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Structural changes in the knee during weight loss maintenance after a significant weight loss in obese patients with osteoarthritis: a report of secondary outcome analyses from a randomized controlled trial

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SUMMARY

Objective: To compare structural knee joint changes in obese patients with knee osteoarthritis (OA) that after an intensive weight loss therapy were randomized to continuous dietetic support, a specialized knee exercise program, or 'no attention' for 1 year.
Methods: 192 obese individuals with knee OA underwent an intensive 16-week weight loss program with subsequent randomization to one of the three treatment groups. Changes in cartilage loss, bone marrow lesions (BMLs), synovitis, and effusion were assessed using semi quantitative assessments of magnetic resonance imaging (MRI) obtained at weeks 0 and 68 applying the BLOKS score.
Results: During the 52 weeks maintenance period the continuous dietary maintenance group support on average gained 1.1 kg (95% CI: −0.3:2.5) body mass, the exercise group gained 6.6 kg (95% CI 5.4:7.8) and the no-attention group gained 4.8 kg (95% CI: 2.9:6.7). There were no statistically significant between-group differences in changes in cartilage loss, synovitis or effusion at the follow-up (analysis of covariance; ANCOVA, $P > 0.16$), while there was an increased number of medial tibiofemoral BMLs in the exercise group (ANCOVA, $P = 0.015$) compared to both diet (difference: −0.21 [95%CI −0.40:−0.03]) and "no attention" (difference: −0.26 [95%CI −0.44:−0.07]) groups.
Conclusion: In this 1 year follow-up after weight-loss in obese knee OA patients, we found a potentially increased number of BMLs in the exercise group compared to the diet and no attention groups, with no between-group differences in changes in cartilage loss, synovitis or effusion. These findings should be interpreted with caution for exercise compliance, MRI methodology and follow-up time.
(ClinicalTrials.gov identifier: NCT00655941)

Introduction

The association between knee osteoarthritis (OA) and obesity is well known[1,2], and obesity is an important factor in the development of OA[2,3]. Accordingly, weight loss is recommended as treatment of choice[4] and the short-term results of weight loss on symptoms are comparable to that of a joint replacement[5]. There are no definitive data on whether weight loss is beneficial for reducing structural OA progression, but available data from different study designs support the notion that intensive dietary-induced weight loss and exercise interventions slow disease progression[4]. However, because knee OA is a slowly progressive disease it is generally agreed that structural disease modifying effects of an intervention should be assessed at the earliest after 1 year[6]. In relation to weight loss, this represents a challenge as maintaining weight loss is difficult.

Maintaining weight loss is typically achieved through continuous dietary counseling or exercise programs, which each

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and in combination have been shown to result in positive clinical long term (18 months) results in patients with knee OA[7]. While the evidence in favor of weight loss and weight loss maintenance with respect to symptomatic relief is indisputable, the effects of weight loss maintenance on structural disease progression are not well documented. Anandacoomarasamy *et al.*[8] showed that weight loss was associated with reduced loss of cartilage thickness and proteoglycan content over 12 months in a cohort of mixed OA and non-OA obese individuals. Other structural changes are also known to characterize OA such as bone marrow lesions (BMLs), cartilage loss, synovitis, and effusion. The effects of weight loss and weight loss maintenance on these structures are unknown.

The present study is a secondary report from a randomized trial and the present study purpose was to compare changes in magnetic resonance imaging (MRI) based assessments of multi-tissue changes in knee OA patients that after an intensive weight-loss therapy entered either (1) 1 year of continuous dietetic support from a dietician, (2) 1 year of a specialized knee exercise program or (3) a 1 year 'no attention' control group.

Patients & methods

Study design

This is a secondary report of MRI outcomes from the CAROT study – Influence of weight loss or exercise on CARtilage in Obese knee osteoarthritis patients Trial (ClinicalTrials.gov identifier: NCT00655941). The CAROT study was designed as a pragmatic randomized controlled trial, with pain and treatment response as primary outcomes and blinded outcome assessors[9]. In the CAROT study knee OA patients were included and were all given an initial 16 week intensive diet intervention, inducing a clinically significant weight loss, i.e., >10%[10–13]. Following the 16-week weight loss program the participants were enrolled in a 52-week maintenance program with random assignment to either (1) continued dietary consultancy, (2) knee exercise therapy, or (3) a no attention control group. Thus, the total study duration was 68 weeks (16 weeks weight loss phase + 52 weeks maintenance phase). The participant's most symptomatic knee at inclusion was designated as the target knee for assessments throughout the study.

Participants

CAROT participants were recruited from November 2007 to August 2008 from the outpatient clinic at the Department of Rheumatology, Frederiksberg Hospital, Denmark, through advertisements in newspapers and on the website of the Parker Institute. Additionally, local general practitioners were informed about the possibility of assigning patients to the project. All participants were prescreened *via* telephone using a series of standard questions concerning eligibility according to criteria of inclusion and exclusion.

Eligibility criteria for the CAROT study were age above 50 years, clinical knee OA confirmed by radiography (osteophytes and/or joint space narrowing assessed by a radiologist), and a BMI>30 kg/m^2. Exclusion criteria were: lack of motivation to lose weight, inability to speak Danish, planned anti-obesity surgery, or receiving pharmacologic therapy for obesity. The participants were asked not to change any medication or nutritional supplement during the study. The study was performed in compliance with the Helsinki Declaration, was approved by the ethics committee of the Capital Region of Denmark [H-B-2007-088], and all participants gave written informed consent.

Interventions and randomization

Initial weight loss program

The 16-week dietary program consisted of a low-energy-diet of normal food plus meal replacements (The Cambridge Weight plan, UK) and nutritional education. The details of the dietary program are described elsewhere[10,12]. Following the first 16 weeks of intensive dietary therapy, participants were randomly assigned with the use of minimization to one of three subsequent treatment groups with an equal allocation ratio (1:1:1). The concealed allocation was carried out on all patients entering the study at week 0 into blocks of 24 participants, consecutively enrolled by the recruiting staff at the Parker Institute, resulting in eight participants in each group per 24 enrolled. Thus, participants were randomly assigned at week 0 – independent of the first 16 weeks – to either (1) a continued dietary maintenance program, (2) exercise therapy lead by an experienced physical therapist, or (3) a no attention control group receiving no intervention for the 52 weeks maintenance period. For each block of patients enrolled, a randomization list was drawn up by the Biostatistician and given to the secretariat at the Parker Institute. After the patients had completed the first 16 weeks of dietary program, the secretariat informed the participants, when to meet with the dietician or physical therapist (i.e., securing concealed allocation), or if they did not have to meet until week 68. This way the random assignment prevented prior knowledge of forthcoming allocations by study participants and those recruiting them to the trial.

Continuous dietary program

The dietary maintenance intervention focused on long-term lifestyle modifications. Participants attended sessions lasting approximately 60 min. The participants were weighed and formula products were handed out (The Cambridge Weight Plan). Participants were advised to use one formula product a day to enhance weight loss. The educational themes in the sessions were: energy expenditure and energy balance, macronutrients, satiety, digestion, motivation, and diet planning. The group treatment provided a combination of empathy, social support, and friendly competition. The dietician aimed to maximize adherence by reinforcing positive dietary changes and addressing barriers to adherence. Attendance to the sessions was recorded.

Exercise program

The 3 days/week exercise program prescribed to each participant randomized to the exercise group consisted of a warm-up phase (10 min), a circuit training phase (45 min), and a cool down/stretching phase (5 min). The exercise intervention was divided into four periods of 12 weeks and one period of 4 weeks (total 52 weeks). The exercise program was designed to gradually transfer the intervention from supervised facility-based exercises to unsupervised home-based exercises. The participants alternated between attendance to exercise at the facility and performing exercises at home. During the first 12 weeks the intervention was facility-based 2 days/week, and concurrently the participants were encouraged to perform the exercises at home 1 day/week. In the second 12 weeks period the participants exercised at the facility 1 day/week and at home 1–2 days/week. During the third 12 weeks period the participants exercised at home 3 days/week, and attended one facility-based exercise session once every second week, substituting one home exercise session. In the fourth 12 weeks period the participants exercised at home 3 days/week, attended one facility-based exercise session once every 3 weeks, substituting one home exercise session,

and during the final 4 weeks the participants met at the facility once, and exercised at home 2–3 days/week. In this way the participants were gradually going from supervised to unsupervised exercise. If a participant did not appear at the facility-based sessions, supervision was attempted by phone by the responsible physiotherapist. The exercise program was designed according to the individualized goal-based OA standard, also referred to as 'neuro-muscular training'[14]. The aim of the individualized goal-based program was to improve knee function and reduce pain. Functional exercises during weight-bearing were applied, emulating activities of daily life. The quality of the performance in each exercise was emphasized, and the level of training and progression was guided by the patient's performance. Attendance at facility-based sessions and self-reported home-based exercise sessions was recorded.

No-attention group program

The control group served as a usual-care comparison group and no attention from the study was provided to the participants after the first 16 weeks of therapy.

Mechanical axis assessment (alignment)

Mechanical axis alignment was measured using a six camera stereophotogrammetric system (Vicon MX, Vicon, UK) with markers placed on anatomical landmarks (second metatarsal head, lateral malleolus, posterior aspect of calcaneus, lateral aspect of the leg, lateral femoral epicondyle, lateral aspect of the thigh, bilaterally on anterior and posterior superior iliac spines) according to the Plug-in-Gait biomechanical model (Vicon MX, Vicon, UK), and anthropometric measurements (height, leg length, and knee and ankle diameters) to determine joint centers. The mechanical axis alignment was defined as the frontal plane knee joint angle expressed in the local joint coordinate system. This procedure yields estimates of mechanical axis alignment similar to full-limb weight-bearing radiographs ($R^2 = 0.54$) but without exposure to radiation[15]. A knee was defined as a varus when alignment was $>0^\circ$ and valgus when $<0^\circ$.

Magnetic resonance image acquisition

MRI was obtained at week 0, 16, and 68 on the target knee using an MRI (1.5 T) whole body scanner (Philips Intera; software release 12.1.5.0) with a send/receive flex medium or large coil fixed to the leg. The MRI protocol used for image acquisition was: Sagittal 3D FLASH gradient-echo (reconstructed to 3 mm slices, TR21ms, TE8.4ms, FA20°, FOV160 × 160 mm, matrix 512 × 512), sagittal non fat sat DUAL turbo spin echo proton density and T2-weighted sequence (4 mm slices, TR2531.3ms, TE15/100, FOV 170 × 170 matrix 256 × 256), coronal T1 turbo spin echo (3 mm slices, TR500ms, TE17ms, FOV150 × 150 mm, matrix 512 × 512) and STIR (3 mm slice, TR1797 TI9ms, TE55ms, FOV150 × 150 mm, matrix 512 × 512).

Outcome measures

The MRI based multi-tissue structural outcomes were changes from week 0–68 in cartilage, BMLs, effusion, and synovitis assessed semi-quantitatively using a comprehensive scoring method, the Boston–Leeds Osteoarthritis of the Knee Score (BLOKS)[16].

The major structural outcome was changes from week 0–68 in cartilage loss assessed by the Cartilage 1 score of the BLOKS[16]. For this assessment the sagittal FLASH and proton/T2 weighted dual turbo spin echo sequences were used. Because it is difficult to separate fluid and cartilage on a FLASH sequence, minor cartilage losses are difficult to detect reliably. We partly compensated for this by using the corresponding sagittal proton/T2 weighted dual turbo spin echo sequence to verify the score from the FLASH sequence and to adjust for potential joint fluid between the cartilage layers. Cartilage loss were scored semi-quantitatively grading the size of any cartilage loss in the four of the nine regions: the medial and lateral weight bearing femoral and medial and lateral tibial regions, graded on a 0–3 scale based on extent of regional involvement; 0 = none; 1 = <10% of the region cartilage surface area; 2 = 10–75% of the region cartilage surface area; 3=>75% of region cartilage surface area. We decided to collate the four regions into a medial tibiofemoral region (medial weight bearing femoral region + medial tibial region), and a lateral tibiofemoral region (lateral weight bearing femoral region + lateral tibial region). The maximal score in the collated regions was considered for analyses together with the number of loss in the region.

The minor structural outcomes were changes from week 0–68 in the BML size score, the number of BMLs, effusion, and synovitis as assessed semi-quantitatively using the relevant scores of the BLOKS[16].

The coronal T1 and STIR images were used for BML size scoring. BMLs appear as ill-defined signal intensity changes in the subchondral bone that are hypointense on T1 images and hyperintense on STIR images[17], and evidence support that combining the two is highly effective for the evaluation of BML[18,19], even though some data suggests that T2w FS sequences might be more sensitive[18]. Due to time restraints in the MRI scanner and the use of a coronal STIR sequence the imaging protocol did not allow for the assessment of BMLs in patella. BMLs were assessed in four of the nine regions of the knee as described[16]: the lateral and medial weight bearing femoral regions and lateral and medial tibial regions. BML sizes were graded on a 0–3 scale based on the extent of regional involvement; 0 = none, 1 = less than 10% of the region; 2 = 10–25% of the region; 3 = more than 25% of the region. We decided to collapse the four regions into a medial tibiofemoral region (medial weight bearing femoral region + medial tibial region), and a lateral tibiofemoral region (lateral weight bearing femoral region + lateral tibial region). To overcome that there can be several BMLs in each region only the maximal size score in a region was considered for analyses together with the number of BMLs in the region.

Effusion and synovitis were evaluated on the proton/T2 weighted and STIR images. Effusion was assessed in the suprapatellar bursa and scored as follows: 0 = physiological; 1 = small; 2 = medium; 3 = large. The non-contrast enhanced synovial thickening around the infra-patellar fat pad was assessed as a sign of synovitis and scored as: 0 = normal; 1 = mild; 2 = moderate; 3 = severe synovitis. Further, presence of synovial thickening (synovitis) in five regions of the knee was scored separately: (1) infrapatellar fat pad, (2) medial posterior-condylar, (3) lateral posterior-condylar, (4) medial recess, and (5) lateral recess. The number of 'present' scores indicates the extent of synovitis in the knee and was considered for analyses.

HG performed all BLOKS assessments under the supervision of MB. MB is a trained radiologist (8 years) and HG was a non-specialized MD who had a total of 3 years within MSK radiology. Intra- and inter-reader reliability were assessed by HG and MB (Kappa coefficients: cartilage: inter-reader: 0.59; intra-reader: 0.81. BML: inter-reader: 0.65; intra-reader: 0.66. Effusion: inter-reader: 0.51; intra-reader: 0.72. Synovitis: inter-reader: 0.66; intra-reader: 0.70).

Statistical methods

The primary aim was to investigate group differences 1 year after the intensive weight loss intervention, i.e., after the 68 weeks of study participation. For all the outcomes, a general linear model (ANCOVA) was used to compare the changes from week 0–68 weeks between groups with a factor for group and adjusted for the level at week 0 as a covariate. The dependent variables (change from baseline) were generated by subtracting the week 0 value from the value at the 68-week assessment. Pairwise comparisons between groups of the changes from week 0 at week 68 were performed. To assess the adequacy of the linear model(s) describing the observed data - as well as checking the assumptions for both the systematic and random part of the model – we investigated the model features *via* the predicted values and the studentized residuals; i.e., the residuals had to be normally distributed (around zero), and be independent of the predicted values.

The analyses were done in two steps. Firstly we analyzed the 'As observed' population defined as participants that completed the 68 weeks assessment with valid and complete measurements were performed. Secondly, the sensitivity of the initial analyses was tested by repeating the analyses on the modified ITT (mITT) population – defined as all randomized participants with valid measurements at week 0, replacing missing data after 68 weeks with the week 0 value. As the results were unchanged we present the results from the mITT analyses.

As sensitivity analyses, we also analyzed the changes from week 0 on the 'As observed' population (defined as above) using a mixed effects model allowing for imbalanced data with fixed effects defined as group (Control, Diet, and Exercise) and week (16 and 68), and participants contributing to the random effects. The models were adjusted for the week 0 value.

All analyses were done applying SAS software (v. 9.2; SAS Institute Inc., Cary, NC, USA), and statistical significance was accepted at $P < 0.05$ (two-sided). Despite multiple tests, no statistical adjustments were applied, as this study does not have a key hypothesis, but is more exploratory in its purpose.

Results

After screening of potential participants 192 individuals were included in the overall trial and randomized (Fig. 1). Of the randomized patients, BLOKS scoring of the week 0 MR-images was not possible in five cases due to poor image quality (Diet: 4; Exercise: 1), resulting in 187 participants with complete week 0 observations defining the mITT population (Table I). Of these, 174 (93%) completed the first (16 weeks) phase. During the following 52 weeks maintenance period, 16 participants (9.1%) dropped out of the study with an overweight of dropouts in the no attention and exercise groups ($n = 9$ and 6, respectively), yielding a total of 159 participants completing the study [Fig. 1]. Of these, BLOKS scoring of the follow-up MR-images was not possible in 15 cases (9.4%) due to poor image quality, resulting in 146 participants with complete follow-up observations after the entire 68 weeks study period. The missing follow-up BLOKS scores were equally distributed among the three group (six participants in the Diet and Exercise groups and five participants in the No-attention group). There were no statistically significant differences between groups in terms of age ($P = 0.34$), body mass ($P = 0.28$) and BMI ($P = 0.26$).

During the 52 weeks maintenance period the participants enrolled in the continuous Dietary maintenance group succeeded in maintaining the weight loss with an average weight regain: 1.1 kg (95% CI: −0.3 to 2.5). The knee exercise group on average regained 6.6 kg (95% CI 5.4–7.8) and the no-attention group regained 4.8 kg (95% CI: 2.9–6.7). The group differences in weight loss/regain were statistically significant ($P < 0.0001$) in favor of dietary maintenance.

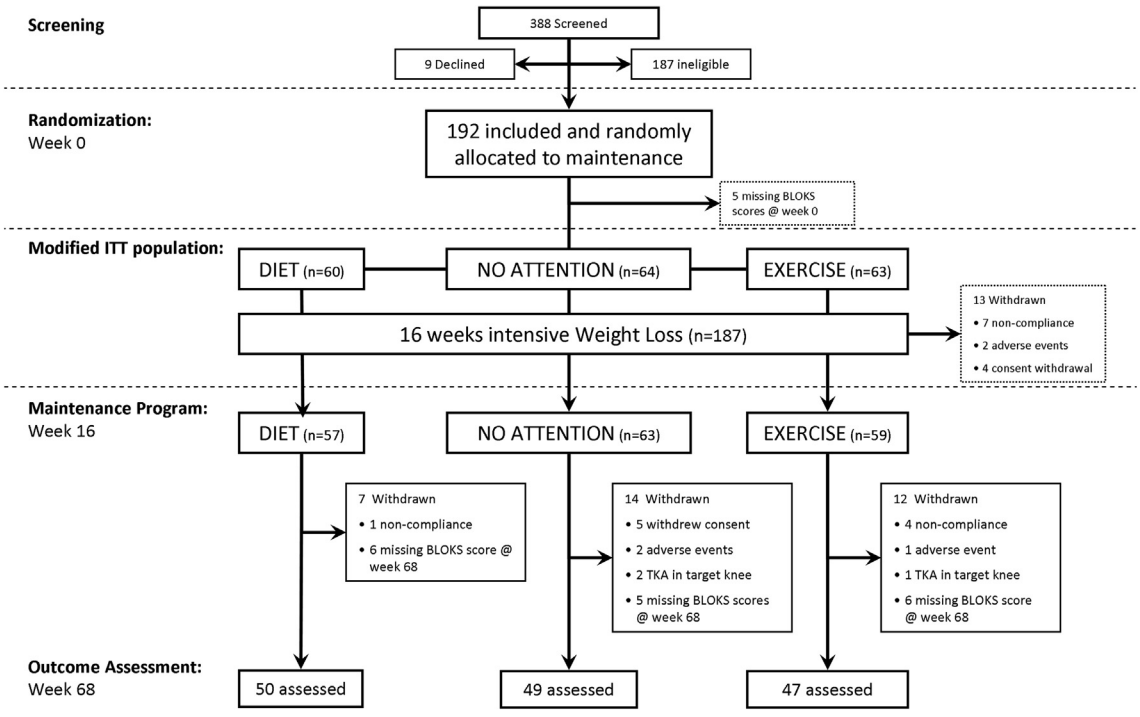

Fig. 1. Enrollment of patients and completion of the study.

Table I
Characteristics of the patients at week 0

Variable	"No attention"			Diet			Exercise		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Age, y	64	63.1	6.8	60	64.6	6.6	63	64.4	5.8
Body mass, kg	64	105.0	16.1	60	102.5	14.1	63	100.9	14.0
Body mass index, kg/m^2	64	37.9	5.3	60	37.3	4.5	63	36.5	4.4
K/L, 0–4	64			60			63		
0, *n* (%)	0	(0%)		1	(2%)		0	(0%)	
1, *n* (%)	4	(6%)		3	(5%)		9	(14%)	
2, *n* (%)	24	(38%)		23	(38%)		23	(37%)	
3, *n* (%)	25	(39%)		22	(37%)		21	(33%)	
4, *n* (%)	11	(17%)		11	(18%)		10	(16%)	
Alignment, degrees	64	6.1	0.7	60	5.6	0.6	63	5.9	0.6
Cartilage loss									
Medial tibiofemoral max score, 0–3	64	1.89	0.89	60	1.78	0.94	63	1.75	1.00
Medial tibiofemoral number of loss, *n*	64	1.73	0.57	60	1.73	0.61	63	1.62	0.68
Lateral tibiofemoral max score, 0–3	64	1.39	0.63	60	1.40	0.72	63	1.44	0.62
Lateral tibiofemoral number of loss, *n*	64	1.75	0.53	60	1.75	0.57	63	1.75	0.51
BML									
Medial tibiofemoral max score, 0–3	64	1.25	1.08	60	1.10	1.02	63	0.92	1.00
Medial tibiofemoral number of BML, *n*	64	1.30	1.16	60	1.10	1.04	63	0.89	0.95
Lateral tibiofemoral max score, 0–3	64	0.39	0.68	60	0.45	0.70	63	0.40	0.83
Lateral tibiofemoral number of BML, *n*	64	0.34	0.60	60	0.37	0.52	63	0.27	0.54
Effusion score	64			60			63		
Effusion, 0–3	64	0.70	0.77	60	0.78	0.76	63	1.03	0.84
Synovial thickening									
Synovitis score, 0–3	64	0.91	0.66	60	0.78	0.61	63	0.92	0.73
Number of Synovitis Sites, *n* (0–5)	64	2.86	1.19	60	2.87	1.02	63	2.63	1.20

K/L: Radiographic disease severity assessed by the Kellgren & Lawrence scale.

Compliance to maintenance programs

During the 52 weight loss maintenance weeks, the median number of attendances at the Dietary session was 32 out of 52 possible (61.5%). The median attendance rate with the facility-based Exercise sessions was seven attendances out of 47 possible (13.8%) and the median reported home-based exercise completion was four out of 109 scheduled home sessions (3.7%).

Imaging outcomes

There were no group differences in the changes in either of the BLOKS assessments of cartilage loss (major outcome), medial BML size score, lateral BML size score and count, synovial thickening and effusion (Table II). There were no statistically significant group differences in the maximal medial tibiofemoral BML score ($P = 0.168$, Table II).

Table II
Changes in imaging outcomes from week 0–68

Variable	Control	Diet	Exercise	ANCOVA			*P*-value
Change from week 0 at week 68 in:	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Control vs Diet	Control vs Exercise	Diet vs Exercise	
				Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Cartilage loss							
Medial tibiofemoral max size score	−0.06 (−0.15:0.04)	−0.13 (−0.23:−0.04)	−0.05 (−0.15:0.04)	0.08 (−0.06:0.21)	−0.01 (−0.14:0.13)	−0.08 (−0.22:0.05)	0.412
Medial tibiofemoral number of losses	−0.09 (−0.19:0.01)	−0.10 (−0.20:0.003)	−0.04 (−0.14:0.06)	0.01 (−0.13:0.15)	−0.05 (−0.19:0.09)	−0.06 (−0.20:0.08)	0.660
Lateral tibiofemoral max size score	−0.02 (−0.11:0.08)	−0.04 (−0.13:0.06)	−0.03 (−0.12:0.07)	0.02 (−0.12:0.15)	0.01 (−0.13:0.14)	−0.01 (−0.14:0.13)	0.973
Lateral tibiofemoral number of losses	−0.11 (−0.20:−0.01)	−0.01 (−0.11:0.08)	−0.001 (−0.10:0.10)	−0.09 (−0.23:0.04)	−0.11 (−0.24:0.03)	−0.02 (−0.15:0.12)	0.235
BML							
Medial tibiofemoral max size score	−0.14 (−0.26:−0.02)	−0.02 (−0.14:0.11)	0.02 (−0.11:0.14)	−0.13 (−0.30:0.05)	−0.16 (−0.33:0.02)	−0.03 (−0.20:0.14)	0.168
Medial tibiofemoral number of BMLs	−0.10 (−0.23:0.03)	−0.05 (−0.18:0.08)	0.16 (0.03:0.29)	−0.05 (−0.23:0.14)	−0.26 (−0.44:−0.07)	−0.21 (−0.40:−0.03)	0.015
Lateral tibiofemoral max size score	−0.11 (−0.23:−0.01)	−0.00 (−0.11:0.11)	−0.01 (−0.11:0.10)	−0.11 (−0.27:0.04)	−0.11 (−0.27:0.04)	0.00 (−0.15:0.16)	0.320
Lateral tibiofemoral number of BMLs	−0.07 (−0.17:0.02)	0.03 (−0.07:0.13)	0.03 (−0.07:0.12)	−0.10 (−0.24:0.03)	−0.10 (−0.24:0.03)	0.00 (−0.14:0.14)	0.223
Effusion score							
Effusion	−0.01 (−0.15:0.14)	−0.14 (−0.28:0.01)	−0.08 (−0.23:0.06)	0.13 (−0.07:0.34)	0.08 (−0.12:0.28)	−0.05 (−0.26:0.15)	0.434
Synovial thickening							
Synovitis score	0.04 (−0.08:0.16)	0.12 (0.001:0.25)	0.05 (−0.07:0.17)	−0.08 (−0.26:0.09)	−0.00 (−0.17:0.16)	0.08 (−0.09:0.25)	0.567
Number of Synovitis Sites	−0.02 (−0.24:0.20)	0.02 (−0.21:0.24)	0.05 (−0.17:0.27)	−0.03 (−0.35:0.28)	−0.07 (−0.38:0.25)	−0.03 (−0.35:0.29)	0.919

95% CI: 95% Confidence Interval.

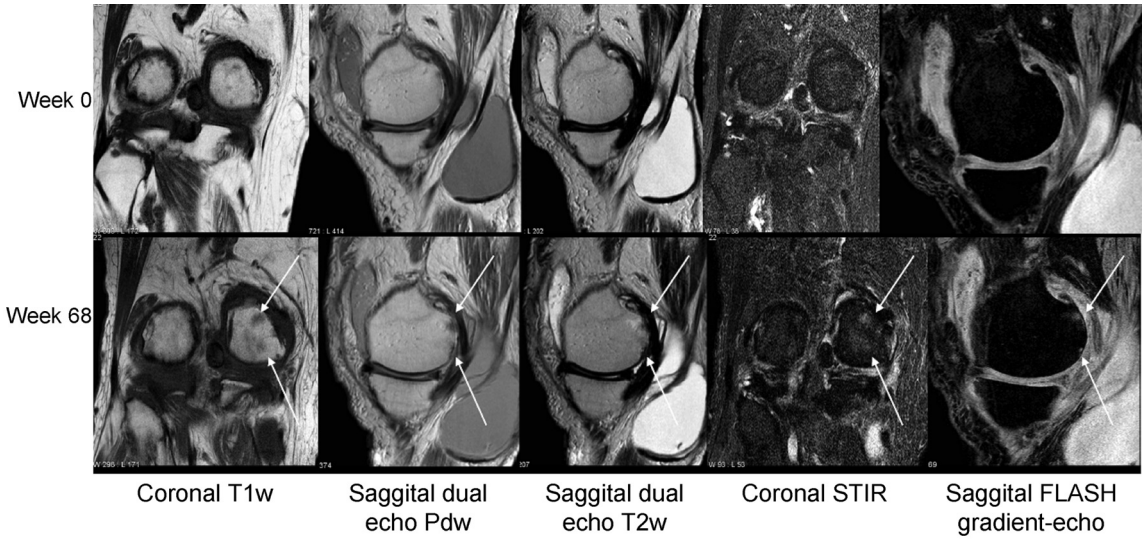

Fig. 2. MR-images from a representative case showing longitudinal change in BMLs. Top row images are baseline images. Bottom row images are images obtained at week 68. Note the progression of and increased number of BMLs in the posterior part of the medial femoral condyle (arrows).

There was a statistically significant difference between groups in the change in medial tibiofemoral BML count (ANCOVA, $P = 0.015$, Table II) in which the Exercise group demonstrated an average increase in medial tibiofemoral BML counts of 0.16 (95% CI: 0.03–0.29, see Fig 2 for representative example), whereas the Diet and Control groups showed no change over time in medial tibiofemoral BML counts (mean change −0.05 [95% CI: −0.18 to 0.08]; $P = 0.463$ and −0.10 [95% CI: −0.23 to 0.03]; $P = 0.139$, respectively). The results from the sensitivity analyses (Appendix 1) did not confirm this finding from the main analyses.

Discussion

This is the first study to investigate the effects of different weight loss maintenance programs on structural disease progression in obese individuals with knee OA. We found no between-group differences in the major structural outcome, cartilage loss, or in most of the minor structural outcomes BML size, effusion and synovitis. We observed an increase in the number of medial tibiofemoral BMLs in the group randomized to the exercise maintenance program compared with the dietary weight loss maintenance and no attention maintenance programs, where no detectable changes were observed.

These results must be interpreted with caution. An average increase of 0.16 in the medial tibiofemoral BML count in the exercise group should be related to the average count at week 0 that was approximately 0.9. This roughly corresponds to a 17% increase in counts, which might reflect that one out of six participants in the exercise group had an additional BML at week 68. The clinical relevance of this is unknown, but the BML progression in the exercise group is in line with the previously reported natural history of BML increase over time in patients with knee OA[20]. It is important to note that the compliance with the exercise program was poor; leaving only a few of the patients actually receiving an adequate exercise stimulus that can be expected to have any structural effects. Therefore these results do not prove exercise *per se* as being structurally detrimental, because we were unable to assess the actual effects of exercise. Possible explanation could be natural course of progression, regression to the mean, or that the exercise group gained more weight during the 1 year follow-up than the other groups, however so did the no attention group. Repeating the statistical analysis of the medial tibiofemoral BML count adjusting for the weight regain did not change the results (data not shown). However, the sensitivity analysis did not confirm the findings (Appendix 1), which downgrade our confidence in the finding.

From the present study, it becomes apparent that it is important to ensure proper motivation to exercise and to optimize contextual factors – particularly in an obese population among whom commencing an exercise program may seem extremely challenging and strenuous. Exercise training programs have been shown to be effective in reducing symptoms and disability in knee OA[21], and exercise is associated with a number of positive 'side effects' beneficial for the individual – provided sufficient compliance with the programs. Only a few studies have investigated exercise in obese patients with knee OA[7,22], and these studies show similar effects on symptoms and disability as studies in non-obese populations with significantly better attendance rates than the present study. One explanation for our low exercise attendance may lie in the recruitment process in which motivation for a dietary-induced weight loss was explicitly a part of the inclusion criteria, whereas motivation for exercise was not emphasized. The few studies of exercise in obese patients with knee OA[7,22] have not reported any effects on structural disease parameters to compare with. In contrast, compliance to our dietary maintenance program was high (average 62%) in which the weight loss was maintained over the 12 months maintenance period. Yet, the dietary maintenance program was not associated with any beneficial structure modifying effects different from the other maintenance groups.

It is possible that the semi quantitative BLOKS scoring of structural changes in OA knee is not sensitive to changes within the time frame of this study. The BLOKS is standardized and well recognized[16] to assess longitudinal structural changes. However, it is possible that group differences could be detected in the present study by application of more sensitive methods, such as within-grade semi quantitative scoring[23] or longer follow-up time. Also, we only assessed BMLs in the tibiofemoral regions, and it is a possible limitation that BMLs in the Trochlea region and patellar were not assessed. A potential caveat in the interpretation of these results also lies in the research design where all patients were

given an initial weight loss intervention at the beginning of the trial – independently of subsequent group allocation for maintenance. The effects of this initial weight loss may carryover for the remaining 52 weeks. Further, the CAROT study was powered to detect symptomatic change – not the present MRI variables. The variation and sensitivity to change of the BLOKS variables used in the present study was unknown beforehand, and it is likely that the study was underpowered. The likelihood of a false positive finding (BML counts in exercise group) is not negligible due to the multiple statistical tests.

In conclusion, this study showed no differences between obese patients with knee OA who after a 16 weeks weight loss participated in either dietary, exercise or no-attention weight loss maintenance programs for 1 year, in changes in semi quantitative assessment of structural damage of the knee. One exception was a potential slightly increased number of medial tibiofemoral BML in the exercise-based maintenance group consistent with the natural history of increasing BML over time in knee OA. These findings needs to be confirmed and should be interpreted with caution for exercise compliance, MRI methodology and follow-up time. The majority of the structural variables assessed showed no or limited progression, possibly indicating a halt in the disease progression as a consequence of weight loss.

Author contributions

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

Study conception and design: Henriksen, Christensen, Lohmander, Bliddal.

Data acquisition: Gudbergsen, Boesen.

Data analysis and interpretation: Henriksen, Christensen, Hunter, Gudbergsen, Boesen, Lohmander, Bliddal.

Role of the funding sources

Funding sources had no role in the design, collection, and interpretation of the data or the decision to submit for publication.

Declaration of interests

Marius Henriksen, Henning Bliddal, and Robin Christensen received travel grants to attend scientific meetings from the Cambridge Manufacturing Company. David Hunter, Henrik Gudbergsen, Mikael Boesen, and L Stefan Lohmander declare no conflict of interest in relation the present study.

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Appendix 1

Changes in imaging outcomes from week 0 at week 68 analyzed with a mixed model with group (control, diet and exercise) and week (week 16 and 68) as fixed effects, participant contributing to random effects, and adjusted for the value at week 0. The analyses were on the 'as observed' population, i.e., no imputations for missing data or drop outs.

Variable Change from week 0 at week 68 in:	Mixed model						
	Control	Diet	Exercise	Control vs Diet	Control vs Exercise	Diet vs Exercise	*P*-value for group
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Cartilage loss							
Medial tibiofemoral max size score	−0.10 (−0.19:−0.01)	−0.15 (−0.24:−0.07)	−0.09 (−0.18:0.01)	0.06 (−0.06:0.17)	−0.01 (−0.13:0.10)	−0.07 (−0.18:0.04)	0.44
Medial tibiofemoral number of losses	−0.08 (−0.17:0.01)	−0.13 (−0.22:−0.04)	−0.13 (−0.22:−0.04)	0.05 (−0.06:0.16)	0.05 (−0.06:0.16)	0.00 (−0.11:0.11)	0.62
Lateral tibiofemoral max size score	−0.02 (−0.11:0.07)	−0.06 (−0.15:0.03)	−0.02 (−0.12:0.07)	0.03 (−0.08:0.15)	0.00 (−0.110.12)	−0.03 (−0.15:0.08)	0.80
Lateral tibiofemoral number of losses	−0.11 (−0.20:−0.02)	−0.01 (−0.10:0.08)	−0.04 (−0.13:0.05)	−0.10 (−0.21:0.01)	−0.07 (−0.18:0.05)	0.03 (−0.08:0.14)	0.21
BMLs							
Medial tibiofemoral max size score	−0.13 (−0.24:−0.02)	−0.06 (−0.17:0.05)	−0.01 (−0.13:0.10)	−0.07 (−0.21:0.07)	−0.12 (−0.26:0.02)	−0.05 (−0.19:0.10)	0.26
Medial tibiofemoral number of BMLs	−0.06 (−0.18:0.06)	−0.04 (−0.16:0.07)	0.05 (−0.07:0.18)	−0.02 (−0.17:0.13)	−0.12 (−0.27:0.04)	−0.10 (−0.25:0.06)	0.28
Lateral tibiofemoral Max size score	−0.09 (−0.19:0.01)	−0.01 (−0.11:0.09)	−0.09 (−0.19:0.01)	−0.08 (−0.20:0.04)	0.00 (−0.12:0.13)	0.08 (−0.04:0.21)	0.34
Lateral tibiofemoral number of BMLs	−0.02 (−0.11:0.07)	0.02 (−0.07:0.11)	−0.03 (−0.122:0.06)	−0.04 (−0.15:0.07)	0.02 (−0.10:0.13)	0.05 (−0.06:0.17)	0.64
Effusion score							
Effusion	0.16 (0.03:0.29)	−0.11 (−0.23:0.02)	0.07 (−0.21:0.06)	0.26 (0.10:0.43)	0.23 (0.06:0.40)	−0.03 (−0.20:0.14)	0.004
Synovial thickening							
Synovitis score	0.00 (−0.11:0.12)	0.11 (−0.01:0.22)	0.01 (−0.11:0.13)	−0.11 (−0.25:0.04)	−0.01 (−0.16:0.14)	0.10 (−0.05:0.25)	0.30
Number of Synovitis Sites	−0.06 (−0.28:0.15)	−0.01 (−0.22:0.20)	0.10 (−0.12:0.31)	−0.06 (−0.32:0.21)	−0.16 (−0.43:0.10)	−0.10 (−0.37:0.16)	0.48

95% CI: 95% Confidence Interval.

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