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Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial

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SUMMARY

Objectives: To evaluate in a prospective, randomized clinical trial (RCT), symptom response among obese knee osteoarthritis (OA) patients following a feasible, intensive weight-loss program for 16 weeks.
Methods: Eligible patients were obese [body mass index (BMI) > 30 kg/m^2]; >50 years old, with primary knee OA.
Participants were randomized to either a very-low-energy diet (VLED) or a low-energy diet (LED) (415 kcal/day and 810 kcal/day, respectively), using commercially available formula foods – only for the first 8 weeks, managed by dieticians. The 8 weeks were followed by an additional 8-week period of a hypo-energetic diet consisting of normal food plus meal replacements (1200 kcal/day). The primary endpoint was the number of patients responding according to the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT–OARSI) responder criterion. The statistical analysis was based on a non-responder intention-to-treat (ITT) population (baseline observation carried forward).
Results: One hundred and ninety two patients (155 (80.7%) females) with a mean age 62.5 years [standard deviation (SD) 6.4; range 50–78 years]; average BMI 37.3 (SD 4.8) were included. At 16 weeks, similar proportions of the VLED and LED groups, 59 (61.5%), and 63 (65.6%) patients, respectively, met the OMERACT–OARSI responder criteria, with no statistical significant difference between the groups ($P = 0.55$). Combining the groups the pooled estimate was 64% meeting the responder criteria [95% confidence interval (CI) 57%, 70%]. There was an overall reduction in pain, corresponding to an average pain reduction on the visual analogue scale (VAS) of 11.1 (95%CI 13.6, 8.5) in the combined groups. At week 16 weight loss in the combined groups was 12.8 kg (95%CI: 11.84–13.66; $P < 0.001$). 71% lost ≥10% body weight in both diet groups, with a pooled estimate of 74% (95%CI: 68–80%).
Conclusion: No clinically significant differences were found between the 415 kcal/day and 810 kcal/day diets.
A 16-week formula-diet weight-loss program resulted in a fast and effective weight loss with very few adverse events resulting in a highly significant improvement in symptoms in overweight patients with knee OA.
ClinicalTrials.gov Identifier: NCT00655941.

Introduction

In osteoarthritis (OA) the knee is the most commonly affected weight-bearing joint with the cardinal symptoms of pain and loss of function[1,2]. Decreased mobility leading to muscle atrophy, an accelerated decline in physical function, and the inability to engage in activities of daily living such as walking and climbing stairs are clinical consequences that often lead to loss of independence and

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poor quality of life[3]. It is estimated that knee OA causes pain and functional problems in more than 10% of the population older than 54 years, and one in four will be severely functionally disabled[4]. Risks of incident OA are obesity, generalized OA, knee malalignment and synovitis[5].

The lifetime risk of symptomatic knee OA rises with increasing Body Mass Index (BMI), with a risk of 2 in 3 among those who are obese[6]. The incidence of obesity is increasing, and at the same time the age profile of the population changes towards older age. This leads to an expected accumulation of patients having concomitant OA and obesity[7,8]. OA is thus one of many diseases in which obesity must be taken into serious account for future healthcare planning[9]. There is evidence that by treating the obesity of patients with co-occurring OA effectively, the functional status is dramatically improved, with the short-term result equal to that of a joint replacement[9,10]. Based on meta-regression analyses, significant weight loss is an effective symptom reducing therapy in knee OA patients with concomitant obesity[11]. As a consequence the OARSI guidelines recommend that patients with knee OA who are overweight should be encouraged to lose weight and maintain their weight at a lower level[12].

As a more intensive weight-loss strategy could result in a more pronounced clinical effect[11] the aim of our study was to compare whether there would be an advantage in using a Very-Low Energy Diet (VLED, 415 kcal/day), compared to a low-energy diet (LED, 810 kcal/day) on short-term followup in obese patients with knee OA. The primary objective was to compare the number of responders among obese OA patients following a feasible, intensive 16 week weight-loss program, according to the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT–OARSI) response criteria[13,14].

Patients and methods

Study design

This was a prospective, pragmatic randomized clinical trial (RCT), with blinded outcome assessors: the CAROT-study (Influence of weight loss or exercise on *car*tilage in *o*bese knee osteoar*t*hritis patients: a RCT, ClinicalTrials.gov identifier: NCT00655941.). The present report is based on the first trial phase of 16 weeks, initiating weight loss using dietary intervention with a LED, evaluating outcomes at two pre-specified time-points. The primary endpoint was the number of patients responding according to the OMERACT–OARSI responder criterion after 16 weeks of treatment[13].

Patient selection

Patients were recruited from November 2007 until August 2008 from the outpatients' clinic at the Department of Rheumatology at Frederiksberg Hospital, Frederiksberg. General practitioners in the local area were informed about the possibility to assign patients to the project. The study was advertised in newspapers and on the website of *The Parker Institute*. All potential trial participants were contacted by telephone and asked a series of standard questions according to the pre-specified eligibility criteria. The study was approved by the local ethical committee of The Capital Region of Denmark [H-B-2007-088] and the RCT was done according to the Helsinki criteria. The study was designed as a pragmatic trial – a RCT whose purpose is to inform decisions about effectiveness when used in normal practice; i.e., excluding as few patients as possible from participation and being directly relevant to healthcare practitioners[15]. Eligibility criteria were obesity (BMI > 30 kg/m^2); more than 50 years of age, primary knee OA diagnosed according to the American College of Rheumatology criteria[16], with clinical signs and symptoms as well as radiologically or arthroscopically verified OA in one or both knees. Exclusion criteria were: previous or planned total knee replacement (TKA) in the target knee; surgical procedures as e.g., arthroscopy or injections into a knee within 3 months prior to enrolment; pharmacological therapy with weight reducing drugs; lack of motivation to lose weight; inability to speak Danish fluently; or a mental state impeding compliance with the program. Patients with other medical illnesses were included provided they could manage the transport to the outpatients' clinic on their own. No patient was excluded due to their medical disease. The patients were asked not to change any nutritional supplements or OA medication during the 16-week period of the study.

Treatment, randomization, and blinding

Subjects were randomly assigned to either 8 weeks of LED (810 kcal/day) or a very-low-energy diet (VLED; 415 kcal/day) in a supervised dietary program[17]. Following this all-provided formula-diet period, all patients were instructed to follow an additional 8-week period of a hypo-energetic diet consisting of normal food plus meal replacements (anticipated approximately 1200 kcal/day in total). Both groups received identical nutritional instructions and behavioral therapy provided by an experienced dietician at weekly sessions (1.5 h/week) throughout the 16 weeks to reinforce and continuously stimulate the patients' decision about weight reduction and to encourage a high degree of compliance. During the 16-week intensive dietary treatment, the amount of attention given to the groups was exactly the same, in order to reduce the risk of performance bias. The LED consisted of meal replacements, nutrition powder and bars (The Cambridge Diet, *the Cambridge Health and Weight plan* UK), which were taken three times a day. The nutrition powder was dissolved in skimmed milk (7.5 dL of milk a day). The VLED consisted of the same meal replacements as LED, but the nutrition powder was dissolved in water, giving the patients only 415 kcal/day. Participants attended in groups of eight, and although they knew they were receiving diets in the range 415–810 kcal/day, they were not overtly aware of the dietary group to which they had been allocated. The LED used in this study *The Cambridge Health and Weight Plan* is not on sale in Denmark, so the patient had no foreknowledge of the products and its energy content. The formula-diet sachets the participants were provided with did not show the energy content. Both dietary programs met all recommendations for daily intake of vitamins and minerals. Daily intake of protein was at least 43.2 g, essential fatty acids 3 g, and linolenic acid 0.4 g. Dietary fiber intake was 7.2 g a day at least. Patients were advised to use a fiber supplement to avoid constipation. The second phase of the study was an 8 weeks (assumed) fixed energy diet program using 1200 kcal a day including two Cambridge products. All patients were taught to make diet plans eating 5–6 small meals a day. The principles of the diet were low-fat, low-sugar and high-fiber. Patients were encouraged to eat at least 300 g of vegetables a day and two portions of fruit. During this phase all groups received the same nutritional education along with recipes for low energy meals.

Blocks were enrolled for randomization based on 24 patients consecutively included during the study period. Randomization was done based on minimization[18], according to (1) gender [M/F], (2) BMI [$\geq$30, $\geq$35, and $\geq$40, respectively] and (3) age-ensuring homogeneity between intervention groups. In order to implement the allocation sequence, the groups were concealed until interventions were assigned. Each randomization list was drawn up by the statistician and given to the secretariat at The Parker Institute who subsequently informed the patients (who already had

their baseline measurements done and signed the informed consent), when to meet with the dietitian (i.e., thus securing a concealed allocation). This way the random assignment prevented foreknowledge of forthcoming allocations by study participants and those recruiting them to the trial[19]. The blinding was maintained throughout the trial.

Assessment of efficacy

The primary outcome of this study was the number of patients responding to therapy according to the OMERACT–OARSI responder criteria[13,20]. The criteria are defined as high improvement in pain or function (≥50%) and an absolute change ≥ 20%, or an improvement in at least 2 of the 3 following: pain ≥ 20% and absolute change ≥ 10%; function ≥ 20% and absolute change ≥ 10%; patient's global assessment ≥ 20% and absolute change ≥ 10%[14]. The three items of the OMERACT–OARSI responder criteria were assessed using a 10 cm visual analogue scale (VAS) with separate results for pain, disability and global evaluation of the patient.

The secondary outcome was the changes in symptoms of knee OA, as perceived by patients prior to and after intervention (week 16), this was monitored by the following questionnaires: the Knee injury and Osteoarthritis Outcome Score (KOOS)[21,22], being a normalized score, 100 indicating no symptoms and 0 indicating extreme symptoms, and the Short-Form-36 (SF-36)[23]. In order to assess the 8-week efficacy the KOOS and the OMERACT–OARSI related questionnaires were filled out by the patients at the 8 week visit.

The following are exploratory outcomes. The changes in body weight were examined as an independent predictor of changes in the symptoms of knee OA. At baseline and after 8 and 16 weeks the body weights of all patients were measured on a decimal weighing scale (TANITA BW-800, 'Frederiksberg Vægtfabrik', Copenhagen, Denmark). Height was measured using a stadiometer, rounding off the values to the nearest 0.5 cm. Body composition was measured with Dual-energy X-ray (DEXA-Lunar DPX IQ Full Body Bone Densitometer) scanning at baseline and after 16 weeks of intervention. Bi-plane weight-bearing semi-flexed (15°) radiographs were taken of the target knee (in case of bilateral symptoms we used the most symptomatic knee); one in the posteroanterior view and one in the lateral-medial view. They were obtained at baseline, using a Philips Optimus apparatus, and the same radiographers using a standardized protocol carried out all examinations at the same department of radiology.

Assessment of safety

Reporting of adverse events was elicited with a non-leading question at all clinic visits, including baseline. All events were coded according to the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. Routine laboratory tests, including measurement of serum glucose levels for estimating effects on glucose homeostasis and administration of liver function tests, were performed at baseline and together with each of the subsequent outcome assessments (i.e., week 8 and 16).

Sample size and power considerations

Patients included in this study were destined to participate in a subsequent 1-year maintenance program, ClinicalTrials.gov Identifier: NCT00655941. No specific sample size calculation was performed.

Statistical analysis

All data analyses were carried out according to a pre-established analysis plan; all analyses were done applying SAS software (v. 9.1.3 Service Pack 4; SAS Institute Inc., Cary, NC, USA). All descriptive statistics and tests are reported in accordance to the recommendations of the "*Enhancing the QUAlity and Transparency Of health Research*" (EQUATOR) network: the CONSORT statement[24]. In order to evaluate the empirical distributions of the continuous outcomes, visual inspection was used to suggest whether the assumption of normality was reasonable. The PROC UNIVARIATE statement was used for summarizing the data. All analyses were conducted according to the intention-to-treat (ITT) principle; i.e., analyzing participant outcomes according to the group to which they were randomized, even if some participants did not receive dietary attention. This was done based on a basic imputation technique, replacing missing data with the value at baseline carried forward[25]. Two sided significance tests were used.

Proportions were compared by estimating the risk difference with 95%CIs for each dichotomous outcome; including a Wald-*Z*-test testing the hypothesis that there was no difference between the proportions[26]. For sensitivity, if the Wald-test indicated statistical significance ($P < 0.10$) a χ^2-test with continuity correction or Fisher's exact test were applied when appropriate. Changes in the continuous outcome data, assumed sampled from a normal distribution, were analyzed using two-sample *t*-test for means, using the Satterthwaite approximation assuming unequal variances by default. The PROC TTEST was used for these with corresponding mean differences and 95%CIs. If the assumption of normality was not reasonable, we analyzed the data with the nonparametric *Wilcoxon Rank Sum* test using PROC NPAR1WAY; in this case the mean difference was replaced with median differences using the ROBUSTSCALE option based on the interquartile range applicable for estimating robust 95% CIs.

Results

Patient characteristics

The total number of persons prescreened *via* telephone during the 9 months recruitment period was 388 (Fig. 1). Of these, 187 (48%) of 388 were ineligible, and 9 (2%) of 388 declined to participate at the screening visit, leaving 192 patients randomized and included (Table I). The typical knee OA patient participating in this study was a 62-year old woman, with a BMI of 37, representing 25–30 kg of excess body weight. The K–L score and the KOOS scores were as shown in Table I. Of the 192 patients 170 (89%) had bilaterally knee OA, with 21 (12%) having a TKA on the contra laterally knee. Of the 192 patients being randomized, 175 (91%) completed the study (returned for the final data collection at week 16). The 17 study participants who did not complete the study were not significantly different from those who remained in terms of age, sex, BMI, initial radiographic score, knee pain or physical function. Retention of participants was not significantly different between the two groups (VLED and LED). In the first 8 weeks 14 participants dropped out; 12 due to non-compliance (VLED, 8; LED, 4) and 2 due to adverse events. In the second 8-week period, three participants dropped out due to non-compliance (VLED, 2; LED, 1); none due to adverse events (Fig. 1). In the VLED group, adherence was 91%, defined as attendance at the 8-week followup, and 90% after 16 weeks (defined as attendance at week 16). For those randomized to the LED diet, adherence was 94% after 8 weeks and 93% after 16

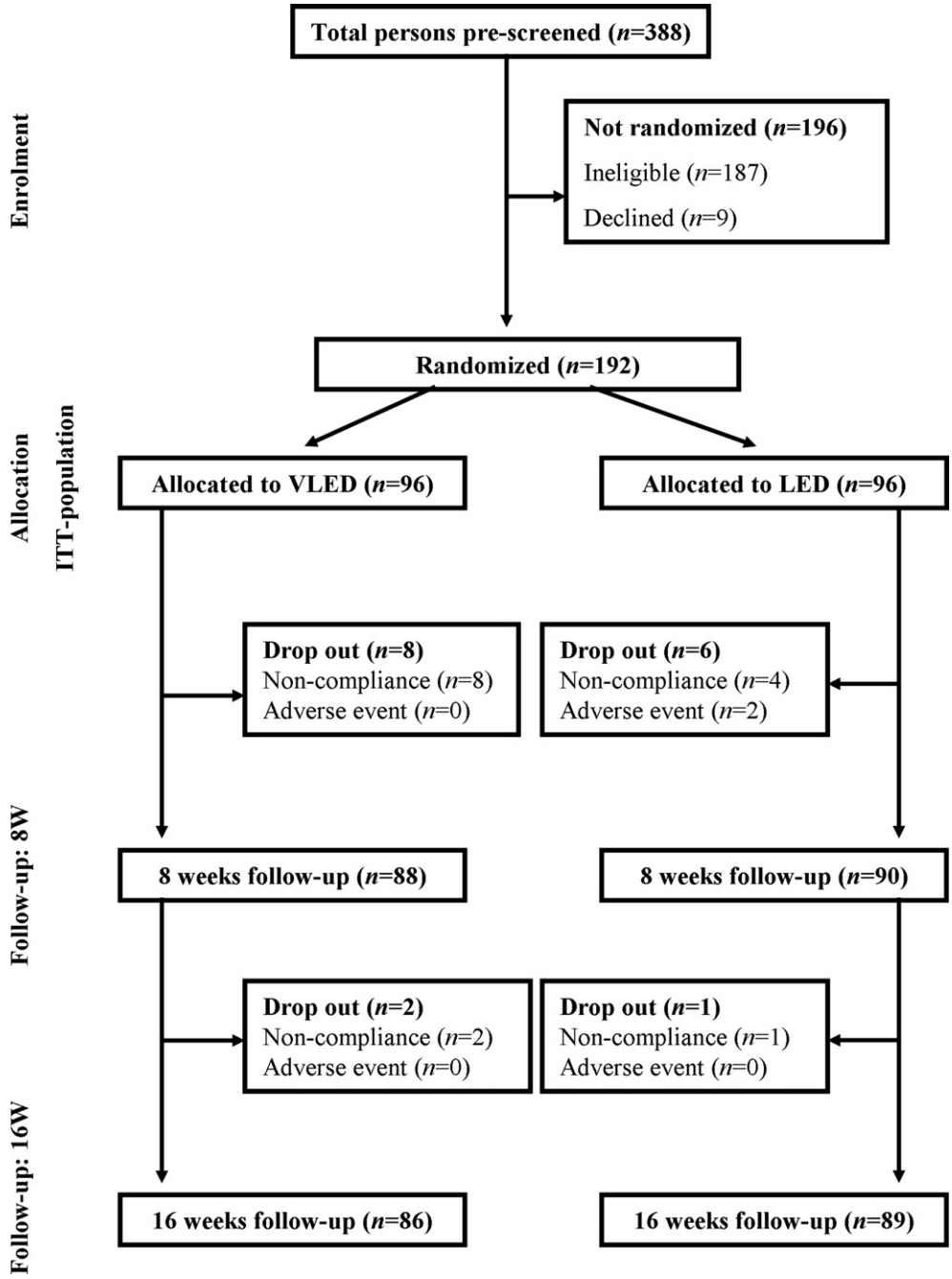

Fig. 1. Progress of participants through CAROT-study. Abbreviations: ITT, Intention-to-treat population.

weeks. There was no statistical significant difference in adherence between the two intervention groups.

Both groups (VLED and LED) lost on average 12% of their initial body weight, with 57 (59.4%) of 96 loosing ≥10% of their body weight in the LED group after 8 weeks and 66 (68.8%) of 96 in the VLED group (Table II, Fig. 2). After 16 weeks there were 71 (74.0%) of 96 having lost ≥10% of their body weight in both the VLED group and in the LED group (Table II). The changes in body weight corresponded to a highly significant reduction in BMI of 4.8 kg/m^2 in the VLED group and 4.0 kg/m^2 in the LED group ($P < 0.001$). Only part of the participants was above the World Health Organization (WHO) definition of morbid obesity (BMI ≥ 40). On the suggestion of the reviewer, we have added a *post-hoc* analysis of the weight loss for this group of participants ($n = 43$), weight-loss average 12.4 kg (95%CI: −14.7 to −10.2), corresponding to 10.8%.

Primary outcome

At 16 weeks, proportions of the VLED and LED groups, 59 (61.5%), and 63 (65.6%) patients, respectively, met the OMERACT–OARSI responder criteria (Table II), with no statistical significant difference between the groups; −4.2%point (95%CI: −18.0 to 9.0; $P = 0.55$). Combining the groups the pooled estimate was 64% meeting the OMERACT–OARSI responder criteria (95%CI: 57–70%) after 16 weeks. After the first 8 weeks 55 (57%) of 96 in the LED

Table I
Baseline characteristics of the patients in the ITT population

Characteristic	Treatment		Combined
	VLED $N = 96$	LED $N = 96$	Total $N_{Total} = 192$
Female, no. (%)	78 (81.3%)	77 (80.2%)	155 (80.7%)
Age (years)	61.8 ± 6.4	63.3 ± 6.3	62.5 ± 6.4 (50.0–77.9)
Duration (years)*	3.0 [1.0; 4.5]	3.0 [1.0; 4.0]	3.0 [1.0; 4.0] (1.0–29.0)
Height (m)	1.66 ± 0.08	1.66 ± 0.08	1.66 ± 0.08 (1.48–1.91)
Weight (kg)	104.1 ± 15.6	102.3 ± 14.4	103.2 ± 15.0 (76.0–145.3)
BMI (kg/m^2)	37.5 ± 5.4	37.1 ± 4.1	37.3 ± 4.8 (30.1–54.0)
Lean body mass (kg)†	50.8 ± 8.2	50.8 ± 9.1	50.8 ± 8.7 (37.1–78.4)
Lean body mass (%)†	50.2 ± 5.8	50.9 ± 5.5	50.5 ± 5.7 (38.0–67.7)
Fat mass (kg)†	48.1 ± 10.5	46.2 ± 8.3	47.1 ± 9.5 (30.7–80.7)
Fat mass (%)†	47.1 ± 6.1	46.3 ± 5.7	46.7 ± 5.9 (28.8–59.7)
Bone mineral content (%)†	2.8 ± 0.4	2.8 ± 0.3	2.8 ± 0.4 (1.9–4.3)
Current smokers no. (%)	12 (12.5%)	7 (3.6%)	19 (9.9%)
Plasma glucose (mmol/L)	5.9 ± 0.7	6.1 ± 1.0	6.0 ± 0.9 (4.8–11.1)
C-reactive protein (mg/L)*	4.1 [2.3; 8.1]	4.6 [2.4; 7.1]	4.4 [2.4; 7.7] (0.7–58.6)
Kellgren and Lawrence radiographic reading, no. (%)‡			
Grade 1	7 (7.4%)	10 (10.5%)	17 (9.0%)
Grade 2	38 (40.0%)	33 (34.7%)	71 (37.4%)
Grade 3	35 (36.8%)	33 (34.7%)	68 (35.8%)
Grade 4	15 (15.8%)	19 (20.0%)	34 (17.9%)
KOOS			
Pain	57.2 ± 17.2	57.4 ± 15.1	57.3 ± 16.1 (11.1–100)
Symptoms	60.2 ± 16.7	61.2 ± 17.6	60.7 ± 17.1 (14.3–96.4)
ADL	59.0 ± 16.9	60.8 ± 17.9	59.9 ± 17.4 (4.7–98.5)
Sports/recreation	19.6 ± 18.1	25.6 ± 21.1	22.6 ± 19.9 (0–100)
QOL	36.9 ± 16.5	39.5 ± 16.5	38.2 ± 16.5 (0–81.3)
OMERACT–OARSI items			
Pain	43 ± 20	42 ± 20	43 ± 20 (2–94)
Disability	45 ± 21	42 ± 22	43 ± 22 (1–93)
Global	33 ± 21	35 ± 24	34 ± 23 (0–93)
SF-36 score			
Physical component	33.3 ± 8.9	34.3 ± 8.5	33.8 ± 8.7 (11.7–60.9)
Mental component	52.6 ± 11.9	54.2 ± 11.5	53.4 ± 11.7 (16.4–73.0)

Plus–minus values are means ± SD and (minimum–maximum) unless otherwise stated. The BMI is the weight in kilograms divided by the square of the height in meters. The KOOS is a normalized score, 100 indicating no symptoms and 0 indicating extreme symptoms. The three items of the OMERACT–OARSI responder criterion can range from 0 to 100 on a VAS. Scores for the Medical Outcomes Study 36-items Short-Form General Health Survey (SF-36) can range from 4 to 71 for the physical component and from 2 to 74 for the mental component. For the OMERACT–OARSI and SF-36, higher scores indicate more severe disease.
Abbreviations: VLED, Very-low-energy diet; LED, low-energy diet; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, Function in daily living; QOL, Quality Of Life; OMERACT, the Outcome Measures in Rheumatology; OARSI, The Osteoarthritis Research Society International; SF-36, short-form-36.
* Presented as median, interquartile range [Q_1;Q_3] and (minimum–maximum).
† Lean body mass, fat mass and bone mineral content was measured using Dual-Energy X-ray Absorptiometry.
‡ Only 91 evaluations in each group.

group and 62 (65%) of 96 in the VLED group met the OMERACT–OARSI responder criterion (Fig. 2).

Secondary outcomes

KOOS

There was an overall improvement in all five subgroups in the KOOS score for both the LED and the VLED groups, all of minimal perceptible clinical improvement (8–10 points)[27] (Table II). The groups showed no difference in effect, with a pooled average for pain 9.72 (95%: 7.72–11.72; $P < 0.001$), symptoms 9.04 (95%: 7.17–10.91; $P < 0.001$), Function in daily living (ADL) 11.07 (95%: 9.11–13.03; $P < 0.001$), sports/recreation 8.60 (95%: 5.79–11.40; $P < 0.001$) and quality of life (QOL) 8.58 (95%: 6.33–10.83; $P < 0.001$), respectively. The greatest improvement in both groups was seen in the Activity of Daily Living subgroup of the KOOS.

SF-36

There was an overall improvement in both the physical and mental component of the SF-36 in both the VLED and the LED group. There was a statistically significant greater improvement in the mental component of the SF-36 in the VLED group compared to the LED group ($P = 0.01$) (Table II).

Safety

As presented in Table III the most statistically significant difference in adverse event reported in the VLED and LED group was epigastric pain 12 (12.5%) and 4 (4.2%); $P = 0.035$.

Five serious adverse events occurred during the study. These were mostly cardiovascular events as seen regularly in this age group. However, one patient in the LED group experienced bradycardia, and was briefly hospitalized. This patient had lost more than 14 kg within 8 weeks, while not adjusted her dosage of metoprolol medication. When her dosage of metoprolol had been adjusted, she was discharged from hospital with no further events of bradycardia, and continued in the study.

One patient in the LED group developed an allergic reaction and was excluded after the first week, this was probably due to allergy towards the formulated diet, and the patient was not hospitalized.

Discussion

The present study showed a highly significant improvement in symptoms in obese patients with knee OA following a 16-week intervention consisting of a LED program leading to a majority of the participants losing more than 10% of their body weight. The

Table II
Primary and secondary outcomes

Variable	Treatment		Comparison	
	VLED $N = 96$	LED $N = 96$	Difference in means (95%CI)	*P*-value
Primary outcome				
OMERACT–OARSI response at end of followup, no. (%)	59 (61.5%)	63 (65.6%)	−4.2 (−18.0 to 9.0)	0.55
Pain	−11.6 ± 1.90	−10.5 ± 1.83	1.10 (−4.11 to 6.32)	0.68
Disability	−14.44 ± 2.25	−12.75 ± 1.93	1.69 (−4.16 to 7.54)	0.57
Global	−9.64 ± 2.12	−11.54 ± 2.09	−1.90 (−7.78 to 3.96)	0.52
Secondary outcomes				
Δ Weight (kg)	−13.3 ± 0.65	−12.22 ± 0.59	1.08 (−0.67 to 2.81)	0.22
Δ Weight (%)	−12.94 ± 0.59	−11.96 ± 0.55	0.98 (−0.61 to 2.56)	
Δ BMI (kg/m^2)	−4.79 ± 0.23	−4.02 ± 0.21	0.34 (−0.27 to 0.96)	0.27
Losing ≥ 10% body weight, no. (%)	71 (74.0%)	71 (74.0%)	0.0 (6.0 to −12)	1.0
KOOS				
Δ Pain	8.88 ± 1.47	10.56 ± 1.42	1.68 (−2.35 to 5.72)	0.41
Δ Symptoms	9.26 ± 1.33	8.82 ± 1.37	−0.44 (−4.21 to 3.33)	0.82
Δ ADL	11.01 ± 1.50	11.13 ± 1.33	0.12 (−3.84 to 4.08)	0.95
Δ Sports/recreation	8.75 ± 1.81	8.44 ± 2.24	−0.31 (−6.0 to 5.37)	0.91
Δ QOL	8.31 ± 1.64	8.85 ± 1.60	0.54 (−3.98 to 5.06)	0.81
SF-36				
Δ Physical component	5.57 ± 0.83	6.07 ± 0.81	0.50 (−1.79 to 2.78)	0.67
Δ Mental component	4.43 ± 0.82	1.32 ± 0.89	−3.11 (−5.49 to −0.73)	0.01

Change in outcomes from baseline after 16 weeks in knee OA patients who were randomized to either the VLED or LED.
Values are mean ± standard error (SE) unless otherwise stated.
Abbreviations: VLED, Very-low-energy diet; LED, low-energy diet; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, Function in daily living; QOL, Quality Of Life; OMERACT, the Outcome Measures in Rheumatology; OARSI, The Osteoarthritis Research Society International; SF-36, short-form-36.

positive results were demonstrated by some 60% of the participants fulfilling the OMERACT–OARSI responder criteria for symptom improvement at 16 weeks. The results fulfilled the expectations of an intensive dietary program in these patients[9,11] and were similar to the effect on OA symptoms by weight loss previously shown in trials using LEDs, nutrition class or weight reducing drugs for 8–72 weeks[10,28–33]. Several circumstances may explain why we did not find a difference in the weight losses between the LED and VLED groups. While dieting, individuals on both LEDs and VLEDs will show a decrease in energy expenditure probably due to a lowering of the basic metabolic rate (BMR) and a lower physical activity level. The reduced BMR is probably an adaptive mechanism to protect the organism during starvation, and as such it also slows the weight loss during dieting. One likely explanation as to why the VLED group did not lose significantly more weight than the LED group is that the VLED group experienced a greater degree of fall in energy expenditure than did the LED group. Another explanation could be lower compliance in the VLED group compared with that in the LED group. The VLED gives only 415 kcal and a lower supply of dietary protein. This could result in more hunger and more occasions of

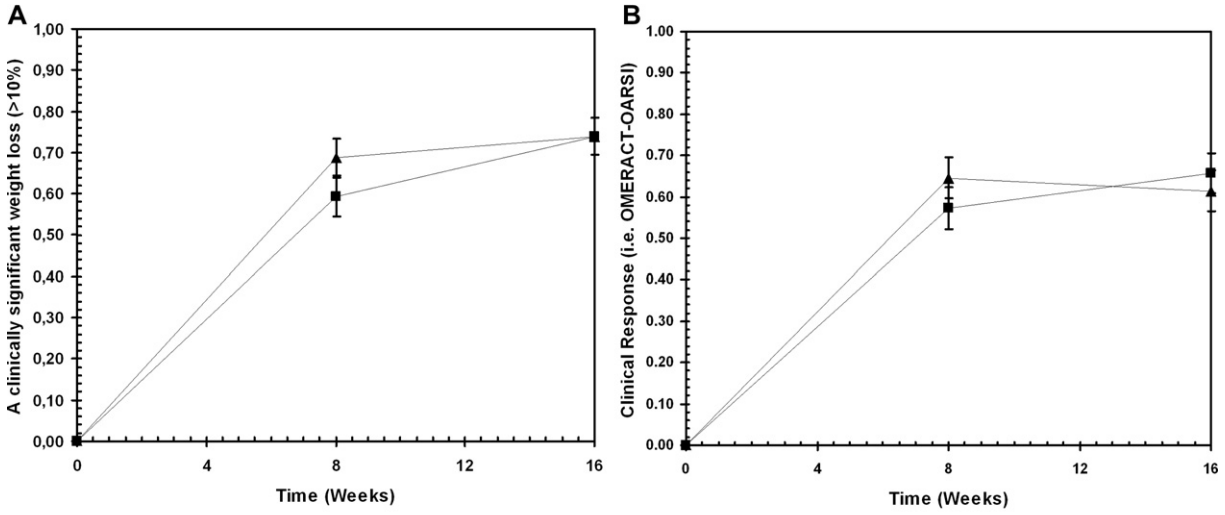

Fig. 2. Clinical efficacy following 16 weeks therapy. A: Proportion of patients loosing ≥10% of their body weight after 8 and 16 weeks. B: Proportion of patients responding to therapy according to the OMERACT–OARSI responder criterion after 8 and 16 weeks. ▲ = VLED, ■ = LED. A response according to the guidelines of the OMERACT–OARSI was classified as a high improvement in pain or function (≥50%) and an absolute change ≥ 20%, or an improvement in at least 2 of the 3 following: pain ≥ 20% and absolute change ≥ 10%; function ≥ 20% and absolute change ≥ 10%; patient's global assessment ≥ 20% and absolute change ≥ 10%.

Table III
Adverse events amongst patients in the ITT population at week 16

Variable	VLED $N = 96$	LED $N = 96$	Risk difference (95%CI)
Abdominal and intestinal symptoms			
Nausea	7 (7.3%)	6 (6.3%)	1.0 (−6.1 to 8.1)
Diarrhoea	4 (4.2%)	3 (3.1%)	1.0 (−4.3 to 6.3)
Constipation	28 (29.2%)	25 (26.0%)	3.1 (−9.5 to 15.8)
Wind/Flatulence	34 (35.4%)	29 (30.2%)	5.2 (−8.1 to 18.5)
Epigastric pain	12 (12.5%)	4 (4.2%)	8.3 (0.6 to 16.1)*
Vomiting	4 (4.2%)	3 (3.1%)	1.0 (−4.3 to 6.3)
Abdominal pain	8 (8.3%)	7 (7.3%)	1.0 (−6.5 to 8.6)
Heartburn	6 (6.3%)	2 (2.1%)	4.2 (−1.5 to 9.8)
Biliary symptoms	2 (2.1%)	4 (4.2%)	−2.1 (−7.0 to 2.8)
Musculoskeletal symptoms			
Cramps	6 (6.3%)	5 (5.2%)	1.0 (−5.5 to 7.6)
Joint paint	7 (7.3%)	11 (11.5%)	−4.2 (−12.4 to 4.1)
Back pain	11 (11.5%)	12 (12.5%)	−1.0 (−10.2 to 8.1)
Swollen joints	10 (10.4%)	7 (7.3%)	3.1 (−4.9 to 11.1)
Sciatic pain	9 (9.4%)	6 (6.3%)	3.1 (−4.5 to 10.7)
Central nervous system and psychiatric symptoms:			
Dizziness	19 (29.8%)	12 (12.5%)	7.3 (−3.1 to 17.6)
Headache	12 (12.5%)	6 (6.3%)	6.3 (−1.9 to 14.4)
Anxiety	5 (5.2%)	4 (4.2%)	1.0 (−4.9 to 7.0)
Sleeplessness	15 (15.6%)	10 (10.4%)	5.2 (−4.3 to 14.7)
Fatigue	14 (14.6%)	12 (12.5%)	2.1 (−7.6 to 11.8)
Mood changes	10 (10.4%)	4 (4.2%)	6.3 (−1.1 to 13.6)*
Depressive tendencies	6 (6.3%)	3 (3.1%)	3.1 (−2.8 to 9.1)
Skin and subcutaneous symptoms:			
Dry skin	18 (18.8%)	12 (12.5%)	6.3 (−4.0 to 16.5)
Allergic rash	11 (11.5%)	8 (8.3%)	3.1 (−5.3 to 11.6)
Redness	3 (3.1%)	6 (6.3%)	−3.1 (−9.1 to 2.8)
Eczema	6 (6.3%)	7 (7.3%)	−1.0 (−8.1 to 6.1)
Perianal itching	3 (3.1%)	7 (7.3%)	−4.2 (−10.4 to 2.1)
Skin irritation	8 (8.3%)	5 (5.2%)	3.1 (−4.0 to 10.2)
Urticaria	2 (2.1%)	2 (2.1%)	0.0 (−4.0 to 4.0)
Miscellaneous symptoms:			
Sensitive to cold	18 (18.8%)	14 (14.6%)	4.2 (−6.4 to 14.7)
Influenza	4 (4.2%)	3 (3.1%)	1.0 (−4.3 to 6.3)
Hair loss	7 (7.3%)	6 (6.3%)	1.0 (−6.1 to 8.1)
Bad breath	17 (17.7%)	8 (8.3%)	9.4 (−0.1 to 18.8)
Toothache	10 (10.4%)	9 (9.4%)	1.0 (−7.4 to 9.5)

Data is presented as proportions no%; mean. Difference is estimated *via* the risk difference.
Abbreviations: VLED, Very-low-energy diet; LED, low-energy diet.
*$P < 0.05$.

non-compliance where other food is eaten, which would lead to less weight loss in this group. Compliance with LED and VLED programs is difficult; nevertheless, it is the cornerstone of successful treatment.

Thus, this trial further supports the recommendation that "patients with hip and knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower level"[12]. The proportion of OMERACT–OARSI responders according to the Kellgren–Lawrence score of the worst compartment of the knee was KL 1 (71%), 2 (62%), 3 (68%), 4 (59%), respectively (n.s.). Patients with even severely affected knees (K–L grades > 3) can lose weight using this program, and have a significant relief in symptoms to the same extent as the patients with K–L grades 0–2, leading to the motto; "bad knees are no excuse for not losing weight".

This phase of our study focused on the dietary intervention and it may be discussed whether a concomitant exercise program might provide additional benefits. In any case, the patients showed improvement in both ADL and sports/recreation subgroup of the KOOS scale with the greatest improvement in ADL of the five subgroups, suggesting a more active lifestyle.

In the group of patients loosing more than 10% of their body weight 75% were responders according to the OMERACT–OARSI responder criteria, compared to only 30% in the group of patients loosing less than 10% of their body weight ($P < 0.0001$) corresponding to a Number Needed to Treat (NNT) of 3. The relief caused by the weight loss was in the same range as that predicted by a metaanalysis[11] and substantiates the notion that a weight loss of 10% might be the best way of treating knee OA in obese patients. Indeed, according to published metaanalyses of the overall efficacy, the weight loss may give the participants as effective or even better symptomatic treatment than e.g., light exercises[29] or NSAIDs[34]. Indirect comparisons have not yet been published on the various therapies in OA, but according to other studies the size of responses on Non-steroidal anti-inflammatory drug (NSAID) vs placebo is 65.4% and 45.9%, respectively[13].

In our study, we experienced a very good compliance with a low drop-out rate; 91% of the participants remained in the study after 16 weeks, meaning that the program was well accepted by the patients.

In general, the intensive diets gave few and mild adverse effects. One serious adverse event presumably happened due to a too large dose of metoprolol in a patient. The reduction of e.g., antihypertensive and antidiabetic medications during intensive diets represents the only challenge for the treating physician[35] and with this reservation any individual irrespective of age, sex, weight or BMI may be enrolled into a program of this type whatever other medical conditions may be present. All participants were asked not to change their medication, and almost all claimed not to have done this. However, in this pragmatic trial, we did not issue diaries for control purposes and thus have no data on the actual consumption over the 16 weeks. The end points were registered on days without such medication, i.e., the patients were fasting from the night before.

This study showed an effect after 16 weeks of intervention, but it remains to be shown that patients will adhere to such program over the coming years. By experience, most patients will regain their lost weight when left on their own[36], however, a maintenance of the weight loss would be expected to be mandatory for continuous relief[37]. There is still a challenge in getting the patients to maintain their weight on a lower level. Exercise was shown to be beneficial for weight maintenance[38]. Thus, following an initial intensive weight-loss program, an exercise intervention together with a continuous weight management program would probably be the best treatment for continuous weight management of the obese with knee OA. There is a need for this type of maintenance studies in knee OA patients. A possible effect of weight loss on structural damage is yet to be shown, and the evidence for long term effects of weight loss and weight maintenance on OA is sparse.

In conclusion, our dietary program resulted in a fast and effective weight loss with very few adverse events resulting in a highly significant improvement in symptoms. Within this timeframe, weight loss by dietary programs is at least as effective as, and may be advocated before considering surgical or pharmacological treatments, which are associated with less advantageous safety profiles[39,40]. The program used in this study could be administered to patients of all ages; concurrent medical diseases were not a barrier to successful weight loss. In fact, such rapid weight loss only presents one major challenge to the treating physician: to reduce medication such as analgesics/NSAID's and for the components of the metabolic syndrome, especially antihypertensive and antidiabetic medications, which may in some cases be withdrawn altogether.

Conflict of interest

AR Leeds is employed as medical director of the Cambridge Manufacturing Company [Cambridge Diet®]. Pia Christensen, Henning Bliddal, Birgit Falk Riecke and Robin Christensen received travel grants to attend scientific meetings from the Cambridge Manufacturing Company.

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Supplementary material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.joca.2010.02.012.

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