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Hayashi, D
Englund, M
Roemer, FW
et al.

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Knee Malalignment is Associated with an Increased Risk for Incident and Enlarging Bone Marrow Lesions in the More Loaded Compartments: The MOST Study

Daichi Hayashi[1], **Martin Englund**[2,3], **Frank W. Roemer**[1,4], **Jingbo Niu**[2], **Leena Sharma**[5], **David T. Felson**[2], **Michel D. Crema**[1,6], **Monica D. Marra**[1], **Neil A. Segal**[7], **Cora E. Lewis**[8], **Michael C. Nevitt**[9], and **Ali Guermazi**[1]

[1]Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, MA 02118, USA

[2]Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, Boston, MA 02118, USA

[3]Lund University, SE-221 85 Lund, Sweden

[4]Department of Radiology, Klinikum Augsburg, Augsburg 86156, Germany

[5]Division of Rheumatology, Northwestern University, Chicago, IL 60611, USA

[6]Department of Radiology, Hospital do Coração (HCor) and Teleimagem, São Paulo, SP, Brazil

[7]Department of Orthopaedics and Rehabilitation, The University of Iowa, Iowa City, IA 52242, USA

[8]Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL 35205, USA

[9]Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA 94107, USA

Abstract

Objective—To examine the relationship of knee malalignment with occurrence of incident and enlarging bone marrow lesions (BMLs) and regression of BMLs.

Corresponding author: Daichi Hayashi, MBBS, PhD, Department of Radiology, Boston University School of Medicine, 820 Harrison Avenue, FGH Building 3rd Floor, Boston, MA 02118, USA, Tel: +1-617-414-4957, Fax: +1-617-638-6602, dhayashi@bu.edu.

Author contributions:

- **a.** Conception and design, acquisition of data, analysis and interpretation of data: All authors
- **b.** Drafting the article or revising it critically for important intellectual content: All authors
- **c.** Final approval of the version to be published: All authors
- **d.** Literature search: DH, ME, FWR
- **e.** Statistical expertise: JN
- **f.** Guarantor of the integrity of the study: AG (guermazi@bu.edu)

Competing interests

Ali Guermazi received consulting fees from Genzyme, Norvartis, AstraZeneca, Merck Serono and Stryker. He is the President of Boston Imaging Core Lab (BICL), LLC. Frank Roemer is the CMO of BICL and received consulting fees from Merck Serono and National Institute of Health. Michel Crema and Monica Marra are shareholders of BICL. Other authors declared nothing to disclose.

Methods—Subjects from the Multicenter Osteoarthritis Study aged 50–79 years with or at high risk of knee osteoarthritis were studied. Full-limb radiographs were taken at baseline and hip-knee-ankle mechanical axis was measured. Baseline and 30-month MRI of knees (n=1782) were semiquantitatively assessed for BMLs. Outcome was defined as a change in BML score in femoral/tibial condyle in medial/lateral compartments. Medial compartment in varus alignment and lateral compartment in valgus alignment were combined to form 'more loaded' compartment, while lateral compartment in valgus and medial compartment in varus were combined to form 'less loaded' compartment. Relative risk (RR) of BML score increase or decrease in relation to malalignment was estimated using a log linear regression model with the Poisson assumption, adjusting for age, gender, body mass index, physical activity scale for the elderly, race and clinic site. Further, results were stratified by ipsilateral meniscal and cartilage status at baseline.

Results—Baseline varus alignment was associated with higher risk of BML score increase from baseline to follow-up in the medial compartment (adjusted RRs [95%CI]: 1.5 [1.2–1.9]) and valgus alignment in the lateral compartment (1.4 [1.0–2.1]). Increase in BML score was more likely in the more loaded compartments (1.7 [1.4–2.0]) in malaligned knees. Regardless of ipsilateral cartilage or meniscus status, adjusted RR for BML score increase was higher in the more loaded compartments of malaligned knees than those with neutral alignment. Decrease in BML score was less likely in the more loaded compartments in malaligned knees (0.8, [0.7–1.0]).

Conclusion—Knee malalignment is associated with increased risk of incident and enlarging BMLs in the more loaded compartments of the tibiofemoral joint.

Keywords

bone marrow lesion; malalignment; osteoarthritis; knee; MRI

Introduction

Subchondral bone marrow lesions (BML), defined by MRI as ill-defined signal alterations directly adjacent to cartilage, are a common feature of knee osteoarthritis. Although understanding of BML pathophysiology is limited, the importance of BMLs for structural progression in OA, as well as associations with pain, has been recognized [1–4]. Recent studies showed that changes in MRI-detected subchondral BMLs are associated with limb malalignment [5], cartilage loss [2, 3] and MRI meniscal derangement in an ipsi-compartmental manner [6]. Also, changes in BMLs are associated with fluctuations in knee pain in patients with knee OA, and pain resolution occurs more frequently when BMLs become smaller [7].

Malalignment of the lower limb, in either the valgus or varus direction, has been found to influence the load distribution across the articular surfaces of the knee joint [8]. It has been shown that varus alignment is associated with an increased risk of incident tibiofemoral OA [9, 10]; valgus alignment was found to have a borderline [9] or no [10] association with incident OA. Varus and valgus have each been associated with subsequent progression in the biomechanically stressed compartment. It has been suggested that BMLs are a result of increased mechanical loading [11]. A recent study evaluated the relationship between mechanical loading, as indicated by the external knee adduction moment (KAM) during walking, and BMLs in people with medial knee OA [12]. A significant relationship between peak KAM and medial tibial BMLs and between KAM impulse and medial compartmental BMLs was found. Results from this study support the hypothesis that greater mechanical loading of the medial compartment plays a role in the pathogenesis of BMLs in medial tibiofemoral OA. A recent study by Englund et al [13] investigated the association between meniscal pathology and incident or enlarging BMLs in knee OA. The authors demonstrated a potent effect of meniscal pathology on both, the development and enlargement of subchondral BML in the ipsilateral knee compartment.

Based on the hypothesis that subchondral BMLs are a result of increased mechanical loading, we performed a study to examine the relationship of knee malalignment with the occurrence of incident and enlarging BMLs in the more loaded compartments of the tibiofemoral (TF) joint. As an additional analysis, we examined if there was any relationship between malalignment and regressing BMLs.

Materials and Methods

Study design and subjects

The Multicenter Osteoarthritis (MOST) Study is a prospective cohort study of 3,026 individuals aged 50 to 79 years with or at high risk of knee OA. Those considered at high risk included persons who were overweight or obese, those with knee pain, aching or stiffness on most of the last 30 days, a history of knee injury that made it difficult to walk for at least 1 week, or previous knee surgery. Subjects were recruited from two US communities, Birmingham, Alabama and Iowa City, Iowa. The study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Campus.

Subjects were excluded from MOST if they screened positive for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Reiter’s syndrome, had renal insufficiency that required hemo- or peritoneal dialysis, a history of cancer (except for non-melanoma skin cancer), had or planned to have bilateral knee replacement surgery, were unable to walk without assistance, or were planning to move out of the area in the next 3 years. Assessments at the baseline and 30-month follow-up were performed using the same protocol, and each included a telephone interview and clinic visit. Subjects completed a survey on physical activity, the physical activity scale for the elderly (PASE) at baseline, and had their height and weight measured at every clinic visit.

Our study sample included all subjects who met the selection criteria (Figure 1). This meant our sample included subjects who were selected for subcohort study of progressive whole knee radiographic OA, and also those selected for matched case-control study of incident whole knee radiographic OA in the parent MOST study. As explained in the documentation published by the MOST study, this study design could lead to bias in the findings [14]. We therefore took additional measures to address this issue, as detailed in the ‘statistical analysis’ section below.

Radiographic acquisition and malalignment measures

All subjects at baseline and 2,662 subjects at 30-month follow-up underwent weight-bearing postero-anterior fixed flexion view knee radiographs using the SynaFlexer positioning frame (Synarc, San Francisco, CA)[15, 16]. A musculoskeletal radiologist (who is not a co-author) and a rheumatologist (DTF) with over 10 years experience each in reading study films and over 30 years of clinical experience graded all baseline postero-anterior films independently according to the Kellgren-Lawrence (K-L) grading, blinded to clinical and MRI data. For subjects who had both baseline and follow-up radiographs, disagreements in radiographic reading among the readers were adjudicated by a panel of three readers (DTF, aforementioned radiologist and another rheumatologist who is not a co-author). The weighted kappa coefficient of inter-observer reliability for the K-L grade readings was 0.79.

Full-limb radiographs of both legs were obtained at baseline using a 14-in × 51-in cassette [17]. The mechanical axis was defined as the angle formed by the intersection of a line from the center of the head of the femur to the center of the tibial spines and a line from the center of the talus to the center of the tibial spines [17]. The interobserver intraclass correlation coefficient for the mechanical axis was 0.99 (p<0.0001). Varus alignment was defined as a hip-knee-ankle (HKA) angle <179°; 179 to 181° was considered neutral and valgus alignment was defined as a HKA angle >181°. Additionally, since there is little evidence at which angle the mechanical load will be significantly different, and there is a possibility that our choice of cut-offs may not be optimal, we performed two additional analyses. Firstly, sensitivity analyses were done to see how different cut-off values affect our results. In addition to the original definition for varus and valgus as described above, we used 178°, 177°, 176°, and 175° as alternative cutoffs for varus and 182°, 183°, 184°, and 185° for valgus. Secondly, we used the HKA angle as a continuous variable without having arbitrary cut-offs. For the latter, malalignment indicating loading was defined as the degrees of HKA measurement away from neutral (180°) towards the compartment of interest (i.e. towards varus for medial compartment, and towards valgus for lateral compartment). HKA <180° indicated varus, while HKA >180° indicated valgus. Mathematically, malalignment indicating loading was defined as [180 - HKA] for the medial compartment, and [HKA - 180] for the lateral compartment.

MRI acquisition

At baseline and follow-up, MRI scans were obtained with a 1.0T MR system (OrthOne™, ONI Medical Systems, Wilmington, MA) with a circumferential transmit-receive extremity coil using a fat-suppressed (FS) fast spin echo (FSE) proton density-weighted (PD-w) sequence in two planes: sagittal, repetition time (TR) = 4,800 ms, echo time (TE) = 35 ms, 3 mm slice thickness, 0 mm interslice gap, 30 slices, 288 × 192 matrix, number of excitations (NEX) = 2, 140 × 140 mm field of view (FOV), echo train length (ETL) = 6; and axial, (TR = 4,680 ms, TE = 13 ms, 3 mm slice thickness, 0 mm interslice gap, 26 slices, 288 × 192 matrix, NEX = 2, 140 × 140 mm FOV, ETL = 10). Also, a short-tau inversion recovery (STIR) sequence in the coronal plane was obtained (TR = 8,448 ms, TE = 17 ms, TI = 100 ms, 3 mm slice thickness, 0 mm interslice gap, 34 slices, 256 × 192 matrix, two NEX, 140 × 140 mm FOV, ETL = 8).

MRI Assessment

MRI findings of knee OA were semiquantitatively assessed with the Whole Organ MRI Score (WORMS) method [18] by four musculoskeletal radiologists (AG, FWR, MDC, and MDM) who were experts of standardized semiquantitative MRI assessment of knee OA. Readers were blinded to clinical and radiographic data including the alignment status, and unaware of the study hypothesis, and read the paired images separately with knowledge of time sequence.

Subchondral BMLs were scored from 0 to 3 based on the extent of subregional involvement (0 = none; 1 = <25% of the subregion; 2 = 25–50%; 3 = >50%) at baseline and at 30-month follow-up in five tibiofemoral regions of the medial and lateral compartment, respectively. In a modification of WORMS developed for longitudinal readings, a within-grade change of BMLs was also recorded, which designates definite change that does not fulfill the criteria for a full-grade increase or decrease, i.e. within-grade worsening was assigned a score increase of 0.5, while a within-grade improvement was assigned a score decrease of 0.5, compared to the baseline score. Thus, any score change of ≥0.5 was considered change in BML size. The weighted kappa of inter-reader reliability for BML assessment as described above was 0.62. Subjects were excluded from the analysis if there was one or more missing scores from any of the subregions relevant to this study. An increase from baseline to follow-up in the maximum subregional BML score within each compartment was regarded as an incident BML (if there was no BML at baseline) or an enlarging BML (if there was a pre-existing BML at baseline). A longitudinal decrease in the maximum BML score was considered a regressing BML. For the latter, only knees with at least one subregional BML score>0 at baseline were included.

Meniscal status was graded separately on a scale of 0–4, and we defined a grade of 1 (minor radial or parrot-beak tear) or higher as a meniscal lesion in our analysis. Additionally, medial or lateral meniscal extrusion were graded on a scale of 0–2, and grade of 1 (≤50% from the midposterior coronal slice when the medial tibial spine was depicted to its maximum extent) or higher was also counted as 'meniscal lesion' in our analysis. Also, cartilage morphology was graded on a scale of 0–6. We defined a grade of 2 (partial thickness focal defect <1cm in greatest width) or higher as a cartilage lesion in any of the following five tibiofemoral regions in the medial and lateral compartment, respectively: anterior, posterior, and central surface of the tibial plateau and the central and posterior articular surface of the femur.

Statistical analysis

We first performed analyses using all subjects who were eligible for this study. Relative risk (RR) of an increase in BML score in the medial, lateral and 'more loaded' (=combination of medial compartment in varus alignment and lateral compartment in valgus alignment) compartments in relation to malalignment was estimated using a log linear regression model with the Poisson assumption. We used generalized estimating equations to account for correlation between two knees from the same subject, and controlled for age, gender, body mass index, overall score of the physical activity scale of the elderly (PASE) [19] at baseline, race, clinic site for radiographic acquisition and MRI selection status [14]. We adjusted for overall PASE scores because all activities that were components of the PACE questionnaire (i.e. walking, light/moderate/strenuous recreational activities, muscle strength/ endurance activities, light/moderate/heavy house work, home repairs, lawn work or yard care, outdoor gardening, caring for another person, and work for pay or volunteer including work that requires standing) could involve weight-bearing activities such as walking and knee bending, and any weight-bearing activities would be relevant for mechanical loading of the knee joint. Adjustments for baseline meniscus and cartilage status were not made because these were thought to be a causal intermediate for BML development or enlargement [13, 20]. However, we performed analyses stratified by ipsilateral meniscus and cartilage status at baseline, i.e. (i) no meniscus or cartilage lesions, (ii) only meniscus lesions present; (iii) only cartilage lesions present; and (iv) both meniscus and cartilage lesions present. We performed secondary analyses stratified by the absence or presence of BMLs at baseline (i.e. incident or enlarging BML, as described earlier). Analysis of incident BML involved only the subregions within a compartment that had no BMLs at baseline, and categorizing each of these as change/no change.

Additionally, we performed separate sensitivity analyses to examine if combining the two subcohorts of the MOST (i.e. subjects who were selected for progressive knee radiographic OA study, and those selected for the matched case-control study of incident knee radiographic OA) resulted in a bias in our findings [14]. We used the same regression model as above, adjusting for age, gender, BMI, physical activity scale, race and clinic site. All statistical analyses were performed using SAS for Windows, version 9.1. Statistical significance was set at $p<0.05$.

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Results

The study sample consisted of 1881 knees from 1422 persons (61.3% women). Demographic characteristics of the subjects and the knees are summarized in Table 1. At baseline, BMLs were found in 647 medial compartments (31.2%) and 323 lateral compartments (21.7%). At the 30-month follow-up visit, 360 knees (19.2%) had an incident and/or enlarging BMLs in the tibial and/or femoral condyle of the medial compartment. The corresponding numbers for the lateral compartment was 164 (8.7%). Meniscal and cartilage pathology at baseline were more frequent in the medial than the lateral compartment (Table 2). The additional sensitivity analyses included 540 knees for the progressive OA study and 401 knees for the incident OA study.

Increase in BML score was more likely in the more loaded compartments in malaligned knees (adjusted RR=1.7, 95% CI 1.4–2.0, Table 3). This finding was also true in the sensitivity analyses involving subjects who were selected for the progressive OA study (adjusted RR=2.0, 95%CI 1.7–2.7) and those for the incident OA study (adjusted RR=2.1, 95%CI 1.2–3.6). Moreover, this finding was consistent across the different cut-off values used for the definition of malalignment, and results of the analysis using the HKA angle as a continuous variable also supported these findings (Table 3).

Regardless of the status of ipsilateral cartilage or meniscus, adjusted RR for BML score increase was higher in the more loaded compartments of malaligned knees than those with neutral alignment in the analysis involving all subjects, but statistical significance was reached only when there was baseline cartilage damage alone (Table 4). Similar findings were found in the sensitivity analyses, but statistical significance was mostly not reached.

For regressing BMLs, decrease in BML score was less likely in the more loaded compartments in malaligned knees (adjusted RR=0.8, 95% CI 0.7–1.0, Table 5). This finding was also true in subjects selected for progressive OA study (RR=0.6, 95%CI 0.4–0.8) but not for those selected for incident OA study (RR=1.5, 95%CI 1.0–2.2). When alternative cut-offs for the definition of malaligment was used, statistical significance was lost in most cases, but statistical significance remained in the analysis using the HKA angle as a continuous variable (Table 5).

Discussion

The present study demonstrated firm evidence that increased mechanical load due to malalignment of the knee joint is a risk factor for incident or enlarging BMLs in the affected compartment of the tibiofemoral joint (i.e. medial compartment if varus, and lateral compartment if valgus). Also, BMLs in the more loaded compartment are less likely to regress than those in knees with neutral alignment.

Results of the sensitivity analyses were, in general, consistent with the analyses using all subjects. However, we note that the likelihood of BML regression was higher in the more loaded compartment of malaligned knees in subjects selected for incident OA study. This was contradictory to the finding with all subjects and that with subjects for progressive OA study. We are uncertain how this phenomenon can be explained. We speculate that, because no knees in the incident OA study had radiographic OA at baseline, BMLs present in those knees might not show typical pattern of longitudinal changes (under the influence of increased mechanical load) that are characteristic to OA-associated BMLs. Nevertheless, the key finding of this study, i.e. relative risk of BML score increase is higher in the more loaded compartment, remained true in all analyses. We therefore think that MRI selection procedure did not result in a notable bias in our analysis. Thus, our discussion presented hereafter will be based on the results of the analysis involving all eligible subjects.

We assessed the increased mechanical load due to malalignment in two ways: by using different cut-off points to define varus and valgus, and also by using HKA angle as a continuous variable without an arbitrary cut-off. Regardless of the cut-off values, results consistently showed that the relative risk of BML score increase at follow-up is higher in the more loaded compartments and the statistical significance remained in all cases. This finding was also supported by the analysis using HKA angle as a continuous variable. We thus believe the cut-off of <179° for varus and >181° for valgus, which were also used in previous publications based on the MOST dataset, is an appropriate choice to maintain the comparability of analytic results regarding malalignment. Therefore, our discussions are based on this definition of varus and valgus.

At baseline, almost half of the subjects of the present study had varus alignment of the knee (46.4%), which is approximately 2.4 times more frequent than valgus alignment (19.7%). Correspondingly, at follow-up, there was a larger number of both incident (158 vs. 94) and enlarging (202 vs. 70) BMLs in the medial compartment than the lateral compartment at follow-up. Overall, BML score increase was 2.2 times more likely to occur in the medial compartment compared to the lateral compartment (19.2% vs. 8.7%). These figures support our hypothesis that the increased mechanical load will lead to development and progression of BMLs in the affected (i.e. "more loaded") compartment. Our finding is in line with a recent study by Segal et al which demonstrated that elevated tibiofemoral articular contact stress predicts risk for BML worsening at 30-month follow-up in persons with or at high risk of knee OA [21]. In that study, the peak (maximum) and mean spatial contact stresses acting on each compartment of each knee were calculated from the discrete element analysis-computed contact stress distributions. While this approach offers more direct way of assessing mechanical load at the tibiofemoral joint, influence of the meniscal status was not taken into account in their analytic model.

Studies by Englund et al. showed that varus alignment is a risk factor for the development of medial meniscal pathology [20] and that meniscal pathology is a risk factor for both incident and enlarging subchondral BMLs [13]. Their findings support the hypothesis that abnormal biomechanical loading patterns created by knee malalignment may lead to meniscal pathology and increased focal stress on articular cartilage, which in turn results in cartilage loss [22, 23], bone alterations including trabecular bone changes [24], increased bone mineral density [25] and the development of BMLs [13]. Although association between malalignment and incident/enlarging BMLs was not the primary focus in this study, the authors also assessed the effects of malalignment on the development of incident or enlarging BMLs in the medial and lateral compartments of the tibiofemoral joint. Their data showed that the frequency of increased BML score in the medial compartment was much higher in varus knees (183/280, 66%) compared with neutral knees (65/280, 24%). Likewise, in the lateral compartment, BML score increase was more frequently seen in valgus knees (47/125, 38%) than in neutral knees (34/125, 27%). However, in this publication authors did not report RRs of incident/enlarging BMLs in regard to alignment of the lower limb. Also, this study did not consider regressing BMLs.

In the present study, we calculated adjusted RRs for incident/enlarging and regressing BMLs with respect to alignment of the lower limb. Our analyses were adjusted for age, sex, BMI, level of physical activity, race, clinic site, and MRI selection status. We then stratified our analyses according to the presence or absence of meniscus and/or cartilage pathology (Table 4). Although adjusted RR for BML score increase in the more loaded compartment was greater than 1.0 regardless of ipsilateral meniscal or cartilage status, we have only found borderline significance for knees without any meniscal or cartilage pathology, or those with both meniscal and cartilage pathology. This is despite the fact that there were a large number of BMLs in the latter group to have sufficient statistical power for the analysis. Overall, it seems that the association of alignment with incident or enlarging BML is not much influenced by the status of meniscus and cartilage. With regard to BML regression, we have shown that it is less likely to occur in the more loaded compartment. This finding is in accordance with our finding regarding the association between increased mechanical load and higher risk of BML incidence/progression.

From these data, although we have shown strong associations between malalignment and BML score increase, we cannot conclude whether or not the malalignment is the direct cause of BML score increase. To date, a link between meniscal pathology and BML score increase [13], as well as that between meniscal pathology and cartilage loss [23, 26], and that between cartilage loss and BML score increase [2], has been demonstrated. Moreover, a link between malalignment and compartment-specific cartilage loss [26–28], and the development of meniscal lesion or extrusion [20] has also been shown. However, the pathway of pathogenesis linking all these features still need to be more carefully evaluated in studies using multiple time points. Lastly, the Poisson assumption did not hold so well for the BML regression study. Thus, the results of our analysis regarding the association between BML regression and the malalignment may need to be confirmed by further studies.

An important limitation is a relatively small number of knees with incident or enlarging BMLs with only ipsilateral meniscal pathology (Table 4). Analysis of data concerning these knees lack power and consequently may be less reliable than ideal. Further, pre-existing moderate to large BMLs may be less likely to further enlarge (ceiling effect). These knees typically have more frequent meniscal pathologies and cartilage damage biasing the estimate of effect toward the null.

In summary, this prospective study provides strong evidence that knee malalignment is associated with an increased risk of incident and enlarging BMLs in the more loaded compartments of the tibiofemoral joint. Although the possibility remains that BMLs are epiphenomenon of cartilage damage, our data suggest BML may result from increased mechanical load imposed on joint cartilage and subchondral bone in a compartment-specific manner, since alignment is a factor influencing load distribution. The risk of BML regression also seems to be affected by the knee malalignment.

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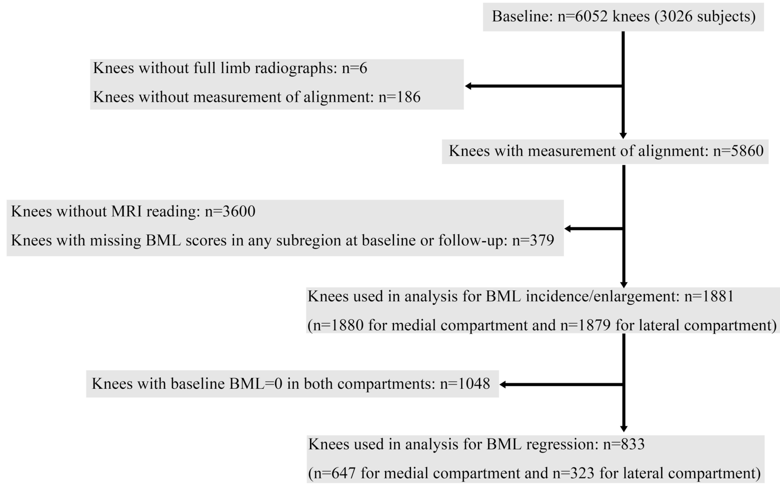

Figure 1.
Flow chart showing the subject inclusion criteria.

Table 1

Demographic characteristics of the subjects at baseline.

	Incident/enlarging BML study	Regressing BML study
Subject-based characteristics		
Total number of subjects	1422	733
Age, year, mean (SD)	62.1 (7.9)	62.8 (8.0)
White, N (%)	1243 (87.4)	640 (87.3)
Female, N (%)	872 (61.3)	435 (59.4)
Body mass index, kg/m^2, mean (SD)	29.9 (4.8)	30.1 (4.9)
Physical activity scale for the elderly	178.5 (87.1)	177.8 (87.6)
Clinic site: Birmingham, AL	643 (45.2)	307 (41.9)
Iowa City, IA	779 (54.8)	426 (58.1)
Knee-based characteristics		
Total number of knees	1881	833
Kellgren Lawrence Grade, N(%)		
0	873 (46.4)	224 (26.9)
1	310 (16.5)	116 (13.9)
2	353 (18.8)	186 (22.3)
3	280 (14.9)	244 (29.3)
4	64 (3.4)	652 (7.4)
missing	1 (0.1)	1 (0.1)
Malalignment, N(%)		
Varus (<179°)	873 (46.4)	429 (51.5)
Neutral (179–181°)	637 (33.9)	252 (30.3)
Valgus (>181°)	371 (19.7)	152 (18.3)

Table 2

Number of incident and/or enlarging bone marrow lesions (BML) at follow-up, and prevalent meniscus and cartilage pathologies at baseline by compartment of the tibiofemoral joint

	Medial compartment	**Lateral compartment**
	n/N (%)	**n/N (%)**
BML incident or enlargement	360/1880 (19.2%)	164/1879 (8.7%)
BML incident	158/1233† (12.8%)	94/1556‡ (6.0%)
BML enlargement	202/647† (31.2%)	70/323‡ (21.7%)
Meniscal damage	644/1880 (34.2%)	209/1879 (11.1%)
Cartilage damage	1225/1880 (65.2%)	888/1879 (47.3%)

Missing values due to incomplete BML scoring in †medial (n=1) and ‡lateral (n=2) compartments.

Table 3

Adjusted relative risk (RR) of bone marrow lesion score increase (i.e. occurrence of incident or enlarging BMLs) using different cutoffs for malalignment and the HKA angle as a continuous variable

		BML score increase			
Definition of varus/valgus	**Compartment**	N_{ie}	**n (%)**	**Crude RR (95%CI)**	**aRR* (95%CI)**
Varus <179°, valgus >181°	More-loaded	1243	278 (22.4)	2.0 (1.6–2.4)	1.7 (1.4–2.0)
	Neutral	1273	145 (11.4)	1.0 (ref)	1.0 (ref)
	Less-loaded	1243	101 (8.1)	0.7 (0.6–0.9)	0.6 (0.5–0.8)
Varus<178°, Valgus>182°	More-loaded	873	208 (23.8)	2.0 (1.7–2.4)	1.7 (1.4–2.0)
	Neutral	2013	244 (12.1)	1.0 (ref)	1.0 (ref)
	Less-loaded	873	72 (8.3)	0.7 (0.5–0.9)	0.6 (0.4–0.8)
Varus<177°, valgus>183°	More-loaded	557	142 (25.5)	2.0 (1.7–2.3)	1.6 (1.4–1.9)
	Neutral	2645	342 (12.9)	1.0 (ref)	1.0 (ref)
	Less-loaded	557	40 (7.2)	0.6 (0.4–0.8)	0.5 (0.3–0.6)
Varus<176°, valgus>184°	More-loaded	367	102 (27.8)	2.1 (1.8–2.5)	1.7 (1.4–2.1)
	Neutral	3025	399 (13.2)	1.0 (ref)	1.0 (ref)
	Less-loaded	367	23 (6.3)	0.5 (0.3–0.7)	0.4 (0.3–0.6)
Varus<175°, valgus>185°	More-loaded	227	74 (32.6)	2.5 (2.0–3.0)	2.0 (1.6–2.4)
	Neutral	3305	435 (13.2)	1.0 (ref)	1.0 (ref)
	Less-loaded	227	15 (6.6)	0.5 (0.3–0.8)	0.4 (0.2–0.7)
HKA angle	indicating loading**	-	-	1.1 (1.1–1.2)	1.1 (1.1–1.2)

*adjusting for age, sex, BMI, physical activity scale for the elderly, race and clinic site, MRI selection status

N_{ie} = number of knees without BMLs at baseline + number of knees with BMLs (WORMS score >0) at baseline excluding those with highest WORMS score (which cannot worsen at follow-up)

N_r = number of knees with bone marrow lesions (WORMS score >0) at baseline

**Malalignment indicating loading was defined as the degrees of HKA measurement away from neutral (180 degrees) towards the compartment of interest (towards varus for medial compartment, and towards valgus for lateral compartment). HKA <180 indicates varus, while HKA >180 indicates valgus. Mathematically, malalignment indicating loading was defined as 180 – HKA for medial compartment, and HKA -180 lateral compartment.

Table 4

Adjusted relative risk (RR) of bone marrow lesion (BML) score increase in the more loaded compartment, stratified by the presence of meniscus and/or cartilage pathology at baseline.

	No ipsilateral meniscal or cartilage pathology			Ipsilateral meniscal pathology only			Ipsilateral cartilage pathology only			Both ipsilateral meniscal and cartilage pathology		
Compartment	**N**	**n (%)**	**aRR* (95%CI)**	**N**	**n (%)**	**aRR* (95%CI)**	**N**	**n (%)**	**aRR* (95%CI)**	**N**	**n (%)**	**aRR* (95%CI)**
More loaded	336	22 (6.6)	1.7 (0.9–3.1)	31	6 (19.4)	N/A **	390	77 (21.0)	1.4 (1.0–1.8)	484	172 (35.5)	1.2 (0.9–1.6)
Less loaded	662	30 (4.5)	1.1 (0.6–1.9)	16	1 (7.1)	N/A **	475	49 (10.3)	0.7 (0.5–1.0)	86	20 (23.3)	0.8 (0.5–1.3)
Neutral	556	22 (4.0)	1.0 (ref)	39	2 (5.1)	1.0 (ref)	483	68 (14.1)	1.0 (ref)	193	53 (27.5)	1.0 (ref)

* adjusting for age, sex, body mass index, and physical activity scale for the elderly, race and clinic site, MRI selection status

** Due to very small numbers of lesions available for analysis, our statistical model did not converge.

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Table 5

Adjusted relative risk (RR) of bone marrow lesion score decrease (i.e. regression of BMLs) using different cutoffs for malalignment and the HKA angle as a continuous variable

		BML score decrease			
Definition of varus/valgus	**Compartment**	**N_{ie}**	**n (%)**	**Crude RR (95%CI)**	**aRR* (95%CI)**
Varus <179°, valgus >181°	More-loaded	493	149 (30.2)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
	Neutral	300	112 (37.3)	1.0 (ref)	1.0 (ref)
	Less-loaded	177	66 (37.3)	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Varus<178°, Valgus>182°	More-loaded	391	115 (29.4)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
	Neutral	460	164 (35.7)	1.0 (ref)	1.0 (ref)
	Less-loaded	119	48 (40.3)	1.1 (0.9–1.5)	1.1 (0.9–1.5)
Varus<177°, valgus>183°	More-loaded	280	81 (28.9)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
	Neutral	621	218 (35.1)	1.0 (ref)	1.0 (ref)
	Less-loaded	69	28 (40.6)	1.2 (0.9–1.6)	1.2 (0.9–1.6)
Varus<176°, valgus>184°	More-loaded	216	64 (29.6)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
	Neutral	713	244 (34.2)	1.0 (ref)	1.0 (ref)
	Less-loaded	41	19 (46.3)	1.4 (0.9–1.9)	1.4 (0.9–2.0)
Varus<175°, valgus>185°	More-loaded	149	38 (25.5)	0.7 (0.6–1.0)	0.8 (0.6–1.0)
	Neutral	797	275 (34.5)	1.0 (ref)	1.0 (ref)
	Less-loaded	24	14 (58.3)	1.7 (1.2–2.4)	1.8 (1.3–2.6)
HKA angle	indicating loading**	-	-	0.9 (0.9–1.0)	0.9 (0.9–1.0)

*adjusting for age, sex, BMI, physical activity scale for the elderly, race and clinic site, MRI selection status

N_{ie} = number of knees without BMLs at baseline + number of knees with BMLs (WORMS score >0) at baseline excluding those with highest WORMS score (which cannot worsen at follow-up)

N_r = number of knees with bone marrow lesions (WORMS score >0) at baseline

**Malalignment indicating loading was defined as the degrees of HKA measurement away from neutral (180 degrees) towards the compartment of interest (towards varus for medial compartment, and towards valgus for lateral compartment). HKA <180 indicates varus, while HKA >180 indicates valgus. Mathematically, malalignment indicating loading was defined as 180 – HKA for medial compartment, and HKA -180 lateral compartment.