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Is Weight Loss Associated with Less Progression of Changes in Knee Articular Cartilage among Obese and Overweight Patients as Assessed with MR Imaging over 48 Months? Data from the Osteoarthritis Initiative[1]

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Purpose: To investigate the association of weight loss with progression of cartilage changes at magnetic resonance (MR) imaging over 48 months in overweight and obese participants compared with participants of stable weight.

Materials and Methods: The institutional review boards of the four participating centers approved this HIPAA-compliant study. Included were *(a)* 640 participants (mean age, 62.9 years ± 9.1 [standard deviation]; 398 women) who were overweight or obese (body mass index cutpoints of 25 and 30 kg/m^2, respectively) from the Osteoarthritis Initiative, with risk factors for osteoarthritis or mild to moderate radiographic findings of osteoarthritis, categorized into groups with *(a)* weight loss of more than 10% (n = 82), *(b)* weight loss of 5%–10% (n = 238), or *(c)* stable weight (n = 320) over 48 months. Participants were frequency-matched for age, sex, baseline body mass index, and Kellgren-Lawrence score. Two radiologists assessed cartilage and meniscus defects on right knee 3-T MR images at baseline and 48 months by using the modified Whole-Organ Magnetic Resonance Imaging Score (WORMS). Progression of the subscores was compared between the weight loss groups by using multivariable logistic regression models.

Results: Over 48 months, adjusted mean increase of cartilage WORMS was significantly smaller in the 5%–10% weight loss group (1.6; 95% confidence interval [CI]: 1.3, 1.9; P = .002) and even smaller in the group with less than 10% weight loss (1.0; 95% CI: 0.6, 1.4; P = .001) when compared with the stable weight group (2.3; 95% CI: 2.0, 2.7). Moreover, percentage of weight change was significantly associated with increase in cartilage WORMS (β = 0.2; 95% CI: 0.02, 0.4; P = .007).

Conclusion: Participants who lost weight over 48 months showed significantly lower cartilage degeneration, as assessed with MR imaging; rates of progression were lower with greater weight loss.

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Osteoarthritis is the most common joint disease in the United States, affecting more than 50% of the population aged 75 years or more (1). Obese women have nearly four times and obese men have five times the risk for knee osteoarthritis when compared with women and men of normal weight (2). Overweight and obesity are defined by using the body mass index ([BMI] weight in kilograms divided by height in square meters), with cutoff points of 25 and 30 kg/m^2, respectively (3). The association between obesity and osteoarthritis is caused biomechanically by increased joint loading (4–7) and alterations in gait patterns and systemically by metabolic factors that frequently occur in obese patients and during weight gain (8) and that may impair cartilage homeostasis and cause systemic and local inflammation (9–11). Acceleration of cartilage degeneration and worsening of clinical symptoms are associated with obesity (12,13), a condition that affects approximately 36% of the U.S. population older than 20 years (14) and therefore is of substantial public health importance.

Previous studies have found correlations between progression of changes in knee cartilage detected with magnetic resonance (MR) imaging and clinical symptoms and BMI (15,16); these correlations underline the fact that the potentially modifiable risk factor of obesity may contribute to the risk for osteoarthritis (17). Weight gain is associated with exacerbation of knee joint degeneration, especially with worsening cartilage and meniscal degeneration over 48 months, when compared with stable weight (18).

On the other hand, weight loss is associated with reduced cartilage volume loss within the medial tibia (19). In addition, participants who lose weight have been shown to have less of an increase in cartilage T2 relaxation time, suggesting less cartilage deterioration over 48 months when compared with stable-weight participants, as detected with compositional MR imaging; this modality depicts molecular changes, such as decrease in glycosaminoglycan content and increase in water content in the extracellular matrix, that precede morphologic cartilage lesions (20). Weight change was also significantly associated with change in cartilage composition in the medial tibia and in Western Ontario and McMaster Universities Arthritis Index (WOMAC) subscales for pain and disability in obese and overweight individuals (21). Nevertheless, to our knowledge, the effect of weight loss on the morphologic degeneration of knee joint tissues has not been assessed. MR imaging is the most sensitive modality with which to depict subtle morphologic abnormalities, and it can reveal early structural osteoarthritic findings, including cartilage and meniscus defects (22–24).

Thus, we hypothesized that different degrees of weight loss have different effects on the progression of morphologic abnormalities of the knee joint detected with 3-T MR imaging over 48 months in obese or overweight persons with risk factors for osteoarthritis or mild to moderate radiographic findings of osteoarthritis in comparison with stable-weight participants.

Advances in Knowledge

- Progression of knee cartilage abnormalities, as detected with MR imaging, was significantly decreased in obese and overweight participants at risk for or with mild to moderate osteoarthritis who had a decrease in body mass index of at least 5% over 48 months when compared with that in participants without weight loss ($P = .002$).
- The amount of weight change was significantly associated with the progression of cartilage abnormalities ($P = .007$).

Implication for Patient Care

- Weight loss is associated with a reduced risk for progression of cartilage, as detected with MR imaging; thus, weight loss is a potential therapeutic option in patients with mild to moderate osteoarthritis and in those who are at risk for osteoarthritis.

Materials and Methods

Database and Participants

Participants were selected from the Osteoarthritis Initiative ([OAI] *http://www.oai.ucsf.edu*), a prospective multicenter cohort study of healthy participants with or without risk factors for or with symptomatic knee osteoarthritis. Informed consent was obtained from all participants; the study was compliant with the Health Insurance Portability and Accountability Act and was approved by the local institutional review boards of all participating centers. Participants were recruited from February 2004 until May 2006.

Complete BMI data for baseline and 12-, 24-, and 48-month follow-up were available for 4526 study participants. Of those, we excluded participants with a baseline Kellgren-Lawrence score higher than 3 in the right knee,

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Abbreviations:
BMEP = bone marrow edema pattern
BMI = body mass index
CI = confidence interval
ICC = intraclass correlation coefficient
OAI = Osteoarthritis Initiative
PASE = Physical Activity Scale for the Elderly
WOMAC = Western Ontario and McMaster Universities Arthritis Index
WORMS = Whole-Organ Magnetic Resonance Imaging Score

Author contributions:
Guarantors of integrity of entire study, A.S.G., T.M.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.S.G., B.J.S., G.B.J., N.C., J.B.G., J.M.W., T.M.L.; clinical studies, A.S.G., B.J.S., J.B.G., J.M.W., T.M.L.; statistical analysis, A.S.G., B.J.S., G.B.J., J.B.G., J.M.W., C.E.M.; and manuscript editing, A.S.G., B.J.S., M.C.N., G.B.J., J.B.G., J.M.W., L.F., C.E.M., T.M.L.

Conflicts of interest are listed at the end of this article.

representing end-stage osteoarthritis (n = 227); those with rheumatoid arthritis developing during study follow-up (n = 7); and those with a baseline BMI less than 25 kg/m^2 (n = 1048), in order to focus on only overweight and obese persons (Fig 1).

To clearly distinguish between stable-weight and weight loss groups, we excluded participants with weight gain of more than 3%, those with weight loss of 3%–5% from baseline to 48 months (n = 1155), and those with irregular weight change who cycled through weight loss and weight gain periods over 48 months (n = 84). To accomplish this last exclusion, we calculated the annual rate of change in BMI over 4 years with a linear regression model and categorized participants into a group with a steady weight change trajectory and a group with an irregular weight change, defined as those with root mean square error of the regression line of their weight change above the 95th percentile.

Through use of the Charlson comorbidity questionnaire developed by Katz et al (25,26), participants with cancer, cardiac failure, and/or other severe diseases developing during the study period were excluded. Furthermore, we excluded participants with missing clinical MR imaging studies at baseline (n = 24) or at 48 months (n = 384). The remaining participants (n = 1597) were grouped according to the percentage of weight loss over 48 months. Groups were as follows: stable weight

Figure 1

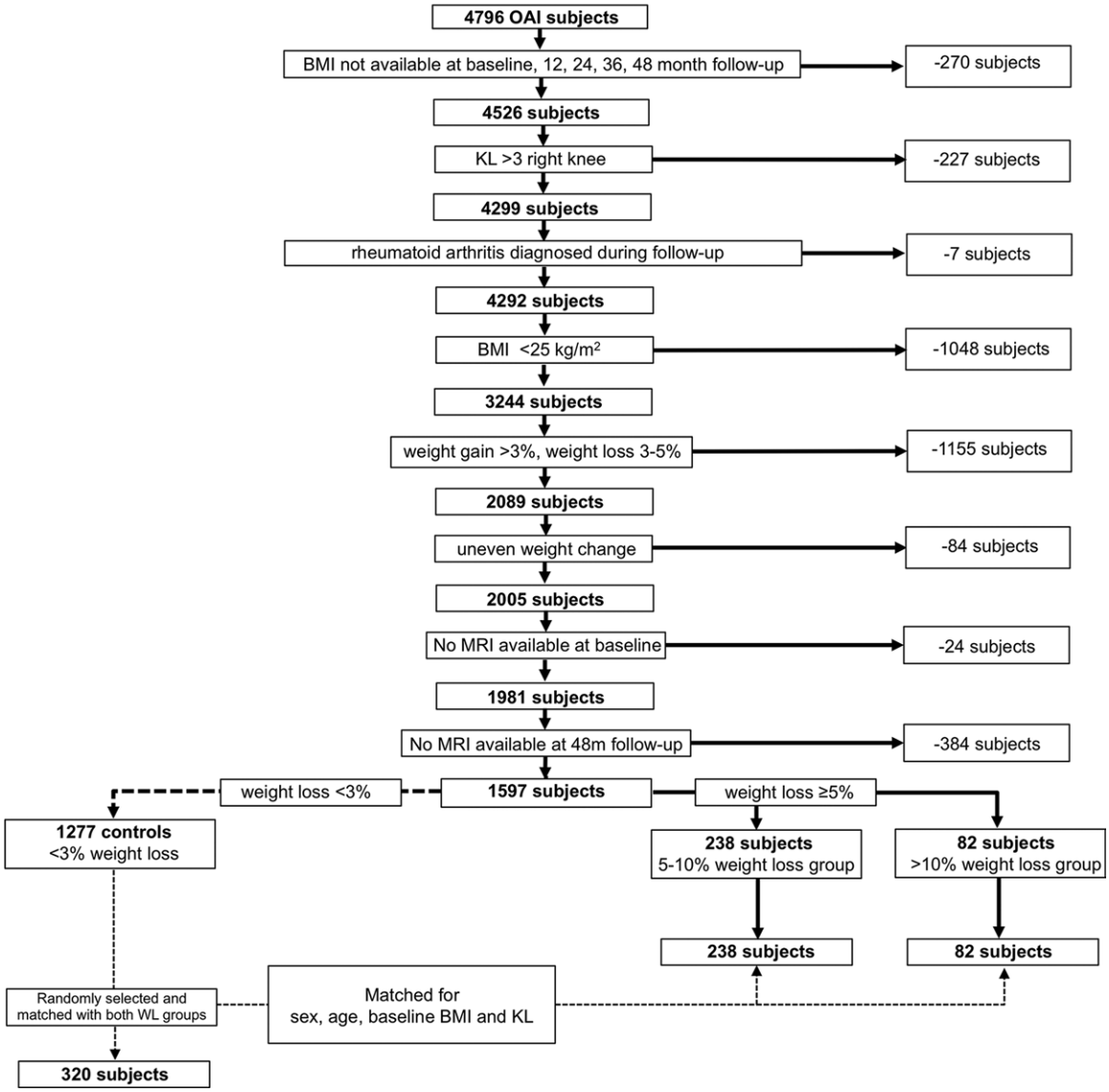

Figure 1: Flowchart shows participant selection from OAI database. *KL* = Kellgren-Lawrence score.

(BMI change <3%, n = 1277), moderate weight loss (BMI decrease of 5%–10% [referred to hereafter as 5%–10% weight loss], n = 238), and substantial weight loss (BMI decrease >10%, n = 82). The weight loss groups were chosen on the basis of the weight loss goals of previous studies (≥5% weight loss in the Arthritis, Diet, and Activity Promotion Trial study; ≥10% in the Intensive Diet and Exercise for Arthritis study) (27–29), which suggest that these thresholds reflect the minimal amount of weight loss needed to improve clinical outcome (pain and function) in patients with knee osteoarthritis.

To perform frequency matching between the stable-weight group and the weight loss groups, we sorted these participants into groups based on sex (male or female), age (10-year strata from 45 to 65 years and one 14-year stratum from 65 to 79 years), baseline BMI (BMI in 2.5 kg/m^2 strata), and Kellgren-Lawrence score (score in strata of 0/1 and 2/3). Participants with stable weight were randomly selected from each stratum and were frequency-matched to participants from the combined weight loss groups for these age, sex, baseline BMI, and Kellgren-Lawrence score groups. For each participant in each weight loss group, one participant with stable weight was selected. Thus, the final group sizes were 238 participants in the 5%–10% weight loss group, 82 in the more than 10% weight loss group, and 320 in the stable weight group.

An a priori power analysis was calculated on the basis of our previous study evaluating the differences in cartilage Whole-Organ Magnetic Resonance Imaging Score (WORMS) between obese participants and participants with normal weight (15); this was done to determine the appropriate size of each subgroup to analyze differences between the groups. After matching the participants, we ensured that the stable weight and weight loss groups did not differ regarding medications influencing metabolic factors, such as antihypertensive medication, diabetic medication or insulin, or lipid-lowering medication (eg, statins or other), which have been reported to affect cartilage degradation. A previous study (15) showed a 44% prevalence of cartilage defects in participants with normal weight (n = 36) compared with a 72% prevalence in obese participants (n = 69). The criterion for significance had been set at .05; therefore, to reach a power of 0.90, a minimum of 72 participants in each group would be required. Thus, we included all eligible participants available within the two weight loss groups to ensure that group sizes were adequate for the comparison.

Knee pain and function were assessed by using the WOMAC Osteoarthritis Index (30), which quantifies pain, stiffness, and physical function (30). This well-established and validated questionnaire was administered yearly to all 4796 participants in a standardized manner.

Physical activity levels were measured by using the Physical Activity Scale for the Elderly (PASE) questionnaire. This well-established instrument (31,32) yields a numeric score and is used to assess three domains of physical activity over a period of 7 days (household, occupational, and leisure activities). Participants completed the questionnaire on the same day as their MR imaging examination. The PASE questionnaire has been validated in older and younger persons (31–33).

MR Imaging

MR images of the right knee were obtained by using identical 3-T imagers (Trio; Siemens, Munich, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, Ohio) at four sites (Ohio State University, Columbus, Ohio; University of Maryland School of Medicine, Baltimore, Md; University of Pittsburgh, Pittsburgh, Pa; and Memorial Hospital of Rhode Island, Pawtucket, RI). The following four sequences were used for the imaging analysis: *(a)* two-dimensional intermediate-weighted fast spin-echo sequence in the coronal plane (repetition time msec/echo time msec, 3700/29; field of view, 140 mm; matrix, 310 × 384); (*b*) two-dimensional proton density–weighted fast spin-echo sequences with fat suppression in the sagittal plane (3200/30; field of view, 160 mm; matrix, 314 × 448); *(c)* three-dimensional dual-echo steady-state gradient-echo sequence (16.3/4.7; flip angle, 25°; field of view, 140 mm; matrix, 307 × 384); and *(d)* three-dimensional T1-weighted fast low-angle shot gradient-echo sequence (20/7.57; flip angle, 12°; field of view, 160 mm; matrix, 512 × 512). Further details regarding the MR imaging sequences are available in the OAI MR protocol (34).

Image Analysis

All baseline and 48-month follow-up images were individually and independently read by two radiologists (A.S.G., B.J.S.; each with 5 years of experience) blinded to patient information and time point information of the images they were assessing. Moreover, they read the images in a random fashion, with a random order to the time points. In case of diverging findings (n = 82), a consensus reading was performed with a third board-certified musculoskeletal radiologist (T.M.L., 24 years of experience). The images were evaluated for three osteoarthritis features by using the semiquantitative WORMS grading system (35), modified as previously described (18,36): Meniscal defects were graded from 0 to 4 in each of the three subregions of the medial and lateral meniscus (anterior, body, and posterior). The meniscal defects and abnormalities were graded according to the WORMS subscale from 0 to 4 (0 = intact, 1 = intrasubstance signal abnormalities, 2 = nondisplaced tear, 3 = displaced or complex tear, 4 = maceration). The meniscal tears were further categorized into radial, vertical, horizontal, flap, bucket handle, meniscocapsular, root tear, extrusion, and others.

Cartilage defects were scored from 0 to 6, and bone marrow edema patterns (BMEPs) were scored from 0 to 3 in the same six regions (patella, trochlea, medial femur, lateral femur, medial tibia, and lateral tibia). For each subscale (WORMS cartilage, meniscus, BMEP), a sum score was calculated by adding the scores of all subregions of each knee (37).

Statistical Analyses

Statistical analyses were performed by using Stata software, version 13.1

(Stata, College Station, Tex). Analyses were performed by using only the consensus readings in the models. To reduce the possibility of type I error due to multiple testing, we used the Bonferroni correction, and $P \leq .017$ ($0.05 \div 3$ because there are three pairwise comparisons among the groups) was considered to indicate significance for the analyses that compared the parameters between the three groups. Differences in characteristics between participants with stable weight and those with 5%–10% weight loss and those with more than 10% weight loss were evaluated separately by using one-way analysis of variance (parametric testing) and χ^2 tests (categorical variables). Multivariable linear regression models adjusting for age, sex, baseline BMI, Kellgren-Lawrence score, and WOMAC and PASE scores were used to compare means of baseline WORMS subscores and increase of WORMS subscores of each weight loss group separately (5%–10% weight loss, >10% weight loss) with those in the group with stable weight (independent variable, group assignment; outcome variable, mean baseline WORMS parameters).

Associations of increases in WORMS subscores (increase in cartilage, meniscus, and BMEP subscores over 48 months) with weight change over 48 months were assessed by using multivariable regression models adjusting for age, sex, baseline BMI, Kellgren-Lawrence score, and WOMAC and PASE scores in all participants (independent variable, percentage of BMI change, outcome variable: increase of WORMS parameters).

Logistic regression models adjusted for age, sex, baseline BMI, Kellgren-Lawrence score, and WOMAC and PASE scores were used to estimate odds ratios for the progression of WORMS subscores for cartilage, menisci, and BMEP and to compare participants with stable weight and those who lost weight (5%–10% weight loss and >10% weight loss). The outcome variable for the subscores for cartilage, menisci, and BMEP was participants with no changes in joint structure over 48 months (ΔWORMS subscore = 0) versus participants with increases in joint structure over 48 months (WORMS subscore > 0), as previously defined (38,39).

In a separate analysis, participants were categorized as overweight (BMI of 25–30 kg/m^2) or obese (BMI >30 kg/m^2) according to their BMI at baseline, and logistic regression analyses with WORMS subscale summary scores were repeated.

The intra- and interreader reproducibility of WORMS grading was assessed for each time point (baseline or 48 months) by using 20 participants who were randomly selected; this was separately evaluated by both radiologists (A.S.G., B.J.S.), who were blinded to time point and patient information. Interreader intraclass correlation coefficients (ICCs) were calculated for each WORMS subscore (cartilage, meniscus, and BMEP). After at least 2 weeks, each radiologist repeated the same WORMS gradings once again the same way. Intrareader ICCs were calculated to compare each WORMS subscore (cartilage, meniscus, and BMEP).

Table 1

Baseline Participant Characteristics

Characteristic	All Participants (n = 640)	Stable Weight Group (n = 320)	5%–10% Weight Loss Group 238	>10% Weight Loss Group (n = 82)
Mean age (y)*	62.9 ± 9.1	62.9 ± 8.7	62.7 ± 9.5	63.6 ± 9.4
Female sex	398 (62.2)	197 (61.6)	150 (63.0)	51 (62.2)
Mean baseline BMI (kg/m^2)*	29.8 ± 3.3	29.9 ± 3.3	29.6 ± 3.3	30.0 ± 3.8
Baseline KL score				
0	196 (30.6)	104 (32.5)	73 (30.7)	19 (23.2)
1	119 (18.6)	54 (16.9)	47 (19.7)	18 (22.0)
2	219 (34.2)	116 (36.3)	78 (32.8)	25 (30.5)
3	106 (16.6)	46 (14.4)	40 (16.8)	20 (24.4)

Note.—Participants in the three different groups were frequency-matched for age, sex, baseline BMI, and Kellgren-Lawrence (KL) score. Unless otherwise noted, data are the numbers of participants, with percentages in parentheses.

* Data are mean ± standard devitation.

Results

Participant Characteristics

Baseline participant characteristics are presented in Table 1. After 48 months, participants in the more than 10% weight loss group lost 4.62 kg/m^2 ± 1.92 on average, participants in the 5%–10% weight loss group lost 2.13 kg/m^2 ± 1.21 on average, and the overall BMI in the stable weight reference group remained almost unchanged, with an increase of 0.08 kg/m^2 ± 0.97. In addition, the severity of morphologic knee abnormalities (WORMS cartilage, menisci, and BMEP) at baseline did not significantly differ between groups ($P \geq .017$ for each) (Table 2).

Change of Cartilage, Meniscal, and BMEP WORMS over 48 Months

Participants with more than 10% weight loss showed significantly lower odds of progression on the overall WORMS cartilage subscore over 48 months when compared with stable weight participants (sum of all cartilage compartments subscales; odds ratio, 0.34; 95% confidence interval [CI]: 0.20, 0.60; $P <$ .001) (Table 3); however, the odds were not significantly lower for the comparison between the 5%–10% weight loss group and the stable weight group (odds ratio, 0.76; 95% CI: 0.54, 1.07; $P = .1$). Adjusted mean increase in the global WORMS cartilage subscore over 48 months was significantly smaller in the 5%–10% weight loss group (cartilage $\text{WORMS}_{5\%-10\%\text{WLG}}$, 1.6; 95% CI: 1.3, 1.9; $P = .002$) and even smaller in the group with more than 10% weight loss (cartilage $\text{WORMS}_{>10\%\text{WLG}}$, 1.0; 95% CI: 0.6, 1.4; $P = .001$) when compared with the group with stable weight (cartilage

Table 2

WORMS Grades at Baseline

Variable	Stable Weight Group	5%–10% Weight Loss Group	*P* Value for 5%–10% Weight Loss Group versus Stable Weight Group	>10% Weight Loss Group	*P* Value for >10% Weight Loss Group versus Stable Weight Group	*P* Value for >10% Weight Loss Group versus 5%–10% Weight Loss Group
Cartilage						
WORMS sum	6.6 (6.1, 7.1)	6.8 (6.1, 7.5)	.4	7.0 (6.6, 8.0)	.3	.9
LFC	0.6 (0.5, 0.7)	0.7 (0.6, 0.9)	.2	0.4 (0.2, 0.6)	.6	.2
LT	0.8 (0.6, 0.9)	0.9 (0.7, 1.0)	.9	0.6 (0.4, 0.8)	.7	.9
MFC	0.9 (0.7, 1.0)	1.0 (0.8, 1.2)	.3	0.9 (0.7, 1.0)	.3	>.99
MT	0.6 (0.5, 0.7)	0.5 (0.3, 0.6)	.4	0.3 (0.1, 0.5)	.8	.7
P	2.0 (1.7, 2.1)	2.2 (1.9, 2.5)	.9	1.4 (0.9, 1.9)	.2	.3
T	1.3 (1.1, 1.5)	1.5 (1.3, 1.7)	.9	0.9 (0.7, 1.4)	.7	.5
Meniscus						
WORMS sum	2.1 (1.9, 2.4)	2.0 (1.6, 2.3)	.3	2.5 (1.9, 3.1)	.6	.3
Sum of medial meniscus scores	1.1 (0.9, 1.3)	1.0 (0.8, 1.3)	.7	1.6 (1.1, 2.0)	.6	.2
Sum of lateral meniscus scores	1.2 (0.9, 1.4)	1.2 (0.8, 1.5)	.9	0.7 (0.5, 1.5)	.1	.3
BMEP						
WORMS sum	2.3 (2.0, 2.5)	2.0 (1.7, 2.3)	.2	2.7 (2.0, 3.0)	.4	.2

Note.—Data are the mean, with 95% CI in parentheses. Multivariable linear regression models were adjusted for age, sex, race, baseline BMI, Kellgren-Lawrence score, WOMAC score, and PASE score. LFC = lateral femoral condyle; LT = lateral tibia; MFC = medial femoral condyle; MT = medial tibia; P = patella; T = trochlea; WORMS sum score = sum of all knee compartments.

Table 3

Odds Ratio for WORMS Subscale Progression between Participants with Weight Loss and Those with Stable Weight

	Stable Weight Group versus 5%–10% Weight Loss Group		Stable Weight Group versus >10% Weight Loss Group	
Variable	Odd Ratio	*P* Value	Odd Ratio	*P* Value
Change in cartilage over 48 months				
WORMS sum	0.76 (0.54, 1.07)	.1	0.34 (0.20, 0.60)	<.001
LFC	0.77 (0.45, 1.30)	.3	0.24 (0.08, 0.73)	.2
LT	0.92 (0.56, 1.51)	.7	0.41 (0.17, 1.00)	.049
MFC	0.74 (0.45, 1.22)	.2	0.36 (0.15, 0.90)	.028
MT	0.39 (0.20, 0.76)	.005	0.16 (0.01, 0.40)	.001
P	0.71 (0.47, 1.09)	.2	0.32 (0.15, 0.70)	.004
T	0.72 (0.46, 1.11)	.2	0.37 (0.20, 0.80)	.021
Change in menisci over 48 months				
WORMS sum	0.70 (0.46, 1.02)	.084	0.42 (0.22, 0.83)	.007
Sum of medial meniscus scores	0.81 (0.53, 1.39)	.5	0.38 (0.21, 0.96)	.041
Sum of lateral meniscus scores	0.70 (0.22, 1.35)	.5	0.30 (0.21, 1.01)	.3
Change in BMEP over 48 months				
WORMS sum	1.03 (0.71, 1.49)	.9	0.39 (0.20, 0.74)	.004

Note.—Data in parentheses are 95% CIs. Multivariable logistic regression adjusting for age, sex, baseline BMI, Kellgren-Lawrence, WOMAC, and PASE scores. LFC = lateral femoral condyle; LT = lateral tibia; MFC = medial femoral condyle; MT = medial tibia; P = patella; T = trochlea; WORMS sum score = sum of all knee compartments.

$WORMS_{SWG}$, 2.3; 95% CI: 2.0, 2.7) (Table 4). This was consistent with lower cartilage degeneration in both weight loss groups over 48 months. Moreover, percentage of weight change was significantly associated with the amount of WORMS cartilage increase (β = 0.2; 95% CI: 0.02, 0.4; P = .007), demonstrating that for every 1% of weight loss there was 0.2-point lower increase in WORMS cartilage over 48 months (Table 5).

In analyses of specific articular regions, the odds of progression for the WORMS cartilage subscale in the medial tibia were significantly lower in both weight loss groups than in the stable weight group (5%–10% weight loss: odds ratio, 0.39 [95% CI: 0.20, 0.76; P = .005]; >10% weight loss: odds ratio, 0.16 [95% CI: 0.01, 0.40; P = .001]) (Fig 2), consistent with lower cartilage degeneration in participants with weight loss compared with those with stable weight over 48 months. Increase in the WORMS cartilage subscale in the medial tibia in the group with more than 10% weight loss was significantly smaller than that in the group with stable weight (P = .006) (Table 4, Fig 3).

Table 4

Adjusted Mean Change in WORMS Grades over 48 Months*

Variable	Stable Weight Group	5%–10% Weight Loss Group	*P* Value for 5%–10% Weight Loss Group versus Stable Weight Group	>10% Weight Loss Group	*P* Value for >10% Weight Loss Group versus Stable Weight Group	*P* Value for >10% Weight Loss Group versus 5%–10% Weight Loss Group
Change in cartilage over 48 months						
WORMS sum	2.3 (2.0, 2.7)	1.6 (1.3, 1.9)	.002	1.0 (0.6, 1.4)	.001	.1
LFC	0.3 (0.2, 0.5)	0.2 (0.1, 0.3)	.06	0.2 (0.01, 0.4)	.2	.8
LT	0.3 (0.2, 0.5)	0.3 (0.1, 0.4)	.7	0.1 (0.02, 0.3)	.1	.2
MFC	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	.4	0.2 (0.04, 0.4)	.4	.6
MT	0.4 (0.2, 0.5)	0.2 (0.04, 0.3)	.026	0.02 (0.01, 0.06)	.006	.3
P	0.5 (0.4, 0.6)	0.4 (0.2, 0.5)	.1	0.3 (0.06, 0.5)	.2	.7
T	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	.05	0.2 (0.03, 0.4)	.068	.4
Change in menisci over 48 months						
WORMS sum	0.9 (0.6, 1.1)	0.6 (0.3, 0.9)	.1	0.7 (0.1, 1.5)	.5	.9
Sum of medial meniscus scores	0.4 (0.2, 0.5)	0.2 (0.04, 0.4)	.2	0.4 (0.2, 0.7)	.9	.5
Sum of lateral meniscus scores	0.5 (0.1, 0.7)	0.3 (0.1, 0.5)	.5	0.2 (0.05, 0.7)	.3	.7
Change in BMEP over 48 months						
WORMS sum	0.6 (0.4, 0.8)	0.7 (0.4, 0.9)	.9	0.5 (0.01, 0.9)	.6	.5

Note.—Data are mean, with 95% CI in parentheses. Multivariable linear regression models were adjusted for age, sex, race, baseline BMI, Kellgren-Lawrence score, WOMAC score, and PASE score. BMEP = bone marrow edema pattern; LFC = lateral femoral condyle; LT = lateral tibia; MFC = medial femoral condyle; MT = medial tibia; P = patella; T = trochlea; WORMS sum score = sum of all knee compartments.

Table 5

Associations between Amount of Weight Change and Increase in WORMS Subscores

Change in WORMS	Adjusted* Regression β	*P* Value
Cartilage	0.2 (0.02, 0.4)	.007
P	0.01 (−0.003, 0.03)	.1
T	0.01 (−0.01, 0.004)	.1
MFC	0.002 (−0.01, 0.01)	.8
LFC	0.01 (−0.002, 0.03)	.1
MT	0.02 (0.01, 0.04)	.01
LT	0.007 (−0.01, 0.02)	.4
Menisci	0.02 (−0.01, 0.06)	.2
BMEP	0.004 (−0.04, 0.03)	.8

Note.—Data in parentheses are 95% CI. BMEP = bone marrow edema pattern; LFC = lateral femoral condyle; LT = lateral tibia; MFC = medial femoral condyle; MT = medial tibia; P = patella; T = trochlea.

* Multivariable linear regression adjusting for age, sex, baseline BMI, Kellgren-Lawrence score, WOMAC score, and PASE score.

In addition, in the medial tibia, the amount of weight change was significantly associated with WORMS cartilage increase (β = 0.02; 95% CI: 0.01, 0.04; *P* = .01) (Table 5), again showing that for every 1% of weight loss there was a 0.02-point lower increase in WORMS cartilage in the medial tibia over 48 months.

Moreover, the participants with more than 10% weight loss had significantly lower odds of progression of cartilage WORMS in the patella (odds ratio, 0.32; 95% CI: 0.15, 0.70; *P* = .004) compared with participants with stable weight, whereas the odds were not significantly lower in the comparison of the 5%–10% weight loss group with the stable weight group (odds ratio, 0.71; 95% CI: 0.47, 1.09; *P* = .2).

Weight loss was associated with 58% lower odds of worsening of meniscal pathologic abnormality in the group with more than 10% weight loss and with 30% lower odds of such worsening in the 5%–10% weight loss group when compared with the stable weight group; however, these comparisons reached significance only in the group with more than 10% weight loss (sum of both menisci subscales; 5%–10% weight loss: odds ratio, 0.70 [95% CI: 0.46, 1.02; *P* = .084]; >10% weight loss: odds ratio, 0.42 [95% CI: 0.22, 0.83; *P* = .007]) (Fig 4). At baseline, the frequency of radial tears, vertical tears, horizontal tears, complex tears, and meniscal root tears did not differ between the stable weight group and the weight loss groups (*P* > .017 for each comparison). The odds of developing the following outcomes were significantly lower in the more than 10% weight loss group than in the stable-weight group (radial tears, *P* = .011; horizontal tears, *P* = .015; complex tears, *P* = .007; meniscal root tears, *P* = .012; as well as maceration of the meniscus, *P* = .002). Moreover, no significant difference was found between the 5%–10% weight loss group and the stable weight group for the odds of developing different types of tears (*P* ≥ .017).

Figure 2

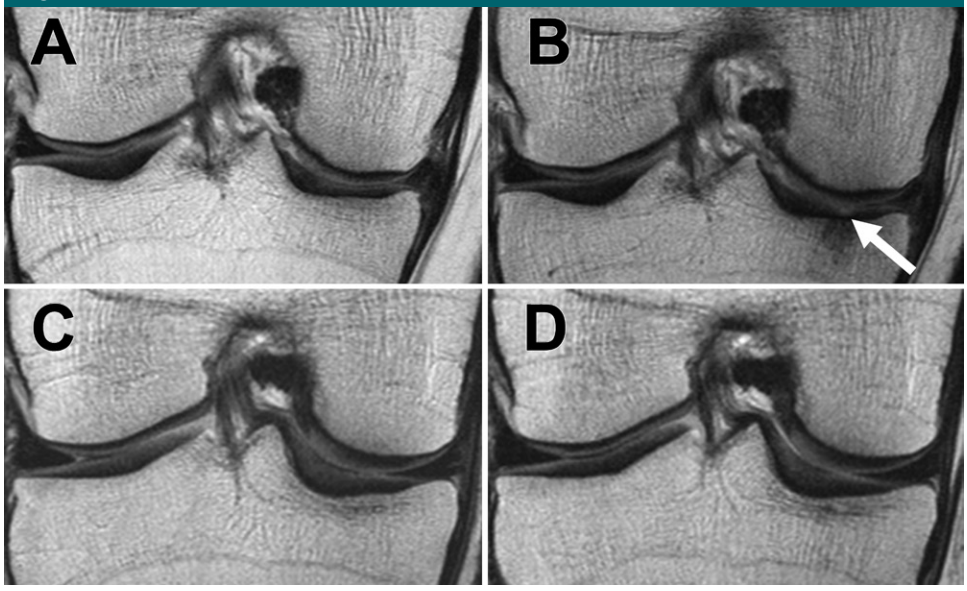

Figure 2: MR images of the right knee obtained with the coronal proton density–weighted fast spin-echo fat-suppression sequence at, *A, C,* baseline and, *B, D,* after 48 months. Patients were an obese 65-year-old woman with stable weight and mild knee pain (WOMAC pain subscale score of 3 at baseline; baseline BMI, 33.1 kg/m^2) (*A* and *B*) and an obese 64-year-old woman with weight loss over 48 months and mild knee pain (approximately 10.9% decrease in BMI; WOMAC pain subscale score of 5 at baseline; baseline BMI, 33.7 kg/m^2) (*C* and *D*). The woman with stable weight developed a full-thickness focal cartilage defect at the medial tibia (arrow) (baseline cartilage WORMS grade 0 in *A* and 2.5 in *B*). In contrast, no cartilage defects were detected at baseline or 48-month follow-up in the woman with weight loss (cartilage WORMS grade 0 in *C* and *D*).

The odds of BMEP progression were 61% lower for participants with more than 10% weight loss than for participants with stable weight (>10% weight loss: odds ratio, 0.39; 95% CI: 0.20, 0.74; P = .004); however, no significant differences were found between the participants with 5%–10% weight loss and those with stable weight (P = .9).

In separate analyses of overweight and obese participants, those with a BMI of 25–30 kg/m^2 who lost more than 10% of their weight showed significantly lower odds of overall cartilage worsening compared with overweight participants with stable weight (odds ratio, 0.34; 95% CI: 0.16, 0.68; P = .003) (Table 6); however, no significant differences were found between participants with stable weight and obese participants (BMI >30 kg/m^2). In overweight participants, odds of meniscal worsening were significantly lower in participants with more than 10% weight loss (odds ratio, 0.32; 95% CI: 0.13, 0.77; P = .011) compared with those with stable weight. In obese individuals, the odds of BMEP worsening were significantly lower in the group with more than 10% weight loss (odds ratio, 0.24; 95% CI: 0.08, 0.67; P = .006) than in the stable weight group.

Reproducibility

The ICCs for intraobserver agreement were 0.85 (95% CI: 0.79, 0.93) and 0.87 (95% CI: 0.81, 0.94) for meniscus WORMS, 0.87 (95% CI: 0.81, 0.92) and 0.84 (95% CI: 0.78, 0.95) for cartilage WORMS, and 0.89 (95% CI: 0.85, 0.91) and 0.86 (95% CI: 0.80, 0.95) for BMEP WORMS. The ICCs for interobserver agreement were 0.83 (95% CI: 0.76, 0.91) for meniscus WORMS, 0.80 (95% CI: 0.74, 0.87) for cartilage WORMS, and 0.88 (95% CI: 0.81, 0.94) for BMEP WORMS.

The ICCs for intraobserver agreement for progression were 0.83 (95% CI: 0.77, 0.93) and 0.84 (95% CI: 0.79, 0.92) for meniscus WORMS, 0.85 (95% CI: 0.80, 0.91) and 0.81 (95% CI: 0.77, 0.91) for cartilage WORMS, and 0.85 (95% CI: 0.80, 0.89) and 0.83 (95% CI: 0.78, 0.90) for BMEP WORMS. The ICCs for interobserver agreement for progression were 0.80 (95% CI: 0.69, 0.90) for meniscus WORMS, 0.78 (95% CI: 0.73, 0.85) for cartilage WORMS, and 0.86 (95% CI: 0.77, 0.90) for BMEP WORMS.

Discussion

In our study, the amount of weight loss was significantly associated with reduced risk for progression of cartilage defects over 48 months detected with MR imaging in 640 obese and overweight participants. Moreover, obese and overweight participants with weight loss showed lower progression of meniscal defects over 48 months than did participants in the weight-matched stable-weight reference group. After participants were classified into two groups

Figure 3

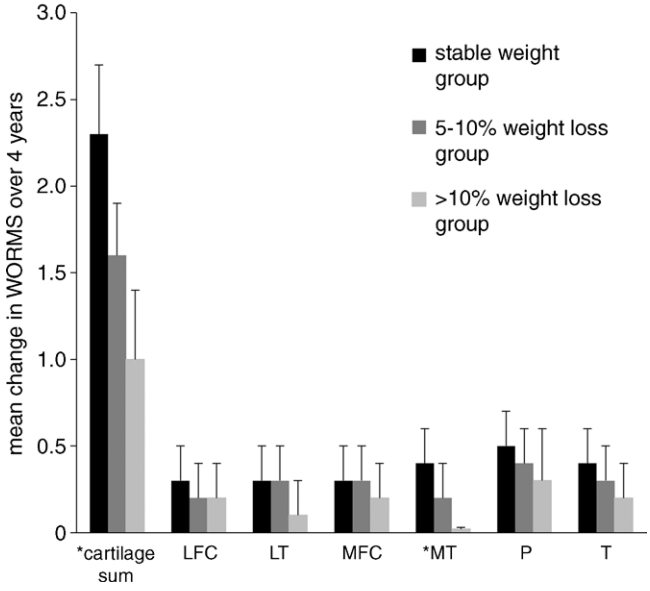

Figure 3: Mean change in WORMS (± standard error of the mean) over 4 years in the groups with stable weight, 5%–10% weight loss, and more than 10% weight loss in the subgroups. Cartilage sum = sum of all compartments; *LFC* = lateral femoral condyle; *LT* = lateral tibia; *MFC* = medial femoral condyle; *MT* = medial tibia; *P* = patella; *T* = trochlea. * indicates significant differences between the groups after logistic regression analysis ($P < .017$).

with different degrees of weight loss, the group with a substantial amount of weight loss (>10% weight loss) showed significantly lower odds of cartilage degeneration when compared with the stable-weight reference group, whereas the odds were not significantly lower when we compared the 5%–10% weight loss group with the stable-weight group. These findings suggest that a larger amount of weight loss is more beneficial for cartilage than is moderate or no weight loss. Both weight loss groups showed reduced cartilage degeneration in the medial tibia, which supports the hypothesis that weight loss is most protective for the weight-bearing regions (19,40). Weight loss was especially associated with reduced progression of cartilage and meniscal defects in the overweight individuals (BMI, 25–30 kg/m^2).

A recent study has shown that overweight and obesity are associated with greater vertical loading rates (7) and increased risk for total knee replacement surgery, with the strongest associations in younger patients (41). Moreover, several studies have previously shown that meniscus defects and cartilage loss are more prevalent within the medial compartment (42,43), overall indicating that medial osteoarthritis occurs more frequently than lateral osteoarthritis (44). Thus, it has been hypothesized that weight loss as a lifestyle intervention might show the strongest protective effect in this weight-bearing region (19). Our regional analyses, showing strong associations for the medial tibia, support this hypothesis.

Our findings also show that the amount of weight loss is associated with the amount of increase in WORMS subscores over 48 months. Similarly, previously investigators reported that the percentage of weight loss is significantly associated with change in cartilage volume (19) and composition (40) of the medial tibia. However, in the previous studies, participants were followed up within a very inhomogeneous and shorter period of time, and the study cohorts were substantially smaller than our overall study cohort. Thus, the results of our study, which show differences in the progression of cartilage changes detected via use of morphologic MR imaging averaged over all compartments, as well as in the patella, and regarding the progression of meniscal defects, were not evident in these previous studies because of shorter observation periods and smaller study cohorts. In other previous studies, varus alignment has been attributed to intensifying the effect of obesity on osteoarthritis progression at the medial tibiofemoral joint compared with other lower extremity joints (45). However, the literature is inconsistent regarding the effects of obesity and risk factors, such as malalignment (46). Another study showed that obesity increases the risk for progression in especially varus-aligned extremities (47). Previous studies have shown that the medial compartment in general is exposed to higher rates of cartilage loss in people with osteoarthritis, which could be attributed to a greater proportion of ground reaction forces by the medial tibiofemoral compartment even in normally aligned knees (40,48).

To our knowledge, our study is the first to longitudinally examine the association between weight loss and progression of morphologic knee joint abnormalities, including cartilage and meniscal defects, as well as BMEP, over 48 months. In a previous study with mostly overweight and obese participants, both elevated cartilage T2 values (assessed with compositional MR imaging and indicating very early molecular changes) and cartilage abnormalities were associated with knee pain (49). Associations between cartilage degeneration and pain have also been demonstrated previously (49–51). This may be due to increased stress on the subchondral bone because cartilage itself does not contain any nociceptors. Our findings—that weight loss is associated with less progression of morphologic cartilage defects and other osteoarthritic changes—therefore emphasize the relevance

Figure 4

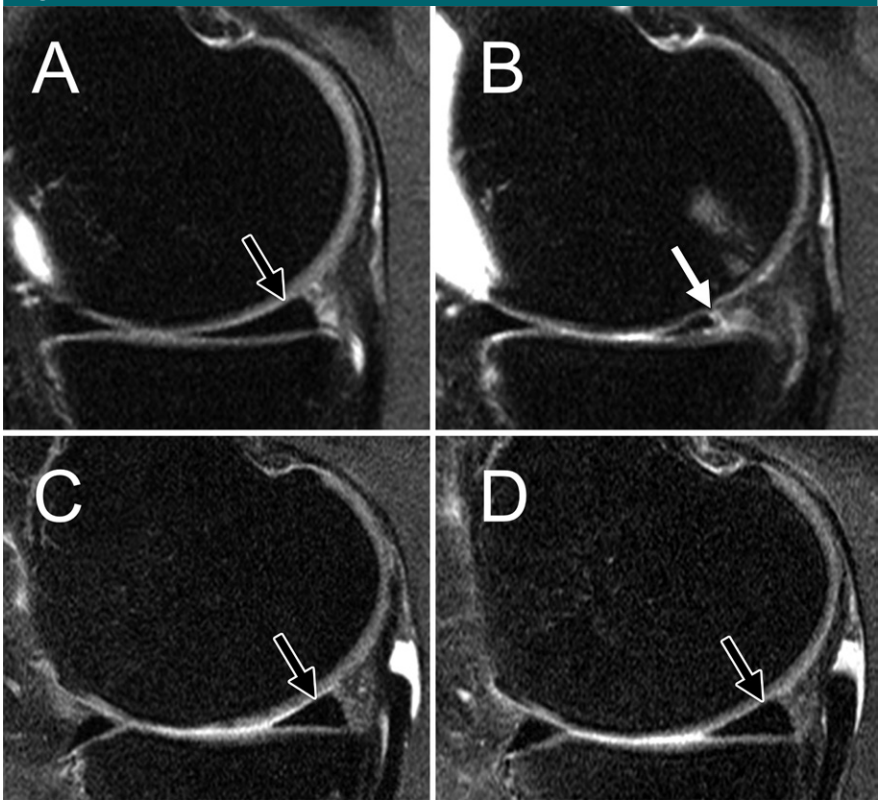

Figure 4: MR images of the right knee obtained with sagittal intermediate-weighted fast spin-echo fat-suppression sequence at, *A, C,* baseline and, *B, C,* after 48 months**.** Patients were an obese 57-year-old woman with stable weight and mild knee pain (WOMAC pain subscale score of 5 at baseline; baseline BMI, 31.4 kg/m^2) *(A, B)* and an obese 59-year-old woman with weight loss (approximately 8.5% decrease in BMI) over 48 months and mild knee pain (WOMAC pain subscale score of 6 at baseline; baseline BMI, 32.1 kg/m^2) *(C, D)*. The woman with stable weight developed a maceration of the medial meniscus (arrow) (medial meniscus WORMS of grade 0 in *A* and grade 4 in *B*) and thinning of the cartilage of the medial femoral condyle. In contrast, no meniscal defects (arrows) were seen on *C* or *D* (medial meniscus WORMS grade 0) in the participant with weight loss.

of lifestyle interventions in obese and overweight individuals regarding joint degeneration as detected with MR imaging and clinical outcome, such as knee pain.

Regarding the subchondral bone, the literature is inconsistent. Some studies have shown strong associations between the presence of BMEPs and the development of pain (52–54), whereas others have shown no association (55–57). Our findings suggest less progression of BMEPs in participants with substantial weight loss compared with stable-weight participants, which is in line with the findings of a previous study that showed the opposite effect in patients with weight gain (18). However, given the inconsistency in the previous literature, caution is needed in estimating the clinical relevance of associations between weight loss and MR findings over time.

Although a previous study showed that in patients with a meniscal tear weight loss caused a reduction of pain and cartilage loss (10), to our knowledge, no study has assessed the association between progression of meniscal degeneration and weight loss, as is demonstrated in our study. When we looked at overweight participants separately in comparison with participants with stable weight, odds of worsening were lower in the overweight cohort; this finding suggests that weight loss could be especially beneficial in this highly prevalent weight group. These results may be explained by changes in dynamic joint loading through weight loss because weight loss may cause decreased loading and shear stress on the menisci (58) (the primary functions of the meniscus is to serve as a shock absorber and to provide load bearing in the joint [59]). The occurrence of meniscal tears may impair these functions, causing increased stress in the knee joint (60,61). Meniscal tears alter whole joint kinematics and shift the mechanical stress distribution in the surrounding structures, including the cartilage. Previous studies showed that meniscus abnormalities are associated with pain (52), suggesting that the impairment of joint mechanics of the knee may be associated with the development of symptoms. Consequently, less worsening of meniscal degeneration in the group with substantial weight loss compared with the stable weight group could affect the progression of clinical symptoms differently within the groups. In addition, weight loss seems to decrease the production of proinflammatory adipocytokines, which contribute to meniscal and cartilage degeneration. However, additional studies analyzing the serologic and biomechanical effects of weight loss are needed to further investigate these mechanisms (10,62).

Our study had limitations, including the lack of clinical metrics as an outcome measure. Moreover, our study was a retrospective analysis of the weight loss of participants included in the OAI, and analyses did not consider methods and weight loss regimens used, including diet, exercise, or bariatric surgery. This is a major limitation of our study and may have introduced confounding effects into our analysis that cannot be estimated because different regimens may have different effects on joint structures (eg, cartilage health might develop differently in participants starting a rigorous exercise training program compared with participants undergoing bariatric

Table 6

Odds Ratio of Progression of WORMS for Weight Loss Groups Compared with Stable Weight Group in Subgroup Analyses Differentiating between Overweight and Obese Participants

	Stable Weight Group versus 5%–10% Weight Loss Group		Stable Weight Group versus >10% Weight Loss Group	
Variable	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Change in cartilage over 48 months				
BMI 25–30 kg/m^2 (n = 386)	0.75 (0.46, 1.22)	.2	0.34 (0.16, 0.68)	.003
BMI >30 kg/m^2 (n = 254)	1.26 (0.72, 2.21)	.4	0.55 (0.24, 1.23)	.15
Change in Menisci over 48 months				
BMI 25–30 kg/m^2 (n = 386)	0.69 (0.39, 1.19)	.2	0.32 (0.13, 0.77)	.011
BMI >30 kg/m^2 (n = 254)	1.06 (0.55, 2.05)	.9	0.45 (0.15, 1.36)	.16
Change in BMEP over 48 months				
BMI 25–30 kg/m^2 (n = 386)	1.26 (0.74, 2.15)	.4	0.74 (0.35, 1.56)	.4
BMI >30 kg/m^2 (n = 254)	1.22 (0.68, 2.18)	.5	0.24 (0.08, 0.67)	.006

Note.—Logistic regression analysis adjusting for age, sex, baseline BMI, and Kellgren-Lawrence score, WOMAC score, and PASE score.

surgery). Yet, the only statistical trend found in the previous assessment of structural knee abnormalities and different types of weight loss (exercise, diet, and diet combined with exercise) was a beneficial effect for both dietary groups regarding progression of BMEP (63). Of note, this previous study was performed over a much shorter period, which may explain the lack of differences between cartilage thickness and volume, as well as the denuded area, between the groups with different weight loss methods.

In another study, participants of both diet groups (diet and exercise group and diet-only group) showed a significantly greater reduction of the inflammatory marker interleukin-6 when compared with the exercise group, suggesting less inflammation and therefore less osteoarthritis progression in the dietary groups (29). Moreover, in the same study, both dietary groups showed lower compressive forces when compared with those in the exercise group; this comparison reached the level of significance in the diet group and showed a statistical trend in the diet and exercise group (29). A similar effect may have been introduced by the fact that analyses did not control for medication, yet we found no significant differences between the stable weight and weight loss groups regarding the use of antihypertensive medication, diabetic medication or insulin, or lipid-lowering medication (eg, statins). Because our study was retrospective, conclusions regarding causation between weight loss and progression of cartilage abnormalities may not be drawn from our results. A prospective study would be required to validate our results.

Of the potential study participants identified in the OAI, 384 dropped out of the study and did not undergo follow-up MR imaging after 4 years. It is unknown whether any of these participants underwent total knee arthroplasty. This limitation of the OAI study may have introduced a bias to our analyses. Moreover, because most participants reported their right leg to be the dominant leg (92.2%), we assessed the MR imaging examinations for the right leg only, which may have introduced a bias to the analyses as well. In addition, only participants in whom MR imaging could be performed were included in the OAI study; thus, participants who had issues with fitting into the MR imaging bore or the MR imaging knee coil because of their body size were excluded from this study, which may have caused a selection bias. Finally, WORMS has limited sensitivity in the detection of subtle changes of cartilage defect sizes over time because changes may not be reflected by an increase in the WORMS subscale if they are too subtle to cause a difference in the score. Biochemical metrics (eg, T2 or T1ρ mapping) are more sensitive regarding these subtle changes. The additional evaluation with quantitative assessment, such as cartilage volumetry, and biochemical metrics may yield more detailed information on cartilage degenerative disease.

In summary, our study showed that weight loss was significantly associated with reduced progression of knee cartilage and meniscal degeneration in obese and overweight individuals with risk factors for osteoarthritis or mild to moderate radiographic evidence of osteoarthritis. Our findings suggest that weight loss may have a protective effect on knee cartilage and menisci and that greater weight loss may be even more beneficial for knee joint health in obese and overweight individuals.

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