2 ± 1.9	27.2 ± 2.1	33.3 ± 2.5
Men, no. (%)	11 (30.6)†	33 (42.3)†	58 (69.0)†	37 (53.6)†
Baseline K/L score, no. (%)				
0	36 (100)	58 (74.4)	59 (70.2)	43 (62.3)
1	0 (0)	20 (25.6)	25 (29.8)	26 (37.7)
36-month followup K/L score, no. (%)				
0	34 (94.4)	57 (73.1)	52 (61.9)	38 (55.1)
1	2 (5.6)	18 (23.1)	30 (35.7)	30 (43.5)
2	0 (0)	3 (3.8)	2 (2.4)	1 (1.4)
Baseline OA risk factors other than overweight/ obesity (self-reported), no. (%)				
Knee symptoms in the past 12 months	0 (0)	68 (87.2)†	78 (92.9)†	50 (72.5)†
History of knee injury	0 (0)	38 (48.7)	49 (58.3)	30 (43.5)
History of knee surgery	0 (0)	18 (23.1)	17 (20.2)	9 (13.0)
Family history of knee replacement surgery	0 (0)	16 (20.8)	16 (19.3)	8 (11.6)
Heberden's nodes	0 (0)	15 (19.2)	19 (22.6)	10 (14.7)

* OA = osteoarthritis; BMI = body mass index; K/L = Kellgren/Lawrence.
† Statistically significant differences between the groups ($P < 0.05$).

($P > 0.05$). The frequency of knee symptoms in the past 12 months was the only OA risk factor that was significantly different between the 3 BMI groups with OA risk factors ($P < 0.05$).

Focal knee lesions. Baseline prevalence and severity of focal knee lesions as well as incidence (BMEP: incidence and remission) and progression (BMEP: progression and regression) of focal knee lesions over 36 months are listed for all 4 groups in Table 2.

The greatest baseline prevalence of meniscal lesions (WORMS Max >0) and tears (WORMS Max >1) was found in group C (subjects with OA risk factors and overweight) and group D (subjects with OA risk factors and obesity),

Table 2. Baseline prevalence and severity of focal knee lesions as well as incidence (BMEP: incidence and remission) and progression (BMEP: progression and regression) of focal knee lesions over 36 months in the right knees of normal controls (group A), subjects with OA risk factors and normal weight (group B), subjects with OA risk factors and overweight (group C), and subjects with OA risk factors and obesity (group D)*

	Group A (n = 36)	Group B (n = 78)	Group C (n = 84)	Group D (n = 69)
Meniscus				
Baseline prevalence of lesions, no. (%)	16 (44.4)	39 (50.0)	57 (67.9)	50 (72.5)
Baseline prevalence of tears, no. (%)	5 (13.9)	23 (29.5)	32 (38.1)	21 (30.4)
Baseline severity of lesions, mean ± SD	0.64 ± 0.87	1.00 ± 1.25	1.31 ± 1.25	1.25 ± 1.16
Incidence of lesions over 36 months	2/20 (10.0)	6/39 (15.4)	9/27 (33.3)	3/19 (15.8)
Progression of lesions over 36 months	1/16 (6.3)	11/39 (28.2)	18/57 (31.6)	14/50 (28.0)
Cartilage				
Baseline prevalence of lesions, no. (%)	27 (75.0)	55 (70.5)	67 (79.8)	63 (91.3)
Baseline prevalence of grade ≥2 lesions, no. (%)	15 (41.7)	41 (52.6)	47 (56.0)	47 (68.1)
Baseline severity of lesions, mean ± SD	1.46 ± 1.23	1.87 ± 1.64	1.99 ± 1.57	2.34 ± 1.46
Incidence of lesions over 36 months	0/9 (0.0)	5/23 (21.7)	4/17 (23.5)	1/6 (16.7)
Progression of lesions over 36 months	3/27 (11.1)	15/55 (27.3)	23/67 (34.3)	31/63 (49.2)
BMEP				
Baseline prevalence of lesions, no. (%)	15 (41.7)	25 (32.1)	40 (47.6)	41 (59.4)
Baseline severity of lesions, mean ± SD	0.75 ± 0.94	0.51 ± 0.82	0.88 ± 1.01	1.04 ± 1.01
Remission of lesions over 36 months	1/15 (6.7)	1/25 (4.0)	3/40 (7.5)	4/41 (9.8)
Incidence of lesions over 36 months	4/21 (19.0)	12/53 (22.6)	11/44 (25.0)	8/28 (28.6)
Regression of lesions over 36 months	0/15 (0.0)	0/25 (0.0)	2/40 (5.0)	6/41 (14.6)
Progression of lesions over 36 months	3/15 (20.0)	12/25 (48.0)	10/40 (25.0)	16/41 (39.0)

* Values are the number/total (percentage) unless otherwise indicated. BMEP = bone marrow edema pattern; OA = osteoarthritis.

Table 3. Comparison of baseline prevalence and severity of focal knee lesions and total WORMS progression over 36 months in the right knees of normal controls (group A) versus subjects with OA risk factors and normal weight (group B), subjects with OA risk factors and overweight (group C), and subjects with OA risk factors and obesity (group D)*

	Group B vs. group A		Group C vs. group A		Group D vs. group A	
	OR (95% CI)	Adjusted *P*	OR (95% CI)	Adjusted *P*	OR (95% CI)	Adjusted *P*
Meniscus						
Baseline prevalence of lesions	0.94 (0.41–2.16)	0.883	1.85 (0.79–4.31)	0.155	2.52 (1.06–5.97)†	0.037†
Baseline prevalence of tears	1.64 (0.40–6.71)	0.495	2.13 (0.51–8.95)	0.304	1.77 (0.47–6.63)	0.399
Total WORMS progression over 36 months	2.18 (0.44–10.76)	0.340	4.48 (0.89–22.53)	0.069	2.87 (0.63–13.05)	0.173
Cartilage						
Baseline prevalence of lesions	0.87 (0.35–2.14)	0.754	1.34 (0.53–3.40)	0.532	3.58 (1.16–11.07)†	0.027†
Baseline prevalence of grade ≥2 lesions	1.10 (0.34–3.58)	0.872	1.46 (0.43–4.94)	0.540	2.31 (0.77–6.92)	0.136
Total WORMS progression over 36 months	3.26 (0.89–11.94)	0.075	4.39 (1.22–15.79)†	0.024†	8.74 (2.43–31.45)†	0.001†
BMEP						
Baseline prevalence of lesions	0.65 (0.20–2.12)	0.477	1.38 (0.41–4.59)	0.605	2.11 (0.71–6.25)	0.180
Total WORMS progression over 36 months	1.24 (0.33–4.72)	0.751	1.14 (0.28–4.60)	0.852	2.27 (0.64–8.06)	0.204
Meniscus: baseline severity of lesions		0.858		0.382		0.318
Cartilage: baseline severity of lesions		0.427		0.225		0.049
BMEP: baseline severity of lesions		0.732		0.286		0.102

* Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for differences in baseline prevalence and total Whole-Organ Magnetic Resonance Imaging Score (WORMS) progression over 36 months between the respective groups by using logistic regression models, adjusting for sex, age, and osteoarthritis (OA) risk factors other than body mass index (BMI). Differences in baseline severity of focal knee lesions between the respective groups were assessed with multivariate regression models, adjusting for sex, age, and OA risk factors other than BMI. BMEP = bone marrow edema pattern.
† Statistically significant differences between the respective groups ($P < 0.05$).

with the lowest prevalence in group A (normal controls) (Table 2). Significant differences in the baseline prevalence of meniscal lesions and tears were only found for the prevalence of meniscal lesions between group D versus group A (OR 2.52, 95% CI 1.06–5.97) (Table 3).

The greatest baseline prevalence of cartilage lesions (WORMS Max >0) and of grade ≥2 cartilage lesions (WORMS Max >1) was observed in group D, while the lowest prevalence of grade ≥2 lesions was found in group A (Table 2). Similar to meniscal lesions, significant differences in the baseline prevalence of cartilage lesions were only observed between group D versus group A (OR 3.58, 95% CI 1.16–11.07) (Table 3).

The greatest prevalence of BMEP (WORMS Max >0) was found in group D, with the lowest prevalence found in group B (Table 2). However, differences in the baseline

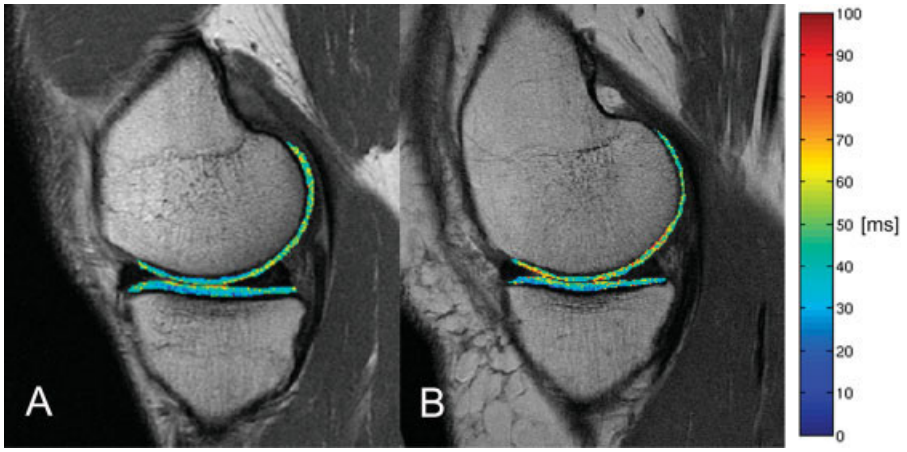

Figure 1. T2 color maps of the medial femur and medial tibia compartments of the right knee overlaid with the first-echo images of the multislice multiecho sequence. **A,** Representative normal control, and **B,** representative subject with osteoarthritis (OA) risk factors and obesity. Blue indicates low cartilage T2 values and red indicates high cartilage T2 values. The subject with OA risk factors and obesity showed elevated T2 values compared to the normal control in the medial femur compartment.

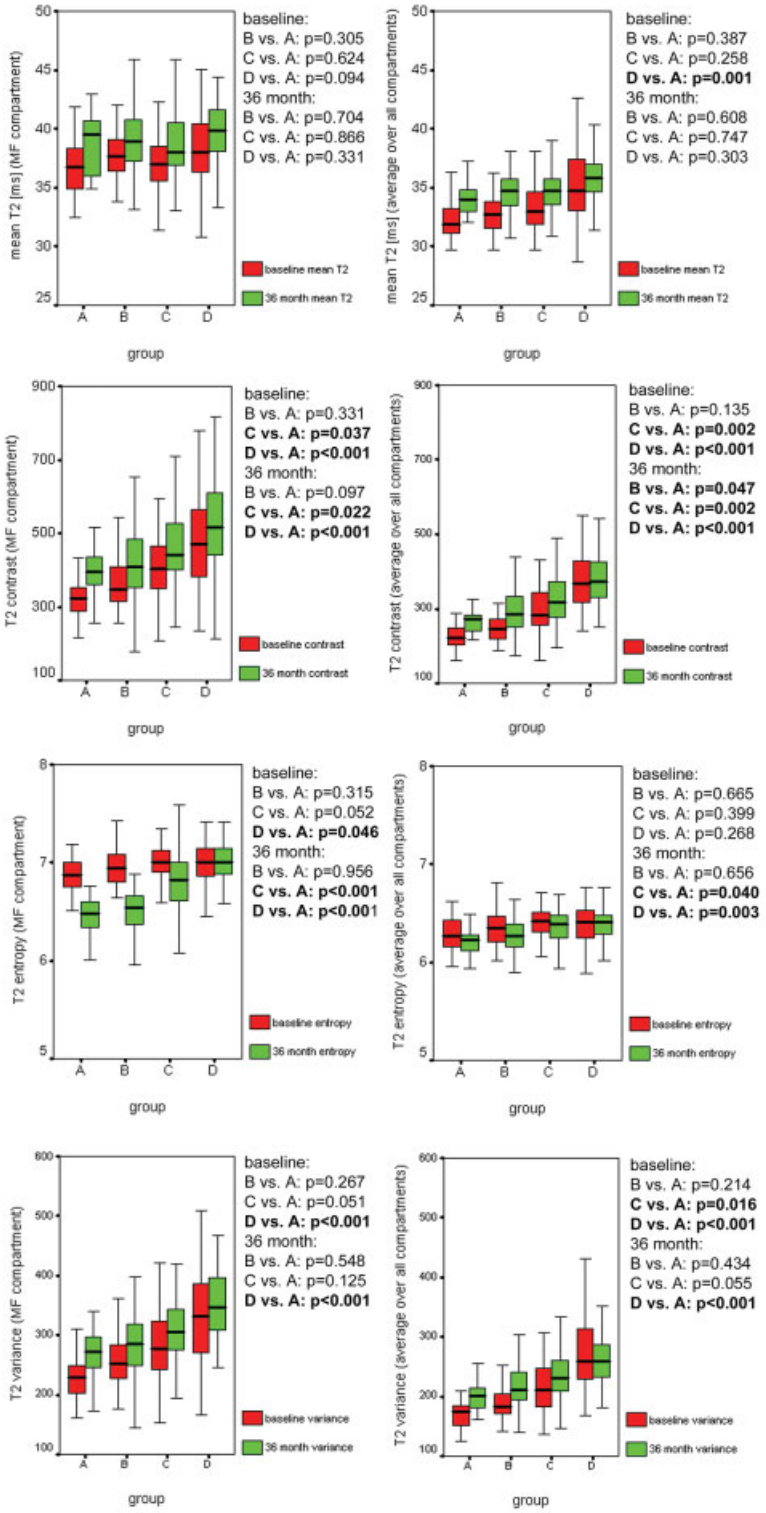

Figure 2. The boxplots show knee cartilage T2 measurements at baseline and 36-month followup for the medial femur (MF) compartment and the average over all compartments in normal controls (group A), subjects with osteoarthritis (OA) risk factors and normal weight (group B), subjects with OA risk factors and overweight (group C), and subjects with OA risk factors and obesity (group D). Differences in T2 measurements of group A versus groups B, C, and D were assessed with multivariate regression models, adjusting for sex, age, and OA risk factors other than body mass index. *P* values in bold indicate statistically significant differences between the respective groups ($P < 0.05$).

Table 4. Changes in knee cartilage T2 measurements over 36 months for the medial femur compartment and the average over all compartments in normal controls (group A), subjects with OA risk factors and normal weight (group B), subjects with OA risk factors and overweight (group C), and subjects with OA risk factors and obesity (group D)*

	Changes in T2 measurements over 36 months, mean ± SD				Multivariate regression models, *P*		
	Group A (n = 36)	Group B (n = 78)	Group C (n = 84)	Group D (n = 69)	Group B vs. group A	Group C vs. group A	Group D vs. group A
Medial femur compartment							
Δmean T2	1.9 ± 1.7†	1.2 ± 2.6†	1.9 ± 3.4†	1.7 ± 5.7†	0.244	0.556	0.582
ΔT2 contrast	71 ± 69†	75 ± 138†	68 ± 137†	46 ± 138†	0.455	0.677	0.857
ΔT2 entropy	−0.45 ± 0.20†	−0.47 ± 0.28†	−0.18 ± 0.28†	−0.01 ± 0.15	0.577	0.002‡	< 0.001‡
ΔT2 variance	42 ± 41†	36 ± 83†	37 ± 78†	8 ± 97	0.629	0.612	0.097
Average over all 5 compartments							
Δmean T2	2.1 ± 1.0†	1.6 ± 5.1†	2.1 ± 3.9†	0.4 ± 4.3	0.281	0.522	0.042‡
ΔT2 contrast	43 ± 39†	58 ± 90†	36 ± 110†	−27 ± 155	0.915	0.573	0.013‡
ΔT2 entropy	−0.08 ± 0.14†	−0.08 ± 0.18†	−0.00 ± 0.19	−0.01 ± 0.12	0.803	0.098	0.068
ΔT2 variance	30 ± 25†	31 ± 74†	19 ± 81†	−35 ± 118†	0.515	0.292	0.001‡

* Differences in changes in knee cartilage T2 measurements between the respective groups were assessed with multivariate regression models, adjusting for sex, age, and osteoarthritis (OA) risk factors other than body mass index.
† Statistically significant ($P < 0.05$) change of respective T2 measurement over 36 months (paired *t*-test).
‡ Statistically significant differences between the respective groups ($P < 0.05$).

prevalence of BMEP between the groups were not statistically significant ($P > 0.05$) (Table 3).

Groups C and D showed the greatest severity of focal knee lesions at baseline (Table 2). Differences in severity of focal knee lesions at baseline reached only statistical significance ($P < 0.05$) for cartilage lesions between group D versus group A (Table 3).

Since the incidence and progression of focal knee lesions over 36 months had partly low counts per group (Table 2), we analyzed the incidence and progression combined per group. Total WORMS progression of meniscal lesions and BMEP was not significantly different between the 4 groups ($P > 0.05$) (Table 3). However, groups C and D showed a significantly greater total WORMS progression of cartilage lesions over 36 months compared to group A (Table 3). The OR for group C versus group A was 4.39 (95% CI 1.22–15.79), and for group D versus group A was 8.74 (95% CI 2.43–31.45).

T2 measurements. In the medial femur compartment and averaged over all 5 compartments, the highest mean T2, T2 contrast, T2 entropy, and T2 variance at baseline were observed in groups C and D, while group A showed the lowest values (Figures 1 and 2). Of all baseline T2 measurements, T2 contrast and T2 variance showed the strongest statistically significant differences between group C versus group A and group D versus group A, respectively ($P < 0.05$) (Figure 2).

While T2 entropy decreased, mean T2, T2 contrast, and T2 variance increased over 36 months in the 4 subject groups in the medial femur compartment (Figure 2 and Table 4). Similar results were found for the average over all 5 compartments, with the exception that T2 contrast and T2 variance did not increase, but decreased in group D (Figure 2 and Table 4). The smallest, mostly nonsignificant changes in T2 measurements over 36 months were observed in group D (Table 4). Consequently, differences in changes of T2 measurements over 36 months between group D versus group A were statistically significant ($P < 0.05$) for T2 parameters, as shown in Table 4. However, differences in T2 variance at 36-month followup remained statistically significant ($P < 0.05$) between group A versus group D, as well as differences in T2 contrast between group A versus groups B, C, and D (Figure 2). Interestingly, T2 entropy decreased considerably in groups A and B despite mean T2 increase (Table 4). These changes resulted in statistically significant ($P < 0.05$) differences in T2 entropy at 36-month followup between group D versus group A and group C versus group A (Figure 2).

DISCUSSION

Obese subjects with OA risk factors but no radiographic OA showed a higher prevalence and severity of meniscal and cartilage lesions compared to normal controls. Furthermore, overweight and obese subjects had a greater progression of cartilage lesions over 36 months. Being overweight or obese was associated with more heterogeneous cartilage according to T2 texture analysis. T2 entropy remained constantly elevated in overweight and obese subjects over 36 months in contrast to normal controls and subjects with OA risk factors and normal weight, who showed a considerable decrease in T2 entropy despite the mean T2 increase.

We found a higher prevalence and severity of meniscal and cartilage lesions in obese subjects than in normal controls. Furthermore, overweight and obese subjects showed a significantly greater total WORMS progression of cartilage lesions over 36 months compared to normal controls. These findings suggest an advanced degenerative joint disease in subjects with high BMI and are consistent with previous studies (6–10,27,36). However, most of these studies have been limited to assessing subjects with

clinically symptomatic and/or radiographic knee OA, while the findings in our study were observed in subjects without pain and without radiographic OA.

Previous cross-sectional studies have reported elevated cartilage mean T2 relaxation times and higher values of T2 texture parameters contrast, entropy, and variance in subjects with OA risk factors and mild OA compared to normal controls (18,21,22). High T2 contrast signifies that many pixels with different T2 values are neighboring. Higher T2 entropy means that it is more likely to find any combination of T2 relaxation time co-occurrence. High T2 variance signifies a high dispersion of co-occurrences of T2 relaxation times. In this study, we analyzed normal controls and normal weight, overweight, and obese subjects with OA risk factors and found the highest values of mean T2, T2 contrast, T2 entropy, and T2 variance in overweight/obese subjects at baseline and 36-month followup. These findings suggest that elevated BMI is associated with advanced cartilage matrix degeneration. Mean T2 was only significantly different between normal controls versus obese subjects for the average over all 5 compartments. T2 texture parameters revealed multiple statistically significant differences between normal controls versus normal weight, overweight, and obese subjects. Therefore, T2 texture parameters may be more sensitive compared to mean T2 values to detect BMI-associated cartilage matrix degeneration. While WORMS grading showed cross-sectionally only statistically significant differences between normal controls versus obese subjects, T2 texture measurements demonstrated statistically significant differences not only between normal controls versus obese subjects, but also between normal controls and overweight subjects. Therefore, T2 measurements may be useful, since they offer interesting insights into the condition of cartilage matrix beyond morphologically detectable focal knee lesions.

The smallest, mostly nonsignificant changes in T2 measurements over 36 months were observed in the obese subjects, suggesting a ceiling effect for cartilage T2 measurements. Little is known about the kind of T2 changes over time. Linear and nonlinear increases as well as temporary and permanent ceiling effects are possible. Future studies with even longer followup times are needed to fully understand the significance of our findings, e.g., studies using the 48-month followup data from the OAI. The nonobese subject groups showed significant increases of mean T2, T2 contrast, and T2 variance over 36 months. These results are consistent with a recent study by Baum et al (12). They reported significant mean T2 increases over 24 months in normal controls and nonobese subjects (BMI <27 kg/m^2) with OA risk factors. Interestingly, T2 entropy considerably decreased over 36 months in normal controls and subjects with OA risk factors and normal weight despite increasing mean T2 values. This leads to significant differences in T2 entropy between normal controls versus overweight and obese subjects at 36-month followup. Higher T2 entropy means a more uniform distribution of probabilities of T2 relaxation time co-occurrences, i.e., it is more likely to find any combination of T2 relaxation time co-occurrence. Therefore, we observed a relatively homogeneous cartilage T2 increase over 36 months in normal controls and subjects with OA risk factors and normal weight, while T2 entropy remained constantly elevated in overweight and obese subjects. Since elevated T2 entropy is associated with osteoarthritic changes (18–21), our findings suggest advanced cartilage matrix degeneration in overweight and obese subjects, which is also reflected by the significantly greater progression of cartilage lesions as assessed by WORMS grading.

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is used to assess the relative distribution of glycosaminoglycans in cartilage (37). Glycosaminoglycans are lost in the early phase of cartilage degeneration. The negatively charged contrast agent gadopentetate dimeglumine distributes within the cartilage matrix in an inverse relationship to the concentration of negatively charged glycosaminoglycans. Therefore, the concentration of gadopentetate dimeglumine reflects the content of glycosaminoglycans of cartilage. Previous studies have demonstrated a relationship between BMI and dGEMRIC (11,38,39). The knee dGEMRIC index was associated with clinical knee OA in obese adults (38). Tiderius et al reported a negative correlation between dGEMRIC and BMI in the knees of subjects with OA, but no correlation in asymptomatic knees (39). While these studies have been limited to assessing subjects with clinically symptomatic knee OA, the findings in our study were observed in subjects without pain and without radiographic OA. Therefore, the results of our study suggest a high sensitivity of T2 relaxation times as a biomarker for early cartilage matrix degeneration. Furthermore, T2 measurements have the advantage of being less time consuming than dGEMRIC, which requires the intravenous injection of gadopentetate dimeglumine and a penetration time into the cartilage of approximately 90 minutes.

This study had some limitations. First, the incidence and progression of focal knee lesions had partly low counts per group. This may result from limitations with the WORMS grading system to measure the incidence and progression of focal knee lesions (40–42). There is an ongoing discussion on how best to measure the incidence and progression of focal knee lesions. For this study, we combined the incidence and progression for the statistical analysis, since the partly low counts of incidence and progression of focal knee lesions per group limited a reliable separate analysis of the incidence and progression of focal knee lesions. However, the statistically significant ORs of total WORMS progression (Table 3) had relatively large 95% CIs, which seems to result from still low counts per group and consequently limits the informative value of these analyses. Second, malalignment is a known OA risk factor (43,44). Malalignment significantly affects the prevalence and severity of focal knee lesions and cartilage T2 measurements. However, the baseline data collected by the OAI only included goniometer alignment readings, which have been found to be inaccurate (45). Therefore, we did not adjust for malalignment in the statistical analysis, which is a limitation of our study. Third, the T2 texture parameters contrast and variance showed relatively high reproducibility errors. This may limit the validity of these parameters. Lastly, the comparison of baseline and 36-month followup T2 measurements requires

reliable and accurate MRI, which is challenging. However, in the OAI, rigorous quality assurance methods were established to allow a high quality of cartilage T2 measurements over 36 months (46).

In conclusion, increased BMI is associated with more severe cartilage degeneration as assessed by both morphologic and quantitative MRI measurements in the preclinical phase of OA. Cartilage T2 relaxation time measurements may be a sensitive biomarker for monitoring cartilage quality in subjects at risk for developing knee OA, since they offer interesting insights in the condition of cartilage matrix beyond morphologically detectable focal knee lesions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Baum had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Baum, Joseph, Nevitt, McCulloch, Link.

Acquisition of data. Baum, Joseph, Nardo, Virayavanich, Arulanandan, Alizai, Carballido-Gamio, Nevitt, Lynch, McCulloch, Link.

Analysis and interpretation of data. Baum, Joseph, Nardo, Virayavanich, Arulanandan, Alizai, Carballido-Gamio, Nevitt, Lynch, McCulloch, Link.

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