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### Permalink

<https://escholarship.org/uc/item/0fk37993>

### Journal

Journal of Magnetic Resonance Imaging, 41(5)

### ISSN

1053-1807

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### Publication Date

2015-05-01

### DOI

10.1002/jmri.24630

Peer reviewed

# Weight Loss Over 48 Months is Associated with Reduced Progression of Cartilage T2 Relaxation Time Values: Data from the Osteoarthritis Initiative

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**Purpose:** To assess whether changes in knee cartilage MR-based T2 relaxation times are associated with weight loss in individuals with risk factors for knee osteoarthritis (OA) compared with controls with stable weight.

**Materials and Methods:** One hundred twenty-seven individuals with risk factors for knee OA were studied: 62 subjects had a body mass index (BMI) decrease  $\geq 10\%$  over 48 months and 65 controls had a BMI change  $< 3\%$ . Cartilage segmentation from five knee compartments at baseline and 48-month follow-up was performed, and T2 maps were generated. The association of change in T2 values over 48 months in the weight-loss group versus the control group was assessed using multiple linear regression models.

**Results:** Weight loss was associated with significantly smaller increases in cartilage T2 in the medial femoral condyle ( $P = 0.035$ ) and overall medial compartment ( $P = 0.006$ ) compared with the controls. In a subgroup analysis comparing weight-loss subjects who were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and overweight (BMI 25–30 kg/m<sup>2</sup>) at baseline, obesity was associated with smaller increases in cartilage T2 values in the medial femoral condyle ( $P = 0.022$ ), lateral femoral condyle ( $P = 0.015$ ), patella ( $P = 0.002$ ), and globally across all compartments ( $P = 0.002$ ).

**Conclusion:** A decrease in BMI of  $\geq 10\%$  was associated with a slower progression of T2 values in individuals with risk factors for OA, suggesting a beneficial impact of weight loss on cartilage matrix degeneration.

**Key Words:** magnetic resonance imaging; weight loss; T2 relaxation time; cartilage; osteoarthritis

**J. Magn. Reson. Imaging 2015;41:1272–1280.**

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OSTEOARTHRITIS (OA) IS the most common joint disorder in the United States, with knee OA being the most prevalent site (1). It has been estimated that almost 28% of adults over age 45 have evidence of radiographic knee OA, with the numbers increasing to approximately 37% of adults over age sixty (2). Body mass index (BMI) is one of the most strongly associated risk factors for knee OA, and individuals with a BMI  $\geq 30$  kg/m<sup>2</sup> are more likely to develop symptomatic knee OA than those with a BMI  $< 25$  kg/m<sup>2</sup> (odds ratio: 6.07) (1,3). The prevalence of knee OA and its association with obesity is of growing concern, as knee OA and obesity are among the most frequent comorbid conditions in older Americans (4,5). Weight loss significantly reduces knee joint loads during walking (6,7), and studies suggest that weight loss at any stage in adulthood can halt the accumulation of knee OA risk that can result from a high BMI (4). Recently, a positive association between BMI and MR-based patellofemoral cartilage T2 relaxation time measurements was demonstrated, indicating that high BMI has a detrimental impact on the cartilage (8). However, it is not well understood how weight loss specifically impacts cartilage integrity and degeneration. Furthermore, it is unclear whether having a BMI in the obese or overweight range at any point in one's life precludes improvement in cartilage T2 values with weight loss. Studies looking at cartilage degeneration in obese individuals have shown smaller rates of degeneration (as measured by T2 progression)

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Contract grant sponsor: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); Contract grant numbers: U01-AR059507, P50-AR060752; Contract grant sponsor: National Institute of Arthritis and Musculoskeletal and Skin Diseases; Contract grant numbers: N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, N01-AR-2-2262.

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Received October 15, 2013; Accepted February 20, 2014.

DOI 10.1002/jmri.24630

View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).

compared with nonobese individuals, possibly due to extensive damage done before the study period (9). Therefore, this raises the question as to whether knee cartilage health in obese persons is beyond the salvage of weight loss, motivating the need to explore the impact of weight loss on knee cartilage health using new in vivo imaging technologies. One such technology is MRI-based T2 relaxation time. By measuring markers of cartilage health such as water content and collagen integrity quantitatively, T2 relaxation time enables us to detect and monitor early cartilage degeneration (10–14); most importantly T2 relaxation time can detect changes in cartilage health even before focal morphological changes occur (15).

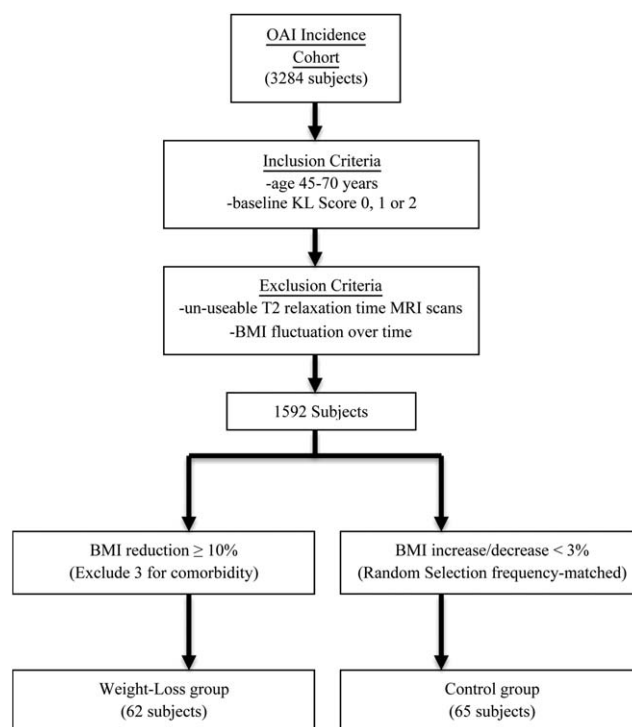
In terms of determining whether weight loss is beneficial for maintaining cartilage biochemical composition, longitudinal assessment of substantial weight loss and the subsequent impact on cartilage T2 relaxation parameters has yet to be performed. The aims of our present study were, therefore, to (i) examine the association of weight loss and concurrent change in T2 relaxation time measurements over a period of 4 years by comparing T2 changes in subjects with a BMI decrease of more than 10% with T2 changes in frequency-matched controls who were weight stable over the same period, and (ii) to investigate cartilage T2 changes in individuals who were obese at baseline and controls who were overweight at baseline, when both groups had a BMI decrease of more than 10% over the same time period.

## MATERIALS AND METHODS

### Subjects

The data used in this study were obtained from the publically available Osteoarthritis Initiative (OAI) database (<http://www.oai.ucsf.edu>). The OAI is a large, ongoing, nationwide, longitudinal prospective study sponsored by the National Institutes of Health. It combines clinical, serologic, and primarily knee joint imaging data obtained annually from 4796 patients between 45 and 79 years old, over a period of 8 years. In this study, we analyzed subsets of subjects from the OAI Incidence subcohort. The study was HIPAA compliant and all subjects provided informed consent. The local institutional review boards approved all the study protocol, amendments, and informed consent documentation. Specific OAI datasets used were baseline clinical dataset 0.2.2, baseline imaging dataset 0.E.1, 48-month follow-up clinical dataset 6.2.1, and 48-month follow-up imaging dataset 6.E.1.

Participants included in the present study were men and women ages 45 to 70 years who did not have symptomatic knee OA in either knee at baseline. Symptomatic knee OA, as outlined in the OAI Study Design Protocol, is defined as a clinical diagnosis of knee osteoarthritis with implications for prevention, requiring both the presence of frequent knee symptoms and radiographic findings reflecting the pathology of osteoarthritis. However, these subjects had characteristic risk factors that placed them at



**Figure 1.** Schematic illustration showing creation of the subgroups. Sixty-two weight-loss subgroup subjects and sixty-five control subgroup subjects were included in this study based on our inclusion and exclusion criteria and weight change classification. OAI = Osteoarthritis Initiative; BMI = body mass index; KL = Kellgren-Lawrence.

increased risk for developing OA, which included the following: (i) previous knee injury or surgery, (ii) family history of total knee replacement, (iii) Heberden's nodes, (iv) knee symptoms in the past 12 months (defined as either [a] frequent knee symptoms, [b] frequent use of medication to treat knee symptoms, or [c] infrequent knee symptoms [pain, aching, or stiffness] in or around the knee at any time in the past 23 months but not on most days for at least 1 month), (v) overweight, and (vi) frequent knee bending activity (9). We only included subjects with a baseline Kellgren-Lawrence (KL) score of 0, 1, or 2 in the right knee and excluded those who did not have technically optimal T2 multiecho sequences of the right knee at baseline and at 48 months. Given our age, BMI, KL score, and image quality criteria, we excluded a total of 1692 subjects from the original pool of 3284 subjects.

From the eligible subjects, we identified two groups defined by BMI change from baseline to 48 months: a weight-loss group who had a BMI reduction  $\geq 10\%$  and a weight stable control group with a BMI increase or decrease of  $< 3\%$  (Fig. 1). We considered a BMI reduction of 10% relevant because the beneficial health impact of a weight loss of that magnitude is well documented in a previous study (16). Furthermore, only subjects without substantial BMI fluctuations ( $< 5\%$  change in BMI between any two 12-month time points) over the 4-year period were eligible for this study. We excluded 3 subjects from the weight-loss group who developed cardiac failure, cancer and/or other severe diseases over the course of

the 48-month study period that may have been responsible for the weight loss. This assessment was based on annual administration of a comorbidity questionnaire asking about new onset of these conditions at each visit. One subject diagnosed with cancer before initiation of the study, and who was treated and stable at baseline and at 48-month follow-up, was included in the study. A summary of the subject selection criteria is shown in Figure 1.

Sixty-two eligible subjects were included in the weight-loss group. Sixty-five weight stable controls were selected from subjects in the OAI Incidence Cohort who met the inclusion criteria but did not exhibit any large change or fluctuations in BMI over the 4 years of the study. Controls were frequency matched, in a 1 to 1 ratio, to the weight-loss group by randomly selecting controls from 5-year age strata. An a priori power analysis was performed to ensure an appropriate number of individuals would be included in the study. Using preliminary data gathered in healthy controls ( $n = 36$ , baseline BMI =  $22.7 \pm 1.5$ , follow-up BMI =  $23.4 \pm 2.1$ ) (9), the standard deviation of change in mean T2 measurements over 36 months was found to be 1.7 in the medial femoral compartment ( $\Delta$  mean T2 =  $1.9 \pm 1.7$ ). From these data, it was determined that a sample size of 46 patients per group would achieve a power  $>0.8$ . Therefore, including 62 subjects in the weight-loss group and 65 in the control group is conservative given the parameters of the power analysis.

### MR Imaging

MR images were obtained using one of four identical 3.0 Tesla (T) (Siemens Magnetom Trio, Erlangen, Germany) scanners and quadrature transmit-receive coils (USA Instruments, Aurora, OH) at four clinical sites (Ohio State University, Columbus, OH; University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; and Memorial Hospital of Rhode Island, Pawtucket, RI). A sagittal two-dimensional (2D) multislice, multiecho (MSME) sequence was acquired and used for measuring T2 relaxation time values. Sequence parameters were: a pulse repetition time (TR) of 2700 ms, seven echo times (TEs 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms), field-of-view (FOV) = 12 cm, bandwidth of 250 Hz/pixel, in-plane spatial resolution of  $0.313 \text{ mm} \times 0.446 \text{ mm}^2$ , slice thickness of 3.0 mm, and 0.5-mm gap. Detailed information about the sequences is available in the OAI MR protocol (17).

### Image Analysis

The sagittal 2D MSME images of the right knee were transferred to a remote workstation (SPARC; Sun Microsystems, Mountain View, CA). Using in-house spline-based software developed with MATLAB (MathWorks, Natick, Massachusetts) cartilage was semi-automatically segmented at the patella, medial femoral condyle, lateral femoral condyle, medial tibia, and lateral tibia compartments in the first echo images of the MSME sequence. This method has previously

been shown to be a highly reproducible way of segmenting cartilage regions of interest (ROI) (18). Each compartment had a range of 8–15 sections, and all sections with well-visualized artifact-free cartilage were segmented.

In each segmented cartilage compartment mean T2 values at baseline and 48 months were calculated using an interactive display language routine; the T2 relaxation time was estimated by fitting an exponential function to the signal intensity at different echo times as follows:  $SI(TE) \sim \exp(-TE/T2)$ , where  $SI(TE)$  is the signal intensity as a function of echo time, and T2 is the transverse relaxation time. Previous studies have suggested that dropping the first echo from the MSME sequence minimizes errors in calculated T2 values for cartilage (19). Therefore, a mono-exponential decay model was used (20), and the last six (20, 30, 40, 50, 60, and 70 ms) echo images were used to generate the T2 data.

To maximize reproducibility in segmentation technique, all readers were required to undergo image and data analysis core initial training at the start of the study. Readers on the segmentation team (A.T.S. and T.P.) met on a weekly basis with the project's lead postdoctoral researcher (H.L.), who had 5 years of cartilage segmentation experience, to review the segmented sequences. Inter-reader reproducibility was confirmed in baseline T2 maps of randomly selected subjects, on which both readers on the segmentation team segmented all five compartments. Inter- and intra-reader reproducibility errors for T2 measurements of each compartment were calculated on a percentage basis as the root mean square average of the single coefficients of variation per knee, according to Stehling et al (21). Reproducibility results for global T2 measurements indicated an inter-reader reproducibility error for mean T2 of 3.33%, and an intra-reader reproducibility error for mean T2 of 1.11%.

### Statistical Analysis

Statistical analysis was performed using STATA version 12.0 software (StataCorp LP, College Station, TX). The differences in subject characteristics (i.e., mean age, BMI, KL Score, etc.) between the control and weight-loss groups were determined using Student's independent t-tests and chi-square tests. Changes in BMI over the course of the study were analyzed using a regression analysis. Associations between baseline T2 and gender were assessed using Student's independent t-tests, and associations between baseline T2, baseline BMI, and age were assessed using regression analyses. Changes in mean T2 measurements over 48 months ( $\Delta$  mean T2) were computed by subtracting baseline T2 measurements from 48-month follow-up T2 measurements. In addition, the relationship between  $\Delta$  mean T2 and  $\Delta$  BMI was analyzed using Spearman correlations. Multiple linear regression models were used to assess the association of differences in  $\Delta$  mean T2 between (a) the weight-loss and control groups, and (b) the overweight and obese subjects within the weight-loss group. Models were adjusted for age, sex, and baseline KL score (1 and 2)

Table 1  
Subject Characteristics and Descriptive Statistics\*

	All	Control group (weight change < 3%)	Weight-loss group (weight loss ≥ 10%)	P-value <sup>†</sup>
n	127 (100%)	65 (51.18%)	62 (48.82%)	
Age (years)*	55.15 ± 6.38	53.78 ± 4.57	56.09 ± 6.89	0.156
Sex (females)*	71 (55.91%)	38 (58.46%)	33 (53.23%)	0.893
Baseline BMI (kg/m <sup>2</sup> )*	27.27 ± 3.16	24.38 ± 3.39	27.49 ± 2.98	<b>0.0005</b>
48-month BMI (kg/m <sup>2</sup> )	23.05 ± 2.71	24.36 ± 3.34	23.07 ± 2.68	<b>0.036</b>
BMI change (kg/m <sup>2</sup> )	-2.22 ± 2.47	-0.026 ± 0.464	-4.35 ± 1.60	<b>&lt;0.0001</b>
Percent BMI change (%)	-7.68 ± 8.65	-0.072 ± 1.90	-15.704 ± 5.00	<b>&lt;0.0001</b>
Baseline KL Score*				0.053
KL = 0	79 (62%)	45 (69%)	34 (55%)	
KL = 1	27 (21%)	15 (23%)	12 (19%)	
KL = 2	21 (17%)	5 (8%)	16 (26%)	
Previous right knee injury	34 (27%)	18 (28%)	16 (26%)	0.619
Previous right knee surgery	11 (9%)	3 (5%)	8 (13%)	0.103
Frequent knee bending activity	91 (72%)	47 (73%)	44 (71%)	0.759
Family history (knee replacement)	23 (18%)	12 (19%)	11 (18%)	0.852
Heberden's nodes	35 (28%)	20 (31%)	15 (25%)	0.442
Knee symptoms (pain, aching, or stiffness, past 12 months)	27 (21%)	9 (14%)	18 (29%)	<b>0.030</b>

\*Logistic regression models used for statistical analysis were adjusted for age, gender, baseline BMI, and baseline KL score to account for differences between groups.

<sup>†</sup>P-values < 0.05 are in bold.

and baseline BMI (1). Results were expressed as changes in T2 (ms), with 95% confidence interval (CI) and adjusted P-value. A P-value of less than 0.05 was considered a statistically significant difference.

## RESULTS

### Subject Characteristics

Mean age, baseline BMI, follow-up BMI, baseline KL score, and gender distribution are listed in Table 1. Sixty-two subjects from the weight-loss group (mean age, 56.09 ± 6.89 years) and 65 subjects from the control group (mean age, 53.78 ± 4.57 years) were included in the study with a mean baseline BMI of 27.49 kg/m<sup>2</sup> ± 2.98 (BMI range, 21.9–34.3 kg/m<sup>2</sup>) and 24.38 kg/m<sup>2</sup> ± 3.39 (BMI range, 19.4–37.0 kg/m<sup>2</sup>), respectively. After 48 months, mean BMI for the weight-loss group was 23.07 kg/m<sup>2</sup> ± 2.68, and 24.36 kg/m<sup>2</sup> ± 3.34 for the control group. The overall average change in BMI for all subjects was -2.22 kg/m<sup>2</sup> ± 2.47. Changes in mean BMI over the 48-month study period were -0.026 kg/m<sup>2</sup> ± 0.464 for the control group and -4.35 kg/m<sup>2</sup> ± 1.60 for the weight-loss group. The mean percent change in BMI was 15.70% ± 5.00, and 0.07% ± 1.90 for the weight-loss group and control group respectively.

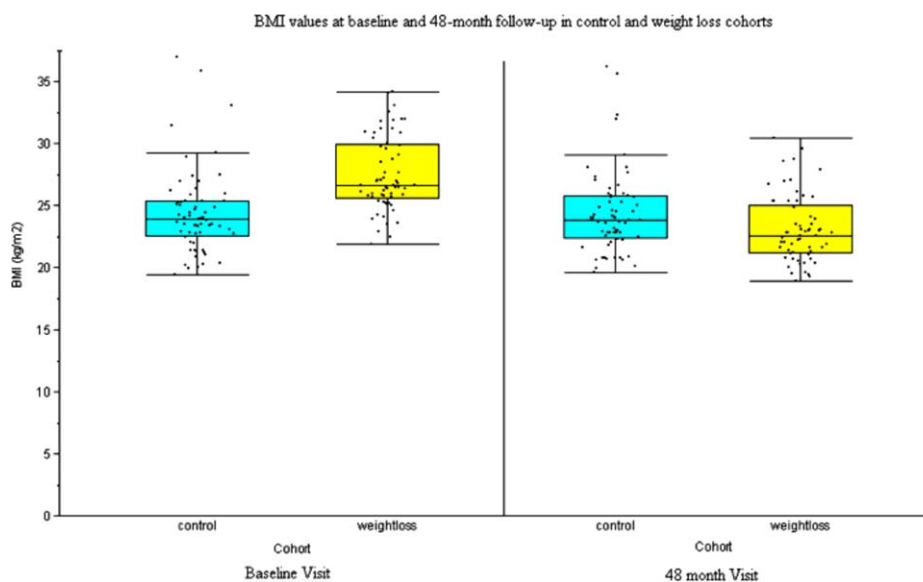
There were no statistically significant differences in mean age or gender distribution between the two study groups ( $P = 0.156$  and  $P = 0.893$ , respectively). As defined by the inclusion criteria, all subjects had KL scores ≤ 2 at baseline in the study knee; while the weight-loss group had more subjects with KL scores of 1

and 2 at baseline, the difference in distribution of scores between the groups did not reach significance ( $P = 0.053$ ). As shown in Figure 2, the weight-loss group had statistically significant higher BMI than the control group at baseline ( $P < 0.001$ ), and statistically significant lower BMI than the controls at 48 months ( $P = 0.036$ ). There was no statistically significant change in the mean BMI of the control group over the 48 months of the study (0.077 kg, 95% CI [-0.078, 0.232],  $P = 0.992$ ).

### T2 Relaxation Time Measurements

At baseline, there were no statistically significant differences in T2 relaxation time measurements between the weight-loss and control groups in any of the knee compartments studied (Table 2). Across all subjects, we observed no statistically significant differences in global baseline or Δ mean T2 values by gender ( $P = 0.242$  and  $P = 0.540$ , respectively). We also performed correlations between T2 values and age and found that global T2 values were significantly higher in patients who were older at baseline (coef = 0.103,  $P = 0.035$ , 95% CI [0.007, 0.199]). However, there were no statistically significant differences in Δ mean T2 by age (coef = -0.044,  $P = 0.181$ , 95% CI [-0.108, 0.021]). Within both the weight-loss and weight stable groups, there was a similar but weak correlation between global baseline T2 values and BMI, as individuals with higher baseline BMI values also had higher baseline T2 values. However, this was not statistically significant (coef = 0.155,  $P = 0.166$ , 95% CI [-0.066, 0.388] in the control group, and coef = -0.233,  $P = 0.088$ , 95% CI [-0.036, 0.502] in the weight-loss group).





**Figure 2.** The average BMI at baseline and 48-month follow-up were analyzed for each group. At baseline, the weight-loss group had a statistically significant higher mean BMI ( $27.49 \pm 3.00 \text{ kg/m}^2$ ) compared with the control group ( $24.38 \pm 3.45 \text{ kg/m}^2$ ) (odds ratio: 1.36,  $P < 0.005$ ). However, at 48-month follow-up the weight-loss group had a statistically significant lower mean BMI ( $23.14 \pm 2.72 \text{ kg/m}^2$ ) than the control group ( $24.36 \pm 3.39 \text{ kg/m}^2$ ) (odds ratio: 0.873,  $P = 0.036$ ), as might be expected because the weight-loss group lost  $\geq 10\%$  baseline BMI. No statistically significant changes in weight are noted in the control group.

### Changes in T2 Relaxation Time Measurements Over 48 Months

The results from all knee compartments demonstrate less of an increase in mean T2 values over 48 months

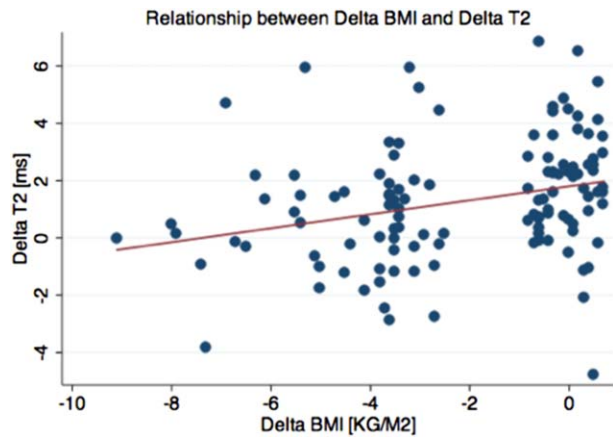
in the weight-loss group compared with the control group, suggesting less progression of cartilage degeneration in the weight-loss group (Table 2). Over 48 months, changes in mean cartilage T2 were

Table 2  
Mean T2 Relaxation Times at Baseline and Changes in Mean T2 Measured in Five Separate Knee Compartments Comparing Weight-Loss and Control Subjects\*

	Control group	Weight-loss group	Adjusted mean difference*	95% CI	P-value <sup>a</sup>
Global (all compartments)					
Baseline mean T2 (ms)	$32.80 \pm 3.01$	$32.75 \pm 3.18$	-0.561	(-1.760, 0.638)	0.356
Change in mean T2 (ms)	$2.52 \pm 2.18$	$1.56 \pm 1.79$	-0.754	(-1.540, 0.033)	0.060
Lateral femoral condyle					
Baseline mean T2 (ms)	$34.27 \pm 2.32$	$34.42 \pm 2.23$	-0.182	(-1.024, 0.660)	0.669
Change in mean T2 (ms)	$2.35 \pm 2.43$	$1.88 \pm 2.30$	-0.094	(-0.948, 0.760)	0.828
Lateral tibia					
Baseline mean T2 (ms)	$29.94 \pm 2.15$	$29.86 \pm 2.35$	-0.357	(-1.278, 0.563)	0.443
Change in mean T2 (ms)	$1.45 \pm 2.30$	$0.71 \pm 1.84$	-0.641	(-1.490, 0.208)	0.137
Lateral compartment					
Baseline mean T2 (ms)	$32.09 \pm 2.07$	$32.17 \pm 2.01$	-0.165	(-0.961, 0.632)	0.683
Change in mean T2 (ms)	$1.89 \pm 2.01$	$1.35 \pm 1.93$	-0.454	(-1.230, 0.321)	0.248
Medial femoral condyle					
Baseline mean T2 (ms)	$37.44 \pm 2.38$	$37.68 \pm 2.55$	-0.287	(-1.209, 0.636)	0.539
Change in mean T2 (ms)	$1.86 \pm 1.98$	$0.67 \pm 2.06$	-0.866	(-1.669, -0.063)	<b>0.035</b>
Medial tibia					
Baseline mean T2 (ms)	$31.60 \pm 2.73$	$31.88 \pm 2.49$	-0.241	(-1.289, 0.806)	0.649
Change in mean T2 (ms)	$2.23 \pm 2.58$	$1.35 \pm 2.80$	-1.055	(-2.151, 0.040)	0.059
Medial compartment					
Baseline mean T2 (ms)	$34.65 \pm 2.28$	$34.25 \pm 4.95$	-0.895	(-2.369, 0.580)	0.232
Change in mean T2 (ms)	$2.02 \pm 1.95$	$0.95 \pm 1.91$	-1.110	(-1.891, -0.329)	<b>0.006</b>
Patella					
Baseline mean T2 (ms)	$32.78 \pm 3.81$	$32.95 \pm 3.15$	-0.944	(-2.169, 0.282)	0.130
Change in mean T2 (ms)	$3.81 \pm 5.28$	$2.48 \pm 3.51$	-0.020	(-1.340, 1.300)	0.976

\*The associations between T2 parameters and weight loss of  $\geq 10\%$  of baseline BMI over 48 months were assessed using linear regression models (adjusted for age, gender, baseline BMI, and baseline KL scores); reported values represent absolute differences in T2 values.

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



**Figure 3.** Scatterplot of change in mean T2 relaxation times versus change in BMI over 48 months in medial femoral condyle compartment ( $r = 0.344$ ,  $P < 0.001$ ).

significantly smaller statistically in the weight-loss group in the medial femoral condyle compartment ( $-0.866$  ms, 95% CI  $[-1.669, -0.063]$ ,  $P = 0.035$ ) and the overall medial compartment ( $-1.110$  ms, 95% CI  $[-1.891, -0.329]$ ,  $P = 0.006$ ), with similar trends observed in the medial tibia compartment ( $-1.055$  ms, 95% CI  $[-2.151, 0.040]$ ,  $P = 0.059$ ) and in the global average across all compartments ( $-0.754$  ms, 95% CI  $[-1.540, 0.033]$ ,  $P = 0.060$ ).

Analysis of BMI change versus  $\Delta$  mean T2 relaxation times in the medial femoral condyle compartment showed that with greater weight loss, there was significantly less increase in T2 observed over 48 months,

( $r = 0.344$ ,  $P = 0.0001$ ; Fig. 3); a similar trend was seen in all compartments, and significance was found in the patella ( $P = 0.03$ ), overall medial compartment ( $P = 0.001$ ), and globally across all compartments ( $P = 0.001$ ).

**Subgroup Analysis**

An additional analysis was performed comparing  $\Delta$  mean T2 over 48 months in overweight subjects (BMI 25.0–29.9 kg/m<sup>2</sup>) and obese subjects (BMI  $\geq 30$  kg/m<sup>2</sup>) within the weight-loss group. A total of 36 overweight subjects and 14 obese subjects were analyzed with a baseline mean BMI of 26.73 and 31.83 kg/m<sup>2</sup>, respectively. There was no statistically significant difference in percent of BMI loss between the obese and overweight subgroups (16.85% versus 16.36%, respectively,  $P = 0.105$ ), however, total weight loss in kilograms was higher in the obese cohort compared with the overweight group (5.35 kg versus 4.39 kg, respectively).

The results from all knee compartments demonstrate a smaller increase in cartilage T2 values over 48 months among those who were obese at baseline compared with those who were overweight at baseline, when both groups lost over 10% of their baseline BMI (Table 3). Smaller increases in cartilage T2 times over 48 months were significantly associated with higher baseline BMI (obese subgroup) globally across all compartments ( $-1.841$  ms, 95% CI  $[-2.981, -0.702]$ ,  $P = 0.002$ ), in the lateral femoral condyle compartment ( $-1.987$  ms, 95% CI  $[-3.565, -0.409]$ ,  $P =$

**Table 3**  
Subgroup Analysis Comparing Overweight (BMI 25–29.9 kg/m<sup>2</sup>) and Obese (BMI  $\geq 30$  kg/m<sup>2</sup>) Individuals in the Weight-Loss Group\*

	Obese (n = 14)	Overweight (n = 36)	Adjusted mean difference*	95% CI	P-value <sup>a</sup>
<b>Global (all compartments)</b>					
Baseline mean T2 (ms)	33.49 ± 3.74	32.53 ± 3.30	1.340	(-0.888, 3.568)	0.232
Change in mean T2 (ms)	0.76 ± 1.90	1.92 ± 1.73	-1.841	(-2.981, -0.702)	<b>0.002</b>
<b>Lateral femoral condyle</b>					
Baseline mean T2 (ms)	34.49 ± 2.31	34.46 ± 2.43	0.085	(-1.459, 1.629)	0.912
Change in mean T2 (ms)	1.04 ± 1.67	2.27 ± 2.65	-1.987	(-3.565, -0.409)	<b>0.015</b>
<b>Lateral tibia</b>					
Baseline mean T2 (ms)	29.84 ± 2.39	29.86 ± 2.61	0.082	(-1.853, 2.016)	0.932
Change in mean T2 (ms)	0.87 ± 1.83	0.70 ± 1.91	-0.281	(-1.679, 1.116)	0.687
<b>Lateral compartment</b>					
Baseline mean T2 (ms)	32.27 ± 2.22	32.17 ± 2.16	0.024	(-1.457, 1.506)	0.974
Change in mean T2 (ms)	0.98 ± 1.64	1.56 ± 2.16	-1.230	(-2.543, 0.083)	0.066
<b>Medial femoral condyle</b>					
Baseline mean T2 (ms)	39.03 ± 2.54	37.22 ± 2.43	1.571	(-0.152, 3.294)	0.073
Change in mean T2 (ms)	-0.11 ± 2.08	1.11 ± 1.86	-1.678	(-3.096, -0.259)	<b>0.022</b>
<b>Medial tibia</b>					
Baseline mean T2 (ms)	32.77 ± 2.90	31.72 ± 2.15	1.072	(-0.710, 2.853)	0.232
Change in mean T2 (ms)	1.48 ± 3.54	1.16 ± 2.71	-0.997	(-3.099, 1.106)	0.344
<b>Medial compartment</b>					
Baseline mean T2 (ms)	35.90 ± 2.46	33.63 ± 5.94	3.758	(0.108, 7.408)	<b>0.044</b>
Change in mean T2 (ms)	0.68 ± 2.26	1.04 ± 1.79	-1.055	(-2.420, 0.309)	0.126
<b>Patella</b>					
Baseline mean T2 (ms)	34.67 ± 3.29	32.50 ± 2.91	2.406	(0.296, 4.515)	<b>0.026</b>
Change in mean T2 (ms)	-0.12 ± 3.41	3.09 ± 2.53	-3.209	(-5.201, -1.217)	<b>0.002</b>

\*The associations between T2 parameters and baseline BMI of subjects in the weight-loss group were assessed using linear regression models (adjusted for age, gender, and baseline KL scores); reported values represent absolute differences in T2 values.

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

0.015), in the medial femoral condyle compartment ( $-1.678$  ms, 95% CI  $[-3.096, -0.259]$ ,  $P = 0.022$ ), and in the patella compartment ( $-3.209$  ms, 95% CI  $[-5.201, -1.217]$ ,  $P = 0.002$ ). A similar trend was seen in the overall lateral compartment ( $-1.230$  ms, 95% CI  $[-2.543, 0.083]$ ,  $P = 0.066$ ). Interestingly at baseline, mean T2 values were higher in the obese compared with the overweight cohort, but these differences were only statistically significant in the patella  $34.67$  ms versus  $32.50$  ms ( $P = 0.026$ ) and overall medial compartment  $35.90$  ms versus  $33.63$  ms ( $P = 0.044$ ). Differences were not statistically significant in other compartments.

## DISCUSSION

The results of this study showed an association between changes in mean knee cartilage T2 values and weight loss of greater than 10% of baseline BMI compared with weight stable individuals with risk factors but no OA. Statistically, significantly smaller increases in cartilage mean T2 relaxation times were seen in the medial femoral condyle compartment and overall medial compartments in individuals who lost  $\geq 10\%$  of their baseline BMI over a 4-year period, as compared to individuals who had  $< 3\%$  change in BMI over the same time period. Similar changes in mean cartilage T2 relaxation times were observed in all other compartments studied, with trends observed globally across the entire knee and in the medial tibia compartment. These results suggest that weight loss was a contributing factor to these individuals' slower progression of cartilage T2 relaxation times compared with individuals who did not lose weight, suggesting a slower rate of cartilage degeneration.

Increases in T2 relaxation times are indicative of progressive cartilage degeneration; T2 values increase as water content increases and collagen is degenerating (22), and can therefore serve as surrogate markers to quantify hyaline cartilage water content and collagen integrity. Because the process of cartilage loss is characterized in stages—first by degradation of portions of the cartilage extracellular matrix, followed by loss of proteoglycan content, changes in water content, and finally molecular changes in collagen structure (10)—early cartilage degeneration can be quantified using T2 relaxation time measurements before morphological cartilage defects are found (11). Given that smaller increases in T2 values were associated with being in the weight-loss group, our findings suggest that weight loss is an effective intervention to slow the earliest stages of cartilage degeneration that lead to the development of OA.

Previous studies have shown that in subjects with minimal baseline cartilage damage, obesity is strongly associated with increased cartilage degeneration (23,24), especially rapid cartilage loss (25). Elevated levels of tibiofemoral articular contact stress have been associated with observed worsening in cartilage morphology (26,27), and the additional mechanical loading of the knee joint in obese individuals may increase this articular stress (28). To investigate

whether weight loss is still of benefit to obese individuals whose cartilage may show more advanced degeneration, a subgroup analysis was performed with obese and overweight subjects within our weight-loss group. Within the obese subcohort, there were statistically significant smaller increases in mean T2 in various knee compartments, suggesting continued benefit of weight loss for obese individuals.

The patterns noted in our findings are consistent with previous studies demonstrating that in the normally aligned ambulating knee, load is disproportionately transmitted to the medial compartment (29). These observed patterns of weight loading are corroborated by radiographic evidence that the medial tibiofemoral compartment has greater prevalence of radiographic osteophytosis and sclerosis compared with the lateral compartments (3). Additionally, recent literature suggests that a mechanical stimulus can induce changes in serum cartilage oligomeric matrix protein associated with cartilage thinning over time, and that these effects are primarily seen in the medial compartments of the knee (30). Similar to previous studies (31), our weight-loss subjects showed the most improvement compared with control subjects in the medial femoral condyle compartment.

From a clinical perspective, using weight loss as an intervention to prevent early OA is supported by other studies, which have suggested that an individual can halt increasing their risk of developing OA by reducing weight at any stage in adulthood (4). We also observed as more weight was lost, mean T2 values increased significantly less, thus suggesting that a greater magnitude of weight loss may be even more beneficial to preserve the cartilage matrix. Given that the higher levels of knee cartilage defects observed with increasing BMI are associated with both objective and self-reported measures of physical disability (32), the potential for improving cartilage health by means of weight loss could have a profound effect upon the quality of life of heavier individuals at risk for OA. Our data further supports this literature citing the benefits of weight loss as a protective intervention for OA in individuals of any weight.

This study was limited by the fact that we were not able to precisely determine how individuals lost weight. We were able to exclude subjects with severe diseases such as progressive cancer and chronic heart conditions, but were limited in assessing the exact contributions of diet and/or physical exercise to our subjects' weight loss plans. Further limitations in this study include our small sample size, which prevented us from performing a matched-pairs analysis with subjects who had similar baseline BMI. Therefore, to account for differences in baseline BMI, we instead controlled for the variable in our regression analysis. In our subgroup analysis, we would have ideally compared obese subjects in the weight-loss group with obese subjects in our control group, but our study is limited by the very small number of obese individuals in the control group. In addition, the longitudinal changes appear relatively small, on the order of 1 ms difference in T2 relaxation times; however, previous studies have shown differences on this order between



patient cohorts with and without disease progression, emphasizing the clinical relevance of those T2 changes (11,33,34). Given that the clinically significant changes in T2 values are relatively small, it is important to acknowledge the inherent limitations of the curve-fitting algorithm used in this and other similar studies. However, rigorous quality assurance is performed in the OAI study and excellent reproducibility data for T2 relaxation time measurements in the order of 1.5–5.3% over 8 years have recently been reported (35). In addition it should be noted that the reported T2 changes in this study were pooled averages over the entire compartments under investigation, and consideration was not given to separating superficial and deep layers of cartilage to look at spatial variation in T2 changes. However, previous studies have demonstrated that performing laminar analysis of cartilage provides limited additional information beyond that provided by bulk measurements alone and that reproducibility of laminar measurements is lower than those of bulk measurements (21,36,37).

In conclusion, our study suggests that weight loss may prevent early cartilage matrix degeneration as measured with MRI based T2 relaxation time. Because T2 relaxation parameters offer noninvasive and safe imaging modalities for evaluating the earliest steps of the cartilage degeneration pathway, they may potentially aid in following the progression of disease and advising patients in a clinical setting before cartilage is lost.

## ACKNOWLEDGMENTS

This study was funded through National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) grants. The study was made possible through support from the Osteoarthritis Initiative, a public-private partnership comprising 5 NIH contracts, with research conducted by the Osteoarthritis Initiative Study Investigators. The study was also funded in part by the Intramural Research Program of the National Institute on Aging, NIH. Private funding partners include Merck Research, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer; the private sector funding for the Osteoarthritis Initiative is managed by the Foundation for the National Institutes of Health. The authors have no financial or personal relationships to disclose.

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