Reducing progression of knee OA features assessed by MRI in overweight and obese women: secondary outcomes of a preventive RCT

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Abstract

Objective: To evaluate the preventive effects of a randomized controlled trial on progression of Magnetic Resonance Imaging (MRI) features of knee osteoarthritis (OA) in overweight and obese women.

Design: In a 2x2 factorial design, the 2.5 years effects of a diet and exercise program and of glucosamine sulphate (double-blind, placebo-controlled) were evaluated in 407 middle-aged women with body mass index ≥ 27 kg/m^2 without clinical signs of knee OA at baseline (ISRCTN 42823086). MRIs were scored with the MRI Osteoarthritis Knee Score (MOAKS). Progression was defined for bone marrow lesions (BMLs), cartilage defects, osteophytes, meniscal abnormalities and meniscal extrusion. Analyses on knee level were performed over the four intervention groups using adjusted Generalized Estimating Equations.

Results: 687 knees of 347 women with mean age 55.7 years (± 3.2 SD) and mean BMI 32.3kg/m^2 (± 4.2 SD) were analyzed. Baseline prevalence was 64% for BMLs, 70% for cartilage defects, 24% for osteophytes, 66% for meniscal abnormalities and 52% for meniscal extrusions. The diet and exercise program + placebo intervention showed significantly less progression of meniscal extrusion compared to placebo only (12% vs 22%, OR 0.50, 95% CI [0.27 – 0.92]). The interventions did not result in significant differences on other OA MRI features.

Conclusions: In subjects at high risk for future knee OA development, a diet and exercise program, glucosamine sulphate and their combination showed small and mainly non-significant effects on the progression of OA MRI features. Only progression of meniscal extrusion was significantly diminished by the diet and exercise program.

Keywords: knee, osteoarthritis, diet, exercise, glucosamine, MRI

Introduction

Knee osteoarthritis (OA) is one of the leading causes of global disability[1], affecting about 10% of men and 13% of women aged > 60 years[2]. Due to the aging population and global epidemic of obesity, the prevalence of symptomatic knee osteoarthritis is likely to rise rapidly, with associated burden for society[1]. Current treatment options can diminish symptoms such as pain and disability, but a curative treatment is not available[3]. Increasing focus on preventive interventions should therefore be highly considered[4, 5].

To meet these demands, the results of the first preventive trial in osteoarthritis research were published recently[6]. The PROOF study (PRevention of knee Osteoarthritis in Overweight Females) evaluated the preventive effects of a diet and exercise program and of oral crystalline glucosamine sulphate on the incidence of knee OA in overweight and obese middle-aged women, without diagnosed knee OA at inclusion. With 2.5 years follow-up, the interventions showed no significant preventive effects on the primary outcome measure, incidence of clinical and radiographic knee OA. Only in a post-hoc analysis with additional data, crystalline glucosamine sulphate with or without the diet and exercise program reduced minimum joint space narrowing of the medial tibiofemoral compartment[7].

Because OA development is a gradual process and radiographic features are late manifestations, MRI features of OA may provide more direct insight in early joint changes[8]. MRI has shown to be more sensitive compared to Kellgren and Lawrence (K&L)[9] grading on posterior-anterior flexed knee radiographs in detecting structural knee OA[10] and is able to detect early OA features in asymptomatic persons without radiographic knee OA[11]. We hypothesized that, compared to clinical and radiographic criteria, MRI would provide more detailed insight in the initial development of knee OA and in the preventive effects of the interventions in this high-risk population. Therefore, the secondary outcome of the PROOF study was pre-defined as the effects of the interventions on OA MRI features[6]. The aim of the present study was to evaluate the preventive effects of a diet and exercise program and of oral glucosamine sulphate on the progression of knee OA MRI features in overweight and obese women between 50 - 60 years, without clinical knee OA at baseline.

Methods

Study design, setting and population

A description of the design and results of the PROOF study (ISRCTN 42823086) has been published previously[6, 7, 12]. This randomized controlled trial evaluated the preventive effects of a diet and exercise program and of oral glucosamine sulphate (double-blind, placebo-controlled) on the development of knee OA in 407 middle-aged (50 - 60 years) women with body mass index (BMI) ≥ 27 kg/m^2, in a 2x2 factorial design with 2.5 years follow-up. Participants were recruited by their general practitioner (GP) and had to be free of clinical knee OA (clinical American College of Rheumatology (ACR)-criteria[13]). They had to master the Dutch language and had to be free of severely disabling co-morbidities, free of inflammatory rheumatic diseases, not under treatment of a physical therapist or GP for knee complaints, not using walking aids, not using oral glucosamine for the last 6 months and free of contraindications for MRI. The Institutional Review Board of Erasmus MC University Medical Center Rotterdam approved the study. All participants gave written informed consent prior to baseline measurements.

Randomization and interventions

In this 2x2 factorial design, eligible patients were randomly assigned to either the intervention group of the diet and exercise program or to the control group and to either daily 1500mg oral crystalline glucosamine sulphate or to placebo. The description of the diet and exercise program, aimed to achieve weight loss in the intervention group, has been presented elsewhere[12]. It provided individual consultations by dieticians trained in Motivational Interviewing[14], who gave tailor-made advices for diet and physical activity. Participants were invited to participate in different physical exercise classes of low impact sports, such as Nordic walking, dancing and aqua jogging. These weekly 1-hour classes were supervised by a local physical therapist and offered during 20 weeks, spread over half a year period. Participants in the control group were not offered an intervention, but for ethical reasons, they were not actively discouraged to lose weight themselves. Crystalline glucosamine sulphate and placebo were provided by Rottapharm Madaus, Monza, Italy (not involved in any way in study design, data collection and statistical analysis) and identical in appearance, smell and taste; subjects and research staff were blinded for allocation. All women were asked to consume one sachet (1500mg powder) per day during the complete 2.5 years of follow-up. During home visits by a research assistant every six months, unused study medication was retrieved and the participants were provided with new supply.

Questionnaires and physical examination

At baseline, participants filled in a questionnaire to record demographic characteristics such as age, postmenopausal status, ethnicity and clinical characteristics such as history of knee injury, physical activity (measured with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH))[15] and knee complaints (“did you experience knee pain in the past 12 months?”). Body weight, body height and presence of Heberden’s nodes on both hands were assessed with a standardized physical examination by a research nurse at baseline and 2.5 years.

Radiography

Posterior-anterior radiographs of both knees were taken at baseline and 2.5 years, using the semi-flexed metatarsophalangeal (MTP) view[16]. K&L grading[9] and medial knee alignment[17] was scored on both radiographs at once (sequence known) by a trained researcher blinded for clinical outcomes and treatment assignment (MR and JR respectively). Normal alignment was defined as angles between 182° and 184°, valgus and varus alignment were defined as angles > 184° and < 182°

respectively[18]. The reproducibility of K&L grading (kappa 0.6) and knee alignment (kappa 0.7) was assessed by the independent scoring of a random subset of 20% of the radiographs by a second blinded researcher (JR or MR).

MRI acquisition and assessment

MRIs of both knees were made at baseline and 2.5 years on a 1.5 Tesla scanner. The MRI protocol included coronal and sagittal non-fat suppressed proton density weighted sequences (slice thickness 3.0 mm/slice gap 0.3 mm), a coronal T2 weighted Spectral Presaturation by Inversion Recovery (SPIR) sequence (slice thickness 5.0 mm/slice gap 0.5 mm), an axial dual spin-echo sequence (slice thickness 4.5mm/slice gap 0.5 mm) and a sagittal 3D water selective (WATS) sequence with fat saturation (slice thickness 1.5 mm). Baseline and follow-up MRIs were scored at once (sequence known) by two blinded researchers (JR human movement scientist, PvdP radiology trainee) using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS)[19]. They evaluated the following OA features: bone marrow lesions and cysts (BMLs), cartilage defects, osteophytes, meniscal abnormalities and meniscal extrusion. We defined meniscal abnormalities as meniscal morphologic abnormalities (tears, maceration, hypertrophy and cysts) and (degenerative) signal abnormalities. Meniscal extrusion was defined separately from meniscal abnormalities. Anterior, medial and lateral extrusion was scored on a 0 - 3 scale for the medial and lateral meniscus, where grade 0 = < 2mm, grade 1 = 2 – 2.9mm, grade 2 = 3 – 4.9mm and grade 3 = > 5mm. For implementing the MOAKS adequately, the two researchers were trained under supervision of an experienced musculoskeletal radiologist (EO: 10 years of experience with musculoskeletal MRI in clinical and research settings). This training has been described in detail previously[20]. The change of the individual OA MRI features was scored using the recently proposed definitions for longitudinal evaluation of OA MRI features (see Appendix table 1)[20], in which the average prevalence-adjusted bias-adjusted kappa (PABAK) values per feature showed ‘substantial’ to ‘nearly perfect agreement’ (range 0.77 – 0.88, observed agreement 89% - 94%)[20]. For the present study, the subregional change scores (1 for progression, -1 for improvement and 0 for no change) were summed over the different MOAKS subregions into an overall measure of change per feature. The summed change scores per feature were dichotomized into progression versus no progression (change score ≥ 1 = progression, change score < 1 = no progression). The tibiofemoral (TF) and patellofemoral (PF) joint were combined for the assessments, as well as the medial and lateral meniscus.

Outcome measures

The outcome measures of this study were pre-defined secondary outcome measures of the original PROOF study. They were defined as the effects of the four intervention groups (diet and exercise program control + placebo group, diet and exercise program control + glucosamine sulphate group, diet and exercise program intervention + placebo group and diet and exercise program intervention + glucosamine sulphate group) on the progression of the following OA MRI features: BMLs, cartilage defects, osteophytes, meniscal abnormalities and meniscal extrusion.

Statistical Analysis

Participants with an available MRI at baseline and 2.5 years of one or both knees were included and analyzed on the basis of a modified 'intention to treat' (ITT) approach, i.e. including all women with available MRIs. Descriptive data were presented as mean ± standard deviation (SD) or as numbers (percentages). Because of a significant interaction between both interventions on the primary outcome (clinical and radiographic knee OA) of the original PROOF study, described extensively in an earlier publication[6], the secondary outcome analyses were performed conform the approach for the primary outcome, over the four separate groups. Subjects in the diet and exercise program control + placebo group were defined as reference. Differences in baseline variables among the groups were analyzed with one-way analysis of variance or with the chi-squared test. We performed uni- and multivariable regression analyses on knee level with Generalized Estimating Equations (GEE), taking into account the association between two knees within one person. Firstly, the unadjusted effects on progression of OA MRI features were determined for the four groups. Secondly, the analyses were adjusted for the presence of the corresponding baseline MRI feature and for possible baseline differences. Since the outcome measure of this paper differs from the primary outcome of the PROOF study, we performed a sensitivity analysis to examine the interaction between the two interventions on the progression of MRI features. In case of no significant interaction, the effects of the two interventions were additionally analyzed with GEE (unadjusted and adjusted). For explorative reasons, we evaluated the progression rates within the four separate groups for the medial and lateral TF joint and the PF joint separately. Statistical analyses were performed with SPSS 21.0 (Chicago, IL). P values of less than 0.05 were considered statistically significant.

Results

Characteristics of the study population

Of the 407 women, 60 (14.7%) were lost to follow-up for current analyses. The main reason was no further time available or interest in the study (48 women, 80%). Other reasons (12 women, 20%) were claustrophobia (3 women), unattainability (6 women) and insufficient MRI quality (1 woman). Two persons deceased during follow-up (death not related to study). Additionally, seven knees were excluded for analyses due to a recent severe knee trauma (n = 1), a prosthetic knee replacement (n = 1) or to inability or unwillingness to continue MRI scanning of the second knee (n = 5). This resulted in the analysis of 687 knees of 347 women. Comparison of baseline characteristics (table 1) between missing and non-missing knees showed a significantly lower prevalence of any cartilage defect in the missing knees (58.3% vs 70.1%, p = 0.020). Mean age was 55.7 ± 3.2 years and mean BMI was 32.3 ± 4.2 kg/m^2. K&L ≥ 2 was present in 6% of the knees. Prevalence of OA MRI features ranged from 24% to 70%. Statistically significant baseline differences between the intervention groups were found for the presence of BMLs (p = 0.015), cartilage defects (p = 0.003) and meniscal extrusion (p = 0.049).

After 2.5 years, both progression of BMLs and cartilage defects was found in 30% of 687 knees, progression of osteophytes was found in 17%. Progression of meniscal abnormalities and meniscal extrusion was found in 28% and 17% respectively.

Intervention effects of the four groups on progression of MOAKS features

Table 2 shows the ORs of the intervention effects for the four groups. The diet and exercise program intervention + placebo group showed statistically significantly less progression of meniscal extrusion compared to the reference group (12% vs 22%, adjusted OR 0.50 [0.27 – 0.92]). The other intervention groups did not demonstrate any statistically significant differences in progression of all of the other OA MRI features.

Interaction and effects of the two interventions on progression of MOAKS features

In contrast to the paper on the primary outcome of the PROOF study[6], there was no statistically significant interaction between the two interventions on progression of any of the different MRI features (p-values ranged from 0.06 – 0.88). Therefore, the effects of the two interventions were additionally analyzed (table 3). The diet and exercise program intervention group demonstrated significantly less progression of meniscal extrusion compared to the control group (13% vs 21%, adjusted OR 0.59 [0.38 – 0.91]. The diet and exercise program intervention did not affect the progression of the other MRI features in comparison to the control group. Glucosamine had no preventive effect on the progression of any of the different MRI features compared to placebo.

Explorative analyses

Progression rates in the medial and lateral TF joint and the PF joint are presented in table 4. Progression rates ranged from 1% in the diet and exercise program intervention + placebo group for lateral meniscus extrusion to 26% in the diet and exercise program intervention + glucosamine group for PF BMLs. Overall, progression rates seemed to be higher in the medial than in the lateral TF joint. For cartilage defects and BMLs, the highest progression rates were found in the PF joint.

Discussion

Summary

This study evaluated the preventive effects of a tailored diet and exercise program and of oral crystalline glucosamine sulphate on progression of OA MRI features over 2.5 years among overweight and obese middle-aged women without clinical knee OA at baseline. The diet and exercise intervention in combination with placebo resulted in significantly less progression of meniscal extrusion compared to placebo only. Also, when analyzing both interventions separately, the diet and exercise intervention showed a significant preventive effect on progression of meniscal extrusion. Progression of the other MRI features was not significantly influenced by glucosamine sulphate, the diet and exercise program, or their combination.

Context and comparison with existing literature

Our baseline results showed a considerable amount of OA MRI features in this high-risk group of women without clinical knee OA. Other MRI studies have analyzed pre-osteoarthritic populations[11, 21-23], but only the study by Sowers et al. was performed in a cohort of women only[23]. The percentages of cartilage lesions in these studies varied from 57 – 81%[11, 21-23], comparable to the amount of lesions in our population (70%). The amount of BMLs ranged between 39 – 75%[11, 21, 22], which is similar to the amount in our study (64%). Only compared to Sowers et al[23], BMLs were more prevalent in our study (64% compared to 39%). This difference is likely due to higher age and BMI in our study and to differences in the semi-quantitative scoring. Sowers et al. did not score bone marrow cysts, while MOAKS scores both bone marrow lesions and cysts. Further, the women in our study showed fewer osteophytes compared to the Framingham Osteoarthritis Study[11] and the Multicenter Osteoarthritis Study (MOST)[21] (24% compared to 74% in the Framingham cohort and almost 100% in MOST). This might be due to differences in age and differences in the semi-quantitative scoring. MOST scored mild osteophytes while we only scored osteophytes grade ≥ 2 as definite osteophyte. Meniscal extrusions (52%) and abnormalities (66%) were more prevalent in our study than in other studies among pre-OA subjects (18% - 24%)[11, 22]. This is likely due to a higher BMI in our study (32.3 kg/m^2 vs 26.7 kg/m^2 – 27.9 kg/m^2), an association that has been found previously in studies evaluating BMI and meniscal abnormities and extrusion[24-26].

Our results showed a lack of significant differences in all outcome measures, except for the progression of meniscal extrusion. Both the analysis of the four separate groups as the two intervention groups showed significantly less progression of meniscal extrusion in the diet and exercise intervention group with or without placebo, compared to the controls. Although the number of knees with progression of meniscal extrusion was relatively low, the relative change was large. The intervention group with or without placebo showed almost half the amount of progression compared to controls. This preventive effect was no longer significant when the diet and exercise intervention was combined with glucosamine (adjusted OR 0.56 [0.31 – 1.03]). In contrast to the interaction on the primary outcome of the PROOF study, there was no significant interaction between the two interventions on the progression of MRI features. Therefore, this finding cannot be explained by such a mechanism and this result is not well understood. Separately, glucosamine did not have a preventive effect on progression of meniscal extrusion.

The non-significance in the diet and exercise group on the four other outcome measures can most reasonably be explained by low adherence for the diet and exercise program and only a mild weight loss. The retention rates for follow-up measurements were high (85%), but only 28% of the initial 203 randomized women in the PROOF study were compliant to the diet and exercise program (≥ 6 dietary consultations and ≥ 7 exercise classes) and showed a weight loss of 1.4 ± 5.2kg versus 0.0 ± 6.7 kg in the control group (p = 0.01)[6]. Although mean attended dietician consultation was 6.9 ± 4.9 and mean attended physical activity class was 7.3 ± 6.3, the amount of attendance varied widely[12]. Instead of strictly dictating the participants about their exercises and diet, the intervention was based on a pragmatic approach in order to simulate everyday clinical practice, but the lack of strict and continued controls might have negatively influenced the adherence rates.

The diet and exercise program showed a preventive effect on the progression of meniscal extrusion. The underlying mechanisms causing extrusion is largely unknown, but is often a sign of meniscus degradation and considered as the end result of pre-existing meniscal damage[27]. Exercise programs can increase upper leg muscle strength and improve knee stability[28, 29], which might both have protective effects on the rate of meniscal extrusion. In addition, physical exercise and a weight lowering diet have local and systemic anti-inflammatory effects[30, 31]. A lower inflammatory joint status may prevent that prevalent meniscal damage like tears, (degenerative) signal abnormalities and maceration results in (end-stage) meniscal extrusion[32].

We have taken into account all levels of extrusion (MOAKS 1 – 3) and not only pathologic extrusion (MOAKS ≥ 2), with the aim to detect all progression in these women without established knee OA. Whether less progression of meniscal extrusion reduces the development of knee OA cannot be concluded from this study. Systematic reviews among knee OA patients showed that meniscal damage (extrusion/maceration) was a prognostic factor for radiographic knee OA but not for clinical knee OA[33, 34]. Both these findings were based on limited evidence and more studies are definitely needed. Longitudinal studies in subjects with and without knee OA showed that meniscal extrusion was an independent predictor of cartilage loss[24, 35-38], due to altering of the load bearing, shock absorbing and stability function of the meniscus[39]. Recently, a narrative review has described the influence of joint inflammation on the pathway from meniscal lesions to osteoarthritis[40] and suggested that joint inflammation has, either direct (meniscal damage) or indirect (obesity or ageing), an important additional negative effect on the rate at which meniscal extrusion leads to cartilage degradation. In this light, influencing joint inflammation through a diet and exercise program might be a worthwhile target in the prevention of knee OA development. The clinical and radiographic long-term follow-up data of the present population (currently being collected) might provide insight whether less progression of meniscal extrusions will result in less clinical and radiographic knee OA.

Strengths and limitations

This study has a number of limitations. Firstly, instead of a true ITT analysis, we used a modified ITT analysis, since only women with baseline and follow-up MRIs available were included. Secondly, the progression of MOAKS features is based on recently developed definitions of longitudinal change per subregion. These are the only developed definitions, but have not been validated yet against clinical and other structural outcomes[20]. In addition, certain feature grades within the MOAKS reflect a wide range of severity[19]. As a result, within-grade progression may remain unnoticed when using the proposed progression definitions. Moreover, we summed all progression scores of the different subregions to score the change of the specific MOAKS feature for the whole knee. Consequently, detailed information about the number of affected regions or the degree of change per subregion is not visible anymore. Also, some subregions might be more at risk for developing progression of certain MOAKS features than others[41]. Therefore, we evaluated progression rates within the randomized groups for the medial and lateral TF-joint and PF-joint separately. Given the low progression rates within these compartments (especially lateral), effect differences between intervention groups were not statistically tested. However, these explorative results suggest that progression rates for the different features in the medial knee compartment are lower among the women in the diet and exercise program intervention + placebo group compared to the controls. Furthermore, they show that the overall progression rates of cartilage defects and BMLs are at least twice as high in the PF-joint compared to the medial and lateral TF-joint. These observations suggest that the PF-joint is predominantly affected in overweight and obese women at risk for knee OA.

Another limitation is represented by the significant baseline differences between groups for the prevalence of OA MRI features. These were evident not only for meniscal extrusions, but especially for BMLs and cartilage defects. Although our statistical analysis adjusted the data for this imbalance, these early MRI features have been shown to predict a greater risk for OA progression[42] and it is therefore unknown whether this influenced the results for both of the interventions.

Furthermore, we are aware of the relatively large number of analyses performed, especially when testing the four different groups. This has resulted in an increased family-wise error rate. This probability might be decreased by the fact that the effects for the two interventions are in line with the results of the four groups, but still a type-I error cannot be fully neglected. However, hopefully the detailed description of these secondary outcome measures will be of valuable input for the design of future preventive OA trials.

As discussed, the poor adherence rate and only mild weight loss may have been improved when more continued contacts were offered during the diet and exercise intervention. Although the approach simulated everyday clinical practice, we recommend more strictly regulated contacts when starting a weight loss intervention in overweight and obese women, to prevent low compliance rates in future preventive studies.

Finally, despite the fact that the included women were free of clinical knee OA at initial screening, 43 of 687 knees (6%) had K&L grade ≥ 2 at baseline. As a very pragmatic design was chosen, with high comparability to clinical practice, these 47 knees were included in the analyses. When we performed the analyses including only knees with K&L grade ≤ 1, the obtained results did not change (data not shown).

Conclusions and implications

This study of overweight and obese middle-aged women without clinical knee OA showed a high prevalence of OA MRI features. In this population at high risk of knee OA development, a diet and exercise program only showed a significant effect on the progression of meniscal extrusion; subjects randomized to a diet and exercise program intervention had less progression of meniscal extrusion compared to controls. Glucosamine sulphate or the combination of glucosamine sulphate and the diet and exercise program did not show preventive effects on progression of any of the MRI features under investigation. Follow-up data of the present population need to confirm whether the women with less progression of meniscal extrusions will subsequently develop less clinical and radiographic knee OA.

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Author contributions

ML contributed to the analysis and interpretation of data, writing of the manuscript and final approval of the article. JR contributed to the conception and design of the study including collection and assembly of data, scoring of the MRIs, analyses and interpretation of data and critical revision of the article for important intellectual content. SBZ contributed to conception and design of the study including obtaining of funding, analyses and interpretation of data and critical revision of the article for important intellectual content.

MvM, BK, PB, EO, DV contributed to the conception and design of the study and to the critical revision of the article for important intellectual content. PvdP contributed to the scoring of the MRIs and to the critical revision of the article for important intellectual content. All authors approved the final version of the manuscript.

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Competing interest statement

All authors declare no conflicts of interest.

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