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Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative

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SUMMARY

Objective: To investigate compositional cartilage changes measured with 3T MRI-based T2 values over 48 months in overweight and obese individuals with different degrees of weight loss (WL) and to study whether WL slows knee cartilage degeneration and symptom worsening.
Design: We studied participants from the Osteoarthritis Initiative with risk factors or radiographic evidence of mild to moderate knee osteoarthritis with a baseline BMI ≥25 kg/m^2. We selected subjects who over 48 months lost a, moderate (BMI change, 5–10%WL, $n = 180$) or large amount of weight (≥10%WL, $n = 78$) and frequency-matched these to individuals with stable weight (<3%, $n = 258$). Right knee cartilage T2 maps of all compartments and grey-level co-occurrence matrix (GLCM) texture analyses were evaluated and associations with WL and clinical symptoms (WOMAC subscales for pain, stiffness and disability) were assessed using multivariable regression models.
Results: The amount of weight change was significantly associated with change in cartilage T2 of the medial tibia (β 0.9 ms, 95% CI 0.4 to 1.1, $P = 0.001$). Increase of T2 in the medial tibia was significantly associated with increase in WOMAC pain (β 0.5 ms, 95% CI 0.2 to 0.6, $P = 0.02$) and disability (β 0.03 ms, 95% CI 0.003 to 0.05, $P = 0.03$). GLCM contrast and variance over all compartments showed significantly less progression in the >10%WL group compared to the stable weight group (both comparisons, $P = 0.04$).
Conclusions: WL over 48 months is associated with slowed knee cartilage degeneration and improved knee symptoms.

Introduction

Obesity is a highly prevalent condition and is a major risk factor for knee OA[1,2]. Biomechanical factors such as increased joint loads and systemic metabolic factors have a negative impact on cartilage degradation[3–5]. Co-occurrence of these factors with obesity accelerates the cartilage degeneration process and worsens clinical symptoms[6,7]. Cartilage degeneration is associated with altered content of proteoglycans and water and degradation of the fibrillar collagen network[8]. Ideally, these findings should be diagnosed at early stages, before irreversible hyaline cartilage damage occurs. MRI-based T2 relaxation time has been identified as an imaging biomarker that provides information on early changes in collagen integrity[9]. Moreover, previous studies have shown that T2 measurements are able to predict changes in cartilage morphology and radiographic OA[10–12].

Studies demonstrated improvement of clinical performance through weight loss (WL)[13,14]. A previous study has shown that T2 relaxation times progress less in subjects with >10% WL of their baseline BMI over 4 years indicating decreased degenerative changes in comparison to controls without WL[15]. However, associations between T2 values in patients loosing weight over time and clinical parameters are not well understood. Another previous

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study found that percentage weight change was significantly associated with change in medial tibial cartilage volume[16], yet this study was limited to investigating cartilage volume only, without compositional imaging, which provides information on early changes in cartilage, even before cartilage volume loss may have taken place[9].

Previous studies have shown that quantitative analysis of cartilage texture using grey-level co-occurrence matrix (GLCM) texture parameters contrast, entropy and variance, allows early detection of compositional and structural changes within the cartilage matrix in subjects with risk for osteoarthritis, before radiographic evidence for OA is present, by providing information on the distribution of T2 pixel values[17,18]. Imaging of homogeneity may visualize early laminar disruption within cartilage, as does laminar analysis, which analyzes the bone and surface layer of cartilage separately[19].

Therefore, in this longitudinal study over 48 months in overweight and obese subjects we analyzed the association of different degrees of WL with changes in symptoms and change in cartilage T2, laminar and GLCM texture analysis parameters as measures of progression of knee cartilage degeneration.

Method

Subjects

The Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu) is an ongoing, longitudinal, prospective, multi-center cohort study with 4796 participants of which subjects for this study were selected. The initiative is sponsored by the U.S. National Institutes of Health (NIH) for investigation of diagnosis, treatment and prevention of OA. Subjects between 45 and 79 years of age with (progression cohort) or are at risk for (incidence cohort) symptomatic knee OA were included into this study. Knee imaging and clinical data were been obtained annually. Informed consent was obtained from all subjects and the study was HIPAA compliant. Study protocols, amendments and informed consent documentations were approved by the local institutional review boards. The following OAI datasets were used: baseline imaging dataset 0.E.1, 48 month follow-up imaging dataset 6.E.1, clinical datasets at baseline 0.2.2, 12 month follow-up 1.2.1, 24 month follow-up 3.2.1 and 48 month follow-up 6.2.2.

For our study, subjects with BMI for baseline, 12, 24, 36 and 48-month follow up were selected from the OAI database (progression and incidence cohort). Subsequently, subjects with missing BMI data at any of the four time points, a baseline Kellgren–Lawrence (KL) score > 3 in the right knee, or rheumatoid arthritis diagnosed during follow-up were excluded from these subjects. Of those, patients with an initial BMI of less than 25 kg/m^2 and a WL of 3–5% were excluded.

Since the trajectory of WL may affect longitudinal changes in joint structures and clinical symptoms, a linear regression model was implemented to assess the annual rate of change in BMI over 4 years. Weight change of the subjects was categorized into “steady” weight and “uneven” weight change, based on the root mean square error (RMSE) of the individual's regression line. In this study, we excluded subjects ($n = 84$) with uneven WL from the overall cohort, which was defined as an RMSE for weight change above the 95th percentile of the RMSE. Reason for this selection criteria was to select patients that follow the linear and steady WL trajectory in order to avoid a bias through subjects that “cycle” through weight gain and WL periods over 48 months and therefore to isolate the effects of continuous steady WL on knee cartilage as good as possible. Also subjects with development of cardiac failure, cancer and/or other severe diseases over the course of the 48-month study period, which could have been responsible for the WL, were excluded using the Katz comorbidity questionnaire[20]. From these subjects only those with right knee MRI T2 mapping sequences available at baseline and 48 months were selected. All subjects that were left after the previous mentioned exclusion criteria ($n = 1981$) were categorized into groups based on their WL over 48 months: moderate (BMI decrease of 5–10%), large amount (BMI decrease of >10%) of WL and stable weight (BMI changes <3%). We randomly selected subjects from among those in the 5–10% weight loss group (5–10%WLG; $n = 180$) and the >10% weight loss group (>10%WLG; $n = 78$) and frequency matched these on sex (m/f), age (10 year strata from 45 to 65 and one 14 year stratum from 65 to 79), baseline BMI (BMI in 2.5 kg/m^2 strata) and KL (KL in strata of 0/1 and 2/3). Subjects with stable weight ($n = 258$) were randomly selected from each stratum in the frequency matching process and matched to the respective WL subjects. This study design was chosen in order to minimize the impact of these covariates (age, sex, baseline BMI and KL) since their impact on the rate of T2 progression is known from previous studies[21–25].

The subject selection process is illustrated in Fig. 1 and subject characteristics are shown in Table I.

An a priori power analysis was performed to calculate the appropriate size of each subgroup in order to analyze differences between the groups. Using preliminary data of our previous study in controls ($n = 65$) and subjects with >10%WL ($n = 62$) over 48 months, the average change of T2 in the medial femur was 1.89 ± 1.98 ms in the control group and 0.67 ± 2.05 ms in the >10% WLG. With these data a comparison between two different WLGs was simulated and we determined a sample size of at least 70 subjects per group would achieve a power >0.9. Therefore we included 78 subjects in the >10%WLG and 180 subjects in the 5–10%WLG in order to ensure adequate group sizes for the comparison.

MR imaging

MR images were acquired 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 (University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Memorial Hospital of Rhode Island, Pawtucket, RI and The Ohio State University, Columbus, OH). T2 values were obtained using sagittal two-dimensional multislice, multiecho sequences with seven echo times (TEs 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms). Further details are available in the OAI MR protocol[26].

Image analysis

Semi-automatic cartilage segmentation of lateral femur, lateral tibia, medial femur, medial tibia and patella compartments was performed as previously described, using an in-house, spline-based software based on MATLAB (MathWorks, Natick, Massachusetts). This algorithm also calculated the mean cartilage thickness of all ROIs for each compartment as previously described[12]. Cartilage was segmented and graded by two trained researchers (M.S. and G.F.), applying this semi-automatic cartilage segmentation tool using the first echo of the MSME sequence and manually correcting the position of control points if needed, in consensus, and under supervision of an experienced radiologist (T.M.L.).

Only artifact-free slices with well-defined boundaries of cartilage were segmented. The trochlea was not segmented because of interfering flow artifacts from the popliteal artery. For each compartment, T2 maps were created and T2 relaxation times were estimated by a mono-exponential decay model as a fitting function

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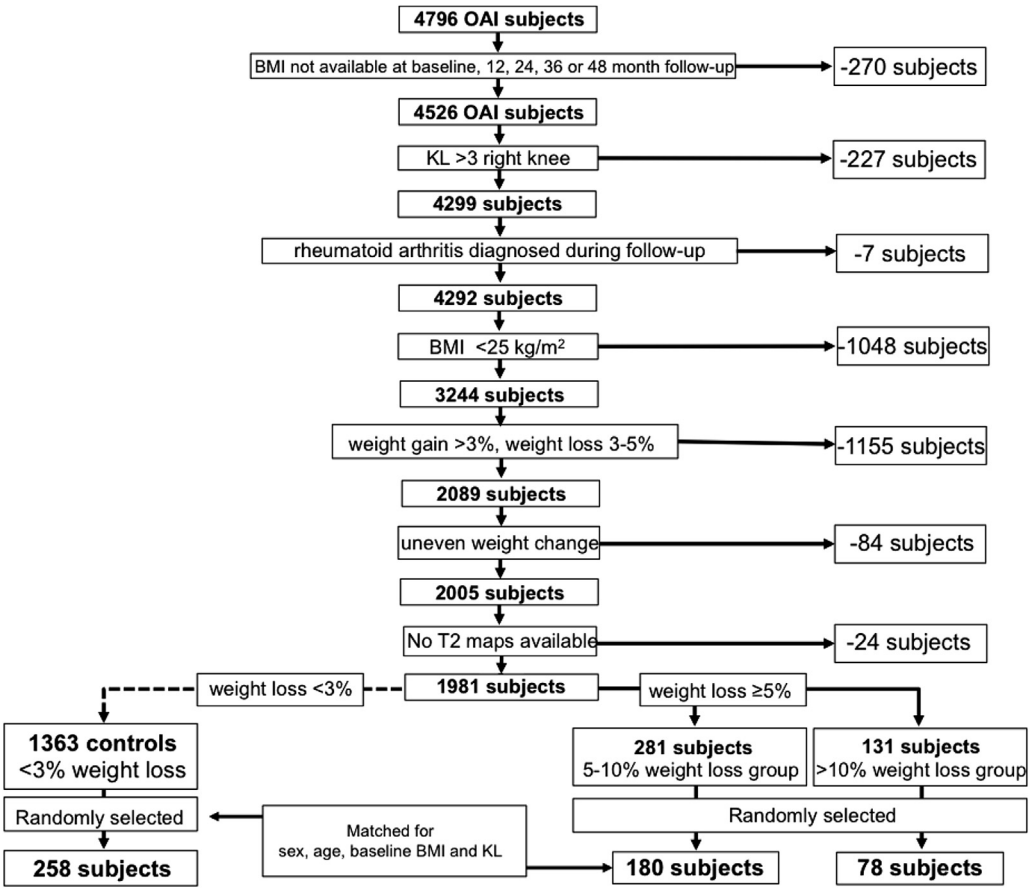

Fig. 1. Patient selection from OAI database.

for the signal intensity at the echo times 20–70 ms. The first echo (10 ms) was not used in order to improve signal-to-noise ratio[27]. Laminar analysis was automatically performed, subdividing the segmented compartments into a superficial and deeper cartilage layer of equal thickness[17]. Superficial layers were orientated to the articular surfaces, deeper layers adjacent to the cartilage–bone interface. The analysis of these cartilage layers separately may provide a more sensitive assessment of T2 measurements and better characterizes cartilage degenerative changes, as previously shown. For correct interpretation of longitudinal data of laminar analysis, cartilage thickness may not show significant cartilage thickness changes over time[19]. Therefore cartilage thickness of each region was calculated based on distance between the cartilage–bone interface and the closest point on the articular surface. The average thickness of each slice was calculated, and averages were summed to determine over all cartilage thickness[28].

Since previous studies have shown that T2 is limited in assessing more advanced degenerative disease[21], we performed an additional sub-analysis in which we excluded all KL = 3 patients and re-analyzed the data (n = 478; number of subjects with KL = 3

Table I
Subject characteristics and differences between SWG and weight loss groups. Subjects were divided into groups based on BMI changes over 48 months

	All	Stable weight*	Weight loss 5–10%*	Weight loss >10%*	*P*-value 5–10% weight loss vs stable weight group	*P*-value >10% weight loss group vs stable weight group
n	516 (100%)	258 (50.0%)	180 (34.9%)	78 (15.1%)		
Age (years; mean ± SD)	62.4 ± 9.2	62.3 ± 8.9	62.5 ± 9.4	62.4 ± 9.7	1.0‡	1.0‡
Sex (females; *n* (%))	314 (60.9%)	156 (60.5%)	109 (60.6%)	49 (62.8%)	1.0†	0.7†
Baseline BMI (kg/m^2; mean ± SD)	30.3 ± 3.5	30.2 ± 3.5	30.2 ± 3.5	30.7 ± 3.6	1.0‡	0.9‡
WOMAC pain (mean ± SD)	2.0 ± 2.6	1.8 ± 2.7	1.9 ± 2.7	2.1 ± 2.5	0.6‡	0.3‡
WOMAC disability (mean ± SD)	1.5 ± 1.2	1.4 ± 1.1	1.5 ± 0.9	1.7 ± 1.4	0.6‡	0.2‡
WOMAC stiffness (mean ± SD)	6.8 ± 9.6	6.7 ± 9.3	6.9 ± 9.3	7.4 ± 9.8	0.8‡	0.1‡
Baseline KL score						
KL = 0 (*n* (%))	204 (39.5%)	107 (41.5%)	70 (38.9%)	27 (34.6%)	0.7	0.5
KL = 1 (*n* (%))	213 (41.3%)	102 (39.5%)	77 (42.8%)	34 (43.6%)	0.8	0.6
KL = 2 (*n* (%))	61 (11.8%)	30 (11.6%)	22 (12.2%)	9 (11.5%)	0.3	0.4
Kl = 3 (*n* (%))	38 (7.4%)	19 (7.4%)	11 (6.1%)	8 (10.2%)	0.8	0.3

* Subjects in the three different groups are matched in terms of age, sex, baseline BMI and baseline KL score.
† Pearson's chi-squared test.
‡ ANOVA.

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excluded for analysis (% of cohort): over all cohort, $n = 38$ (7.4%); stable weight group (SWG), $n = 19$ (7.4%); 5–10%WLG, $n = 11$ (6.1%); >10%WLG, $n = 8$ (10.2%); Table I). This step was undertaken to confirm the results were not caused by a bias in the analysis created by subjects with more severe cartilage defects, since T2 values tend to be less useful in these subjects[21].

In addition to standard T2, we also performed an exploratory analysis of cartilage texture using GLCM texture analysis to evaluate the spatial distribution of T2 values, as described previously[17,18,29,30]. We included two GLCM parameters from the contrast group (contrast and homogeneity), one parameter each from the orderliness group (entropy) and the statistics group (variance), as published previously[17,18]. GLCM contrast expresses the differences of values of neighboring pixels, consequently high GLCM contrast indicates a high probability of neighboring pixels with large differences in T2[31]. GLCM homogeneity decreases exponentially inversely from the contrast value and expresses the similarity of neighboring pixels, indicating that higher GLCM values reflect high similarity between neighboring pixels[17,29]. GLCM variance is a measure of the dispersion of pixel values around the mean T2, meaning that high GLCM variance reflects a high number of pixels with T2 co-occurrences dispersed from the mean T2[18,32]. GLCM entropy is a measure of orderliness regarding the distribution of pixel value co-occurrences, therefore high GLCM entropy indicates that pixel pairs with same T2 values are less likely to be found[17,18,29,30].

WOMAC questionnaires

Knee pain and function were assessed with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[33]. WOMAC subscales for pain, stiffness and disability (5 point scale) at baseline and 48 months, as described previously[34], were investigated in this analysis.

Statistical analysis

Statistical analysis was performed with Stata/IC Version 13.1 software (StataCorp, College Station, TX) using a two-sided 0.05 level of significance.

One-way analysis of variance (ANOVA; for parametric testing) and chi-square tests (for categorical variables) were used to evaluate differences in subject characteristics between subjects with stable weight, 5–10% WL and >10% WL.

All models were checked for the following assumptions that were met (values are provided for the dependent variable baseline over all T2): linearity between the predictor variables and the dependent variables (Lack of Fit $F = 1.42$, $P = 0.33$), normality of the dependent variables and the residuals (Shapiro–Wilk test $P > 0.05$), homogeneity of variances (Levene's test statistic $= 1.61$, $P = 0.20$), absence of influential outliers in the data (max observed: Cook's distance is 0.042 and leverage is 0.049), and absence of multicollinearity (none of predictor variable pairs have correlation above 0.2).

In order to fulfill the assumption of independence, a random data sample was selected. Additionally, the Durbin–Watson statistic (1.98) indicated that the assumption of independence of the errors was satisfied.

The associations between changes in T2 relaxation times and the assignment to different weight loss groups (SW, 5–10%WL, >10%WL) over 48 months were assessed using multivariable regression models adjusting for age, sex, baseline BMI and baseline KL score (independent variables: groups; dependent variable: ΔT2 parameters). The entire T2 analyses were repeated after excluding subjects with KL = 3, using the same statistical approach. Due to the large number of parameters, the analyses were split into the following categories (based on previously published data[15–18]): primary data (compartments: over all, medial tibia, patella; imaging parameter: mean T2, bone layer texture parameters contrast and variance); exploratory data (compartments: lateral femur, lateral tibia, medial femur; imaging parameters: articular layer, texture parameters entropy, homogeneity).

Differences in changes of GLCM texture parameters over 48 months between the SWG and the two weight loss groups were calculated (independent variables: groups; dependent variable: ΔGLCM texture parameters).

Cartilage thickness at baseline and cartilage thickness changes over 48 months and the association with the amount of WL was analyzed by using linear regression models, adjusting for age, sex, baseline BMI and baseline KL score (independent variables: groups; dependent variable: baseline cartilage thickness and Δcartilage thickness, respectively).

Associations of changes in WOMAC subscales (pain, stiffness and disability) or changes in cartilage T2 with weight change over 48 months were assessed using multivariable regression models adjusting for age, sex, baseline BMI and baseline KL score (independent variables: percentage of change in BMI; dependent variable: Δ WOMAC subscales or ΔT2 parameters).

Reproducibility

Both for the intra- and inter-reader reproducibility, T2 measurements were calculated on a percentage basis as the root mean square average of single coefficients of variation (CV) to assess the reproducibility error, as previously described[35].

Inter-reader reproducibility was assessed between the two readers (M.S. and G.F.) in 10 patients and was 1.66% over all compartments. CVs for single compartments were as follows: 1.28% for the lateral femur, 1.11% for the lateral tibia, 1.29% for the medial femur, 2.01% for the medial tibia, and 2.42% for the patella.

For intra-reader reproducibility analysis, the same reader performed repeated T2 measurements in 10 randomly selected patients with readings separated by at least 14 days. Intra-reader CVs were calculated for each compartment using these repeated measurements and compartment specific and over all CVs were as follows: 0.92% for the lateral femur, 1.14% for the lateral tibia, 1.07% for the medial femur, 1.63% for the medial tibia, 2.33% for the patella, and 1.42% over all compartments.

Results

Subject characteristics

Characteristics of all subjects are described in Table I. There were no significant differences in mean age, baseline BMI or gender frequencies between the groups. Distribution of KL score, baseline WOMAC subscales, imaging site and race did not differ significantly between any of the groups ($P > 0.05$, respectively). After 48 months, subjects in the >10%WLG lost 4.22 ± 1.97 kg/m^2 on average while the 5–10%WLG had lost 2.03 ± 1.29 kg/m^2 on average. BMI change of the SWG was 0.08 ± 0.97 kg/m^2. The association between change in BMI and change in WOMAC subscales pain, stiffness and disability is shown in Table IV. The more weight was lost, the more WOMAC subscales improved ($P < 0.05$, respectively).

Change of T2 relaxation time and WL

T2 changes for different groups and compartments are shown in Table II. Increase of global T2 between baseline and 48 month follow-up (ΔT2) was significantly smaller in the medial tibia in the >10%WLG compared to the SWG ($P < 0.001$), as demonstrated in Fig. 2, suggesting less progression of cartilage degeneration over

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time for the >10%WLG in the medial tibia. Yet, there was no significant change of T2 in the 5–10%WLG compared to the SWG ($P > 0.05$). The relationships between percentage of body WL and the change of T2 over 48 months are presented in Table IV (Fig. 3). After adjusting for age, sex, baseline BMI and KL, weight change was significantly associated with change in T2 of the medial tibia (β 0.9 ms, 95% CI 0.4 to 1.1, $P = 0.001$), but not in the medial femur (β 0.2 ms, 95% CI −0.1 to 0.2, $P = 0.8$) or patella (β 0.09 ms, 95% CI −0.07 to 0.3, $P = 0.3$). These results demonstrate that for every 1% of WL there was 0.9 ms less increase of cartilage T2 over 48 months, suggestion less progression of cartilage degeneration the more weight was lost.

In laminar subanalyses, changes of global T2 over 48 months were significantly lower in the >10%WLG compared to the SWG, showing globally slowed cartilage degeneration after >10%WL in the bone layer ($P = 0.03$). Moreover, changes of T2 over 48 months of the bone layer of the patella showed significantly lower values in the >10%WLG ($P = 0.04$) compared to the SWG, suggesting less progression of cartilage degeneration in the patella in the >10% WLG over 48 months.

After excluding subjects with KL = 3 and re-analyzing the dataset, mean T2 of all compartments combined was significantly lower in the >10%WLG compared the SWG ($P = 0.02$) and significance levels of the differences between these two groups in the other compartments improved (Supplemental data).

Changes in GLCM, cartilage thickness and WL

In the >10%WLG, changes in GLCM contrast and variance over all compartments ($P = 0.04$ and $P = 0.04$, respectively) as well as in the patella ($P = 0.01$ and $P = 0.04$, respectively) over 48 months were significantly lower than in the SWG, suggesting less progression of cartilage inhomogeneity and increased orderliness in the >10%WLG.

Decrease of GLCM homogeneity over 48 months was significantly lower in the medial tibia in the >10%WLG compared to the SWG ($P = 0.004$; Table III). We re-analyzed the data with Bonferroni correction, to verify that our significant findings were not caused by the number of hypotheses tested, yet this did not change the results.

Over all compartments, there were no significant differences in baseline cartilage thickness and in cartilage thickness changes over 48 months between the SWG and both WLGs ($P > 0.05$) assessed.

Associations of changes in clinical symptoms and cartilage T2

Increase of T2 in the medial tibia was significantly associated with an increase in the WOMAC subscales for pain (β 0.5 ms, 95% CI 0.2 to 0.6, $P = 0.02$; Table V and disability (β 0.03 ms, 95% CI 0.003 to 0.05, $P = 0.03$). These results demonstrate 0.5 ms increase in cartilage T2 in the medial tibia per point increased on the WOMAC subscore pain scale.

Over all compartments, increase in T2 was significantly associated with increase in the WOMAC subscale for stiffness (β 0.1 ms, 95% CI 0.003 to 0.2, $P = 0.04$). Similarly to the findings in the medial tibia, WOMAC subscale for disability showed a statistical trend (β 0.02 ms, 95% CI −0.002 to 0.4, $P = 0.07$), again, suggesting progression of cartilage degeneration over all compartments being associated with clinical worsening.

Discussion

In this study, the effect of WL on the biochemical composition, texture and thickness of cartilage in individuals with risk factors for OA was analyzed using MR-based T2 relaxation time measurements. We found significantly less increase of cartilage T2 in overweight and obese subjects in the medial tibia over 48 months.

Table II
Comparison of change in global, articular and bone layer T2 relaxation times (mean [95% confidence interval]) over 48 months of the cartilage compartments of the knees between the group with stable weight and weight loss groups. An increase in T2 values indicates a worsening of cartilage degradation*

Parameter	Compartment		Stable weight	5–10% Weight loss	*P*-value 5–10% weight loss vs stable weight group	>10% weight loss	*P*-value >10% weight loss group vs stable weight group
Global ΔT2 (in ms)	all compartments	Baseline mean T2 (ms)	32.4 [32.1, 32.7]	32.5 [32.0, 32.7]	0.8	32.7 [32.2, 33.2]	0.3
		Change in mean T2 (ms)	1.0 [0.8, 1.1]	0.8 [0.6, 1.1]	0.6	0.6 [0.4, 1.0]	0.3
	LF	Baseline mean T2 (ms)	36.3 [35.9, 36.7]	35.8 [35.3, 36.3]	0.3	36.4 [35.8, 37.1]	0.7
		Change in mean T2 (ms)	1.5 [1.2, 1.8]	1.3 [0.8, 1.7]	0.7	1.2 [0.7, 1.6]	0.7
	LT	Baseline mean T2 (ms)	27.1 [26.8, 27.3]	27.3 [27.0, 27.7]	0.3	27.4 [26.7, 28.0]	0.4
		Change in mean T2 (ms)	1.2 [1.0, 1.6]	1.0 [0.7, 1.3]	0.2	1.0 [0.8, 1.2]	0.3
	MF	Baseline mean T2 (ms)	39.7 [39.3, 40.1]	39.2 [38.7, 39.7]	0.2	39.0 [38.6, 39.5]	0.8
		Change in mean T2 (ms)	0.6 [0.2, 1.0]	0.8 [0.4, 1.1]	0.6	0.4 [0.0, 0.9]	0.5
	MT	Baseline mean T2 (ms)	29.1 [28.9, 29.4]	29.3 [28.8, 29.6]	0.6	29.3 [28.7, 29.9]	0.6
		Change in mean T2 (ms)	1.1 [0.8, 1.4]	0.8 [0.4, 1.0]	0.2	−0.3 [−0.9, 0.4]	**<0.001**
	PAT	Baseline mean T2 (ms)	30.5 [30.1, 30.9]	30.7 [30.1, 31.1]	0.7	31.3 [30.5, 32.1]	0.08
		Change in mean T2 (ms)	0.9 [0.5, 1.3]	0.5 [0.3, 1.1]	0.2	0.4 [0.02, 1.0]	0.3
Articular Layer ΔT2 (in ms)	all compartments	Baseline mean T2 (ms)	35.3 [35.0, 35.6]	35.2 [34.8, 35.6]	0.9	35.6 [35.0, 36.2]	0.5
		Change in mean T2 (ms)	1.1 [0.8, 1.3]	1.0 [0.6, 1.3]	0.6	0.9 [0.3, 1.5]	0.3
	MT	Baseline mean T2 (ms)	32.4 [32.1, 32.7]	32.4 [32.1, 32.7]	0.1	32.4 [32.1, 32.7]	0.7
		Change in mean T2 (ms)	1.3 [0.9, 1.6]	0.9 [0.4, 1.3]	0.1	0.0 [−0.2, 0.7]	**<0.001**
	PAT	Baseline mean T2 (ms)	33.1 [32.7, 33.6]	33.4 [32.8, 33.9]	0.5	34.0 [33.1, 34.9]	0.1
		Change in mean T2 (ms)	0.9 [0.4, 1.3]	0.5 [0.0, 1.0]	0.3	0.5 [0.0, 1.1]	0.8
Bone Layer ΔT2 (in ms)	all compartments	Baseline mean T2 (ms)	29.6 [29.3, 29.8]	29.5 [29.2, 29.8]	0.9	29.4 [29.1, 30.2]	0.3
		Change in mean T2 (ms)	1.0 [0.7, 1.1]	0.9 [0.6, 1.1]	0.7	0.4 [0.0, 0.8]	**0.03**
	MT	Baseline mean T2 (ms)	26.4 [26.1, 26.7]	26.5 [26.1, 26.8]	0.9	26.5 [26.0, 27.0]	0.7
		Change in mean T2 (ms)	1.0 [0.6, 1.2]	0.8 [0.4, 1.2]	0.06	−0.2 [−0.5, 0.3]	**<0.001**
	PAT	Baseline mean T2 (ms)	27.9 [27.5, 28.2]	27.9 [27.4, 28.2]	0.9	28.6 [27.9, 29.4]	0.2
		Change in mean T2 (ms)	1.0 [0.6, 1.3]	0.5 [0.3, 0.8]	0.07	0.2 [−0.5, 0.5]	**0.04**

; LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella.

* The associations between ΔT2 relaxation times and WL (5–10% WL and >10% WL) over 48 months were assessed using linear regression models adjusting for age, sex, baseline BMI and baseline KL score. Significant results ($P < 0.05$) are bolded.

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Table III
Comparison of texture parameters over 48 months (mean difference (95% confidence interval)) between groups*

	Stable weight vs 5–10% weight loss	*P*-value	Stable weight vs >10% weight loss	*P*-value
Mean over all compartments				
Δ contrast	10.7 (−9.1, 30.4)	0.4	29.4 (1.5, 58.3)	**0.04**
Δ entropy	0.1 (−0.2, 0.4)	0.7	0.4 (−0.1, 0.9)	0.2
Δ variance	7.0 (−3.9, 17.6)	0.3	14.9 (0.4, 30.2)	**0.04**
Δ homogeneity	−0.02 (−0.06, 0.02)	0.4	−0.04 (−0.1, 0.01)	0.1
Medial tibia				
Δ contrast	1.6 (−28.7, 31.9)	0.8	38.2 (−4.7, 81.2)	0.08
Δ entropy	0.1 (−0.5, 0.4)	0.5	0.5 (−0.2, 1.2)	0.2
Δ variance	4.3 (−16.2, 15.4)	0.8	19.4 (2.1, 42.0)	0.07
Δ homogeneity	−0.006 (−0.08, 0.06)	0.8	−0.1 (−0.2, −0.01)	**0.004**
Patella				
Δ contrast	14.0 (1.5, 58.3)	0.3	42.2 (10.0, 74.4)	**0.01**
Δ entropy	0.4 (−0.1, 0.9)	0.1	0.3 (−0.5, 1.2)	0.5
Δ variance	11.4 (0.4, 30.2)	0.4	23.7 (12.3, 50.1)	**0.04**
Δ homogeneity	−0.09 (−0.1, 0.01)	0.02	−0.04 (−0.1, 0.06)	0.4

* Multivariable regression analysis adjusting for age, sex, baseline BMI and baseline KL score. Significant results ($P < 0.05$) are bolded.

Table IV
Associations between weight change and change in cartilage T2 and clinical symptoms

Parameter	Compartment	Adjusted* regression β (95% CI)	*P*-value
Change cartilage T2 (ms)	all compartments	0.06 (−0.04, 0.1)	0.2
	MT	0.9 (0.4, 1.1)	**0.001**
	MF	0.02 (−0.1, 0.2)	0.8
	PAT	0.09 (−0.07, 0.3)	0.3
Change in WOMAC	Pain	0.4 (0.2, 0.7)	**0.001**
	Stiffness	0.2 (0.01, 0.4)	**0.03**
	Disability	0.1 (0.02, 0.2)	<**0.001**

* Linear regression analysis adjusting for age, sex, baseline BMI and baseline KL score. Significant results ($P < 0.05$) are bolded.

Table V
Associations between change in symptoms and change in cartilage T2

Cartilage compartments	Change in WOMAC	Adjusted* regression β (95% CI)	*P*-value
T2 (ms) over all compartments	Pain	0.04 (−0.02, 1.0)	0.2
	Stiffness	0.1 (0.003, 0.2)	**0.04**
	Disability	0.02 (−0.002, 0.4)	0.07
T2 (ms) of MT	Pain	0.5 (0.2, 0.6)	**0.02**
	Stiffness	0.1 (−0.03, 0.3)	0.11
	Disability	0.03 (0.003, 0.05)	**0.03**

* Linear regression analysis adjusting for age, sex, baseline BMI and baseline KL score. Significant results ($P < 0.05$) are bolded.

Less clinical worsening was associated with both, lower T2 increase over time and a substantial amount of WL. Moreover, especially in the >10%WLG, slower cartilage matrix degeneration through WL over all compartments was found with texture analysis. The highest association of WL and reduced cartilage degeneration was found in the medial tibia, which adds to the hypothesis that WL is most protective in the medial weight-bearing compartments[16,36].

These findings are supported by the GCLM homogeneity parameter measured, which suggests less progression of cartilage degeneration after a large amount of WL, especially within the medial tibia[36]. Also, a previous study has demonstrated that percentage of weight change was significantly associated with change in cartilage volume of the medial tibia, yet although our range of weight change was smaller our over all study cohort was larger[16].

This study is the first to examine the longitudinal association between WL over 48 months, and change in both, cartilage T2 and symptoms. The association found between changes in cartilage T2 in the medial tibia with change in clinical symptoms pain and disability emphasizes WL being an important primary management strategy in obese individuals in order to avoid or slow progression of OA.

Previous studies suggested a link between obesity and progression of OA[37,38] and demonstrated that weight gain was strongly associated with increased[31] and >10%WL was associated with slower progression of cartilage degeneration[15]. Neither of the

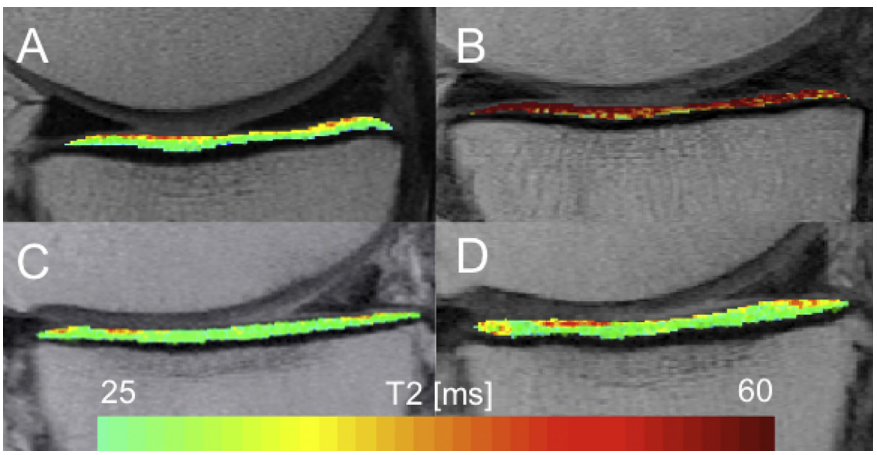

Fig. 2. Representative T2 maps from a subject with stable weight (A, B) and a >10% WL subject (C, D) at baseline (left) and 48 months follow up (right). **Stable weight subject (A, B):** In this subject mean T2 relaxation times increase (red) in the medial tibia. **>10% weight loss subject (C, D):** Only slight progression of cartilage T2 relaxation times. T2 increase is a measure for progression of cartilage degeneration.

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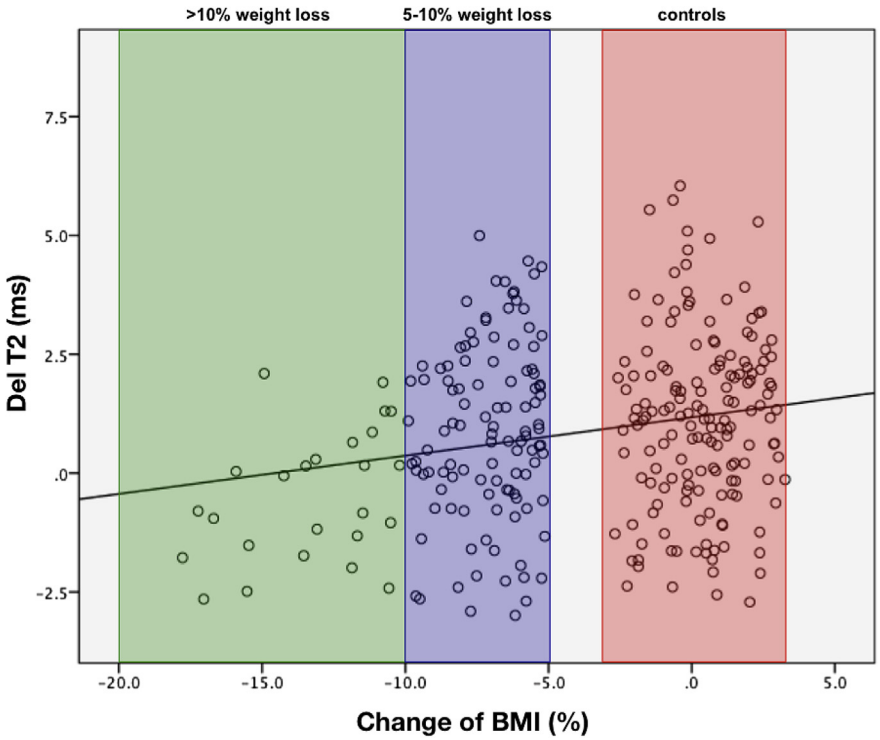

Fig. 3. Scatterplot of change in mean T2 relaxation times vs change in BMI over 48 months in the medial tibial compartment ($r = 0.37$, $P < 0.001$). Group with more than 10% WL is marked green; group with 5–10% WL is marked blue; control group is marked red.

mentioned studies have investigated a group with 5–10%WL, nor have they evaluated cartilage texture analysis, laminar analysis or clinical data[15]. To our knowledge, this is the first study to quantify cartilage composition with texture and laminar analysis in obese subjects after stratifying these in two groups with different amounts of WL.

Nevertheless, similar to the previous study, the >10%WLG had significantly less increase of T2 in the medial tibia. With laminar analysis, less increase of T2 was found in the bone layer over all compartments combined in the >10%WLG compared to the SWG[17], which emphasizes the superiority of laminar analysis in detecting changes in cartilage composition and differences over all compartments in between the groups, compared to using solely mean T2 values as used in previous studies[15]. These results derived from laminar analysis suggest a slowed progression of cartilage degeneration in subjects with >10%WL effects all compartments.

Further previous studies have shown that T2 values are limited in assessing more advanced degenerative disease[21] and interestingly, after excluding subjects with radiographically moderate OA (KL = 3), T2 relaxation times in both cartilage layers significantly decreased in the >10%WLG compared to the controls. These findings underline the global protective effect of WL for the entire joint cartilage matrix, which confirms and broadens previous findings[15]. Additionally, in the >10%WLG, slower cartilage degeneration through WL over all compartments was found with texture analysis, which supports the importance of more sophisticated analysis to increase accuracy in the investigation of cartilage composition.

Moreover, the assessed GLCM parameters of contrast, variance and entropy reflect heterogeneity of the cartilage extracellular matrix[12,18,30]. Previous studies have shown that elevated GLCM parameters suggest cartilage degeneration[18]. Interestingly, significantly less increase of GLCM contrast and variance was found over all compartments as well as at the patella in the >10%WLG compared to controls, suggesting decelerated degenerative changes of cartilage in all compartments[18]. This may be caused by texture parameters showing earlier and stronger signal changes through WL in all compartments. Previous studies confirmed that texture and laminar analysis add valuable information to solely assessed mean T2 values, detecting smaller changes, which may be otherwise masked by over all spatial T2 changes in the collagenous extracellular matrix[18]. This underlines the importance of our findings of texture analysis over all compartments, since in the previous studies no differences in the global T2 changes over all compartments were detected between the >10%WL and the SWG. This study demonstrates that subjects without WL showed more elevated and heterogeneous cartilage T2 compared to subjects that lost a substantial amount of weight over all compartments. Therefore texture analysis was able to detect differences in biomechanical cartilage composition over all compartments while simultaneously cartilage T2 alone was not able to detect differences in changes of cartilage quality.

Our study has limitations, which need to be reported: no additional image analysis was performed assessing morphological changes of MRI findings. Nonetheless, further investigations in which structural MR findings are associated with WL in obese and overweight subjects, are warranted. Moreover, we performed a retrospective analysis of subjects' WL data. Therefore many confounders can only be controlled in a prospective study, such as activity levels, diet, and comorbidities. These confounders might cause issues regarding the analysis, especially at a 5–10%WL cohort. Also, the analysis of effects of weight gain on cartilage degeneration is of great clinical importance and needs to be investigated in future studies.

In summary, our study demonstrated that weight change was significantly associated with change in cartilage composition in the medial tibia and in WOMAC subscales for pain and disability in obese and overweight individuals. Yet, after creating subgroups, only the >10%WLG was associated with significantly decreased

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progression of compositional cartilage degeneration compared to stable weight in individuals with risk factors or mild to moderate radiographic evidence for OA. Based on our findings we hypothesize that WL has a protective effect on cartilage, which is detected in all compartments, and that a larger amount of WL is more beneficial in obese and overweight subjects in order to slow progression of cartilage matrix deterioration and worsening of clinical symptoms.

Author contributions

Alexandra Gersing, M.D (alexandra.gersing@ucsf.edu). and Thomas Link, Ph.D., M.D (thomas.link@ucsf.edu). take responsibility for the integrity of the work as a whole, from inception to finished article.

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Acquisition of data: Solka, Feuerriegel, Gersing, Schwaiger, Heilmeier, Joseph, Link.

Analysis and interpretation of data: Gersing, Solka, Schwaiger, Nevitt, McCulloch, Link.

Drafting of article or revising it critically for important intellectual content: Gersing, Solka, Schwaiger, Joseph, Nevitt, McCulloch, Link.

Final approval of the version of the article to be published: Gersing, Solka, Joseph, Schwaiger, Heilmeier, Feuerriegel, McCulloch, Nevitt, Link.

Competing interest statement

None of the authors have any financial or other interests related to the manuscript submitted to Osteoarthritis and Cartilage that might constitute a potential conflict of interest.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2016.01.984.

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