Osteoarthritis and Cartilage 18 (2010) 746–754

Osteoarthritis and Cartilage

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

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ARTICLE INFO

Article history:
Received 12 October 2009
Accepted 11 February 2010

Keywords:
Knee osteoarthritis
Weight-loss
Diet
Randomized clinical trial

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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1063-4584/$ – see front matter
doi:10.1016/j.joca.2010.02.012

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