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Predictive validity of within-grade scoring of longitudinal changes of MRI-based cartilage morphology and bone marrow lesion assessment in the tibio-femoral joint - the MOST Study

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Abstract

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Authors Contributions

1. All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
2. All authors contributed to drafting the article or revising it critically for important intellectual content.
3. All authors gave their final approval of the manuscript to be submitted.

Additional contributions:

- Analysis and interpretation of the data: FWR, MN, AG, DTF, JN
- Drafting of the article: FWR, MN, DTF; AG, CEL
- Provision of study materials or patients: MN, DTF, CEL, JT, AG, FWR
- Statistical expertise: JN, MN, DTF
- Obtaining of funding: MN, DTF, CEL, JT
- Collection and assembly of data: MN, DTF, CEL, JT, AG, FWR

Competing interests

Dr. Guermazi has received consultancies, speaking fees, and/or honoraria from Facet Solutions, Genzyme, Stryker, Merck Serono, Novartis and Astra Zeneca and is the President of Boston Imaging Core Lab (BICL), a company providing image assessment services. He received a research grant from General Electric Healthcare. Dr. Roemer is Chief Medical Officer and shareholder of BICL. Dr. Roemer has received consultancies, speaking fees, and/or honoraria from Merck Serono and the National Institutes of Health. Dr. Crema is shareholder of BICL.

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Objective—In order to increase sensitivity to detect longitudinal change, recording of within-grade changes was introduced for cartilage morphology and bone marrow lesion (BML) assessment in semiquantitative magnetic resonance imaging (MRI) scoring of knee osteoarthritis. The aim of this study was to examine the validity provided by within-grade scoring.

Design—The Multicenter Osteoarthritis (MOST) Study is a longitudinal study of subjects with or at risk of knee osteoarthritis. Baseline and 30 months MRIs were read according to the modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) system including within-grade changes for cartilage and BMLs. We tested the validity of within-grade changes by whether the 30 month changes in cartilage and bone marrow lesion assessment were predicted by baseline ipsi-compartmental meniscal damage and malalignment, factors known to affect cartilage loss and bone marrow lesions, using ordinal logistic regression.

Results—1867 knees (from 1411 participants) were included. Severe medial meniscal damage predicted partial grade (aOR 4.4, 95%CI 2.2,8.7) but not ≥ full grade (aOR 1.3, 95%CI 0.8,2.2) worsening of cartilage loss and predicted both, partial grade (aOR 9.6, 95%CI 3.6,25.1) and ≥ full grade (aOR 5.1, 95%CI 3.2,8.2) worsening of BMLs. Severe, but not moderate, malalignment predicted ipsicompartmental within-grade (medial cartilage damage: aOR 5.5, 95%CI 2.6,11.6; medial worsening of BMLs: aOR 4.9, 95%CI 2.0,12.3) but not full grade worsening of BMLs and cartilage damage.

Conclusions—Within-grade changes in semiquantitative MRI assessment of cartilage and bone marrow lesions are valid and their use may increase the sensitivity of semiquantitative readings in detecting longitudinal changes in these structures.

Keywords

osteoarthritis; MRI; semiquantitative scoring; WORMS; within grade; validity

Introduction

Magnetic Resonance Imaging (MRI) of the knee is commonly applied as an outcome measure in knee osteoarthritis (OA) longitudinal observational studies and clinical trials. Semiquantitative MRI scoring systems for knee OA, such as the Whole Organ MRI Score (WORMS), the Boston Leeds Osteoarthritis Knee Score (BLOKS) or MRI Osteoarthritis Knee Score (MOAKS), typically define longitudinal change in cartilage morphology and bone marrow lesions (BMLs) within a subregion in terms of differences of at least one full grade change between time points [1–3]. In order to increase the sensitivity to capture longitudinal changes in cartilage morphology and bone marrow lesion size, so-called within-grade changes that do not fulfill the criteria for a full grade difference between time points were introduced [4, 5]. A similar approach applied to radiographic assessment of knee OA has shown increased sensitivity to change using malalignment as a predictor [6]. For MRI readings, to date no comparative evaluation of scoring including and excluding within-grade changes has been performed. Since there is limited data addressing the question of validity of such reading approaches, and large OA studies including multiple time points are currently ongoing, it is important to determine whether within-grade changes should be part of semiquantitative MRI assessment. Information about the value of scoring within-grade changes in cartilage and BML assessment using the WORMS method may potentially be translatable to other SQ scoring systems of knee OA that are applied in a longitudinal fashion. Previous studies testing the validity of imaging- based scoring systems in OA research have used clinical parameters such as pain measures, or imaging based measures such as joint space narrowing, malalignment or meniscal damage [2, 6–8].

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Thus, aim of the present study was to assess the validity provided by scoring within-grade changes in cartilage and BML subregional assessment in comparison to using full grade or greater (≥ full grade) changes only, using baseline knee malalignment and meniscal damage as predictors of compartment-specific structural progression over 30 months of follow-up.

Materials and methods

Study Design and Subjects

Subjects were participants in the Multicenter Osteoarthritis (MOST) Study, a prospective epidemiological study of 3,026 people aged 50 to 79 years with a goal of identifying risk factors for incident and progressive knee OA in a population either with or at high risk of developing OA. They were recruited from the populations of two U.S. communities, Birmingham, Alabama and Iowa City, Iowa through mass mailing of letters and study brochures, supplemented by media and community outreach campaigns. MOST subjects were recruited and enrolled between June 2003 and March 2005. The Health Insurance Portability and Accountability Act-compliant study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco and Boston University School of Medicine. We obtained written informed consent from all participants.

Subjects considered at high risk for knee OA included those 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 one week, or previous knee surgery. Subjects were not eligible to participate in MOST if they screened positive for rheumatoid arthritis, [9] had ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, 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 three years.

In the present study we included all participants with available baseline and 30-month follow-up radiographic and MRI readings. These knees were previously selected for one or more of three substudies in MOST: 1) a cohort study of risk factors for radiographic OA progression consisting of randomly selected knees with either patellofemoral or tibiofemoral OA at baseline; 2) a case-control study of risk factors for incident radiographic OA; and 3) a case-control study of risk factors for onset of new, consistent frequent knee pain at 30 months [10]. A detailed flowchart of subject and knee inclusion is presented in Figure 1.

Radiographs

At baseline, all subjects underwent weight-bearing posteroanterior (PA) fixed flexion knee radiographs using the protocol by Peterfy et al. and a plexiglass positioning frame (SynaFlexer™) [11]. A musculoskeletal radiologist and two rheumatologists all with over 10 years experience reading study radiographs and blinded to clinical data, graded the x-rays according to the Kellgren-Lawrence (KL) scale [12]. Radiographs were presented sequentially with readers blinded to all clinical data and to MR images. Radiographic tibiofemoral OA was considered present if KL grade ≥2 defined as present when there were definite osteophytes and possible narrowing of the joint space. If readers disagreed on the presence of radiographic OA, readings were adjudicated by a panel of 3 readers. In addition, radiographs were assessed for joint space width in the medial and lateral tibiofemoral compartments according to the OARSI atlas (scores 0 to 3).

At the baseline clinic visit long-limb films were acquired with a 14-inch × 51-inch cassette. Mechanical alignment was measured as the angle formed by the intersection of the femoral and tibial mechanical axes. The femoral mechanical axis is the line from the center of the

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femoral head through the center of the knee, and the tibial mechanical axis is drawn as a line from the center of the ankle to the center of the knee. Neutral alignment was defined as 178–182 degrees. Moderate varus malalignment as 3–6 degrees medial deviation from the mechanical axis, and severe malalignment as ≥ 7 degrees deviation. Moderate and severe valgus malalignment was defined accordingly. The inter-observer intraclass correlation coefficient for the mechanical axis was 0.99 ($p<0.0001$)[13].

MRI Acquisition

MRIs were obtained in both knees at baseline and 30-month follow-up with a 1.0 T dedicated extremity unit (OrthOne™, GE Healthcare, Wilmington, MA) at both clinical centers with a circumferential extremity coil using fat-suppressed (FS) fast spin-echo proton density-weighted (PDw) sequences in two planes, sagittal (TR = 4800 ms, TE = 35 ms, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288 × 192 matrix, 2 excitations (NEX), 140 × 140 mm field of view (FOV), echo train length (ETL) = 8) and axial (TR = 4680 ms, TE = 13 ms, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288 × 192 matrix, 2 NEX, 140 × 140 mm FOV, ETL = 8), and a short tau inversion-recovery (STIR) sequence in the coronal plane (TR = 6650 ms, TE = 15 ms, TI = 100 ms, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256 × 192 matrix, 2 NEX, 140 mm^2 FOV, ETL = 8).

MRI Interpretation

Two musculoskeletal radiologists (FWR and AG), with 7 and 9 years experience in standardized semiquantitative MRI assessment of knee OA, blinded to radiographic OA grade and clinical data, graded cartilage status, BMLs, meniscal morphology and meniscal extrusion according to the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system [1]. WORMS scoring is possible with a moderate to high degree of agreement and accuracy using a 1.0T dedicated extremity MRI system compared with a 1.5T large-bore MRI [14]. Baseline and follow-up MRIs were presented paired and sequentially to the readers, with the chronological order known to the readers. All MRI readings were performed over a period of two years. BMLs and cartilage status were scored in each of the 5 subregions in the medial and lateral tibiofemoral compartments, for a total of 10 subregions per knee.

Cartilage morphology and signal were scored semiquantitatively from 0 to 6 in each subregion (0 = normal thickness and signal; 1 = normal thickness but increased signal on PDw or STIR images; 2.0 = partial thickness focal defect <1 cm in greatest width; 2.5 = full thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial-thickness defects intermixed with areas of normal thickness, or a grade 2.0 defect wider than 1 cm but <75% of the region; 4 = diffuse (≥75% of the region) partial-thickness loss; 5 = multiple areas of full thickness loss or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6 = diffuse (≥75% of the region) full-thickness loss). It needs mentioning that the 2.5 grade in WORMS does not represent a within-grade change but a separate grade within the WORMS scale representing a focal full-thickness defect.

BML size was scored from 0–3 based on the extent of regional involvement (0 = none; 1 = <25% of the subregion, 2 = 25–50% of the subregion; 3 = >50% of the subregion). BMLs were defined as poorly-delineated areas of hyperintensity directly adjacent to the subchondral plate on the STIR and PDw FS images [15, 16]. Knees with typical MRI signs of traumatic bone contusions, osteonecrosis, fracture or malignant bone infiltration were excluded from the analysis. However, of all analyzed MRIs only one knee showed a subacute tibial depression fracture at follow-up and was excluded for this reason.

In a modification of WORMS developed for longitudinal readings, the use of coding within-grade changes for cartilage and bone marrow lesion assessment was introduced. A within-

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grade change was defined as a definite visual difference that does not cover a full grade increase or decrease in subregional cartilage damage or BML change [4, 5]. An example of a BML within-grade change is shown in Figure 2.

Meniscal status was graded from 0 to 4 in the anterior horn, the body segment, and the posterior horn of the medial and lateral meniscus.

We examined inter-rater reliability for change in WORMS cartilage and BML scores over 30 months in 10 knees selected by the MOST Coordinating Center at UCSF with the readers blinded for reason for selection to include a range of progression in key features assessed by WORMS. Within grade changes in cartilage scores and BML scores in a subregion were counted as change. Both readers scored all 10 pairs of examinations in known chronological order. Simple Kappa was calculated for agreement on change with the subregion as the unit of analysis. Kappas for no change / change, (including partial grades) were 0.91 (95% confidence interval 0.81–1.00) for cartilage assessment and 0.91 (95% confidence interval 0.84–0.99) for BMLs.

Statistical analysis

The ability of baseline meniscal damage and knee malalignment to predict compartment-specific structural progression was assessed using ordinal logistic regression with generalized estimating equations to account for correlations among two knees per subject and adjusting for age, sex and body mass index. Structural progression was defined as any ipsi-compartmental cartilage loss and BML worsening considering within-grade changes vs no change and ≥ full grade changes vs. no change. A compartment was defined as experiencing “within-grade worsening” if this compartment showed only within-grade worsening in any of the 5 compartmental subregions and no full grade or greater change. A compartment was defined as having “≥ full grade worsening” if only full grade or greater change was observed in any of the 5 compartmental subregions and no within-grade changes were observed. For meniscal damage assessment, analyses were performed using compartments without meniscal damage as the reference. Meniscal damage was stratified into no damage (grade 0), grade 1, 2 and grades 3 and 4 combined. For malalignment assessment, analyses were performed using neutral aligned limbs as the reference and looking at moderate and severe malaligned limbs separately. For this analysis, valgus knees were excluded in the assessment of medial features and varus knees were excluded in the assessment of lateral MRI features. All statistical calculations were performed using SAS® software (Version 9.1 for Windows; SAS Institute; Cary, NC).

Results

There were 1867 knees of 1411 subjects who met our inclusion criteria for this study. On average the subjects were elderly (mean age 62.1 ±7.8 years) and overweight (mean BMI 29.9 ± 4.8), and there were more women than men (61.2% female subjects). The majority (n=1173, 62.8%) of knees did not have established tibiofemoral OA (K/L=0 or 1) at baseline. There were 651 limbs with varus malalignment (34.9%) and 228 knees (12.2%) with valgus malalignment.

In the medial compartment, severe meniscal damage (grades 3 and 4) predicted within-grade worsening of cartilage loss but not ≥ full grade worsening (aORs 4.4, 95% CI 2.2,8.7 and 1.3, 95% CI 0.8,2.2, respectively). Within-grade and ≥ full grade worsening of BMLs in the medial compartment was predicted in a comparable fashion by severe meniscal damage (aORs 9.6, 95% CI 3.6,25.1 and 5.1, 95% CI 3.2,8.2, respectively) (Table 1). In the lateral compartment, severe meniscal damage predicted both within-grade worsening and ≥ full grade worsening in a comparable fashion (aORs 3.8, 95% CI 1.1,13.0 and 3.9, 95% CI

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1.7,9.0, respectively). Few lateral compartments showed within-grade worsening of BMLs only and thus a comparison was not possible for BML assessment and ipsi-compartmental meniscal damage (Table 2).

Severe varus malalignment predicted within-grade worsening of cartilage damage in the medial compartment (aOR 5.5, 95% CI 2.6,11.6), but not ≥ full grade worsening (aOR 1.7, 95% CI 0.9,3.3). Severe valgus malalignment predicted within-grade worsening of cartilage damage in the lateral compartment (aOR 6.3, 95% CI 1.3,30.6) but not ≥ full grade worsening (aOR 0.9, 95% CI 0.2,4.9) (Table 3). Severe varus malalignment predicted both, within-grade and full grade worsening of BMLs in the medial compartment (aORs 4.9, 95% CI 2.0,12.3 and 2.5 95% CI 1.4,4.6, respectively). None of the knees with severe valgus malalignment showed within-grade worsening of BMLs in the lateral compartment only, and thus a comparison was not possible for BML assessment and severe valgus malalignment (Table 4). Moderate valgus malalignment predicted within-grade worsening of BMLs but not cartilage loss, and not ≥ full grade worsening of cartilage damage or BMLs. Moderate varus malalignment predicted neither within-grade nor ≥ full grade worsening of cartilage damage or BMLs.

Discussion

With large longitudinal epidemiologic multicenter osteoarthritis studies such as the Osteoarthritis Initiative (OAI) and MOST ongoing, it is paramount to base image assessment strategies on data-based evidence prior to engaging in large scale reading efforts applying semiquantitative MRI scoring tools. In the current analysis based on data from the MOST study, we showed that more loaded compartments, either due to malalignment or due to severe meniscal damage, are at increased risk for within-grade and ≥ full grade cartilage loss and BML progression.

As radiologic semiquantitative expert assessment of knee MRIs relies on ordinal grading schemes, quite commonly visual definite changes are observed in longitudinal observations that do not fulfill the criteria of a full grade change. Readers usually will code these as “no change” when compared to the previous visit and as a consequence sensitivity to detect change will likely be lower when compared to assessment that enables coding of these subtle changes. An alternative would be to code these within-grade changes as a full grade change, although this would incorrectly assign a higher grade that does not fulfill the defining criteria of that grade. In addition, ceiling effects of scoring will have to be expected in longitudinal assessment over several time points. For these reasons, so-called within-grade coding was introduced that captures these visual changes as being “worse” or “better” than the previous visit but still assigning the correct grade as defined by the scoring system. In a previous analysis from the MOST study looking at radiographic assessment including within-grade scoring of JSN, varus and valgus malalignment strongly predicted the risk of within-grade progression [6]. Although within-grade scoring has been applied for quite some time also in MRI readings, the validity of such an approach has not been systematically shown [4, 5]. While scoring of within grades will increase numbers of subregions and compartments showing change, it is unknown if these recorded changes are meaningful.

As knee malalignment should predict both cartilage loss and BML worsening in the more loaded compartment, and meniscal damage should predict cartilage loss and BML worsening in the affected compartment, we focused on malalignment and meniscal damage to predict compartment-specific structural progression [17, 18]. WORMS cartilage loss scores and WORMS BML worsening scores were compared looking either at within-grade changes only or at full grade changes or greater. We applied the WORMS scale as this has been used in MOST from the beginning and thus we cannot extrapolate if our findings are translatable

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to other scoring systems such as BLOKS or MOAKS [2, 3]. Studies with large numbers of subjects are needed to perform such analyses. Potentially the Osteoarthritis Initiative (OAI) a large ongoing study could answer some of the questions remaining in regard to other scoring systems, such as MOAKS. However, we believe that the basic concept of within-grade scoring, i.e. coding of visual definite changes that do not fulfill the criteria of a full grade change from one time point to the next will be applicable to all scoring systems.

Our finding that severe medial meniscal damage predicted within-grade progression of cartilage damage but not ≥ full grade worsening needs mentioning and seems surprising. This fact is not easily explained and based on our data only speculation to explain this finding is possible. One reason could be that knees that showed > full grade worsening only and no within-grade changes showed more concomitant structural pathology such as effusion, synovitis, meniscal extrusion or ligamentous damage that also might have deleterious effects on cartilage loss and thus diluted the effect of meniscal damage in these knees. Another explanation could be that within grade changes were detected primarily for a different part of the spectrum in comparison to > full grade worsening as the WORMS scale for cartilage scoring clearly is not a linear scale. For example, going from 2 to 3 on the WORMS scale is not the same as going from 5 to 6 [7]. Why this finding was only observed for the medial compartment and not the lateral remains elusive but could be due to the lower numbers of within grade and > full grade worsening in the lateral compartment. Similar explanations might be valid to explain the comparable findings in regard to malalignment and cartilage loss.

Our study has limitations that should be acknowledged. The MRIs were presented sequentially, and readers were aware of the chronological order of images. This might result in a slight tendency to read more change in comparison to a blinded reading. However, it has been shown that scoring without knowing the chronological sequence substantially decreases sensitivity in the detection of clinically relevant changes in comparison to scoring in chronological order and that it does not introduce false positive changes [19, 20]. These studies showed that blinding to time point can lead to misclassification of the longitudinal change in a feature and that it may compromise the assessment of the relation of that feature and its outcome [21]. Within grade scoring is only feasible when the chronological order is known as coding refers specifically to the previous time point. Another possible shortcoming of our study is the fact that we employed 1.0T extremity MRI, which has been questioned to yield inferior image quality when compared to 1.5T or 3T large bore systems. These issues, to the extent they exist, seem not to affect semiquantitative scoring of knee OA. In a comparative exercise scoring knees of subjects who had received a 1.0T extremity MRI scan and a 1.5T large bore examination of the same knee on the same day, we could show good agreement, sensitivity and specificity for all assessed features [14]. Even in a large epidemiologic study like MOST it has to be acknowledged that sample size is not sufficient to assess all associations adequately, which was the case in the present analysis for severe valgus malalignment and cartilage loss and BML worsening in the lateral compartment.

Summarizing our findings, we have shown that severe meniscal damage predicted within grade worsening of cartilage loss but not full-grade or more in the medial compartment, and also medial within grade and full-grade or more worsening of BMLs. In the lateral compartment, severe meniscal damage predicted both within-grade worsening and ≥ full grade worsening in a comparable fashion. Severe varus malalignment predicted within-grade worsening of cartilage damage in the medial compartment, but not ≥ full grade worsening. Severe valgus malalignment predicted within-grade worsening of cartilage damage in the lateral compartment but not ≥ full grade worsening. Scoring of within-grade changes increases number of compartments and subregions showing change and the association of partial grade changes with risk factors and outcomes suggests that they are clinically

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relevant. Based on our findings we recommend considering within-grade assessment in longitudinal evaluation of knee OA using WORMS and potentially other semiquantitative scoring approaches.

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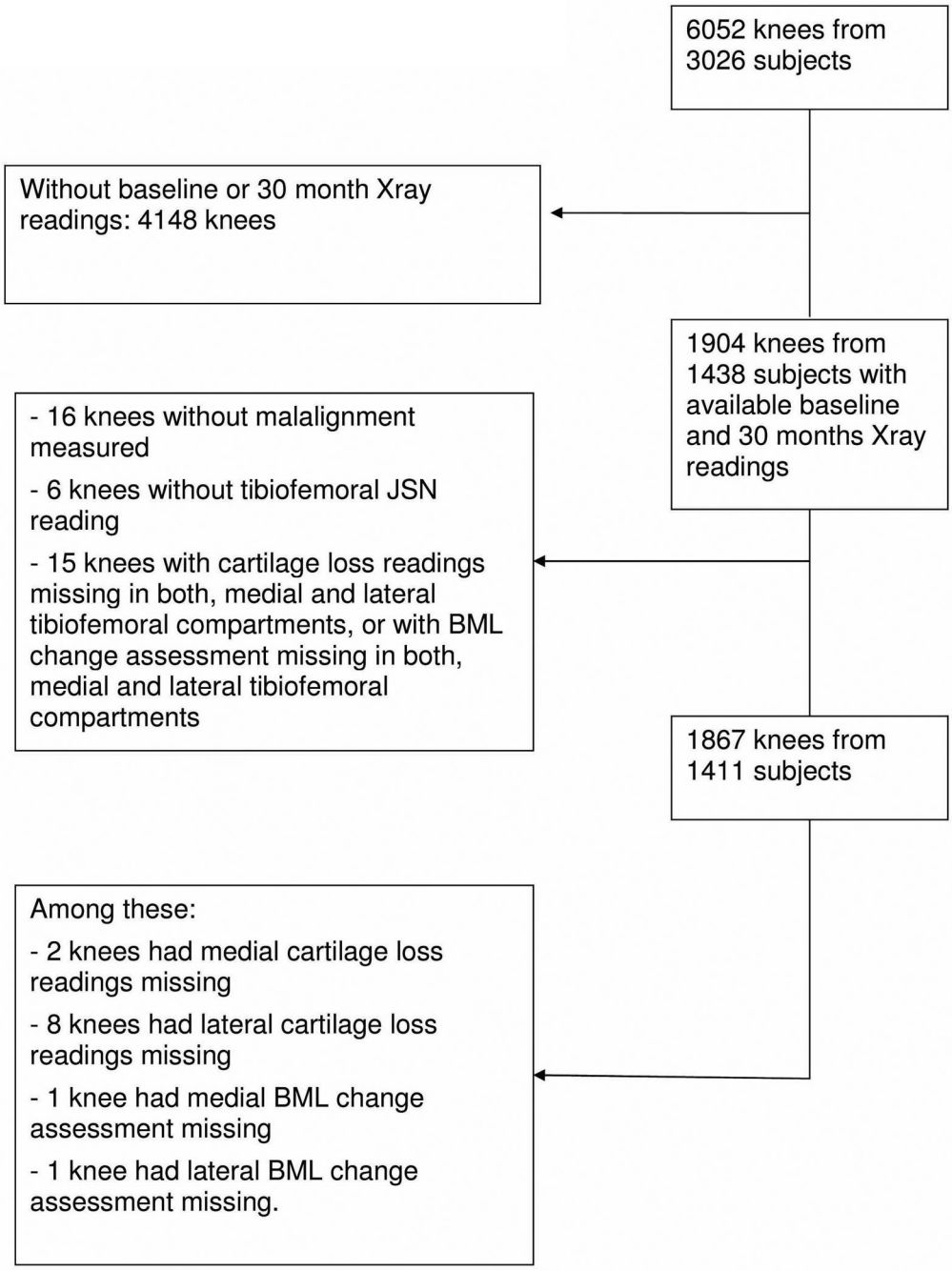

Figure 1.
Flowchart of knee inclusion.

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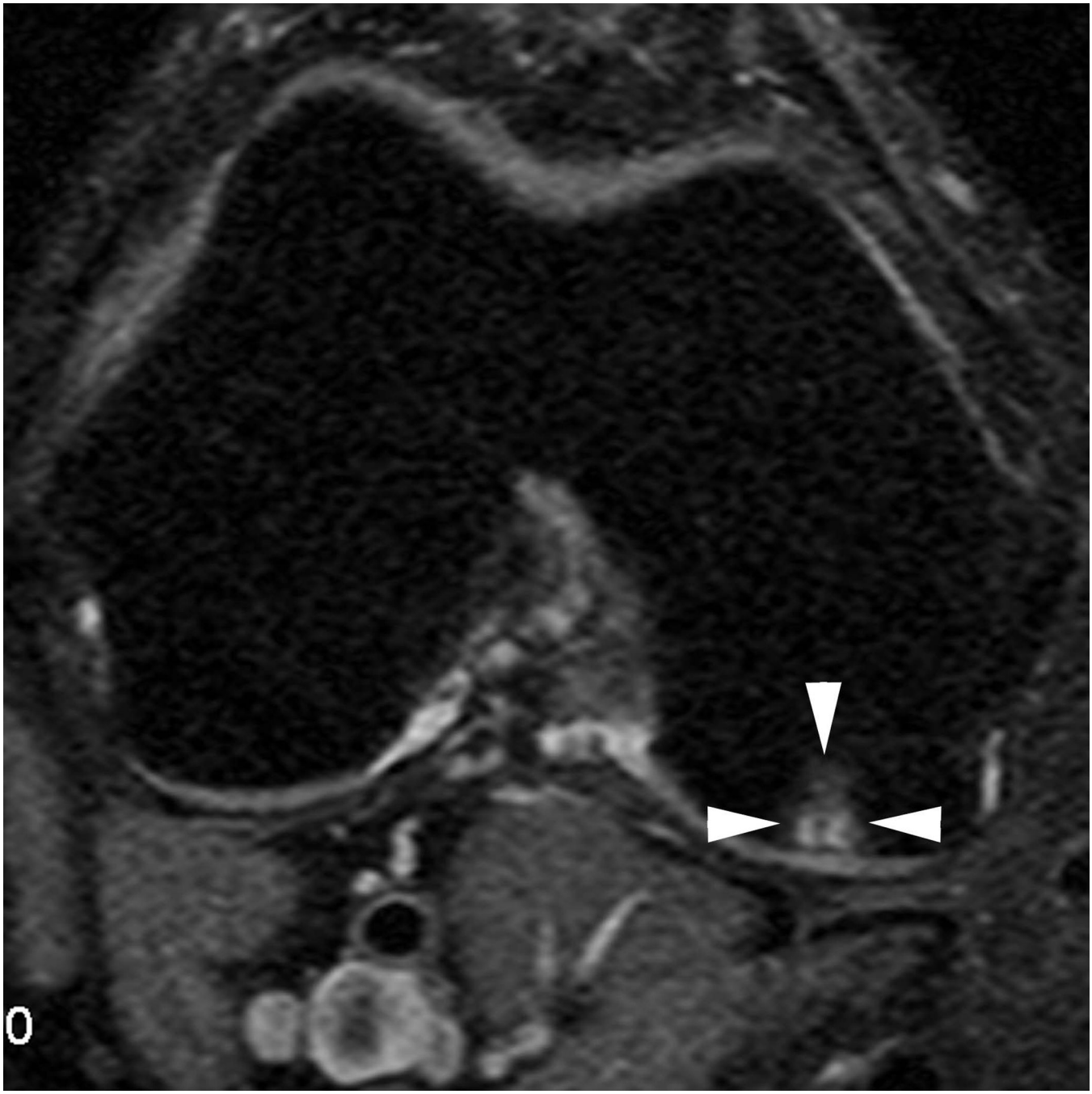

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Figure 2.
Axial proton density weighted fat suppressed image shows within-grade progression of BML in posterior subregion of the medial femur. A. At baseline a small grade 1 BML is depicted (arrowheads). B. At 30 months follow-up, same BML shows discrete but definite increase in size, but still does not fulfill criteria for a full grade change (arrows). Increase in size was coded as within-grade change.

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Table 1

Medial mensical damage and its relation to cartilage loss and BML worsening in the medial tibio-femoral compartment

Meniscal damage (predictor) (max. score in medial compartment)	**Cartilage loss in medial compartment (outcome)**				**[1]Adjusted OR (95% CI)**	
	Total number of knees [2]	**Knees with no change (%)**	**Knees with within-grade worsening only(%)**	**Knees with ≥ full grade worsening(%)**	**Outcome within-grade worsening vs. no change**	**Outcome ≥ full grade worsening vs. no change**
0	1224	1002 (81.9)	43 (3.5)	179 (14.6)	1.0	1.0
1	78	48 (61.6)	6 (7.7)	24 (30.8)	1.0 (0.3,3.7)	1.8 (0.8,3.9)
2	243	139 (57.2)	26 (10.7)	78 (32.1)	2.1 (0.9,4.6)	2.1 (1.3,3.5)
3 and 4	320	185 (57.8)	51 (15.9)	84 (26.3)	4.4* (2.2,8.7)	1.3 (0.8,2.2)

Meniscal damage (predictor) (max. score in medial compartment)	BML worsening in medial compartment (outcome)				[1]Adjusted OR (95% CI)	
	Total number of knees [3]	Knees with no change (%)	Knees with within-grade grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome within-grade worsening vs. no change	Outcome ≥ full grade worsening vs. no change
0	1225	1039 (84.8)	28 (2.3)	158 (12.9)	1.0	1.0
1	78	57 (73.1)	2 (2.6)	19 (24.4)	0.3 (0.03,2.5)	0.9 (0.4,2.0)
2	243	164 (67.5)	14 (5.8)	65 (26.8)	1.5 (0.5,4.7)	1.2 (0.7,2.0)
3 and 4	320	157 (49.1)	34 (10.6)	129 (40.3)	9.6* (3.6,25.1)	5.1* (3.2,8.2)

[1]Adjusting for age, sex, BMI

[2]two knees had medial cartilage loss measurements missing

[3]eight knees had lateral cartilage loss measurements missing

OR – odds ratio, 95% CI- 95% confidence interval

*statistically significant at $p \leq 0.05$

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Table 2

Lateral mensical damage and its relation to cartilage loss and BML worsening in the medial tibio-femoral compartment

Meniscal damage (predictor) (max. score in lateral compartment)	**Cartilage loss in lateral compartment (outcome)**				**[1]Adjusted OR (95% CI)**	
	Total number of knees [2]	**Knees with no change (%)**	**Knees with within-grade worsening only (%)**	**Knees with ≥ full grade worsening (%)**	**Outcome: within-grade worsening vs. No change**	**Outcome: ≥ full grade worsening vs. No change**
0	1654	1432 (86.6)	51 (3.1)	171 (10.3)	1.0	1.0
1	28	18 (64.3)	3 (10.7)	7 (25.0)	1.9 (0.3,12.8)	0.9 (0.2,3.7)
2	81	44 (54.3)	7 (8.6)	30 (37.0)	1.6 (0.4,6.3)	2.9 (1.3,7.0)
3 and 4	96	47 (49.0)	12 (12.5)	37 (38.6)	3.8* (1.1,13.0)	3.9* (1.7,9.0)
Meniscal damage (predictor) (max. score in lateral compartment)	BML worsening in medial compartment (outcome)				[1]Adjusted OR (95% CI)	
	Total number of knees [3]	Knees with no change (%)	Knees with within-grade grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome: within-grade worsening vs. no change	Outcome: ≥ full grade worsening vs. no change
0	1657	1535 (92.6)	18 (1.1)	104 (6.3)	1.0	1.0
1	28	20 (71.4)	0 (0.0)	8 (28.6)	n/a	1.4 (0.4,5.2)
2	81	60 (74.1)	1 (1.2)	20 (24.7)	n/a	1.4 (0.6,3.4)
3 and 4	100	48 (48.0)	9 (9.0)	43 (43.0)	n/a	10.1* (4.5,22.6)

[1] Adjusting for age, sex, BMI

[2] one knee had medial bone marrow lesion change measurements missing

[3] one knee had lateral bone marrow lesion change measurements missing

OR – odds ratio, 95% CI- 95% confidence interval

* statistically significant at $p \leq 0.05$

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Table 3

Malalignment and its relation to cartilage loss

Malalignment (predictor)	**Cartilage loss in <u>medial</u> compartment (outcome)[1]**				**Adjusted OR [3](95% CI)**	
	Total number of knees	**Knees with no change (%)**	**Knees with within-grade worsening only (%)**	**Knees with ≥ full grade worsening (%)**	**Outcome: within grade worsening vs. No change**	**Outcome: ≥ full grade worsening vs. No change**
Neutral (2° valgus – 2° varus)	998	773 (77.5)	48 (4.8)	177 (17.7)	1.0	1.0
Moderate varus (3°-6°)	538	356 (66.2)	50 (9.3)	132 (24.5)	0.9 (0.5,1.6)	1.3 (0.8,1.9)
Severe varus (≥ 7°)	102	57 (55.9)	20 (19.6)	25 (24.5)	5.5* (2.6,11.6)	1.7 (0.9,3.3)
Malalignment (predictor)	**Cartilage loss** in **<u>lateral</u>** compartment (outcome)[2]				Adjusted OR[3](95% CI)	
	Total number of knees	Knees with no change (%)	Knees with within-grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome: within grade worsening vs. No change	Outcome: ≥ full grade worsening vs. No change
Neutral (2° valgus – 2° varus)	997	824 (82.7)	43 (4.3)	130 (13.0)	1.0	1.0
Moderate valgus (3°-6°)	203	147 (72.4)	10 (4.9)	46 (22.7)	0.5 (0.1,1.5)	2.0 (0.8,5.1)
Severe valgus (≥ 7°)	21	14 (66.7)	4 (19.1)	3 (14.3)	6.3* (1.3,30.6)*	0.9 (0.2,4.9)

[1] n = 1638 knees. Valgus knees excluded from analysis

[2] n = 1221 knees. Varus knees excluded from analysis

[3] Adjusting for age, sex, BMI

OR – odds ratio, 95% CI- 95% confidence interval

* statistically significant at $p \leq 0.05$

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Table 4

Malalignment and its relation to BML worsening

Malalignment (predictor)	**BML worsening in medial compartment[1] (outcome)**				**Adjusted OR[3] (95% CI)**	
	Total number of knees	**Knees with no change (%)**	**Knees with within-grade worsening only (%)**	**Knees with ≥ full grade worsening (%)**	**Outcome within grade worsening vs. No change**	**Outcome ≥ full grade worsening vs. No change**
Neutral (2° valgus – 2° varus)	999	798 (79.9)	32 (3.2)	169 (16.9)	1.0	1.0
Moderate varus (3°-6°)	538	360 (66.9)	31 (5.8)	147 (27.3)	0.8 (0.4,1.6)	1.2 (0.8,1.7)
Severe varus (≥ 7°)	101	55 (54.5)	12 (11.9)	34 (33.7)	4.9* (2.0,12.3)	2.5* (1.4,4.6)
Malalignment (predictor)	**BML worsening** in **lateral** compartment[2] (outcome)				Adjusted OR[3] (95% CI)	
	Total number of knees	Knees with no change (%)	Knees with within-grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome: within grade worsening vs no change	Outcome: ≥ full grade worsening vs no change
Neutral (2° valgus – 2° varus)	999	909 (91.0)	18 (1.8)	72 (7.2)	1.0	1.0
Moderate valgus (3°-6°)	206	158 (76.7)	4 (1.9)	44 (21.4)	73.6* (24.0,225.8)	1.1 (0.5,2.4)
Severe valgus (≥ 7°)	22	13 (59.1)	0 (0.0)	9 (40.9)	n/a	8.4 (2.6,27.7)*

[1] n = 1638 knees. Valgus knees excluded from analysis

[2] n = 1221 knees. Varus knees excluded from analysis

[3] Adjusting for age, sex, BMI

OR – odds ratio, 95% CI- 95% confidence interval, BML – bone marrow lesion

* statistically significant at $p \leq 0.05$