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Brief Report

The association between meniscal body extrusion and the development/enlargement of bone marrow lesions on knee MRI in overweight and obese women

Fan Zhang [a,*], Sita M. Bierma-Zeinstra [b,c], Edwin H.G. Oei [d], Aleksandra Turkiewicz [a], Martin Englund [a,e,1], Jos Runhaar [c,1]

[a] Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Orthopaedics, Clinical Epidemiology Unit, Lund, Sweden
[b] Department of Orthopaedics, Erasmus MC University Medical Center, Rotterdam, the Netherlands
[c] Department of General Practice, Erasmus MC University Medical Center Rotterdam, the Netherlands
[d] Department of Radiology & Nuclear Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands
[e] Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, Boston, MA, USA

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ABSTRACT

Objective: To determine the association between meniscal body extrusion and bone marrow lesion (BML) development/enlargement in overweight and obese women at high risk of knee osteoarthritis (OA).
Design: We used baseline and 30 months follow-up data of the PROOF study, Netherlands, comprising overweight or obese women aged 50–60 years, free of clinical knee OA. All subjects (n = 395) completed a questionnaire on knee complaints and physical activity, underwent physical examination, radiography, and repeated 1.5 T MRI of both knees. Using the mid-coronal MRI slice, one observer measured tibial plateau width and meniscal body extrusion of both menisci in both knees. BMLs and meniscal damage were read using the semi-quantitative MOAKS scoring system by another observer. The association between BML development and meniscal extrusion was primarily analyzed with a random-effects logistic regression model adjusted for age, body weight, body height, physical activity, meniscus damage, knee alignment, and tibia width. In addition, we used a fixed-effect regression model for evaluation of knee-specific factors.
Results: In our primary model, there was about 24% increased risk of BML incidence/enlargement per 1 mm extrusion (95% confidence interval [CI] 0.99, 1.57) for medial compartments and 69% risk increase (95% confidence interval [CI] 1.27, 2.25) for the lateral compartments. Results from the fixed-effects regression model were similar, strengthening the validity of the findings.
Conclusions: Meniscal body extrusion is an important factor influencing BML development/enlargement, and thus may be a potential treatment target in knee OA development.

1. Introduction

There is often an unclear relationship between different magnetic resonance imaging (MRI) features of osteoarthritis (OA), e.g. between meniscal extrusion and bone marrow lesions (BMLs).

The most common definition of non-traumatic BML is described as ill-defined signal alterations adjacent to the subchondral plate on MRI [1]. BMLs in the knee are associated with either acute knee trauma [2], or more chronic conditions that may be associated with abnormal load transfer conditions [3] but have also been reported to be due to effects of drugs [4]. The abnormal histological changes in OA-related BMLs include necrosis, edema, trabecular abnormalities and fibrosis [5].

Meniscal extrusion is generally considered as pathological when the external margin of the meniscus body exceeds the margin of the tibial plateau by > 3 mm [6,7]. A previous cross-sectional study has suggested that there is a strong association between meniscal derangement and the presence of ipsilateral BMLs [8]. Further, in subjects with knee OA two previous longitudinal studies have suggested that meniscal pathology,

* Corresponding author. Clinical Epidemiology Unit, Orthopaedics, Remissgatan 4, Wigerthuset, SE-221 85, Lund, Sweden.
E-mail addresses: augustus2000@126.com (F. Zhang), s.bierma-zeinstra@erasmusmc.nl (S.M. Bierma-Zeinstra), e.oei@erasmusmc.nl (E.H.G. Oei), aleksandra.turkiewicz@med.lu.se (A. Turkiewicz), martin.englund@med.lu.se (M. Englund), j.runhaar@erasmusmc.nl (J. Runhaar).
[1] Equal contribution as senior authors.

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including both meniscal maceration and meniscal body extrusion, increases the risk for development of structural changes such as BMLs [9,10]. However, these important observational findings need to be confirmed in more datasets, in particular also in subjects without clinical knee OA at baseline.

Obesity is regarded as an important risk factor for OA development. Thus, the aim of this study was to determine the effect of meniscal body extrusion on the development of new BMLs, or the enlargement of pre-existing BMLs, in a sample of overweight and obese women *without* clinical knee OA.

2. Methods

2.1. Study sample

Data of this study were obtained from baseline and 30 months follow-up data of the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study, the Netherlands [11]. The PROOF trial (ISRCTN 42823086) was originally designed to evaluate the effects of a diet, exercise program and glucosamine sulphate on the development of clinical knee OA. The trial comprises 407 female subjects. The PROOF trial's main inclusion criteria were as follows:

- Age between 50 and 60 years.
- Free of knee OA according to the clinical ACR criteria [12] for knee OA
- Body mass index (BMI) $\geq$27 kg/m2

The subjects completed a questionnaire on knee complaints and physical activity, had a physical examination, and they underwent radiography, and 1.5 T MRI of both knees. The PROOF trial was approved by the ethics committee at the Erasmus MC University Medical Center Rotterdam, the Netherlands.

2.2. MRI protocol

MRIs of both knees were acquired at baseline and 30 months follow-up on a 1.5 T MRI scanner (Siemens Symphony/Magnetom Essenza and Philips Intera scanners were used with a dedicated rigid knee coil). Coronal and sagittal non-fat-suppressed proton density weighted sequences were included in the protocol (slice thickness 3.0 mm/slice gap 0.3 mm/repetition time (TR) 2700 ms/echo time (TE) 27 ms/matrix size (M) 320 $\times$ 320/field of view (FOV) 16.0 cm). Furthermore, a coronal T2 weighted Spectral Presaturation by Inversion Recovery (SPIR) sequence (slice thickness 5.0 mm/slice gap 0.5 mm/TR 5030 ms/TE 71 ms/M 256 $\times$ 256/FOV/16.0 cm), an axial dual spin-echo sequence (slice thickness 4.5 mm/slice gap 0.5 mm/TR 3500 ms/TE 25/75 ms, M 256 $\times$ 256/FOV 16.0 cm) and a sagittal 3D water selective (WATS) sequence with fat saturation (slice thickness 1.5 mm/TR 21.4 ms/TE 8.0 ms/M 320 $\times$ 320/FOV 16.0 cm) were performed.

2.3. MRI measurements

We used the same two-dimensional quantitative measurement method of meniscal body extrusion as in a previous study [12]. In brief, one observer (FZ) blinded to subject characteristics and clinical data, assessed the menisci on mid-coronal intermediate-weighted turbo spin-echo (IW TSE) MR images (both left and right knees). The data gathered included the width of tibial plateau (from the margin of the tibial plateau excluding any osteophytes), both medial and lateral meniscus coronal width and meniscal body extrusion to the closest 0.1 mm using Sante DICOM Editor (64-bit) software. Thirty randomly selected knees were reassessed by the same and another observer for the purpose of reliability.

MRIs were scored for BMLs by two trained readers as well as an experienced musculoskeletal radiologist using the MRI Osteoarthritis Knee Score (MOAKS), which is a semi-quantitative MRI OA scoring method with high inter-observer reliability [12,13]. Baseline and follow-up MRI scans were scored at the same occasion, with known sequence, but with readers blinded for clinical details. Upon reading all MRI scans, evolution of BMLs was defined using previously published definitions [12]. In brief, for each MOAKS defined subregion in the tibiofemoral compartment, incidence/progression of BML over the follow-up period was defined as either the incidence of a cyst or a BML in a compartment without BML at baseline, or increase in the score for the size of the BML, or only in few instances, an increase in the number of BMLs in the compartment when size was unchanged.

Our outcome variable, on compartment level in each knee, was dichotomized (yes/no) into either incident/enlarging BML or *no* incident/enlarging BML (i.e., containing both stationary and regressing BMLs).

2.4. Covariates

Apart from the knee specific covariates: ipsilateral meniscal tear, damage or prior meniscus resection (yes/no), tibia width and knee alignment, we included the following person-specific covariates: age, body weight, body height, and physical activity level. Body weight was measured to the nearest kg and body height to the nearest cm. The physical activity level was assessed using the validated SQUASH (the Short Questionnaire to Assess Health-enhancing physical activity) questionnaire.

2.5. Statistical methods

We used two types of models for statistical analysis. In model 1, a mixed-effects logistic regression, all persons with non-missing data were included. Apart from the knee-specific covariates (ipsilateral meniscus damage, tibial width, and knee alignment), we adjusted for the following person-specific covariates: age, body weight, body height, and physical activity. As sensitivity analysis we repeated this model with adjustment for knee injury during the follow-up period.

In model 2, a fixed-effects logistic regression, only persons with discordant knee outcome were included (i.e. BML progression in one knee but not in the other) [14]. In this model only knee-specific covariates were included, because all potential confounding at the person level (both measured and unmeasured) was taken care of through the model specification. The power in this model is however lower (because no data on between subject variation are used and only persons with discordant knees are included). We consider this model as a sensitivity analysis to evaluate if the results of the mixed-effects model could be confounded by unmeasured person-specific factors.

The presented estimates are odds ratios (ORs) with 95% confidence intervals (95% CIs). As the occurrence of incident/enlarging BMLs was low (less than 10%) these ORs can be interpreted as risk ratios.

3. Results

Twelve subjects out of the baseline cohort had missing or unreadable MR images and were thus excluded. The mean (SD) age of the final study cohort (n = 395) at baseline was 55.7 (3.2) years and the mean (SD) BMI was 32.4 (4.3) kg/m2. Among the 790 knees, 313 (40%) had varus malalignment, anatomical knee alignment angles between 182° and 184° were defined as normal, >184° as valgus alignment and <182° as varus alignment, while 98 (12%) had valgus malalignment, 246 (31.1%) knees were reported an affirmative answer (yes) to the question: "Have you experienced pain in or around the knee during the last 12 months?", 100 (12.6%) had a history of knee injury, and 339 knees (43%) had a Kellgren Lawrence (KL) grade 1, 49 (6%) knees with KL grade 2 and 5 (0.6%) knees with KL grade 3) (Table 1).

The outcome value (incident/enlarging BMLs in the tibiofemoral compartment) was missing in 68 persons (17%), 127 knees (16%) and

Table 1
Characteristics of the study subjects at the baseline exam.

Characteristic	
Women (n = 395)	
Age, mean (SD) years	55.7 (3.2)
Body mass index, mean (SD) kg/m2	32.4 (4.3)
Physical activity[a], mean (SD)	6837 (3714)
Knees (n = 790)	
Varus malalignment, n (%)	56 (7.1)
Valgus malalignment, n (%)	299 (37.8)
History of knee injury, n (%)	100 (12.6)
Kellgren-Lawrence grade ≥1, n (%)	393 (49.7)
Quadriceps muscle strength, mean (SD) Newton	253 (47)
Mild knee symptoms, n (%)	246 (31.1)
Meniscus tear, medial, n (%)	71 (9)
Meniscus tear, lateral, n (%)	39 (5)

[a] Measured with the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) questionnaire.

254 compartments (16%), mainly due to no knee MRI obtained at the follow-up time point. Of the 110 compartments with incidence/progression of BML, in 8 compartments the size of BML at follow-up was graded as 3, in 14 compartments graded as 2 and in the rest of compartments as 1. Of the 110 compartments that had incidence/progression of BMLs, 50 (45%) were diffuse-only (diffuse-only is defined as not having a cyst at follow-up).

Intra-observer reliability (intra-class correlation coefficient) and inter-observer reliability (absolute agreement) for the tibial plateau width, medial and lateral meniscus width, medial and lateral meniscal extrusion ranged from 0.69 to 0.98 and 0.62 to 0.96, respectively.

3.1. Medial compartment

In the primary mixed-effects regression analysis, 63 knees had an incident/enlarging BML with a multivariable OR of 1.24 (95% CI 0.99, 1.57) for the meniscal extrusion parameter, i.e. a 24% increased likelihood of incident/enlarging BML per 1 mm extrusion. The sensitivity analysis with adjustment for knee injury yielded the OR of 1.27 (95% CI 1.02, 1.59). The multivariable effect estimate from the fixed-effect regression model was similar (OR 1.19, 95% CI 0.81, 1.76) for the meniscal extrusion parameter suggesting that there was no substantial confounding from unmeasured person-level factors (Table 2).

3.2. Lateral compartment

In the primary mixed-effects regression analysis 42 knees had an incident/enlarging BML with a multivariable odds ratio of 1.69 (95% CI 1.27, 2.25) per 1 mm larger extrusion. The sensitivity analysis with additional adjustment for knee injury yielded the effect estimate of 1.70 (95% CI 1.27, 2.26) (Table 2).

The multivariable fixed-effects analysis confirmed the findings from the primary model with an odds ratio of 1.89 (95% CI 1.08, 3.31) for the meniscal extrusion parameter.

4. Discussion

BMLs are common and often clinically important features in knee OA [15]. It has also received increased attention as a potential target for drug development. Although its pathogenesis is not fully understood, it may hypothetically often represent pathological changes due to excessive focal loading. In our study, we evaluated the association between meniscal body extrusion (as a measure of meniscal function) and incident/enlarging BMLs in overweight and obese women without clinical knee OA (in contrast to prior longitudinal reports). We used a semi-quantitative measurement technique to evaluate BML development/enlargement, and our findings confirm and extend those from the two prior longitudinal studies in subjects with knee OA that there is an association with incident/enlarging BML in the ipsilateral tibiofemoral compartment [9,10]. This finding supports a biomechanical component or adiposity related inflammation in the development and enlargement of BMLs of the more chronic type in knees with suboptimal meniscal function, in particular as high body weight seems to be associated with increased risk as well (Table 2).

The first longitudinal study in this field is from the Multicenter Osteoarthritis Study (MOST) dataset which suggested higher relative risks were associated with more severe and with lateral meniscal pathology [10]. More recently, findings from an ancillary study including subjects with knee OA only from the Osteoarthritis Initiative (OAI) confirmed the important role of intact meniscus integrity and normal position [9]. In line with the findings from MOST, our point estimates suggest a slightly stronger association between meniscal extrusion and BML development in the lateral compartment maybe due to the fact that PROOF only has overweight and obese subjects. This corroborates the more critical role of the lateral meniscus in load distribution as compared to the medial, and thus loss of lateral meniscus position (in the more concave lateral tibial surface) seems to be more detrimental than the corresponding loss of meniscus function in the medial compartment.

We would like to comment on some limitations. Our study sample size was relatively limited (and we had approximately 16% with missing data on our outcome), and thus the confidence intervals for the effect estimates were wide, but that does not alter our interpretation of results, and our overall conclusion. The estimates from fixed-effects logistic regression model and our sensitivity analyses supported our interpretation. Also, BMLs are known to fluctuate substantially over time, and these were read only at two time points. Thus, we do not fully know the influence of meniscus pathologies on these fluctuations. Finally, a further limitation is that these subjects may have been free of clinical knee OA per ACR criteria at baseline but few of them had radiographic OA (4% of knees with KL grade ≥ 2).

Table 2
The effect on incident/enlarging bone marrow lesions; results from random-effects mixed regression analysis.

	Medial compartment			Lateral compartment		
	Univariable	Multivariable	Multivariable (sensitivity)[a]	Univariable	Multivariable	Multivariable (sensitivity)[a]
Number of knees		672	668		675	671
Number of persons		342	345		342	345
Meniscal extrusion (mm)	1.40 (1.13, 1.75)	1.24 (0.99, 1.57)	1.27 (1.02, 1.59)	1.66 (1.27, 2.17)	1.69 (1.27, 2.25)	1.70 (1.27, 2.26)
Age (years)	1.10 (1.00, 1.20)	1.11 (1.00, 1.22)	1.10 (1.00, 1.22)	0.96 (0.87, 1.07)	0.95 (0.85, 1.06)	0.95 (0.86, 1.06)
Body weight, per 5 kg increase	1.14 (1.03, 1.27)	1.15 (1.02, 1.30)	1.17 (1.04, 1.32)	1.08 (0.96, 1.20)	1.10 (0.96, 1.26)	1.10 (0.96, 1.25)
Body height	1.00 (0.95, 1.04)	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)	1.01 (0.96, 1.06)	0.96 (0.90, 1.03)	0.96 (0.89, 1.02)
Physical activity	0.99 (0.91, 1.07)	0.99 (0.91, 1.07)	1.00 (0.93, 1.08)	1.02 (0.94, 1.11)	1.01 (0.92, 1.10)	1.01 (0.93, 1.10)
Ipsilateral meniscal damage	1.97 (0.90, 4.35)	1.45 (0.61, 3.44)	1.51 (0.64, 3.53)	2.08 (0.70, 6.19)	1.59 (0.49, 5.14)	1.58 (0.49, 5.06)
Tibial width (mm)	1.01 (0.92, 1.12)	0.96 (0.84, 1.09)	0.95 (0.84, 1.07)	1.01 (0.91, 1.12)	1.02 (0.89, 1.17)	1.03 (0.90, 1.18)
Valgus alignment	0.73 (0.39, 1.34)	0.85 (0.47, 1.56)		1.47 (0.75, 2.88)	1.47 (0.74, 2.92)	
Knee injury	0.94 (0.40, 2.20)		0.77 (0.32, 1.86)	1.26 (0.54, 2.91)		0.93 (0.38,2.29)

[a] In the sensitivity analysis adjusted for knee injury instead of valgus alignment (due to sparse data adjusting for both in one model was not feasible).

In conclusion, meniscal extrusion is associated with ipsi-compartmental incident/enlarging BMLs.

Contribution

FZ participated in the design of the study, acquired the data, contributed to statistical analyses, made interpretation of results, and draft the manuscript.

SB-Z acquired the data, made interpretation of the results, and revise the manuscript.

EO acquired the data, made interpretation of the results, and revise the manuscript.

AT participated in the design of the study, analyzed the data, made interpretation of the results, and revised the manuscript.

ME designed the study, interpreted the results, and revised the manuscript.

JR designed the study, acquired the data, interpreted the results, and revised the manuscript.

All authors have approved the final version for submission.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2019.100015.

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