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ORIGINAL ARTICLE

Prevention of Incident Knee Osteoarthritis by Moderate Weight Loss in Overweight and Obese Females

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Objective. **This study evaluated the effect of moderate weight loss on the incidence of knee osteoarthritis (OA) in middle-aged overweight and obese women, without clinical and radiologic knee OA at baseline.**

Methods. **A total of 353 women (87%) with followup data available were selected from the Prevention of Knee Osteoarthritis in Overweight Females study, which evaluated the preventive effect of a diet and exercise intervention and of oral glucosamine sulfate on the incidence of knee OA. This was an exploratory proof-of-concept analysis, which compared the incidence of knee OA between women who reached the clinically relevant weight loss target of 5 kg or 5% of body weight after 30 months and those who did not reach this target.**

Results. **The weight loss group showed a significantly lower incidence of knee OA according to the primary outcome measure, which was composed of the American College of Rheumatology criteria (clinical and radiographic), Kellgren/Lawrence grade ≥2, and joint space narrowing ≥1.0 mm (15% versus 20%; odds ratio 0.5, 95% confidence interval 0.3–0.9). Moreover, the weight loss also positively affected several health measures, such as blood glucose level, body fat percentage, and blood pressure.**

Conclusion. **A reduction of ≥5 kg or 5% of body weight over a 30-month period reduces the risk for the onset of radiographic knee OA in middle-aged overweight and obese women. Because of the slow progression of the disease, a longer followup period will be necessary before the number of prevented cases of knee OA by moderate weight loss becomes clinically more relevant.**

INTRODUCTION

The worldwide prevalence of obesity nearly doubled between 1980 and 2008 (1). According to the most recent estimates by the World Health Organization, 35% of all adults are overweight (body mass index [BMI] ≥25 kg/m^2) and more than 12% are obese (BMI ≥30 kg/m^2) (1). A high BMI is a strong risk factor for the onset of knee osteoarthritis (OA) (2–4) and has been associated with the incidence of both clinical (5–7) and structural (8–13) features of knee OA. Given the high medical costs, productivity costs, morbidity, and disability associated with knee OA, there is an increasing need for preventive measures (14).

In trials among subjects with and without established knee OA, weight loss was shown to have advantageous structure-modifying, systemic, and clinical effects (15–21). In a systematic review on the effects of weight loss on knee OA patients, a weight loss of at least 5% of body weight was indicated for symptomatic relief (22). Losing 5 kg or 5% of body weight has also been indicated as the minimum weight loss necessary for a positive and clinically relevant effect on cardiovascular risk profile, including significant reduction of blood pressure and

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Significance & Innovations

- To our knowledge, this is the first time that the preventive effect of moderate weight loss (5 kg or 5% of body weight) on incident knee osteoarthritis (OA) has been studied.
- This study serves as a proof-of-concept that moderate weight loss can, in fact, prevent incident knee OA in a high-risk population of overweight and obese women.
- This article contributes to preventive studies in OA, which are lacking, especially in a primary care setting.

improved glucose tolerance (23). In subjects without knee OA but with overweight or obesity, and hence at high risk for developing knee OA, the preventive effect of such a clinically relevant weight reduction has never been studied. Using results from the Framingham Osteoarthritis Study, it has been estimated that moderate weight loss (approximately 5 kg) could reduce the onset of knee OA in overweight and obese subjects (24,25).

Recently, the first preventive trial in OA research, the Prevention of Knee Osteoarthritis in Overweight Females (PROOF) study, was undertaken (26). In this randomized clinical trial among middle-aged women with a BMI $\geq$27 kg/m^2 without knee OA at baseline, the effects of a diet and exercise program on the incidence of knee OA over 2.5 years was studied. The diet and exercise program did show favorable effects on body weight in the intervention group during the first year of the intervention, and indications of a preventive effect among subjects compliant with the intervention were found (26). The objective of the diet and exercise intervention was a structural weight reduction of 5 kg or 5% of baseline body weight.

The primary objective of the present study is to evaluate the effects of a clinically relevant reduction in body weight ($\geq$5 kg or 5%), irrespective of the original interventions, on the incidence of clinical and radiologic knee OA after 2.5 years in middle-aged overweight and obese women.

PATIENTS AND METHODS

For this study we used data from the PROOF study. A full description of the study protocol can be found elsewhere (26). In short, this 2.5-year followup study aimed to evaluate the preventive effect of a diet and exercise program and oral glucosamine sulfate (double-blind, placebo-controlled) on the onset of knee OA in a 2 $\times$ 2 factorial design. The study protocol was approved by the Medical Ethical Committee of Erasmus Medical Center. This article was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (27). For the present study, the predefined hypothesis, stating that losing 5 kg or 5% of baseline body weight had a preventive effect on knee OA, was tested.

Fifty general practitioners in Rotterdam, The Netherlands, contacted all women ages 50–60 years registered at their practice. All women who returned the reply card, reported a BMI $\geq$27 kg/m^2, and were interested in participating were sent additional information. One week later, these women were screened by phone to determine whether or not they met the study inclusion criteria. Inclusion criteria were 50–60 years of age, BMI $\geq$27 kg/m^2, not meeting American College of Rheumatology (ACR) criteria for OA (28), no contraindications for magnetic resonance imaging, no rheumatic diseases, not using a walking aid, not under treatment for knee symptoms, mastery of the Dutch language, and not taking oral glucosamine during the past 6 months. Here, ACR criteria concerned the clinical criteria only, since screening at this stage was done by phone. All other references to ACR criteria in the present article refer to those measured with clinical and radiographic data. All women eligible and willing to participate were invited to visit the research institute for informed consent procedure and baseline measurements. The period of recruitment ran from July 2006 until May 2009.

At baseline, body weight and height, waist circumference, and blood pressure were measured. Skin folds of the triceps were measured and used to calculate body fat percentage using the formula by Lean et al (29), which was considered the most reliable method based on simple anthropometric measurements in women.

$$\text{fat percentage} = (0.73 \times \text{BMI} + 0.548 \times \text{triceps skin fold}) + (0.27 \times \text{age}) - 5.9$$

A blood sample was taken to assess total blood cholesterol and glycosylated hemoglobin (HbA_{1c}) concentration, and Heberden's nodes on both hands were assessed. A standardized semiflexed posteroanterior radiograph of both knees was taken according to metatarsophalangeal protocol (30). All subjects filled out a questionnaire that included questions on knee symptoms, number of days with knee pain, past knee injuries, and postmenopausal status. Knee symptoms were defined as having any knee pain in the past 12 months. All measurements were repeated after 2.5 years of followup.

All tibiofemoral compartments of all knees were scored for knee OA by a researcher blinded to clinical outcomes (baseline and followup images at once, with known sequence), using the Kellgren/Lawrence (K/L) scale ($\kappa = 0.6$) (31). Also, alignment of the knee was assessed and varus alignment was defined as having an angle of less than 178 degrees on the baseline radiograph. Minimal joint space width (intraclass correlation 0.67–0.76) was measured digitally on each radiograph in each tibiofemoral compartment independently by 2 blinded researchers (JR and BCdV), according to the Lequesne method (32). Scores with a difference of $\geq$2.0 mm between the 2 readers were reevaluated by both readers at a consensus meeting. Joint space narrowing (JSN) was calculated for each tibiofemoral compartment by subtracting the mean score of both assessors at baseline from the mean score at followup.

Table 1. Baseline characteristics for weight loss and non–weight loss groups*

	Non–weight loss	Weight loss	*P*
Subjects, no.	292	61	
Mean ± SD age, years	55.8 ± 3.2	55.5 ± 3.2	0.42
Mean ± SD BMI, kg/m^2	32.0 ± 4.1	33.4 ± 4.3	< 0.01
Postmenopausal	69	73	0.33
Heberden's nodes in ≥1 finger	28	25	0.58
Knees, no.	584	122	
Kellgren/Lawrence grade 0	52	43	0.11
Kellgren/Lawrence grade ≥1	48	57	
History of knee injury	12	21	0.01
Knee OA symptoms†	31	33	0.75
Varus alignment‡	39	43	0.36

* Values are percentages unless otherwise indicated. BMI = body mass index; OA = osteoarthritis.
† Knee OA symptoms defined as having knee pain in the last 12 months.
‡ Varus alignment of the knee defined as an angle of <178 degrees on the baseline radiograph.

For the analyses, all subjects with the primary outcome measure and followup data on body weight available were selected. Baseline characteristics were tested for significant difference between the weight loss and non–weight loss groups using an independent *t*-test for linear measures and the chi-square test for dichotomous measures. Using the generalized estimating equation (GEE), which takes into account the association between knees within subjects, we compared the incidence of knee OA in subjects who reached the weight loss target of 5 kg or 5% body weight reduction at 2.5 years to subjects who did not. The predefined primary outcome measure was the incidence of knee OA, defined as the incidence of K/L ≥2 or ACR criteria (clinical and radiographic) or JSN ≥1.0 mm in the medial or lateral tibiofemoral compartment. JSN of 1.0 mm was chosen as the cutoff because the population concerned is a population without knee OA and thus with healthy cartilage thickness. We hypothesized that less than 1.0 mm would be of questionable clinical interest in this population. Since the initial screening was done by phone, we anticipated that a proportion of participants would meet the criteria of one of the components of the primary outcome measure at baseline. These participants would be included in the analysis, defining development of knee OA during the followup period as meeting the criteria of one of the other components of the primary outcome measure. As a sensitivity analysis, we also analyzed differences between the weight loss and non–weight loss groups for the separate items of the primary outcome measure. For these analyses, participants who met the criteria for that specific outcome measure at baseline were excluded. All GEE analyses were adjusted for the randomized groups of the initial PROOF study and their interaction and for K/L grade at baseline (0 versus ≥1), since it was shown to be related to the incidence of knee OA (26), and for those factors that were significantly different between the weight loss and non–weight loss groups at baseline. Results from these analyses were presented in odds ratios (ORs) with 95% confidence intervals (95% CIs). Baseline differences between the weight loss and non–weight loss groups were tested using Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. To evaluate the magnitude of the changes in clinical outcomes after a weight reduction of 5 kg or 5% of body weight, changes over the 2.5-year followup period on total cholesterol, HbA_{1c} level, body fat percentage, waist circumference, and blood pressure between the weight loss and non–weight loss groups were assessed using Student's *t*-test. All statistical analyses were performed using SPSS, version 20.0, with a *P* value less than 0.05 regarded as statistically significant.

RESULTS

After 2.5 years, the primary outcome measure and followup data on body weight was available for 353 women (87%). The reasons the remaining 54 participants were lost to followup were as follows: 1 was unavailable, 1 had no radiograph at baseline, 9 had no radiograph at followup, 38 were unwilling and dropped out during followup, 2 dropped out due to glucosamine side effects, 1 had no questionnaire data at followup, and 2 died during the course of the study. The participants who were lost to followup had a slightly lower BMI (mean ± SD 32.3 ± 4.1 versus 33.1 ± 5.0) and more often had a history of knee injury (14% versus 6%). Both of these differences were significant ($P < 0.05$). Of the other variables, there were no significant differences between the participants who were lost to followup and those who completed the study. Of those who completed the study, 61 (17%) fulfilled the weight loss target of 5 kg or 5% body weight. This group was defined as the weight loss group, which we compared to the other 292 participants, called the non–weight loss group. Baseline characteristics of both groups are presented in Table 1.

As expected, there was a proportion of participants with knee OA at baseline, which we knew from the initial screening by phone. A number of participants (3.9%) met ACR criteria at baseline and 6.6% of participants had a K/L grade of 2 or higher. As stated in the Patients and Methods section, these participants were not excluded from the analysis. However, for sensitivity analysis, these

Table 2. Incidence of knee OA for weight loss and non–weight loss groups*

	Incidence No./total no. (%)	Adjusted odds ratio (95% CI)†
Knee OA‡		
Weight loss group	18/122 (15)	0.50 (0.27–0.93)
Non–weight loss group	117/584 (20)	1
Kellgren/Lawrence grade ≥2		
Weight loss group	3/118 (3)	0.27 (0.08–0.90)
Non–weight loss group	33/545 (6)	1
American College of Rheumatology criteria		
Weight loss group	6/122 (5)	0.34 (0.09–1.32)
Non–weight loss group	41/584 (7)	1
Medial joint space narrowing ≥1.0 mm		
Weight loss group	6/122 (5)	0.65 (0.26–1.67)
Non–weight loss group	34/583 (6)	1
Lateral joint space narrowing ≥1.0 mm		
Weight loss group	7/122 (6)	0.74 (0.32–1.70)
Non–weight loss group	40/583 (7)	1

* Weight loss group defined as ≥5 kg or 5% weight loss and non–weight loss group as <5 kg or 5% weight loss. OA = osteoarthritis; 95% CI = 95% confidence interval.
† Analyses adjusted for randomized groups from the Prevention of Knee Osteoarthritis in Overweight Females study and their interaction, Kellgren/Lawrence grade and body mass index at baseline, and past injury. The non–weight loss group served as the reference group.
‡ Primary outcome measure and defined as incidence of Kellgren/Lawrence grade ≥2 or by American College of Rheumatology criteria (clinical and radiographic) or by joint space narrowing ≥1.0 mm.

participants were excluded from the analyses with the separate components of the primary outcome measure as the outcome measure.

At baseline, the mean BMI ($P = 0.01$) and the number of knees with a past injury ($P = 0.01$) were significantly higher in the weight loss group. Hence, the analyses were additionally adjusted for these variables. The weight change in the weight loss group over the 2.5 years of followup was -9.9 ± 5.7 kg on average (range -4.2 kg to -24.7 kg). In the non–weight loss group, subjects gained 1.8 ± 4.0 kg on average (range -4.8 to $+21.2$ kg). The mean change in BMI was <3.6 kg/m^2 in the weight loss group and $+0.7$ kg/m^2 in the non–weight loss group. Incidence figures of knee OA according to the primary outcome and the separate items and corresponding ORs for the weight loss group relative to the non–weight loss group are presented in Table 2.

Incidence according to the primary outcome measure was 20% in the non–weight loss group and 15% in the weight loss group (OR 0.50, 95% CI 0.27–0.93). Also, the difference in the incidence of a K/L grade ≥2 between the non–weight loss group (6%) and the weight loss group (3%) was statistically significant (OR 0.28, 95% CI 0.08–0.90). The other outcome measures showed no significant difference between the 2 groups.

Subjects in the weight loss group had a significant reduction in HbA_{1c} level (-1.4 versus 0.4 mmole/mole; $P = 0.03$), fat percentage (-4.7% versus -0.1%; $P < 0.01$), waist circumference (-7.3 cm versus 1.5 cm; $P < 0.01$), and systolic (-5.3 mm Hg versus 0.2 mm Hg; $P = 0.04$) and diastolic (-7.9 mm Hg versus -2.8 mm Hg; $P < 0.01$) blood pressure over the 2.5-year followup period compared to subjects in the non–weight loss group.

DISCUSSION

To our knowledge, this is the first time that the preventive effect of moderate weight reduction on incident knee OA in a high-risk group of middle-aged women with a BMI ≥27 kg/m^2 has been studied. Previously, 1 study reported a preventive effect of weight loss on cartilage thickness of the knee (18). However, this was an observational study without validated clinical or radiologic OA outcomes, making the results less applicable in clinical practice. Recently, a study reported on the preventive effect of an intensive diet and exercise program on knee pain and showed evidence of a preventive effect of a weight loss intervention on knee pain (33). However, knee OA figures were not presented since no radiographs were taken. Moreover, the present study reports on an effect of moderate weight loss, which makes it more applicable in primary care.

The intention-to-treat analysis of the original PROOF study showed no significant main effects of the diet and exercise program or the glucosamine versus placebo intervention on the incidence of knee OA over 2.5 years. The present study, as a proof-of-concept, shows that a clinically relevant weight reduction of 5 kg or 5% of body weight or more leads to significantly fewer incident cases of knee OA in overweight and obese women.

The PROOF study used a combined outcome measure of radiographic and clinical knee OA features in order to make a preventive randomized trial with a relatively short followup time feasible (26). In the non–weight loss group, 6% of all knees had incident radiographic knee OA (K/L ≥2) over the followup period. This annual incidence of 2.4% is at the high end of the range found in population-based cohorts using the same criterion, such as the

Framingham Osteoarthritis Study (2% in women) (34), the Rotterdam study (1.4% in men and women with a BMI >27.5 kg/m^2), the Chingford Women's Study (2.3% in women ages 45–64 years) (35), and the ROAD study (3.6% in women ages 50–59 years) (36). Only the ROAD study reported higher incidence numbers than our study, but these were calculated on a subject level rather than on a knee level. On a subject level, an annual incidence of 4% was found in the non–weight loss group. The incidence of clinical knee OA (clinical and radiographic) found in the present study (2.8% in the non–weight loss group) was higher than that reported in other studies (1% in women of the Framingham Osteoarthritis Study and 0.3% in middle-aged women) (34,37). This could possibly be explained by the fact that our study was conducted on overweight and obese subjects, who are at higher risk for the onset of knee OA than normal-weight individuals (2,3).

There is an obvious overlap between the incidence of JSN and of a K/L grade $\geq$2, given that JSN is part of the definition of a K/L grade $\geq$2. Nevertheless, we did not find a similar association between weight loss and incident JSN like we found for the incidence of a K/L grade $\geq$2. In addition to JSN, a K/L grade $\geq$2 requires definite osteophytes in the tibiofemoral joint. Previously, surplus fat mass has been linked to osteophyte formation, possibly through circulating leptin levels (38). Since circulating leptin level decrease after weight loss (38), it could be supposed that clinically relevant weight loss would lead to less osteophyte formation. Less osteophyte formation could explain why we found an effect of weight loss on the incidence of a K/L grade $\geq$2, and not for JSN.

At baseline, the weight loss group had a significantly higher BMI and reported a greater number of knees with a history of knee injury. The first was to be expected, since a high BMI is a predictor for greater weight loss (39,40). Probably, the higher prevalence of knees with a history of injury in the weight loss group was also linked to BMI; baseline BMI was significantly higher in subjects with a previously injured knee than in subjects without, and a history of injury was shown to have a nonsignificant effect on all outcome measures when adjusted for BMI at baseline (data not shown). Perhaps the former injury led to a less active lifestyle and, hence, a higher body weight.

Besides effects on the onset of knee OA, moderate weight loss also positively affected several health measures, such as blood glucose level, fat percentage, waist circumference, and blood pressure. Positive alterations in these features have been linked to reduced risk of type 2 diabetes mellitus and cardiovascular morbidity and mortality (41). However, the magnitude of the changes found was not high enough to reduce the 10-year risk of fatal cardiovascular disease (41). Maintenance of body weight in the weight loss group over a prolonged period would possibly lead to greater reductions in these health measures. Other limitations of this study include the observational design, which makes the results less applicable in clinical practice, since the intervention effect of the original randomized controlled trial was adjusted for in the analyses, thereby making this article a proof-of-concept. In addition, a limitation of this study is that an association is found between significant weight loss and the development of knee OA, which does not necessarily mean that a causal relation between these 2 variables exists. Confounding factors could distort this association. For example, a secondary analysis on data derived from the PROOF study showed, among other things, that participants with a relatively low body weight around their 40th year of life were more likely to lose weight during the study (42). This could mean that the group that lost 5 kg or 5% of their body weight is, in fact, a group of participants with an overall healthier lifestyle, which could account for the better health outcomes. However, the changes in health outcomes were measured during the period in which the participants lost weight. It is not expected that their blood pressure and HbA_{1c} level would lower spontaneously.

In conclusion, a reduction of $\geq$5 kg or 5% of body weight over a 30-month period is associated with a reduced risk of the onset of (radiographic) knee OA in middle-aged overweight and obese women. Also, several health measures were positively altered after this moderate weight loss. Due to the slow progress of the disease, a longer followup period will be necessary before the number of prevented cases of knee OA by moderate weight loss becomes clinically relevant.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Runhaar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Runhaar, Vroegindeweij, Oei, Bierma-Zeinstra.

Acquisition of data. Runhaar, van Middelkoop, Bierma-Zeinstra.

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