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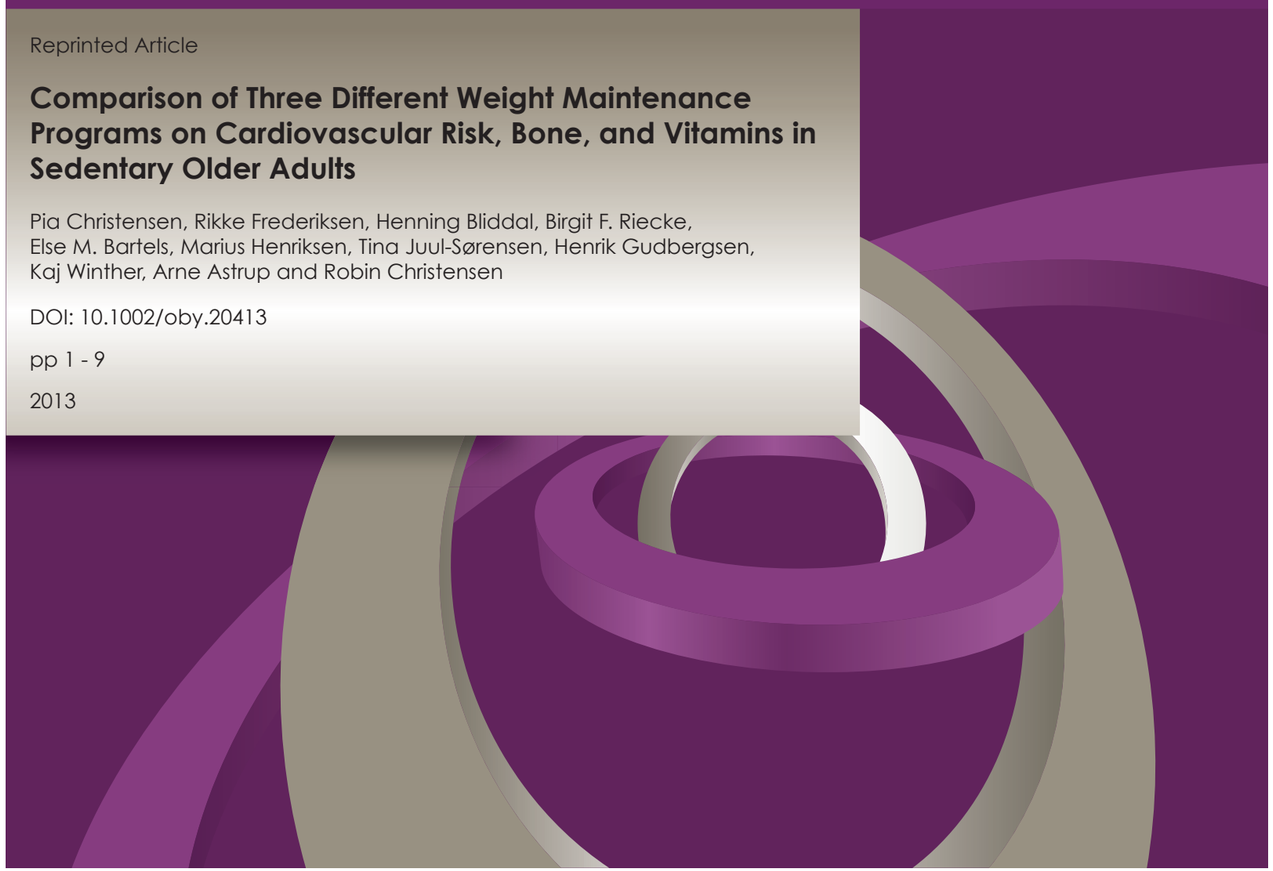

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Obesity

Comparison of Three Different Weight Maintenance Programs on Cardiovascular Risk, Bone, and Vitamins in Sedentary Older Adults

Pia Christensen[1,2], Rikke Frederiksen[1], Henning Bliddal[1], Birgit F. Riecke[1], Else M. Bartels[1], Marius Henriksen[1], Tina Juul-Sørensen[1,3], Henrik Gudbergsen[1], Kaj Winther[4], Arne Astrup[2] and Robin Christensen[1,3]

Objective: Obese patients with knee osteoarthritis (OA) are encouraged to lose weight to obtain symptomatic relief. Risk of vascular events is higher in people with OA compared to people without arthritis. Our aim in this randomized trial was to compare changes in cardiovascular disease (CVD) risk-factors, nutritional health, and body composition after 1-year weight-loss maintenance achieved by [D]diet, [E]knee-exercise, or [C]control, following weight loss by low-energy-diet.

Design and Methods: Obese individuals ($n = 192$, >50 years) with knee OA, 63 years (SD 6), weight 103.2 kg (15.0), body-mass index 37.3 kg/m^2 (4.8), were enrolled into a 68-week weight-loss trial.

Results: Mean changes in weight, in D, E, and C were −11.0, −6.3, and −8.3 kg ($P = 0.002$). Reduction in waist circumference in D, E, and C were −8.4, −4.6, and −7.0 cm ($P = 0.007$). D reduced waist circumference significantly more than E: −3.8 cm (95%CI −6.2 to −1.4; $P = 0.0024$). There was no difference between the groups in changes in CVD risk factors; blood pressure, triglycerides, and cholesterol. Nutritional health was improved in all groups. For markers of bone, no statistical difference was found between the groups.

Conclusions: Dietary support, or control, maintained improvements in cardiovascular risk factors to the same extent and none of the interventions had a detrimental effect on bone.

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Introduction

Obesity with related co-morbidities is associated with reduced life expectancy and increased mortality from cardiovascular disease (CVD) and other causes (1,2). Risk factors such as high blood pressure (BP), abdominal obesity, dyslipidemia, and high blood glucose levels, which all increase with obesity, are strongly, consistently, and directly associated with the risk of major cardiovascular events (3).

Intentional weight loss is known to effectively reduce CVD risk factors and diminishing the risk of developing diabetes (4). Risk of vascular events is higher in people with osteoarthritis (OA) compared to people without OA (5,6), which further speaks in favor of weight loss for overweight patients with OA. Furthermore, weight loss is recommended as treatment option for overweight and obese patients with knee OA to reduce pain and improve function (7,8). Effective weight management is an important goal for everyone, and it is especially important for obese patients with knee OA, as they represent a segment of the population at highest risk for future total knee alloplasty (9).

Weight-loss approaches should be undertaken with care, as they can also be associated with reduced intake of essential nutrients as well as loss of muscle and bone mass (10,11). Therefore, it is important to evaluate both the ability of different lifestyle interventions to

[1] The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen F, Denmark. Correspondence: Robin Christensen (robin.christensen@frh.regionh.dk) [2] Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Frederiksberg, Denmark [3] Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense M, Denmark [4] Department of Clinical Biochemistry, Frederiksberg Hospital, Frederiksberg, Denmark

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induce changes in health outcomes such as waist circumference, weight, fitness, glycemic control as well as cardiovascular risk factors and to assess changes in vitamins and bone metabolism.

This study focuses on the results of the life-style intervention in the CAROT trial (12). The purpose of this study is to test the hypothesis that dietary support after a major weight loss will be associated with better cardiovascular risk factor outcomes, better nutritional status, and less bone loss compared with the specialized knee exercise program or a ''no attention'' control group. Although exercise in some patient groups can induce positive effects on cardiovascular risk factors (13), we speculate that pain and disability associated with knee OA will hinder them from engaging in exercise activities to an extent that may have an impact on the CVD risk profile.

Methods and Procedures

The CAROT study was initially designed to compare improvements in physical function and knee pain in sedentary, obese individuals with OA of the knees after one year of either dietary support, knee exercise, or a ''no attention'' control group, all three groups following a major weight loss. This was a prospective, pragmatic randomized controlled trial (RCT), with blinded outcome assessors: the CAROT study (Influence of weight loss or exercise on CARtilage in Obese knee osteoarthritis patients, ClinicalTrials.gov identifier: NCT00655941). The study was designed as a pragmatic trial, was approved by the local ethical committee of the Capital Region of Denmark [H-B-2007-088], and carried out according to the Helsinki criteria.

Initially all participants went through a 16-week intensive dietary weight loss intervention which has been described in details previously (12,14,15). The dietary weight loss approach applied in the CAROT trial for all participants was a combination of formula diet products, dietetic advice as well as focus on long-term lifestyle changes. In this context, the advantage of formula products is that a dieting person knows exactly how many calories she/he has consumed when eating formula products. This is in contrast to eating conventional food where the energy content is typically underestimated by 40-50% (16). Additionally, formula products must—by legislation—contain a defined minimum amount of essential nutrients to meet the recommended daily intake.

In the intensive 16-week weight loss phase, participants were randomly assigned to either 8 weeks of low-energy diet (LED; 3,400 kJ/day [810 kcal/day]) or a very-low-energy diet (VLED; 1,743 kJ/day [415 kcal/day]) in an all-provided formula-diet period in a supervised dietary program. Both dietary programs met all recommendations for daily intake of macronutrients, vitamins, and minerals (14). This was followed by an additional 8-week period of a hypo-energetic diet consisting of normal food plus two formula products daily (targeting ~1,200 kcal/day in total). All participants were taught how to make diet plans with 5-6 small meals a day; the principles of the diet were in line with the guidelines for healthy eating issued by the Danish National Board of Health, i.e., low fat, low sugar, and high fiber intake. Second phase was 52 weeks where the participants were randomly assigned to either a continued dietary weight maintenance arm, knee exercise, versus the control group receiving no intervention.

Participants and setting

The participants were obese (defined as a body-mass index [BMI] > 30 kg/m^2), more than 50 years of age and had primary knee OA diagnosed according to the American College of Rheumatology criteria (17). Exclusion criteria were lack of motivation to lose weight, inability to speak Danish, planned anti-obesity surgery, total knee alloplasty, and receiving pharmacologic therapy for obesity. The participants were asked not to change any medication or nutritional supplements during the study. Participants were recruited from November 2007 until August 2008 from the outpatients' clinic at the Department of Rheumatology at Copenhagen University Hospital at Frederiksberg, Denmark. 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.

Maintenance phase

D, Diet. The goal of the dietary intervention was to produce and maintain a weight loss of at least 10%, which has been found to be the magnitude of weight loss needed to achieve clinically relevant relief in disease symptoms in the knees (18). The focus of the dietary education was on long-term lifestyle changes and modifications. The education included self-monitoring of eating habits, dietetics, stimulus control, problem solving, and social support. Goals for body weight were advised to be in the range of BMI 24-29 kg/m^2. In the maintenance phase, the focus of the dietician included assisting participants who had reached their weight loss goals to maintain their weight loss, and providing counseling for participants who had a difficult time changing behavior and losing weight. Participants attended weekly sessions for approximately 1 h including weighing and provision of formula products (1 Cambridge Weight Plan product per day).

E, Exercise. The typical exercise intervention 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 aim was to gradually translate the intervention from facility-based exercises to home-based exercises. The participants alternated between attendance to exercise at the facility or performing the exercises at home. In this way, the participants were gradually going from supervised to unsupervised exercise. The aim of the intervention was to improve knee function and reduce pain. Functional weight-bearing exercises were applied, emulating activities of daily life—both light and more vigorous activities. The quality of the performance in each exercise was emphasized, and the level of training and progression was guided by the patient's performance.

C, Control. The control group served as a usual-care comparison group and no attention was provided to the participants after the first 16 weeks of dietary intervention.

Randomization and concealed allocation

In the initial intensive weight loss period, participants were randomly assigned to receive either LED or VLED (14). Following the first 16 weeks of dietary intervention, participants were assigned with the use of minimization to one of three subsequent treatment

groups with an equal allocation ratio (1:1:1) (19). The participants were stratified according to gender, body weight at baseline, and weight loss. The concealed allocation was done on the basis of all the participants entering the study at baseline. Each randomization list was drawn up by a biostatistician (RC) and given to the secretariat at the Parker Institute who subsequently informed the participant having completed the 16 weeks dietary weight loss phase, when and where to meet in the maintenance period, securing a concealed allocation. The random assignment prevented knowledge of forthcoming allocations by study participants and personnel recruiting participants to the trial.

Outcome measures

Waist circumference was measured with a tape measure in cm midway between the lower rib and iliac crest according to WHO recommendations (20). Body weight was measured on digital scales (TANITA BW-800, Frederiksberg Vægtfabrik, Frederiksberg, Denmark). Height was measured to the nearest 0.01 m. BMI was calculated by a person's weight (in kilograms) divided by the square of his/her height (in meters). Bone mineral density (BMD, g/cm^2), bone mineral content (BMC, g), fat mass, and lean body mass were determined by dual energy X-ray absorptiometry (DEXA) using a Lunar DPX IQ Full Body Bone Densitometer (GE Medical Systems, Madison, WI). Pulse and BP was measured using a mercury sphygmomanometer. All measurements were done at baseline and after 68 weeks.

All blood samples were taken after at least a 12-h fast and were analyzed at the Department of Clinical Biochemistry at Frederiksberg Hospital using standardized laboratory procedures. Micronutrient deficiency was defined according to the references from the Department of Clinical Biochemistry: cut-off values were $<$ 50 nmol/l for P-25-OH-Vitamin D3, $<$ 200 pmol/l for P-Cobalamin, $<$ 12 μg/l for P-Ferritin, and $>$ 6.9 pmol/l for parathyroid hormone (PTH). Plasma-25-OH-Vitamin D3 was measured on a Abbott Architect *I*SR using micro particle chemiluminescence immunoassay, plasma-Cobalamin and plasma-Ferritin was measured on a Abbot Architect i2000SR using two step immunoassay with chemiluminescence micro particle technology and plasma-PTH was measured on a Cobas e601 using sandwich immunoassay with chemiluminescence detection.

The metabolic syndrome (MS) definition is based on the National Cholesterol Education Program Adult Treatment Panel (ATP III 2005) (21)—MS is present when three or more of the following conditions occur simultaneously: 1) abdominal obesity defined by waist circumference 102 cm (men), 88 cm (women); 2) dyslipidemia: triglycerides (TG) $\geq$ 1.695 mmol/l; 3) dyslipidemia: high density lipoprotein (HDL) cholesterol $\leq$ 1.036 mmol/l (men), $\leq$ 1.295 mmol/l (women); 4) BP $\geq$ 130/85 mmHg or use of medication for hypertension; 5) fasting plasma glucose $\geq$ 5.55 mmol/l or use of medication for hyperglycemia.

Information on physical activity level was obtained by a questionnaire measuring physical activity on an average weekday as a total 24-h metabolic equivalent (MET) score (22). The questionnaire has been shown to correlate well with physical activity diaries and to reflect maximum oxygen uptake (23). The questionnaire was self-administered and respondents were asked to describe their habitual physical activity and inactivity on an average weekday, by filling out the amount of time spent on nine different intensity levels of physical activity (24). The nine levels consisted of: sleep (0.9 METs), TV viewing and other leisure time sedentary activity (1.0 METs), computer or desk work (1.5 METs), light standing activity, cooking, washing dishes or driving a car (2.0 METs), light cleaning, walking down stairs (3 METs), brisk walking or bicycling to work or for pleasure (4.0 METs), gardening or carrying light objects upstairs (5.0 METs) aerobics, health club exercise, chopping wood or shoveling snow (6.0 METs) and vigorous activity, such as jogging, running, tennis, etc. (>6.0 METs).

Statistical analysis

Statistical analysis was performed with the use of a statistical software package (SAS 9.3 for Windows, Cary, NC). All confirmatory data analyses were carried out according to a pre-specified analysis plan. Descriptive statistics for the continuous variables were summarized as mean $\pm$SD (and minimum and maximum) or median (and interquartile range) and categorical variables as number (%). All analyses were on an intention-to-treat (ITT) basis with baseline observation carried forward for missing data. The adjusted mean differences were estimated using analysis of covariance (ANCOVA) with the baseline value applied as covariate. Categorical outcomes were assessed by using chi-square tests. 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. Changes were generated by subtracting the baseline value from the value at the 68-week assessment. In the case where the main effect of group was statistically significant ($P < 0.05$), pair-wise comparisons of the changes from baseline at the trial's endpoint (week 68) were performed using *t*-tests.

Results

One hundred and ninety-two patients were randomly assigned to one of three interventions with 64 in each treatment group (Supporting Information File 1 show the trial profile). The participants in the three groups were well matched as they were randomized on the basis of their baseline characteristics. During the intensive weight loss period 17 (8.9%) study participants dropped out. There was no significant baseline difference between those who completed versus those who dropped out the trial (data not shown). During the following 1-year maintenance intervention, 16 of the 175 patients who had completed the first phase (9.1%) dropped out of the study. The dropout rate was significantly lower in the diet group (1 patient out of 56, 1.8%) than for participants assigned to the control group (9 patients out of 61, 14.8%; $Z = 2.66$, $P = 0.0078$) and the exercise group (6 patients out of 58, 10.3%; $Z = 1.96$, $P = 0.050$). Adherence to the interventions, defined as the percentage of sessions attended during week 16 and week 68 with the health professionals averaged 22% (median 13.8%) in the exercise group and 59.1% (median 61.5%) in the diet group. The patient characteristics of the 192 individuals included as the ITT population are presented in Table 1. The typical participant was a 63-year old woman, with a BMI of 37.3 kg/m^2 and waist circumference of 111.3 cm.

Forty-six of 64 (71.9%) were classified as having MS at baseline in both the diet and the exercise group, and 47 out of 64 (73.4 %) were classified in the control group. Baseline data on nutritional

TABLE 1 Baseline characteristics of the intention-to-treat population

Characteristic	Diet ($n = 64$)	Exercise ($n = 64$)	Control ($n = 64$)
Age, years	63.0 ± 6.5	62.9 ± 5.8	61.7 ± 6.8
Female, no. (%)	52 (81.3%)	52 (81.3%)	51 (79.7%)
Height, cm	166.0 ± 8.3	166.3 ± 7.9	166.5 ± 8.6
Waist circumference, cm	112.5 ± 10.9	110.0 ± 10.9	111.4 ± 11.0
Metabolic syndrome, no. (%)[a]	46 (71.9%)	46 (71.9%)	47 (73.4%)
Systolic blood pressure, mmHg	140.1 ± 19.0	139.7 ± 19.7	143.1 ± 19.7
Diastolic blood pressure, mmHg	89.1 ± 15.7	85.8 ± 9.4	91.6 ± 20.0
Pulse, bpm	69.2 ± 10.2	70.7 ± 9.5	68.5 ± 11.9
Fasting glucose, mmol/l	6.0 ± 0.8	6.1 ± 1.0	5.9 ± 0.7
Total cholesterol, mmol/l	5.3 ± 1.1	5.0 ± 1.0	5.2 ± 1.1
LDL cholesterol, mmol/l	3.0 ± 0.9	2.8 ± 1.0	3.1 ± 0.9
HDL cholesterol, mmol/l	1.6 ± 0.4	1.6 ± 0.4	1.5 ± 0.5
Triglycerides, mmol/l[b]	1.19 [0.96; 1.62]	1.25 [0.10; 1.72]	1.27 [0.88; 1.72]
C-reactive protein, mg/l[b]	3.8 [2.4; 7.7]	4.5 [1.85; 6.85]	4.1 [2.5; 8.9]
Weight, kg	103.6 ± 14.8	101.0 ± 14.0	105.0 ± 16.1
Body mass index, kg/m^2	37.6 ± 4.5	36.5 ± 4.4	37.9 ± 5.3
MET score[c]	41.8 ± 7.4	41.8 ± 7.3	39.8 ± 7.6
Sedentary activity minutes per day[d]	510 ± 151	503 ± 145	549 ± 149

Data are mean ± SD, except when otherwise indicated.
LDL, low density lipoprotein; HDL, high density lipoprotein; bpm, beats per minute.
[a]The metabolic syndrome is defined according to the American Heart Association criteria.
[b]Presented as median [Q1; Q3].
[c]MET score is the metabolic equivalents score, which is the average score of activities during 24 hours ranging from sleep with a MET score of 0.9 to activities such as running, playing tennis with MET scores >6.0.
[d]Minutes spent daily sitting quietly down, watching television, listening to music or reading, working at a computer or desk, sitting in a meeting, eating.

status and body composition are presented in Table 2. Around 50% of the participants showed vitamin D deficiency at baseline. As a parallel to this, PTH was elevated in about 30% of the participants. About 20% of the participants showed decreased vitamin B12, while ferritin was at normal values.

Effect of intervention on waist circumference and metabolic syndrome

Figure 1 shows the changes in waist circumference. A significant improvement was observed for change in waist circumference in response to the intensive weight loss period. All of the three

TABLE 2 Nutritional status and body composition in the study population at baseline

Variable	Diet ($n = 64$)	Exercise ($n = 64$)	Control ($n = 64$)
P-25-OH-Vitamin D3, nmol/l	45.3 ± 19.1	49.9 ± 19.8	50.8 ± 22.2
P-25-OH-Vitamin D3 <50 nmol/l, no. (%)	32 (52.5%)	28 (45.2%)	27 (42.9%)
P-cobalamins (Vitamin B12), pmol/l	304.1 ± 148.5	288.1 ± 102.8	288.5 ± 93.1
P-cobalamins (Vitamin B12) <200 pmol/l, no. (%)	11 (17.2%)	12 (19.0%)	11 (17.5%)
P-Ferritin, mikg/l[a]	87.5 [60.5; 168.0]	98.0 [48.5; 134.0]	104.0 [61.5; 161.0]
P-Ferritin < 12 mikg/l, no. (%)	1 (1.6%)	1 (1.6%)	0 (0.0%)
P-PTH, pmol/l	6.5 ± 1.7	6.4 ± 2.5	6.2 ± 2.3
P-PTH > 6.9 pmol/l, no. (%)	22 (34.4%)	21 (32.8%)	18 (28.1%)
Lean body mass, g	51053 ± 8447	50266 ± 8511	51309 ± 9348
Fat mass, g	47353 ± 9234	45749 ± 9107	48028 ± 10381
Fat mass, %	46.7 ± 5.8	46.2 ± 6.0	46.9 ± 6.4
Bone mineral content, g	2760.7 ± 426.1	2764.5 ± 445.1	2831.2 ± 516.0
Bone mineral density, g/cm^2	1.20 ± 0.08	1.20 ± 0.09	1.20 ± 0.10

Data are mean ± SD, except when otherwise indicated.
[a]Presented as median [Q1; Q3].PTH, Parathyroid hormone

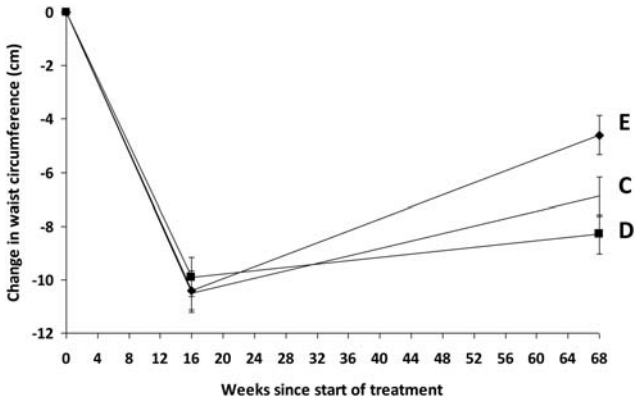

FIGURE 1 Adjusted changes in waist circumference by treatment group. Error bars indicate standard error. D, diet; E, exercise; C, control.

randomized groups successfully maintained a reduction in waist circumference at week 68. As also presented in Table 3, the mean reduction was greater in the diet group than in the exercise group (difference −3.8 [−6.2 to −1.4] cm; $P = 0.0024$). There was no statistically significant difference between the diet and the control group (difference 1.5 [−0.9 to 3.9] kg; $P = 0.22$). A trend toward a statistically significant difference between control and the exercise group (difference −2.2 [−4.7 to 0.2] cm; $P = 0.07$) was observed. For transparent reporting we have also given changes immediately after the intensive weight loss at week 16 in Table 3, but without testing for significant difference. The prevalence of the MS was lower after the maintenance phase at week 68, where only 26 of 64 (40.6%) in the diet group fulfilled the criteria for the syndrome as compared to 35 of 64 (54.7%) in the exercise group and 34 of 64 (53.1%) in the control group ($P = 0.22$).

Effect on components of the metabolic syndrome and related variables

Systolic BP had decreased significantly in all groups at week 68, but no difference was found between groups ($P = 0.60$). Additionally, there was no statistically significant mean difference between the groups for any of the other components defining MS, diastolic BP ($P = 0.29$), fasting blood glucose ($P = 0.97$), TG ($P = 0.36$), or HDL cholesterol ($P = 0.34$; see Table 3). There were significant decreases in body weight in all groups with a statistically significant difference between groups ($P = 0.0023$). The diet group lost more than both the exercise group (mean difference of −4.62 [95% CI: −7.27 to −1.97; $P = 0.0007$] kg) and the control group (mean difference of −2.78 [95% CI: −0.14 to 5.43; $P = 0.039$] kg). No difference was observed between the exercise and control group. The measure of physical activity level—the MET score, did not differ between the three groups at week 68 ($P = 0.34$), neither did the hours spent on sedentary activities during a day ($P = 0.21$).

Effects on nutritional status, body composition, and markers of bone health

Changes in vitamin D, vitamin B12, ferritin, PTH, and changes in fat mass, lean body mass, and markers of bone health, over the study period are given in Table 4. At study end vitamin D levels had increased in all groups, but significantly more so in the diet group than in the exercise and the control group. The mean difference was 9.79 nmol/l (95% CI: 1.98-17.60 nmol/l; $P = 0.014$) between the diet and the exercise group, and the mean difference was 7.90 nmol/l (95% CI: 0.11-15.70 nmol/l; $P = 0.047$) between the diet and the control group, i.e. both in favor of the dietary intervention. No difference was found between the exercise and the control group. Concomitantly, there were significant increases in vitamin B12 in all three groups, and in ferritin in the diet group. Vitamin B12 increased significantly more in the diet than in the control group ($P = 0.027$), and a clear trend in the same direction was seen between the diet and the exercise group ($P = 0.051$). There was no significant difference between groups regarding increment in ferritin ($P = 0.48$). At week 68, PTH (Table 4) had significantly decreased in both the diet group and the control group. This was not the case in the exercise group. Between group difference in PTH was seen, where the diet group ($P = 0.0001$) and the control group ($P = 0.045$) had lower values than the exercise group. A trend toward a difference between the diet and the control group ($P = 0.06$) was also seen, the diet group showing lower values.

Lean body mass had decreased in all groups at week 68 with no difference between the groups ($P = 0.66$). However, the loss of fat mass was larger in the diet group than both the exercise group (mean difference of −4,188 g [95% CI: −6,442 to −1,934 g; $P = 0.0003$]) and the control group (mean difference of −3,007 g [95% CI: −5,248 to −766 g; $P = 0.009$]).

The marker of bone status, BMC, significantly decreased in all groups during the study period. However, there was no difference between the groups ($P = 0.89$). BMD remained stable during the trial period, and did not change in any of the groups between baseline and week 68.

Discussion

Waist circumference and the MS are important cardiovascular risk factors. This study showed a significant reduction in waist circumference after the initial weight loss program and good maintenance in all three intervention groups after one year. This finding is similar to other lifestyle intervention studies showing that it is possible to maintain the positive effect of weight loss in the long-term (4,25). Interestingly, the control group maintained the reduction in waist circumference in the same range as the diet group, indicating that if the initial lifestyle intervention includes the proper tools the participants learn how to adapt to a healthier lifestyle. Therefore, it may not be as important to follow-up as intensely afterwards.

The present results must be interpreted with caution. Most importantly, 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 effects on cardiovascular risk factors over 1 year. Many of the participants in the exercise group expressed dissatisfaction with their group assignment, as they would have preferred to continue with dietetic counseling. This may explain the poor attendance to exercise and subsequent poorer weight loss maintenance. Additionally, the exercise program was designed to target knee OA pain and disability rather than to increase the daily energy expenditure and affect cardiovascular risk factors. The exercise typically advocated for weight loss may not be

TABLE 3 Effects of interventions on components of the metabolic syndrome and related variables

Variable	Diet ($n = 64$), Mean (95% CI)	Exercise ($n = 64$), Mean (95% CI)	Control ($n = 64$), Mean (95% CI)	*P*
Waist circumference, cm				0.0073
Δ from baseline to week 16	−9.9 (−11.3 to −8.6)	−10.4 (−11.8 to −9.1)	−10.5 (−11.9 to −9.1)	
Δ from baseline to week 68	−8.4 (−10.2 to −6.7)	−4.6 (−6.3 to −2.9)	−7.0 (−8.7 to −5.3)	
Metabolic syndrome, no. (%)[a]				0.22
No. (%) at week 16	29 (45.3%)	37 (57.8%)	31 (48.4%)	
No. (%) at week 68	26 (40.6%)	35 (54.7%)	34 (53.1%)	
Systolic blood pressure, mmHg				0.60
Δ from baseline to week 16	−11.9 (−15.5 to −8.3)	−9.4 (−13.1 to −5.8)	−12.9 (−16.5 to −9.3)	
Δ from baseline to week 68	−7.3 (−11.0 to −3.6)	−9.4 (−13.1 to −5.6)	−6.8 (−10.6 to −3.1)	
Diastolic blood pressure, mmHg				0.29
Δ from baseline to week 16	−6.6 (−9.5 to −3.8)	−5.3 (−8.2 to −2.4)	−7.1 (−10.0 to −4.3)	
Δ from baseline to week 68	−4.1 (−7.0 to −1.3)	−0.9 (−3.8 to 2.0)	−2.1 (−4.9 to 0.8)	
Pulse, bpm				0.030
Δ from baseline to week 16	−5.0 (−6.9 to −3.2)	−6.5 (−8.4 to −4.6)	−6.6 (−8.4 to −4.7)	
Δ from baseline to week 68	−4.6 (−6.5 to −2.8)	−4.3 (−6.2 to −2.3)	−1.3 (−3.2 to 0.54)	
Fasting glucose, mmol/l				0.97
Δ from baseline to week 16	−0.38 (−0.50 to −0.27)	−0.22 (−0.34 to −0.10)	−0.36 (−0.48 to −0.25)	
Δ from baseline to week 68	−0.18 (−0.36 to 0.0028)	−0.15 (−0.33 to 0.028)	−0.17 (−0.34 to 0.013)	
Total cholesterol, mmol/l				0.25
Δ from baseline to week 16	−0.30 (−0.49 to −0.12)	−0.34 (−0.53 to −0.16)	−0.44 (−0.62 to −0.26)	
Δ from baseline to week 68	−0.052 (−0.23 to 0.12)	0.023 (−0.15 to 0.19)	−0.18 (−0.35 to −0.008)	
LDL cholesterol, mmol/l				0.23
Δ from baseline to week 16	−0.22 (−0.38 to −0.07)	−0.20 (−0.36 to −0.05)	−0.24 (−0.40 to −0.09)	
Δ from baseline to week 68	−0.014 (−0.15 to 0.12)	0.035 (−0.10 to 0.17)	−0.13 (−0.27 to 0.0077)	
HDL cholesterol, mmol/l				0.34
Δ from baseline to week 16	−0.03 (−0.09 to 0.03)	−0.05 (−0.12 to 0.008)	−0.11 (−0.17 to −0.05)	
Δ from baseline to week 68	0.022 (−0.038 to 0.082)	0.054 (−0.0062 to 0.11)	−0.0098 (−0.070 to 0.051)	
Triglycerides, mmol/l				0.36
Δ from baseline to week 16	−0.19 (−0.29 to −0.08)	−0.15 (−0.26 to −0.04)	−0.30 (−0.40 to −0.19)	
Δ from baseline to week 68	−0.17 (−0.29 to −0.049)	−0.073 (−0.19 to 0.048)	−0.19 (−0.31 to −0.068)	
C-reactive protein, mg/l				0.051
Δ from baseline to week 16	−1.03 (−2.06 to 0.01)	−1.89 (−2.92 to −0.85)	−0.63 (−1.67 to 0.40)	
Δ from baseline to week 68	−1.97 (−3.53 to −0.41)	−2.79 (−4.35 to −1.23)	−0.11 (−1.67 to 1.44)	
Weight, kg				0.0023
Δ from baseline to week 16	−12.0 (−13.5 to −10.5)	−13.0 (−14.5 to −11.5)	−13.3 (−14.8 to −11.8)	
Δ from baseline to week 68	−11.0 (−12.9 to −9.1)	−6.3 (−8.1 to −4.5)	−8.3 (−10.1 to −6.4)	
Body mass index, kg/m^2				0.0018
Δ from baseline to week 16	−4.4 (−4.9 to −3.9)	−4.7 (−5.2 to −4.1)	−4.8 (−5.3 to −4.2)	
Δ from baseline to week 68	−4.1 (−4.7 to −3.4)	−2.3 (−3.0 to −1.7)	−2.9 (−3.6 to −2.3)	
MET score[b]				0.34
Δ from baseline to week 16	2.29 (0.79 to 3.78)	2.98 (1.49 to 4.48)	3.26 (1.72 to 4.79)	
Δ from baseline to week 68	1.04 (−0.55 to 2.63)	2.28 (0.68 to 3.87)	2.66 (1.04 to 4.29)	
Sedentary activity minutes per day[c]				0.21
Δ from baseline to week 16	−37 (−63 to −11)	−49 (−75 to −23)	−40 (−67 to −13)	
Δ from baseline to week 68	−1.3 (−29.1 to 26.6)	−24.4 (−52.2 to 3.5)	−36.1 (−64.6 to −7.7)	

ANCOVA, ANalysis of COVAriance; LDL, low density lipoprotein; HDL, high density lipoprotein; bpm, beats per minute.
[a]The metabolic syndrome is defined according to the American Heart Association criteria.
[b]MET score is the metabolic equivalents score, which is the average score of activities during 24 h ranging from sleep with a MET score of 0.9 to activities such as running, playing tennis with MET scores >6.0.
[c]Minutes spent daily sitting quietly down, watching television, listening to music or reading, working at a computer or desk, sitting in a meeting, eating.

TABLE 4 Effects of the interventions on nutritional status and body composition in the study population

Variable	Diet ($n = 64$), Mean (95% CI)	Exercise ($n = 64$), Mean (95% CI)	Control ($n = 64$), Mean (95% CI)	*P*
P-25-OH-Vitamin D3, nmol/l				0.035
Δ from baseline to week 16	13.8 (10.5–17.1)	13.5 (10.2–16.7)	15.7 (12.5–19.0)	
Δ from baseline to week 68	28.5 (23.0–34.1)	18.7 (13.2–24.2)	20.6 (15.2–26.0)	
P-25-OH-Vitamin D3 <50 nmol/l				0.056
No. (%) at week 16	15 (24.6%)	12 (19.4%)	14 (22.2%)	
No. (%) at week 68	5 (8.2%)	15 (24.2%)	12 (19.0%)	
ΔP-cobalamins (Vitamin B12), pmol/l				0.054
Δ from baseline to week 16	28.8 (10.2–47.3)	59.4 (40.7–78.1)	32.8 (14.1–51.5)	
Δ from baseline to week 68	89.4 (60.4–118.3)	48.5 (19.4–77.6)	42.9 (13.8–72.0)	
P-cobalamins (Vitamin B12) <200 pmol/l				0.28
No. (%) at week 16	7 (10.9%)	8 (12.7%)	6 (9.5%)	
No. (%) at week 68	2 (3.1%)	6 (9.5%)	3 (4.8%)	
P-Ferritin, mikg/l				0.48
Δ from baseline to week 16	7.3 (−5.6 to 20.3)	2.8 (−10.2 to 15.8)	7.2 (−5.8 to 20.2)	
Δ from baseline to week 68	17.5 (3.9–31.1)	5.7 (−8.0 to 19.3)	12.4 (−1.2 to 26.1)	
P-Ferritin < 12 mikg/l				0.44
No. (%) at week 16	0 (0%)	0 (0%)	0 (0%)	
No. (%) at week 68	1 (1.6%)	3 (4.7%)	1 (1.6%)	
P-PTH, pmol/l				0.0006
Δ from baseline to week 16	−1.2 (−1.5 to −0.8)	−0.7 (−1.0 to −0.3)	−0.5 (−0.9 to −0.2)	
Δ from baseline to week 68	−1.02 (−1.4 to −0.67)	−0.03 (−0.38 to 0.32)	−0.54 (−0.89 to −0.19)	
P-PTH > 6.9 pmol/l, no. (%)				0.090
No. (%) at week 16	4 (6.3%)	15 (23.4%)	13 (20.3%)	
No. (%) at week 68	8 (12.5%)	18 (28.1%)	13 (20.3%)	
Lean body mass, g				0.66
Δ from baseline to week 16	−996 (−1,710 to −282)	−1,985 (−2,705 to −1,265)	−1,981 (−2,695 to −1,267)	
Δ from baseline to week 68	−1,010 (−1,456 to −565)	−874 (−1,323 to −424)	−1,169 (−1615 to −723)	
Fat mass, g				0.0010
Δ from baseline to week 16	−9,772 (−10,971 to −8,574)	−10,325 (−11,537 to −9,114)	−10,185 (−11,385 to −8,984)	
Δ from baseline to week 68	−8,985 (−10,569 to −7,401)	−4,797 (−6,398 to −3,195)	−5,978 (−7,565 to −4,391)	
Fat mass, %				0.0003
Δ from baseline to week 16	−5.5 (−6.3 to −4.7)	−5.6 (−6.4 to −4.8)	−5.3 (−6.1 to −4.5)	
Δ from baseline to week 68	−5.1 (−6.0 to −4.1)	−2.4 (−3.4 to −1.4)	−3.0 (−3.9 to −2.0)	
Bone mineral content, g				0.89
Δ from baseline to week 16	−10.2 (−41.5 to 21.2)	−6.8 (−38.5 to 24.8)	−20.1 (−51.5 to 11.3)	
Δ from baseline to week 68	−50.2 (−75.6 to −24.9)	−57.1 (−82.7 to −31.6)	−58.7 (−84.1 to −33.3)	
Bone mineral density, g/cm^2				1.00
Δ from baseline to week 16	0.0028 (−0.0029 to 0.0085)	0.0033 (−0.0024 to 0.0091)	0.0048 (−0.0009 to 0.011)	
Δ from baseline to week 68	−0.0034 (−0.0085 to 0.0018)	−0.0033 (−0.0085 to 0.0019)	−0.0033 (−0.0085 to 0.0018)	

PTH, parathyroid hormone.

feasible for a population with knee pain. This represents a challenge in dealing with individuals with concomitant obesity and knee OA. The poor compliance with the exercise program might very well represent a characteristic which is specific to an obese knee OA population and it raises concern about the feasibility of exercise interventions in these patients. The results of this study emphasize the crucial need to find ways to improve adherence to evidence-based exercise programs for patients with OA.

As previously stated, the risk of vascular events is higher in people with OA compared to people without OA (5). To our knowledge, this is the first randomized trial investigating the effectiveness of a weight loss and exercise lifestyle intervention on cardiovascular risk and nutritional status in an OA population. More than 70% of the participants in our study were classified as having the MS at baseline. Following the intervention only 40.6% of the participants in the diet group, 54.7% in the exercise group, and 53.1% of the

participants in the control group had the syndrome. This is a clinically important finding. Although no statistical significant difference was found between the groups, there was a trend toward a higher number of participants in the diet group experienced resolution of the syndrome following the intervention ($P = 0.22$). The reversal of the MS was usually due to a significant reduction in two components, namely waist circumference and systolic BP.

In several studies it has been shown that there is a relationship between BMC, BMD, and body weight (26). The effect of weight loss on BMC is controversial. Many studies have shown that when weight is lost intentionally or unintentionally, there will be a corresponding reduction in bone mass, which would in turn potentially increase the risk of osteoporosis and the risk of fractures (27-30). On the contrary, some studies show that weight loss—at least short-term (12 weeks) —does not have a negative impact on BMC (31). Loss of BMC has been found to be more related to loss of body fat mass ($r = 0.83$; $P < 0.0001$) than to loss of body weight ($r = 0.63$; $P < 0.0001$) (27). In a study by Pritchard et al. (28), changes in BMC were correlated with fat loss, both in interventions with diet (11.7 g BMC change/kg fat loss), and in interventions with exercise (11.4 g BMC change/kg fat loss). Skov et al. and Jensen et al. (27,29) showed that losses of BMC per kg fat mass loss were 15.8 g/kg and 16.5 g/kg, respectively. Our study showed that decreases in BMC were similar in both the diet, exercise, and control group during the 68-week intervention. The losses of BMC in relation to fat loss was 50.2 g/8.985 kg or 5.59 g/kg (1.8% of initial BMC) in the diet group, 57.1 g/4.797 kg or 11.90 g/kg (2.0%) in the exercise group, and to 58.7 g/5.978 kg or 9.82 g/kg (2.1%) in the control group. We found that the losses of BMC/kg loss of fat mass were smaller than others have previously reported. Additionally, we did not find statistically different changes in BMD at week 68, with a mean change in weight loss ranging from 4.5 kg to 12.9 kg. This lack of change in BMD following a major weight loss indicates that the risk of osteoporosis was not increased.

One risk factor for fractures in older persons with OA may be hypovitaminosis D, as established for the general population (32). In our study, vitamin D increased in all three groups, and fewer participants were deficient in vitamin D at the end of the study compared with baseline, where close to 50% of the participants were deficient (defined by plasma vitamin D3 below 50 nmol/l). The improvements and corrections of these vitamin deficiencies may very likely have been due to the formula products given in the initial phase of the study, as they were enriched with the recommended daily intake of all essential vitamins and minerals. Moreover, the participants were receiving intensive dietetic counseling which could have affected food choices in a positive way leading to a general healthier diet long-term. The participants in the diet group continued to receive one formula product a day during week 16 and 68 containing approximately 1/3 of the recommended daily intake of micronutrients. It is also possible that some of the improvements in vitamin D may be due to liberation of this vitamin from fat tissue during the weight loss (33). The increments in vitamin D may have contributed to the preserved BMD seen in this study. Apart from preserving BMD during weight loss, improvements in vitamin D might have additional positive effects, since vitamin D level has been associated with important CVD risk factors (34), and vitamin D may decrease disease progression in OA as seen in the Framingham cohort study (35).

Following the intervention applied in this study, most of the participants are still obese. Although, intentional and sustained weight loss of only 5% will lead to improvements in obesity-related disorders such as coronary heart disease risk factors and coronary heart disease (36), prevent diabetes mellitus type 2 in subjects with impaired glucose intolerance, and improve the management of hyperglycemia in patients with type 2 diabetes (37), these patients might achieve further benefits by losing additional weight and maintaining their weight at that level.

The strengths of this study include the randomized controlled design, large sample size, high compliance with the initial weight loss intervention, and the low attrition rate at follow-up. An important limitation is that the exercise program provided was not designed to have an effect of components of the MS. We used dual-energy X-ray absorptiometry to monitor bone loss, as it is the standard method of measuring BMD in both research and clinical settings. Thus, one limitation concerning the DEXA scans is that they do not provide any information about bone micro architecture (bone quality), which is an additional determinant of fracture risk (38). Although we acknowledge the limitations associated with the use of risk factors as surrogate measures, rather than monitoring patient-important outcomes (39), these are still the factors monitored in clinical practice when applying current treatment strategies both in lifestyle interventions as well as in pharmacological therapies (40).

In conclusion, dietary support weekly, or control with no attention for a year, both following a major weight loss, maintained improvements in cardiovascular risk factors to the same extent. The dietary support group maintained the reduction in waist circumference significantly better than the exercise group. The number of participants with MS was reduced in all groups. There was a general improvement in nutritional status in all groups, and vitamin D was improved significantly more in the diet group than in the two other groups, and none of the interventions had a detrimental effect on bone health. O

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