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The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes

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SUMMARY

Purpose: Report the radiographic and magnetic resonance imaging (MRI) structural outcomes of an 18-month study of diet-induced weight loss, with or without exercise, compared to exercise alone in older, overweight and obese adults with symptomatic knee osteoarthritis (OA).
Methods: Prospective, single-blind, randomized controlled trial that enrolled 454 overweight and obese (body mass index, BMI = 27–41 kg m^{-2}) older (age ≥ 55 yrs) adults with knee pain and radiographic evidence of femorotibial OA. Participants were randomized to one of three 18-month interventions: diet-induced weight loss only (D); diet-induced weight loss plus exercise (D + E); or exercise-only control (E). X-rays ($N = 325$) and MRIs ($N = 105$) were acquired at baseline and 18 months follow-up. X-ray and MRI (cartilage thickness and semi-quantitative (SQ)) results were analyzed to compare change between groups at 18-month follow-up using analysis of covariance (ANCOVA) adjusted for baseline values, baseline BMI, and gender.
Results: Mean baseline descriptive characteristics of the cohort included: age, 65.6 yrs; BMI 33.6 kg m^{-2}; 72% female; 81% white. There was no significant difference between groups in joint space width (JSW) loss; D −0.07 (SE 0.22) mm, D + E −0.27 (SE 0.22) mm and E −0.16 (SE 0.24) mm ($P = 0.79$). There was also no significant difference in MRI cartilage loss between groups; D −0.10(0.05) mm, D + E −0.13(0.04) mm and E −0.05(0.04) mm ($P = 0.42$).
Conclusion: Despite the potent effects of weight loss in this study on symptoms as well as mechanistic outcomes (such as joint compressive force and markers of inflammation), there was no statistically significant difference between the three active interventions on the rate of structural progression either on X-ray or MRI over 18-months.

Introduction

Obesity is the single most important risk factor for development of severe osteoarthritis (OA) of the knee[1–3]. Because obesity is both a risk factor for OA and has been increasing in prevalence over the past four decades[4,5], it is projected that substantially more

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individuals will be affected by knee OA in the future[6]. In addition to being a leading risk factor for knee OA incidence, obesity also contributes directly towards the genesis of symptoms[7].

Weight reduction has demonstrated the ability to decrease the pain and disability associated with knee OA[8,9]. Recent meta-analyses conclude that a >5% reduction in weight will result in moderate-to-large improvements in self-reported disability[10]. Similarly, exercise also leads to improvement in self reported symptoms[11] and in trials does not appear to harm structure[8] despite recent observational evidence that it may[12]. Mechanistically, weight reduction may lead to reductions in joint loads and inflammatory cytokines[9], and this may be helpful in preserving joint integrity; or at least not leading to more rapid decline as a consequence of increased walking speed and knee joint loading[13]. However, despite solid clinical evidence supporting the efficacy of weight loss for symptom improvement, there is limited evidence from existing studies on the effects of weight loss on articular tissue structures; and to date few of these studies have actually been on persons with definite OA[14,15]. Ding *et al.*[16] demonstrated that excess body fat was associated with greater tibial cartilage loss, and that a greater percentage of lean mass was protective. This study raises important concerns that in the absence of preserving lean mass, weight loss may not be beneficial for preserving joint structures. Further reinforcing the potential concerns of weight loss, large weight loss in morbidly obese persons initiates a faster gait which would tend to increase knee loads or at least partially attenuate the reduction in knee loads[17]. An observational trial of massive weight loss through gastric surgery demonstrated marked improvements in cartilage synthesis and reductions in cartilage degradation biomarkers[14]. In an observational cohort of persons undertaking either non-surgical or surgical intervention for weight loss, weight reduction was associated with improvements in cartilage composition (proteoglycan content) and tissue loss (reduced cartilage thinning) over 12 months[18]. More recently in a randomized trial in obese persons with knee OA, investigators did not find differences between exercise, diet and no attention groups for cartilage loss, synovitis or effusion on magnetic resonance imaging (MRI)[15]. There was however a potentially increased number of bone marrow lesions (BMLs) in the exercise group.

Given that weight loss reduces pain[9], improves function, and reduces knee joint loads, we hypothesized that weight loss would also favorably alter the rate of structural progression in persons with knee OA. Since there is a lack of well controlled data on the effects of weight loss on joint structure, we undertook additional analyses in an existing dataset from subjects who participated in the recently reported Intensive Diet and Exercise for Arthritis (IDEA) trial[9]. The intent of the present investigation was to examine the radiographic and MRI structural outcomes from IDEA; an 18-month study of diet-induced weight loss, with or without exercise, compared to exercise alone in older, overweight and obese adults with symptomatic knee OA.

Materials and methods

Study design

IDEA was a single-blind, single-center, 18-month, randomized controlled trial[9,19]. Participants were randomized into one of the three groups: diet-induced weight loss only (D); diet-induced weight loss plus exercise (D + E); or exercise-only control (E). We designated E as the comparison group because our previous work[20] indicated that aerobic walking or resistance training should be part of the standard-of-care for knee OA patients. The trial design, rationale and primary outcomes are reported elsewhere[9,19].

Study oversight

IDEA was conducted from July 2006 to June 2011 at Wake Forest University and the Wake Forest School of Medicine, Winston-Salem, NC, USA. It was HIPAA (*Health Insurance Portability and Accountability Act*) compliant and approved by the Human Subjects Committee of Wake Forest Health Sciences. Informed consent was obtained from all study participants.

Study sample

The IDEA study consisted of 454 ambulatory (a subsample of 325 persons had repeat X-rays and 105 had repeat MRIs for this analysis), community-dwelling persons age $\geq$ 55 years with: (1) Kellgren–Lawrence (KL) grade 2 or 3 (mild or moderate) radiographic femorotibial OA or femorotibial plus patellofemoral OA of one or both knees[21], (2) pain on most days due to knee OA, (3) 27 $\leq$ body mass index (BMI) $\leq$ 41 kg m^{-2}, and (4) a sedentary lifestyle (<30 min wk^{-1} of formal exercise past 6 months). Participants were recruited from the community over a 37-month period (November 2006 to December 2009). A stratified-block randomization method was used to assign all eligible persons to one of the intervention arms, stratified by BMI and gender.

Interventions

a. *Intensive weight loss intervention*. Both the D and D + E groups received the same dietary intervention. The weight loss goal was a mean group loss of at least 10% of baseline weight. The dietary plan was based on partial meal replacements, including up to two meal-replacement shakes per day (Lean Shake®, provided by General Nutrition Centers, Inc., Pittsburgh, PA). For the third meal, participants followed a weekly menu plan and recipes that were 500–750 kcals, low in fat and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits.

The initial diet plan provided an energy-intake deficit of 800–1000 kcals/day as predicted by energy expenditure (estimated resting metabolism × 1.2 activity factor) with a minimum of 1100 kcals for women and 1200 kcals for men. The calorie distribution goal was 15–20% from protein, <30% from fat, and 45–60% from carbohydrates, consistent with the Dietary Reference Intakes for Energy and Macronutrients[22] and successful weight-loss programs[23]. As follow-up progressed, fewer meal replacements were consumed. Body weight was monitored weekly or biweekly during nutrition education and behavioral sessions: these included from months 1–6, one individual session and three group sessions per month, and from months 7–18, biweekly group sessions and an individual appointment every 2 months.

b. *Exercise*. The exercise intervention was identical for E and D + E. Sixty-minute sessions were conducted 3 days/week for 18 months. During the first 6 months, participation was center-based. After 6-month follow-up (FU6) testing and a 2-week transition phase, participants could remain in the facility program, opt for a home-based program, or combine the two. The 3 days/week program consisted of aerobic walking (15 min), strength training (20 min), a second aerobic phase (15 min), and cool-down (10 min).

c. *Intensive weight loss plus exercise*. Participants randomized to the D + E intervention received both interventions described above.

Measurements and procedures

X-ray acquisition and measurement

Bilateral, posteroanterior, weight-bearing, semiflexed, knee X-rays were acquired at baseline and repeated at 18-month follow-up (FU18) to assess changes in quantitative measures of radiographic joint space width (JSW). All radiographs with paired acquisitions (baseline and FU18) are included in this analysis ($n = 325$). Participants' knees were flexed at 15° using a *SynaFlexer*positioning device (Synarc, San Francisco, CA), and the beam centered on the joint space. The X-ray beam was directed perpendicular to the cassette to pass between the femoral condyles and the patella surfaces. The exact angle of the beam depends upon the degree of flexion of the knee and the participant's individual body habitus and was adjusted between 0 and 15° under fluoroscopy. The focus-to-film distance was held constant throughout the study. This method of acquisition standardizes positioning to optimize reproducibility[24].

The minimum JSW (mJSW) was measured in digitized radiographic images using an automated software application[25–27]. Further, fixed distances were measured between the external and internal border of the medial femorotibial compartment (MFTC). The software automatically determined the tangent to the femoral condyles as the *x*-axis of the coordinate system; the medial and lateral borders were marked manually, perpendicular to this *x*-axis and tangential to the greatest prominence of the medial and the lateral femoral epicondyles. After normalization of the range to 0 (medial epicondyle) and 1 (lateral epicondyle), fixed locations were defined on the *x*-axis to obtain fixed-location measures of JSW, specifically JSW(x) between $x = 0.15$ (external) and $x = 0.30$ (internal) for MFTC[27] (Fig. 1). Based upon superior responsiveness from prior analyses we selected the JSW$x = 0.225$ as the preferred location for the fixed coordinate JSW measure[25].

Because even the above standardized positioning techniques still have potential for malpositioning, positioning accuracy was measured by examining the distance between the anterior and posterior tibial rim. We defined malpositioning as a change in this distance of >2 mm between the baseline and FU18 radiograph.

Full-length X-ray

A full-length A–P radiograph was obtained using the Agfa ADC system (Quantum Q-Rad based imaging) approach. Participants were positioned using the methods of Sharma *et al.*[28] such that both lower extremities were imaged simultaneously. Both tibial tubercles were faced directly forward and the participants' feet were positioned 15 cm apart. Participants stood upright with weight equally distributed to both feet. Alignment was defined as the measure of the angle formed by the intersection of the lines connecting the centers of the femoral head and the intercondylar notch and the centers of the ankle talus and tibial spines. A varus knee was an angle >2° in the varus direction (or a bowlegged appearance), and valgus was an angle < −2° in the valgus direction (or a knock-kneed appearance). A neutral knee was defined as an angle between −2 and 2° in the varus direction[29]. All of the measurements were made by a single physician and using the NIH ImageJ program. Interrater reliability was 0.994.

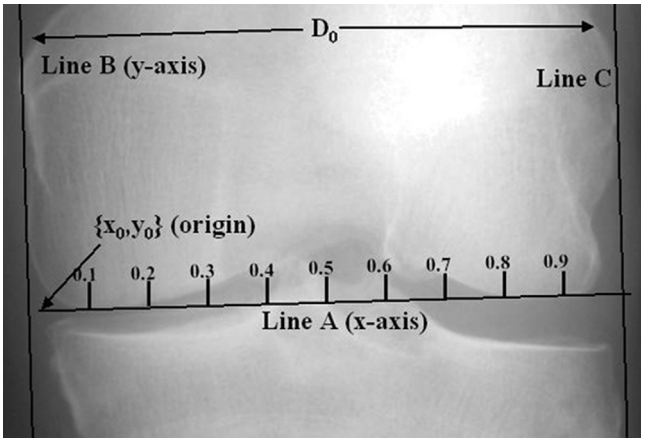

Fig. 1. Landmarks and definition of coordinate system.

MRI acquisition

MRI of the most symptomatic knee was performed on a subsample of study participants with 105 (of 454 participants) having both baseline and follow-up MRI scans acquired. Sample size per group is as follows: (D) $n = 33$, (D + E) $n = 36$, (E) $n = 36$. This subsample was randomly selected during the latter recruitment waves of the study. MRIs were obtained with a 1.5 T (General Electric Healthcare, Milwaukee, WI) scanner using an extremity coil. The following MRI sequences were obtained: (1) Double oblique coronal three-dimensional spoiled gradient-echo (SPGR) with fat suppression; (2) Axial T1-weighted spin-echo (SE); (3) Double oblique coronal T1-weighted SE; (4) Sagittal T1-weighted SE; (5) Sagittal T2-weighted fast spin-echo (FSE) with fat suppression; (6) Double oblique coronal T2-weighted FSE with fat suppression.

Semi-quantitative (SQ) scoring of joint tissue structures. MRIs were read paired and unblinded to timepoint by a musculoskeletal radiologist with 14-year experience in semiquantitative MRI assessment and using the BLOKS method[30]. The following MRI features were scored: (1) BML size; (2) BML Count; (3) Synovitis; and (4) Effusion.

BML size was assessed over nine anatomical sites/subregions at baseline and FU18. Outcomes for each subregion were classified using the semiquantitative scale 0 = "none", 1 = "<10%", 2 = "10–25%", 3 = ">25%", where the % describes the proportion of the subregion affected BMLs. We used a maximum scoring approach that captures the maximum BML score (0–3) recorded among all the subregions. To model the number of BMLs, we simply counted the number of sites in which BML size exceeded 0. Thus, this variable could take values of 0–9.

Hoffa-Synovitis was assessed at baseline and FU18. The synovitis scores were quantified as 0 = "none", 1 = "mild", 2 = "moderate", 3 = "severe". Effusion was captured at baseline and FU18 by a single variable, which takes the values 0 = "normal, no effusion", 1 = "small, ≤33% of maximum potential distention", 2 = "medium, 2 = 33–66% of maximum potential distention", and 3 = "large, 3=>66% of maximum potential distention".

Test–retest reliability of the above readings was performed on 10% of scans ($N = 22$) 1 week apart. Reliability for BML size, 0.72, synovitis 0.66 and effusion 0.61.

Quantitative Cartilage Morphometry. Measurements focused on the MFTC, because (1) it is the most common site of knee OA[28]; (2) changes there are strongly related to BMLs and varus knee alignment[28,31]; and (3) we have additional, well-established measures of joint integrity including JSW and BLOKS[30]. The medial tibial (MT) and central weight-bearing medial femoral (cMF) cartilages were segmented by manual tracing of the total

area of the subchondral bone (tAB) and the area of the cartilaginous joint surface (AC) on a slice-by-slice basis[32,33]. Segmentation of tAB included all areas of cartilage-covered and denuded subchondral bone, but not osteophytes[34,35]. Likewise, AC segmentation excluded osteophyte cartilage. MT was segmented throughout all slices that displayed cartilage; analysis of the femoral condyle was confined to the portion of the condyles that are displayed without relevant partial volume effect in coronal images (cMF)[36]. All segmented data were quality controlled (QC'd) by one expert, by checking all segmented slices of each data set, and corrections of the segmentation were performed if necessary.

The same software used for segmentation and QC readings was used to calculate the size of the tAB, the tAB covered with cartilage (cAB), the denuded bone area (dAB), the area of the cartilage surface (AC), the mean cartilage thickness across the entire tAB (ThCtAB), counting all denuded areas as 0 mm cartilage thickness, the mean cartilage thickness across cAB (ThCcAB), and maximal cartilage thickness [Fig. 2(a)][32]. In addition, subregional measurements were performed by analyzing ThCtAB in central, internal, external, anterior and posterior subregions of MT, and central internal and external subregions of cMF, using a method developed by Wirth *et al.*[37] [Fig. 2(b)].

Statistical analysis

We used a per-protocol analysis to compare change between groups at FU18 as some participants did not have paired image acquisitions at baseline and 18 months. X-ray and continuous MRI outcomes were analyzed using analysis of covariance (ANCOVA) adjusted for baseline values, BMI, and gender. X-ray was also adjusted for inter-rim distance. Ordinal logistic regression was used for the ordinal SQ analyses, adjusting for baseline values, BMI and gender.

For the semi quantitative analysis we used a maximum scoring approach that captures the maximum BML score (0–3) recorded among all the subregions. To model the number of BMLs we fitted a Poisson regression model to the number of subregions with observed BMLs for each individual to determine a randomization group effect, adjusting for baseline BMI, gender, and the number of BMLs reported at baseline. Using maximum synovitis scores over all anatomical locations similar to previous outcomes we performed an ordinal logistic regression for the maximum synovitis score by randomization group, adjusting for baseline BMI, gender, and baseline maximal synovitis score. For effusion due to the small count of participants with "normal" effusion scores, we collapsed "normal" and "small" into a single category. We then performed an ordinal logistic regression for a randomization group effect, adjusting for gender, baseline BMI, and baseline effusion. All analyses were performed assuming a Type I error rate of 0.05 using SAS v9.2 (SAS Institute, Cary, NC).

Results

Demographic characteristics (Table I)

A total of 454 persons with a mean age 66 years and mean BMI of 33.6 kg m^{-2} were participants in the trial. The three groups were well matched for demographic characteristics including age, gender and BMI. Similarly there were no major differences in KL grade or mJSW between groups. The MRI and X-ray subsamples were broadly similar to the overall group for all characteristics (see Table I).

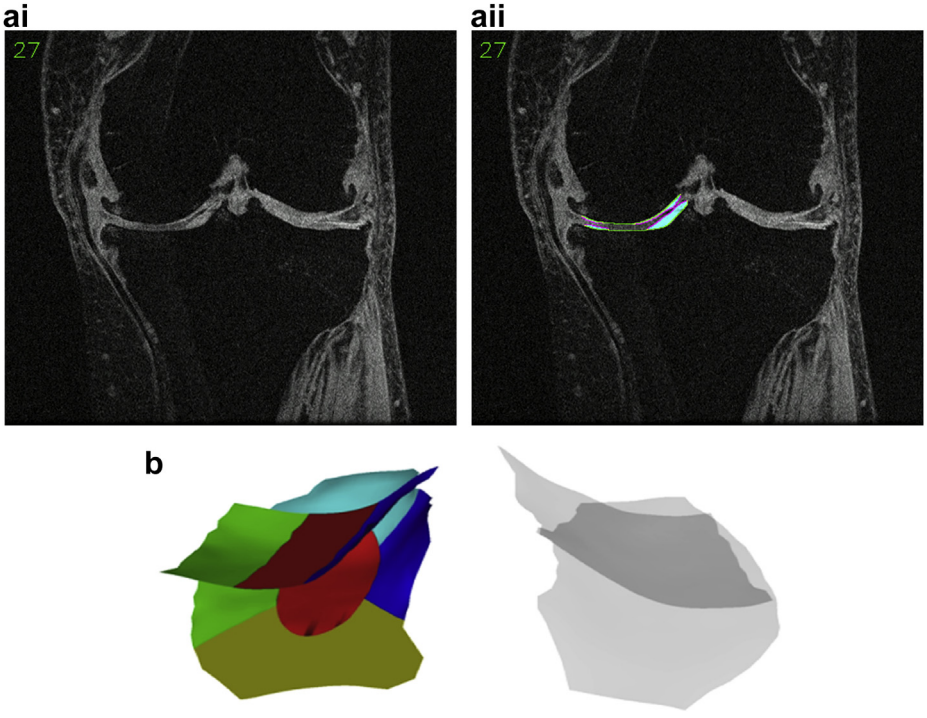

Fig. 2. (a) Sagittal magnetic resonance images (MRI) acquired using SPGR sequence. Both images depict the same slice of the MFTC. The image on the right shows the segmentation of the cartilage (magenta = segmentation of the cartilage surface; green = segmentation of the total area of subchondral bone = tAB) and the filling between the two surfaces in turquoise. The image of the MFTC shows an area of denuded subchondral bone (dAB) in the weight-bearing aspect of the medial femoral condyle (cMF) and medial tibia (MT). (b) Visual display of the medial femorotibial subregions. Posterior view of the femorotibial compartment of the knee (middle), inferior view of the weight-bearing femur (top), and superior view of the tibia (bottom). Color codes for both the femoral and tibial plates: red = central subregion, green = external subregion, blue = internal subregion, yellow = posterior subregion, turqoise = anterior subregion.

Table I
Mean (SD) demographic and clinical characteristics of the study participants at baseline

	Overall ($N = 454$)	Diet only ($N = 152$)	Diet and exercise ($N = 152$)	Exercise only ($N = 150$)	MRI subsample ($n = 98$)*	X-ray subsample ($N = 325$)
Gender (female *N* (%))	325 (72)	108 (71)	109 (72)	108 (72)	72 (73)	240 (74)
Age (mean, SD) yrs	66 (6)	66 (6)	65 (6)	66 (6)	65 (6)	66 (6)
% Non-white	19	16	20	20	16	16
BMI (mean, SD) kg m^{-2}	33.6 (3.7)	33.8 (3.6)	33.5 (3.7)	33.5 (3.7)	33.7 (3.8)	33.4 (3.8)
Kellgren–Lawrence grade of index knee (% grade 2)	48.7%	48.0%	47.4%	50.7%	42.9%	48.3%
mJSW at baseline (mm)	3.61 (1.92)	3.73 (2.09)	3.44 (1.86)	3.67 (1.80)	3.30 (1.77)	3.61 (1.92)
Mechanical alignment (degrees)†	0.30 (4.39)	0.99 (4.82)	−0.28 (4.52)	0.20 (3.74)	−0.21 (3.97)	0.33 (4.40)
WOMAC function (range 0–68)	24.2 (10.9)	24.8 (10.4)	24.6 (11.7)	23.1 (10.3)	22.0 (9.9)	23.5 (10.9)

mJSW = minimum joint space width.
* 105 persons had baseline and 18 months MRIs of whom 98 had adequate quality images for the purposes of analysis.
† Negative numbers indicate valgus alignment.

X-ray (Table II)

The mean rate of change in mJSW in the three groups ranged between −0.18 and −0.28 mm over the 18 months period, with all of the groups demonstrating progression, and with no evidence of a difference between groups.

SQ MRI (Table III)

The odds ratios for BML size indicated no differences between groups. D and D + E tended to have lower maximum BML scores at FU18 than E. For BML lesion count, we observed no significant effect ($P = 0.44$), and the model-adjusted means appeared to demonstrate a slightly higher number of lesions in the E group, especially compared to D. For the maximal synovitis score analysis, we observed a non-significant *P* value ($P = 0.60$) with relatively small averages for all groups using an ordinal logistic regression model. For this model, we collapsed categories 2 and 3 at 18 months, given that only two participants had "severe" synovitis at follow-up. For effusion the *P* value for the comparison between groups was not significant ($P = 0.72$).

Quantitative cartilage morphometry (Table IV)

The quantitative cartilage volume, cartilage thickness and percent denuded area results were broadly consistent across the different regions of the knee with no significant difference at 18-months between groups. The D + E showed a trend for greater loss.

Effect of malalignment on rate of X-ray progression

One of the challenges in assessing structural modification in OA is that a large proportion of participants often do not progress. Selecting those with varus malalignment may identify a subgroup

Table II
X-ray JSW change from baseline to 18 months for mJSW and JSWx = 0.225

	Diet only	**Diet & exercise**	**Exercise only**	*P* value for between group difference
n	129	136	135	
Baseline mJSW mm(SD)	3.73 (2.09)	3.45 (1.86)	3.67 (1.80)	
Baseline JSW225 mm (SD)	4.64 (2.03)	4.30 (1.88)	4.65 (1.87)	
Change mJSW (95% CI)*	−0.28 (−0.54, −0.03)	−0.27 (−0.53, −0.02)	−0.18 (−0.43, 0.07)	0.81
Change JSW225 (95% CI)*	−0.35 (−0.60, −0.09)	−0.23 (−0.48, 0.03)	−0.16 (−0.41, 0.09)	0.56
Adj change mJSW (95% CI)†	−0.30 (−0.54, −0.06)	−0.24 (−0.47, −0.00)	−0.16 (−0.40, 0.07)	0.71
Adj change JSW225 (95% CI)†	−0.39 (−0.63, −0.16)	−0.21 (−0.44, 0.01)	−0.15 (−0.38, 0.07)	0.29
Change weight kg (95% CI)	−8.9 (−10.3, −7.5)	−9.7 (−11.1, −8.3)	−1.7 (−3.1, −0.2)	<0.01
% Change weight (95% CI)	−9.5 (−10.9, −8.0)	−10.5 (−12.0, −9.0)	−1.9 (−3.3, −0.4)	<0.01

* Adjusted for baseline BMI, gender and baseline value of outcome.
† Adjusted for baseline BMI, gender and baseline value of outcome and rim quality control measure.

Table III
SQ MRI measures change from baseline to 18 months

		Diet only	Diet & exercise	Exercise only
	No. of observations	33	36	36
Maximal BML size	Baseline frequency >0 (%)	29 (88)	33 (92)	32 (89)
	OR (95% CI)*	0.44 (0.15–1.23)	0.70 (0.25–1.95)	Referent
BML count	Baseline mean (SD)	2.27 (1.51)	1.53 (1.61)	1.51 (1.71)
	Estimate (95% CI)*	−0.20 (−0.51 to 0.11)	−0.11 (−0.40 to 0.18)	Referent
Maximum synovitis score	Baseline frequency >0 (%)	18 (55)	20 (56)	17 (47)
	OR (95% CI)*	1.78 (0.53–5.96)	1.10 (0.33–3.70)	Referent
Effusion score	Baseline frequency > Normal (%)	32 (97)	59 (98)	35 (97)
	OR (95% CI)*	1.18 (0.47–2.97)	1.46 (0.59–3.61)	Referent
Weight	Change from BL (kg) (95% CI)	−9.8 (−12.7, −6.9)	−10.5 (−14.0, −7.0)	−1.0 (−2.4, 0.3)
	Change from BL (%) (95% CI)	−10.1 (−13.0, −7.1)	−11.2 (−15.1, −7.4)	−1.2 (−2.7, 0.2)

* Adjusted for baseline BMI, gender and baseline value of outcome.

Table IV
Quantitative cartilage MRI measures

Description	Diet only		Diet & exercise		Exercise only		*P* value
	18 months	Change	18 months	Change	18 months	Change	
	Mean, SE (95% CI)	Mean, SE (%)	Mean, SE (95% CI)	Mean, SE (%)	Mean, SE (95% CI)	Mean, SE (%)	
Volume of cartilage (mm^3) over area of aggregate MT + cMF	2583.6, 38.9 (2506.4, 2660.9)	−73.1, 38.9 (−2.8)	2566.9, 37.6 (2492.2, 2641.5)	−89.9, 37.6 (−3.4)	2624.4, 36.9 (2551.2, 2697.6)	−32.3, 36.9 (−1.2)	0.49
Volume of cartilage (mm^3)over area of Media tibia (MT)	1740.9, 25.1 (1691.1, 1790.7)	−23.7, 25.1 (−1.4)	1727.3, 24.3 (1678.9, 1775.5)	−37.4, 24.3 (−2.1)	1757.6, 23.6 (1710.7, 1804.4)	−7.1, 23.6 (−0.4)	0.63
Volume of cartilage (mm^3)of medial fem condyle (cMF)	839.7, 17.5 (804.9, 874.4)	−48.9, 17.5 (−5.5)	837.3, 16.9 (803.6, 870.9)	−51.3, 16.9 (−5.8)	865.5, 16.7 (832.3, 898.7)	−23.2, 16.7 (−2.6)	0.39
Cart thickness (mm) over area of aggregate MT + cMF	2.80, 0.05 (2.71, 2.89)	−0.10, 0.05 (−3.35)	2.77, 0.04 (2.68, 2.86)	−0.13, 0.04 (−4.34)	2.85, 0.04 (2.76, 2.93)	−0.05, 0.04 (−1.66)	0.42
Cart thickness (mm) over area of MT	1.45, 0.02 (1.40, 1.49)	−0.02, 0.02 (−1.56)	1.43, 0.02 (1.39, 1.47)	−0.04, 0.02 (−2.65)	1.46, 0.02 (1.42, 1.50)	−0.01, 0.02 (−0.58)	0.55
Cart thickness (mm) over area of medial fem condyle (cMF)	1.35, 0.03 (1.30, 1.41)	−0.07, 0.03 (−5.13)	1.34, 0.03 (1.29, 1.40)	−0.08, 0.03 (−5.95)	1.39, 0.03 (1.33, 1.44)	−0.04, 0.03 (−2.66)	0.43
Cart thickness (mm) over area of central medial tibia	1.86, 0.04 (1.79, 1.93)	−0.06, 0.04 (−2.89)	1.84, 0.04 (1.77, 1.91)	−0.08, 0.04 (−4.10)	1.89, 0.03 (1.82, 1.95)	−0.03, 0.03 (−1.59)	0.59
Cart thickness (mm) over area of central weight-bearing medial femur	1.47, 0.04 (1.39, 1.55)	−0.10, 0.04 (−6.08)	1.43, 0.04 (1.35, 1.51)	−0.14, 0.04 (−8.66)	1.51, 0.04 (1.43, 1.58)	−0.06, 0.04 (−3.91)	0.37
Cart thickness (mm) over area of aggregate cMT & ccMF	3.33, 0.07 (3.20, 3.46)	−0.15, 0.07 (−4.35)	3.26, 0.07 (3.13, 3.40)	−0.22, 0.07 (−6.23)	3.39, 0.07 (3.26, 3.52)	−0.09, 0.07 (−2.67)	0.37
Avg % MT denuded area	7.31, 0.88 (5.56, 9.05)	1.48, 0.88 (25.34)	2566.9, 37.6 (2492.2, 2641.5)	−89.9, 37.6 (−3.4)	7.10, 0.85 (5.41, 8.80)	1.27, 0.85 (21.81)	0.77
Avg % cMF denuded area	12.38, 1.56 (9.28, 15.48)	2.42, 1.56 (24.36)	1727.3, 24.3 (1678.9, 1775.5)	−37.4, 24.3 (−2.1)	13.11, 1.55 (10.04, 16.18)	3.16, 1.55 (31.70)	0.82
Bone area (cm^2) over area of aggregate MT + cMF	2.87, 0.05 (2.78, 2.96)	−0.10, 0.05 (−3.37)	837.3, 16.9 (803.6, 870.9)	−51.3, 16.9 (−5.8)	2.93, 0.04 (2.84, 3.02)	−0.04, 0.04 (−1.49)	0.44
Bone area (cm^2) over area of MT	1.46, 0.02 (1.42, 1.50)	−0.02, 0.02 (−1.51)	2.77, 0.04 (2.68, 2.86)	−0.13, 0.04 (−4.34)	1.47, 0.02 (1.43, 1.51)	−0.01, 0.02 (−0.50)	0.63
Bone area (cm^2) over area of cMF	1.41, 0.03 (1.35, 1.47)	−0.08, 0.03 (−5.17)	1.43, 0.02 (1.39, 1.47)	−0.04, 0.02 (−2.65)	1.46, 0.03 (1.40, 1.51)	−0.03, 0.03 (−2.32)	0.38
Weight, SD (kg)	87.8, 14.3 (82.4, 93.1)	−8.5, 7.6 (−11.3, −5.7)	80.4, 13.8 (75.4, 85.4)	−10.6, 10.4 (−14.3, −6.8)	90.7, 13.3 (86.0, 95.5)	−1.2, 3.7 (−2.5, 0.1)	<0.01
Weight, SD (%)		−8.6, 7.7 (−11.6, −5.7)		−11.4, 11.3 (−15.5, −7.3)		−1.3, 4.1 (−2.8, 0.1)	<0.01

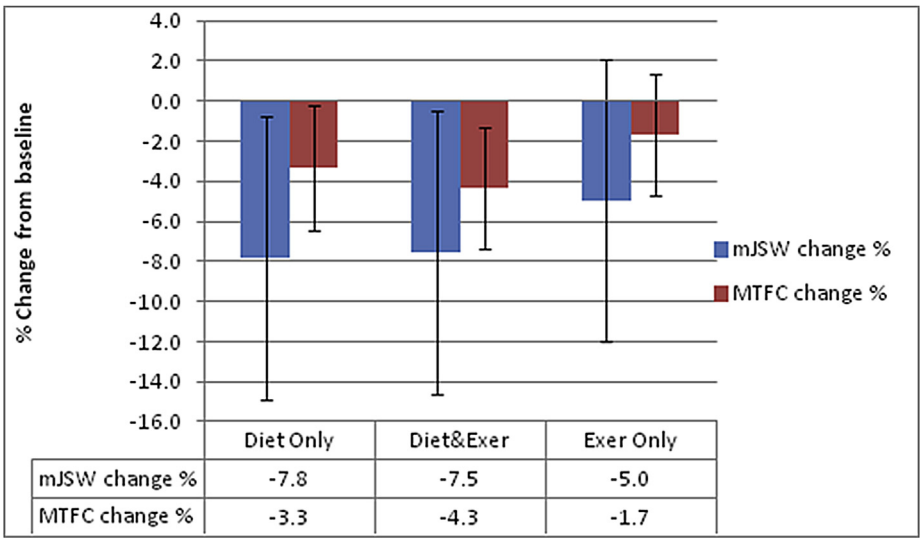

Fig. 3. Percent changes from baseline (95% CI) for mJSW and MTFC thickness.

that is more likely to progress. The alignment measures were well matched between the groups (Table I) with the D group ranging from −11 to 15°, D + E from −13 to 9.6°, and E from −11.3 to 7.3°. The cohort was divided into three broad categories according to their alignment; <−2 = valgus, −2 to +2 = neutral and >2 = varus. Bearing in mind that JSW is a measure in the medial compartment and most of the progression in that compartment will occur in those that are varus aligned, the analysis focused on that subgroup of 113 persons with a varus alignment of >2° {range 2.03–15.41}. With the E group as reference, the D + E estimate was 0.15 (SE 0.17) and D −0.03 (0.17). For the MRI analyses there was no difference found between groups but it is important to recognize that the subsample was too small to draw anything meaningful from these results. Figure 3 compares the main results for change in mJSW and MFTC (Fig. 3).

Discussion

The results of this trial suggest that intensive diet-induced weight loss that averaged 10% of body weight over an 18-month study period, whether through a combination of diet and exercise or diet alone, does not provide a benefit in terms of knee joint structure when compared to exercise alone in individuals with knee OA, despite demonstrating improvements in pain and function[9]. It is important to note, however, that the rates of change (progression) are consistent with prior natural history studies and as such these interventions are unlikely to be doing harm[38,39].

In contrast to our results, previous observational/non-randomized studies have raised the possibility that weight loss could be structure modifying[14,18]. An Australian observational cohort study included 78 persons recruited from both non-surgical and surgical weight loss programs[18]. They found that weight loss was associated with improvements in both the quality (improved dGEMRIC index) and quantity (reduced cartilage thickness losses) of medial articular cartilage. Interestingly, when comparing our sample with this observational study the mean loss in medial cartilage thickness in our sample was similar to that in those defined as losing weight and slowing progression in the other study[18].

Richette *et al.* studied 44 persons undergoing gastric surgery with painful knee OA[14]. Weight loss resulted in a significant increase in N-terminal propeptide of type IIA collagen levels (+32%; $P = 0.002$), a biomarker of cartilage synthesis, and a significant decrease in cartilage oligomeric matrix protein (COMP) (−36%; $P < 0.001$), a biomarker of cartilage degradation. These results suggest a favorable effect of weight loss on cartilage turnover.

There are a number of differences from these studies and our own. As distinct from these uncontrolled studies, we included an active comparator that may itself have structure modifying effects. The weight loss in these studies was largely gained from bariatric surgery, which resulted in ~20% weight loss; substantially more than our mean weight loss of 10%. Importantly, this is an area currently under investigation and we await with great interest the results of other studies with similar objectives to our own[40].

Prior radiographic studies also afford a useful historical comparison with the rates of change we found in this study. Some recent systematic reviews demonstrate that the mean rate of annual narrowing is about 0.15 mm/year[38,41], but importantly greatly varies between studies due to length of follow-up, method of radiographic acquisition, measurement method and radiographic status at time of recruitment. Based upon this literature, for a study of 18 months duration if structural progression is linear one would expect JSW loss of −0.225 mm. All of the groups in the IDEA trial lost JSW at approximately the rate that would be expected compared to the natural history changes. Intriguingly, the small subsample of persons with varus malalignment who are at greatest risk of medial femorotibial progression showed the greatest benefit in the combination diet and exercise group. It is difficult to make too much of this result on a small sample and warrants confirmation in future larger studies. Given variability in the magnitude and timing of weight loss, we are planning secondary analyses to look further at questions such as the dose response relationship between the magnitude of weight loss and structural change.

The inherent appeal in conducting MRI measurements are suggestions from previous data that MRI measures are more responsive[35,39] and that the relation of structure to symptoms may be stronger[42]. The results of SQ MRI analyses show trends suggestive of benefit for both of the dietary groups (D and D + E); however, larger studies will be required to clarify the effect of weight loss is on joint structure.

There are a number of limitations of this study that warrant discussion. The lack of a control group that received no “active” intervention makes disentangling treatment effects challenging. It is quite plausible that the exercise alone group redeemed some

benefit from a joint structure perspective and hence dissecting the benefit from the dietary arms in this study was problematic. The number of persons who had an MRI acquired during the study was small, limiting our ability to make important between group distinctions based upon the size and subsequent power of the analyses. The lack of contrast administration also reduced our ability to detect more subtle changes in synovitis[43].

In summary, in a per-protocol analysis there was no statistically significant difference in the rate of progression in X-ray or quantitative MRI for persons undergoing intensive weight loss through diet, with and without exercise compared to exercise alone despite significant improvements in pain, function, and in biomechanical and inflammatory pathways towards OA in the diet groups[9]. We observed the expected amount of progression in JSW in each group, hence our interventions are unlikely to have caused more rapid progression. This finding is important given the potential concern of promoting joint damage with weight bearing exercise in overweight and obese adults who are not also losing weight. The findings do not denigrate the important symptomatic findings in the same trial and the important implications they have for this pressing public health issue of growing obesity and knee OA prevalence[9].

Contributorship

DJH and SPM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They also conceived the study, participated in its design and coordination, and drafted the manuscript. DB, FE, AG, RFL, BJN, SLM, GDM, ML, PD, CL, JJC, JDW participated in study design and coordination. FE participated in study design and coordination. DB participated in the statistical analyses. All authors read and made comments on previous drafts of the manuscript, and approved the final manuscript.

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Competing interest

AG is President of Boston Imaging Core Lab, LLC and Consultant to Sanofi-Aventis, Merck Serono and TissueGene.

FE is co-owner, CEO and CMO of Chondrometrics GmbH and Consultant to MerckSerono and Abbvie.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.03.034.

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