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Authors

Antony, B
Driban, JB
Price, LL
et al.

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The relationship between meniscal pathology and osteoarthritis depends on the type of meniscal damage visible on magnetic resonance images: data from the Osteoarthritis Initiative

Benny Antony[1,2], **Jeffrey B. Driban**[1], **Lori Lyn Price**[3,4], **Grace H. Lo**[5,6], **Robert J. Ward**[7], **Michael Nevitt**[8], **John Lynch**[8], **Charles B. Eaton**[9], **Changhai Ding**[2], and **Timothy E. McAlindon**[1]

[1]Division of Rheumatology, Tufts Medical Center, Boston, USA

[2]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

[3]The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

[4]Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, USA

[5]Section of Immunology, Allergy, and Rheumatology, Baylor College of Medicine, Houston, TX, USA

[6]Center for Innovations in Quality, Effectiveness and Safety Medical Care Line and Research Care Line; Michael E. DeBakey VAMC, Houston, TX, USA

[7]Department of Radiology, Tufts Medical Center, Boston, USA

[8]Department of Epidemiology and Biostatistics, University of California at San Francisco, USA

Corresponding author and address for reprints: Dr. Benny Antony, Menzies Institute for Medical Research, Private Bag 23, Hobart, Tasmania 7000, Australia, Tel: 61-362-264255, Fax: 61-362-267704, Benny.EathakkattuAntony@utas.edu.au.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Antony had full access to the data in the study and contributed to the conception and design, analysis and interpretation of data, drafting/revisions of the article, as well as final approval of the article. Study design: Driban JB, Lo GH, Nevitt MC, Lynch J, Eaton CB, McAlindon TE; Data Collection: Driban JB, Lo GH, Ward RJ, McAlindon TE; Analysis and interpretation of data: Antony B, Driban JB, Price LL, Lo GH, Ward RJ, Nevitt MC, Lynch J, Eaton CB, Ding C, McAlindon TE; Statistical analysis: Antony B, Driban JB, Price LL, Ding C, McAlindon TE. All authors read and approved the final manuscript.

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[9]Center for Primary Care and Prevention, Alpert Medical School of Brown University, Pawtucket, RI, USA

Abstract

Objective—To determine the association of different types of meniscal pathology with common measures of osteoarthritis severity and progression: knee pain, bone marrow lesion (BML) volume, and end-stage knee osteoarthritis (esKOA).

Design—Participants were selected from an ancillary project to the Osteoarthritis Initiative (OAI) who had at least one knee with symptomatic osteoarthritis. Baseline magnetic resonance images (MRI) were evaluated for meniscal pathology using a modified International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine (ISAKOS) classification system. We collapsed 10 types of meniscal pathology into 5 categories: normal, intrameniscal signal, morphological deformity/extrusion (altered meniscal shape and/or extrusion but no apparent substance loss), tear, and maceration. Outcomes included WOMAC knee pain and BML volume at baseline and after 2-years. We defined the prevalence of esKOA based on a validated algorithm. We performed logistic regression and adjusted for age, sex, and body mass index (BMI).

Results—The 463 participants (53% male) included in the analysis had mean age 63 (9.2) years, BMI 29.6 (4.6) kg/m^2, and 71% had Kellgren-Lawrence grade≥2. Morphological deformity/extrusion and maceration, but no other types of meniscal pathology, were associated with BML volume (morphological deformity/extrusion odds ratio [OR]=2.47,95%CI:1.49,4.09, maceration OR=5.85,95%CI:3.40,10.06) and change in BML volume (morphological deformity/extrusion OR=2.17,95%CI:1.37,3.45, maceration OR=3.12,95%CI:1.87,5.19). Only maceration was associated with baseline WOMAC knee pain (OR=2.82,95%CI:1.79,4.43) and prevalence of esKOA (OR=7.53,95%CI:4.25,13.31).

Conclusions—Based on MRI, morphologic deformity/extrusion and maceration rather than intrameniscal signal or tear were associated with osteoarthritis severity and progression, which highlights the importance of differentiating distinct types of meniscal pathology.

Keywords

Meniscus; tear; bone marrow lesions; knee pain; end-stage knee osteoarthritis

Introduction

Meniscal damage is common among older adults[1] and is an important risk factor for the incidence[2] and progression of knee osteoarthritis (KOA)[3]. Damage to a meniscus can compromise its ability to absorb, transmit, and distribute mechanical stress over a large area of the joint cartilage[4]. Meniscal pathology increases the risk for structural changes commonly associated with KOA (e.g., bone marrow lesions (BML)[5,6], cartilage volume loss[7], and altered subchondral bone mineral density[8]). However, there are different types of meniscal pathology, which range from subtle intrameniscal signal to tears (e.g., horizontal tear, radial tear) and maceration. Certain types of meniscal pathology (e.g., maceration) may alter joint loading more than other types of subtle meniscal pathology (e.g., intrameniscal signal). Hence, certain types of meniscal pathology, like maceration (meniscal destruction),

may influence structural and clinical progression of KOA more than other types of meniscal pathology. Major meniscal pathology (comparable with maceration) is associated with BML progression[5] and knee pain[9] among individuals without KOA. Furthermore, the presence of major meniscal pathology is more likely in knees that receive a knee replacement than among knees that do not[10,11]. While only 5% of adults without KOA have meniscal destruction (e.g. maceration), one in four have at least one type of meniscal pathology, which suggests that certain types of meniscal pathology (e.g., tears) may not be a major catalyst for OA progression[1]. It is important to determine if certain types of meniscal pathology are associated with structural and symptomatic changes because this could help us more efficiently identify individuals at risk for progression.

We aimed to determine the association of different types of meniscal pathology with common measures of OA severity and progression. Specifically, we evaluated knee pain, change in knee pain over 2 years, BML volume, and change in BML volume over 2 years because these measures of OA severity and progression have been previously associated with meniscal pathology in studies that did not account for different types of meniscal pathology[5,6,9,12,13]. We also tested the association of different types of meniscal pathology with a validated definition of end-stage KOA (esKOA), which is a unique outcome that accounts for radiographic disease severity and self-reported knee pain and function[14]. We hypothesize that only certain types of meniscal pathology that severely alter meniscal function (i.e., maceration, change in meniscal shape [morphological deformity/extrusion]) relate to common measures of KOA severity and progression.

Materials and methods

Study sample

We selected a convenience sample of the Osteoarthritis Initiative (OAI) Progression Cohort (n=1390) who attended an OAI visit between August 2007 to April 2009 and consented to participate in the Bone Ancillary Study (n=629). The primary aim of the Bone Ancillary Study was to investigate the influence of bone in the structural progression of OA. The inclusion criteria were a willingness to undergo additional knee imaging (i.e., additional magnetic resonance [MR] scans and dual-energy x-ray absorptiometry). Participants with contraindication for MR imaging were excluded. For the Bone Ancillary Study analyses, the 24-month OAI visit was considered baseline and the 48-month visit was considered as the 2-year follow-up. At baseline, these participants had clinical data and MR images that were assessed for meniscal pathology (n=463) and BML volume (n=first 386 knees based on ID as a convenience). At the follow-up visit, 463 participants had clinical data and 386 participants had MR images that were assessed for BML volume. The reduced sample size was due to time and personnel constraints.

We selected one knee per participant. We used the primary OAI imaging knee as the index knee unless there was a contraindication for MR imaging. According to protocol, the primary OAI imaging knee was the right knee, which underwent a complete set of OAI MR sequences. The contralateral knee had an abbreviated MR scan to reduce participant burden. While everyone in this study sample had at least one knee with symptomatic OA, the primary OAI imaging knee was not always the knee with symptomatic OA.

This study received ethical approval from each OAI clinical site (Memorial Hospital of Rhode Island Institutional Review Board, The Ohio State University's Biomedical Sciences Institutional Review Board, University of Pittsburgh Institutional Review Board, and University of Maryland Baltimore–Institutional Review Board), the OAI coordinating center (Committee on Human Research at University of California, San Francisco), and the Institutional Review Board at Tufts Medical Center and Tufts University Health Sciences Campus. All participants provided informed consent to the OAI and the Bone Ancillary Study.

Magnetic resonance imaging

MR images were acquired at the 24- and 48-month OAI visits with one of four identical Siemens (Erlangen, Germany) Trio 3-Tesla MR systems and a USA Instruments (Aurora, OH, USA) quadrature transmit-receive knee coil at the four OAI clinical sites[15]. For purposes of the Bone Ancillary Study these MR images were considered baseline and 2-year follow-up. The following sequence was used for BML evaluation: sagittal intermediate-weighted, turbo spin echo, fat-suppressed MR sequences (field of view=160 mm, slice thickness=3 mm, skip=0 mm, flip angle=180 degrees, echo time=30 ms, recovery time=3200 ms, 313×448 matrix (interpolated to 512×512), phase encode superior/inferior, × resolution=0.357 mm, and y resolution=0.511 mm). We scored menisci using the same sequences used to evaluate BMLs in addition to the coronal intermediate-weighted 2D turbo spin echo, recovery time of 3850 ms, echo time of 29 ms, slice thickness of 3 mm, and field of view of 140 mm. All images are publicly available (https://oai.epi-ucsf.org).

Meniscal pathology scoring

A single experienced fellowship trained musculoskeletal radiologist (RJW) reviewed the baseline MR images for meniscal pathology by location (i.e., anterior horn, body, and posterior horn) within the medial and lateral menisci using a modified International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine (ISAKOS) meniscal tear classification system[16]. The original ISAKOS scoring was based on viewing of videos of arthroscopy to evaluate the meniscal tear based on the tear depth, location, tear pattern, length, quality of tissue, and percent of meniscus excised. This was modified to focus on the radiological aspect of MR imaging and 10 classifications were made: normal, intrameniscal signal, morphological deformity/extrusion (shape change including meniscal extrusion but no apparent substance loss), horizontal tear, horizontal flap tear, longitudinal- vertical tear, radial tear, vertical flap tear, complex tear, and maceration (destruction). The presence of these 10 pathologies was evaluated systematically in each region of the meniscus and each region was assigned only one pathology. Intrameniscal signal was defined as an increase in signal intensity within a region without other pathologic features. The reader indicated a type of tear when it was the only tear in a region. Meniscal morphological deformity/extrusion referred to the major loss of meniscal integrity with loss of normal contour and no obvious tear as defined by no linear hyperintense signal extending to an articular surface (Supplementary Figure 1). Morphological deformity may occur with displacement (Figure 1c). Other types of pathologies, with the exception of intrameniscal signal, were absent in this category. Hence, if a region had morphological deformity/extrusion and intrameniscal signal change then the region was characterized as morphological deformity/extrusion. The

inter-observer agreement (kappa) of the MRI-based ISAKOS scoring system ranged from 0.56 to 0.92. The intra-observer agreement was kappa >0.81.

BML volume evaluation

A semi-automated segmentation method was used to determine BML volume from baseline and follow-up MR images of the Bone Ancillary Study. We focused on BMLs in the medial and lateral tibia because we hypothesized these regions would be influenced by meniscal pathology more than the femoral regions, which could have BMLs secondary to patellofemoral OA. A detailed description of the segmentation method is published elsewhere[17]. In brief, two readers measured BML volume by using a graphic user interface (MATLAB; MathWorks, Inc., Natick, MA, USA) to identify the crude boundaries of the tibia and femur in each slice of the MR sequence. The program automatically refined the initial bone border and applied a thresholding and curve evolution process twice to segment the areas of high signal intensity, which represent a probable BML. Based on common standards for defining BMLs[18], the software detected subchondral BMLs (i.e., the distance between a BML and the articular surface should be ≤10 mm[18]) that appear on more than one image. Using this criteria, BMLs have been associated with the presence of meniscal pathology[6], knee pain[19,20], and structural progression[20,21].

Validity of this method with OAI images was previously demonstrated[17]. We found a moderate-to-good intra-reader (intraclass correlation coefficient ($ICC_{3,1}$)=0.79 to 0.99) and inter-reader reliability ($ICC_{2,1}$=0.59 to 0.93) for BML volume change[22]. A third reader assessed the accuracy and consistency of all segmentations.

Knee pain evaluation

Knee-specific pain was assessed using the well validated Western Ontario and McMaster Universities osteoarthritis index (WOMAC) pain score[23], which was assessed at baseline and 2-year follow-up visits. WOMAC pain scale is based on 5 questions of knee pain over the past 7 days when performing different activities (e.g., walking, climbing stairs, lying down). These pain questions were assessed with a 5-point Likert scale (0=no pain and 4=severe pain), which were summed for a total WOMAC pain score (range 0–20). WOMAC pain scores are publicly available (Files: AllClinical##_SAS[version 3.2 and 6.2]).

End-stage knee osteoarthritis calculation

We adopted a strategy to define esKOA based on a modified validated algorithm for defining an individual's appropriateness for a total knee arthroplasty (TKA)[14,24]. We defined the state of esKOA at the 36- and/or 48-month OAI visits (1 year and/or 2 year follow-up). The modified algorithm accounts for a participant's radiographic severity, localization of OA (i.e., patellofemoral, medial or lateral tibiofemoral, multiple compartments), knee symptoms, range of motion, and varus/valgus laxity assessments. Radiographic severity and localization were based on Kellgren-Lawrence scoring and OARSI joint space narrowing scores, respectively. Central readers provided the scoring based on bilateral posterior-anterior weight-bearing knee x-rays (Files: kXR_SQ_BU##[version 3.5 and 6.3]). One reader (JL) read MR images to determine the presence of patellofemoral OA (a definite osteophyte with a definite cartilage lesion at the patella or anterior femur[25]) when the

algorithm needed to account for the number of affected compartments. Knee pain and knee function status in participants were assessed with the sum of the WOMAC pain and function scales. We then collapsed the sum of the WOMAC pain and function scales into 4 categories to reflect the slight (scores 0–11), moderate (scores12–22), intense (scores 23–33) and severe (scores ≥34) symptomatology. Patients were classified as having limited mobility or increased instability when they either had a flexion contracture of ≥5 degrees or were graded as having moderate or severe medial or lateral laxity during valgus or varus stress testing with the knee flexed to 20 degrees. All measures were collected following the OAI protocol, which is publicly available (https://oai.epi-ucsf.org; Files: allclinical## [version 1.5, 3.5, 5.5]).

Clinical Data

At baseline, study staff asked participants: “Have you ever injured your right knee badly enough to limit your ability to walk for at least two days?”. A similar question was asked for the left knee. At each annual visit study staff asked a follow-up question: “Since your last annual visit to the OAI clinic about 12 months ago, have you injured your right knee badly enough to limit your ability to walk for at least two days?”. A similar question was asked for the left knee. We defined a history of injury as anyone who reported a history of injury at the baseline, 12-month, or 24-month OAI visits. A similar question was asked for the surgery status of knee and was followed up over the visits. Self-reported physical activity during the previous 7 days was measured using the Physical Activity Scale for the Elderly (PASE). PASE scores from 24-month OAI visit were used to determine physical activity groups from lowest to highest activity levels.

Age, sex, and body mass index (BMI), were recorded based on a standardized protocol (https://oai.epi-ucsf.org). All OAI clinical data are publicly available.

Data analysis

Some types of meniscal pathologies had a low prevalence; therefore, for analyses, we collapsed the 10 original ISAKOS categories into normal, intrameniscal signal, morphological deformity/extrusion, tear (i.e., horizontal, horizontal flap, vertical-longitudinal, radial, radial-longitudinal, complex tear), and maceration. Each of these 5 categories was dichotomized as present or absent. As a secondary post hoc analysis, we also counted the number of regions of the knee with maceration (0–6), which represented the most severe type of meniscal pathology.

To assess the association with types of meniscal pathology and structural progression we assessed BML volumes in 386 knees. Since the BML segmentation program detected small areas of signal intensity on every knee we used a classification and regression tree (CART) to identify a meaningful BML volume cut-off value using medial joint space narrowing progression as outcome as we previously published[20]. A total tibial BML volume less than 1cm^3 was identified as the volume that cannot be classified as meaningful BML. For cross sectional analysis, we collapsed the baseline BML volume into 3 categories: 1) no meaningful BML volume (<1cm^3), 2) small BML volume: below median value of meaningful BML volumes (1.00 to 2.15cm^3), and 3) large BML volume: above median

value of meaningful BML volume (>2.15cm^3). Longitudinally, the change in BML volume was collapsed to 4 groups based on the presence of a meaningful BML volume and quartiles of BML volume change: 1) no meaningful BML volume (<1cm^3) at both time points, 2) regression of meaningful BML volume: baseline BML volume≥1.00 cm^3 & BML volume change≤−0.75 cm^3, (lowest quartile of change), 3) no BML volume change: middle 2 quartiles of the BML volume change (baseline BML volume≥1.00 cm^3 & BML volume change>−0.75 cm^3 & ≤1.00 cm^3), and 4) progression of meaningful BML volume: (baseline BML volume≥1.00 cm^3 & BML volume change>1.00 cm^3). Ordinal logistic regression was performed to determine the association of baseline meniscal pathology with BML volume and change in BML volume.

A large percentage of knees had a WOMAC knee pain score of zero and our analyses failed to meet the assumptions for linear regression modelling; therefore, WOMAC knee pain at baseline was collapsed into 3 categories for cross-sectional analysis: 1) no or little pain (WOMAC pain score 0–1, reference category), 2) mild pain (WOMAC pain score 2–3), 3) moderate-severe pain (WOMAC pain score >3). Longitudinally, we collapsed the change in WOMAC knee pain between the baseline and 2-year follow-up visits into 3 categories based on the presence or absence of pain and a clinically meaningful change in pain (absolute change of 2 or relative change of 40%)[26]: 1) no pain or a meaningful decrease in pain (reference category), 2) pain but no change over time, and 3) meaningful increase in pain. Ordinal logistic regression was performed to determine the association of baseline meniscal pathology with knee pain and change in knee pain over 2 years.

To assess whether the type of meniscal pathology was associated with esKOA we adapted the previously published decision rule[14] and collapsed the inconclusive and inappropriate category into one category that is not esKOA. We defined the original appropriate category as esKOA. Logistic regression was performed to determine the association between baseline meniscal pathology and esKOA. We completed secondary analyses by further adjusting for history of knee injury or surgery, BML and PASE in multivariable analyses.

All parameter estimates were adjusted for age, sex, and BMI. In addition, indicator variables for intrameniscal signal, morphological deformity/extrusion, maceration, and tear were all included in models to explore the independent association of each type of meniscal pathology on structural and clinical progression of KOA. All statistical analyses were performed on SAS 9.4 (Cary, NC, USA).

Results

463 participants from the baseline visit of Bone Ancillary Study were included in the analysis with mean (standard deviation) age of 63 (9) years, 53% male, BMI 29.6 (4.6) kg/m^2, and 86% had any type of meniscal pathology at baseline. 55% participants had intrameniscal signal, 30% morphological deformity/extrusion, 20% maceration and 47% any tear. Prevalence of baseline any knee pain was 73%, baseline BML was 27 %, and the esKOA was 15%. The sample included a wide range of radiographic severity with 14%, 15%, 34%, 28%, and 8% with Kellgren-Lawrence grades 0, 1, 2, 3, 4; respectively. There

were 168 (36%) knees with a history of knee injury and 102 (22%) knees with a history of knee surgery.

Types of meniscal pathology and BML volume

Table 1 provides the cross-sectional associations between types of meniscal pathology and baseline BML volume. Table 2 presents the longitudinal associations between types of meniscal pathology and BML volume change. Overall, the presence of a meniscal pathology, regardless of type, was associated with BML volume (odds ratio [OR]=3.91, 95% confidence interval [95%CI]=1.36,11.24). Morphological deformity/extrusion and maceration were consistently associated with BML volume and change in BML volume. Intrameniscal signal and any tear were not significantly associated with BML volume or change in BML volume.

Having more meniscal regions affected with maceration was associated with greater BML volume than those with a normal meniscus. Further adjusting for surgery or injury cases did not change our conclusion. We did not report the association between BML volume change and any type of meniscal pathology because our analyses failed to meet the assumption for proportional odds.

Types of meniscal pathology and knee pain

Tables 3 and 4 provide the cross sectional and longitudinal associations between meniscal pathology and knee pain, respectively. Overall, the presence of a meniscal pathology, regardless of type, was not significantly associated with knee pain (OR=1.30, 95%CI=0.78,2.18) or change in knee pain (OR=0.89, 95%CI=0.54,1.48). When we assessed the types of meniscal pathology, meniscal maceration was significantly associated with greater knee pain but not with increase in knee pain in longitudinal analysis. Morphological deformity/extrusion was not significantly associated with knee pain cross-sectionally, but showed a trend (p=0.059) towards an increase in knee pain over 2 years. Further adjusting for any history of surgery or injury cases, BMLs and PASE yielded largely similar results.

Types of meniscal pathology and end-stage knee osteoarthritis

Table 5 presents the association of meniscal pathology type with the prevalence of esKOA at the 36- or 48-month OAI visit. Overall, there was no statistically significant association between the presence of meniscal pathology, regardless of type, and the prevalence of esKOA (OR=1.50, 95%CI=0.64,3.54). However, maceration was associated with esKOA. Having more meniscal regions affected with maceration was associated with greater odds of having esKOA than those with a normal meniscus. Intrameniscal signal and any tear were not associated with esKOA.

Discussion

This is the first study to determine the association between different types of meniscal pathology based on the detailed ISAKOS scoring system and common measures of OA severity and progression. We found that meniscal maceration and an altered meniscal shape including meniscal extrusion (morphological deformity/extrusion) rather than intrameniscal

signal or tears were associated with structural changes. Our results also suggest that meniscal maceration is associated with greater knee pain and esKOA.

Abnormalities that severely disrupt load distribution of a meniscus such as altered shape and maceration were associated with BML volume and change in BML volume. Presence and larger number of regions with meniscal maceration was also associated with BML and esKOA suggesting that both number and type of pathology may be important in predicting KOA progression. Roemer et al found that presence of maceration of the meniscal body and medial posterior horn was more likely in knees that received knee replacement than in control knees[10]. Our findings also suggest that severe disruptive pathologies of menisci are associated with structural KOA progression.

Prevalent intrameniscal signal and tear were not associated with BML presence or BML progression or esKOA in our study. The present finding concurs with a previous study, which found that the rate of medial meniscus lesions (tear or intrameniscal signal) was not higher in those who developed incident radiographic KOA compared with control participants[27]. Hence, these pathologies are less disruptive and may not be detrimental in KOA progression over 2 years and conservative treatment can be considered for these pathologies; however, these findings may not be generalizable to acute meniscal tears. In fact, acute meniscal tears in younger athletic populations are key risk factors for incident KOA[28,29].

The presence of a tear alone does not qualify as KOA[25]. A recent consensus-based OA definition noted that the presence of a tear must be accompanied by an osteophyte or full thickness cartilage defect and at least one of the following: BML/cyst, partial thickness cartilage loss, or bone attrition. Similarly, intrameniscal signal alone is not KOA despite representing early degenerative changes in the meniscus and being common among adults[1,30].

We found that meniscal maceration was associated with higher knee pain cross-sectionally but not longitudinally. It is possible that maceration is associated with a severe pain that may not change over time. We found no other associations with knee pain including tears. Further prospective studies are warranted to determine if tear incidence is related to acute knee pain and if a subset of knees can then function without pain. The fact that only meniscal maceration is related to pain in our study may explain discordant findings in prior studies[1,9,13,31]. Inconsistencies among prior studies may be due to the absence of clear-cut definition of different types of meniscal pathology. This highlights the need to differentiate meniscal maceration from other types of prevalent meniscal pathology.

The strength of our study was the use of an algorithm to predict the esKOA, which incorporates measures of pain, function and structural severity. This measure is preferable to TKA, which is a common KOA endpoint, because various factors influence the patient's willingness to undergo TKA; including, financial situations[32].

There was no major difference in the association between meniscal pathology and knee pain after further adjustment for BMLs. There was a significant reduction in the effect size of the association between meniscal pathology and esKOA after further adjustment for BMLs

suggesting a potential mediation. However, these associations remained statistically significant, indicating the independent association of meniscal pathology. BMLs may fall in the causal pathway of the association between meniscal pathology and knee pain or esKOA.

An important limitation is that we did not measure the meniscal pathology at the follow-up visit; therefore, we cannot assess if change in meniscal pathology is associated with change in KOA. Furthermore, we evaluated meniscal pathology with a modified arthroscopy-based scoring system, and we could not measure the meniscal extrusion in this cohort and therefore cannot comment on the influence of extrusion on KOA progression. However, numerous studies have evaluated the importance of meniscal extrusion[3,5,11,33]. While our scoring system enabled us to assess different types of meniscal tears in various regions we unfortunately needed to summarize them as tears because each tear type had a low prevalence. Hence, we could not analyze the specific types of tears nor compartment-specific effect of meniscal pathology on BMLs and knee pain. Furthermore, we did not specifically measure the radial root tear, but they were included in the radial tear category. We are unable to determine the importance of the severity of a tear. We believe this may be important for future studies because our findings suggest that the least severe pathology (intrameniscal signal) is not associated with KOA or KOA progression while more severe types of pathology (meniscal maceration) are. We did not record insufficiency fractures in these subjects and therefore not included in the analyses. This cohort had a large number of KOA cases, which limits our ability to generalize to general population. Despite this limitation, this study provides important insights about meniscal findings that may be associated with changes within the next two years. Further longitudinal studies are required to confirm the effect of different meniscal pathologies on the other structural progression markers such as articular cartilage.

Conclusions

Among the five categories of meniscal pathologies, disruptive pathology (i.e., morphologic deformity/extrusion or maceration) rather than intrameniscal signal or tear was associated with knee pain and structural changes. Meniscal maceration is also associated with a later clinical state that is proxy for esKOA. This suggests that not all meniscal pathology has the same impact on KOA outcomes and therefore, it is important for future studies to differentiate distinct types of meniscal pathology. Similarly, clinicians should be wary of pathologies that impair normal load distribution properties of meniscus because they may relate to KOA severity and progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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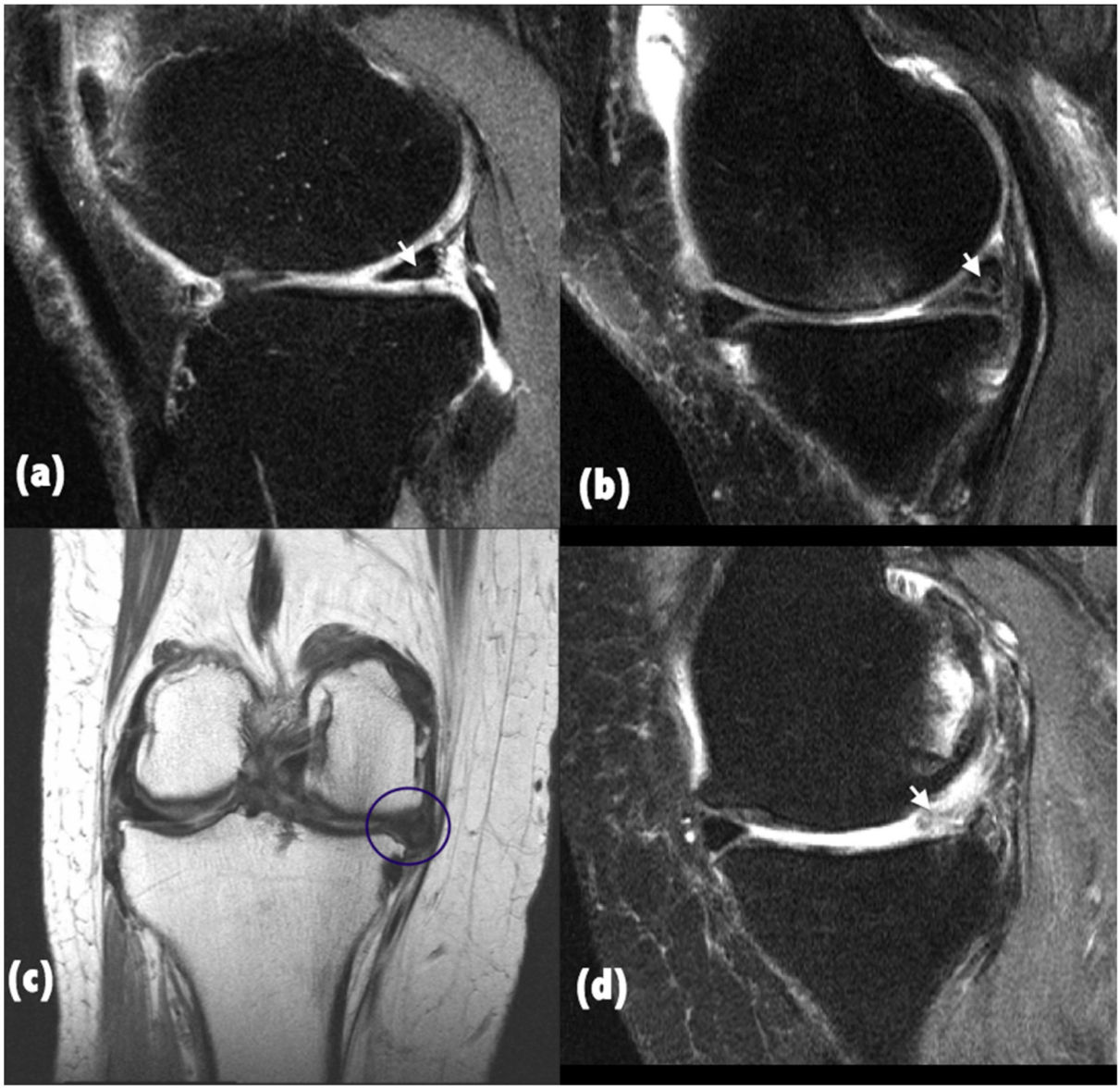

Figure 1.

Different types of meniscal pathologies used in the modified ISAKOS scoring system. (a) Intrameniscal signal, (b) Tear (complex), (c) Morphological deformity/extrusion (often occurs with displacement), (d) Maceration

Table 1

Association between different types of meniscal pathology and total tibial bone marrow lesion volume at baseline (24-month OAI visit).

Menisci (Overall n = 386)	No BML n(%)	Small BML n(%)	Large BML n(%)	Univariable OR (95% CI)	Multivariable* OR (95% CI)
Type of Pathology **					
Intrameniscal Signal (n=212)	154(73)	31(15)	27(13)	1.09(0.69,1.71)	1.25 (0.76,2.08)
Morphological Deformity/extrusion (n=117)	68(58)	25(21)	24(21)	**2.80(1.76,4.47)**	**2.47(1.49,4.09)**
Maceration (n=77)	33(43)	12(16)	32(42)	**7.04(4.22,11.76)**#	**5.85(3.40,10.06)**
Any Tear (n=183)	137(75)	26(14)	20(11)	0.85(0.54,1.33)	0.95(0.58,1.58)
Maceration: Number of Regions Affected **					
0 (n=309)	251(81)	39(13)	19(6)	Reference	Reference
1 (n=37)	20(54)	6(16)	11(30)	**4.18(2.12,8.23)**	**3.86(1.94,7.68)**
2 (n=22)	8(36)	3(14)	11(50)	**10.09(4.36,23.29)**	**8.19(3.48,19.29)**
3 and above (n=18)	5(28)	3(17)	10(56)	**13.89(5.42,35.59)**	**14.48(5.56,37.66)**

OR = odds ratio, 95% CI = 95% confidence interval, BML = bone marrow lesion, OAI= Osteoarthritis Initiative, PASE = physical activity scale for the elderly

[a] No BML: BML volume below 1.00 cm^3

[b] Small BML: Below median of meaningful BML volume: BML volume > 1.00 cm^3 & <2.15 cm^3

[c] Large BML: Above median of meaningful BML volume: BML volume > 2.15 cm^3

* Ordinal regression models were used and adjusted for age, gender and BMI

** Types of pathology were further adjusted for each other in multivariable analysis

Analyses failed to meet the proportional odds assumptions for ordinal logistic regression.

Bold denotes statistical significance at p<0.05

All multivariable models remained statistically significant after further adjustments for injury or surgery and PASE

Table 2

Association between different types and combination of meniscal pathology at baseline and total tibial bone marrow lesion volume change over 2 years.

Menisci (Overall n = 386)	No BML at both times[a] n(%)	Regression of BMLs[b] n(%)	No Change in BMLs[c] n(%)	Progression of BMLs[d] n(%)	Univariable OR (95% CI)	Multivariable[*] OR (95% CI)
Type of Pathology[**]						
Intrameniscal Signal (n=212)	138(65)	19(9)	34(16)	21(10)	1.09(0.72,1.64)	1.21(0.77,1.90)
Morphological Deformity/extrusion (n=117)	60(51)	13(11)	30(26)	14(12)	**2.33(1.52,3.60)**	**2.17(1.37,3.45)**
Maceration (n=77)	26(34)	17(22)	24(31)	10(13)	**3.81(2.39,6.07)**[#]	**3.12(1.87,5.19)**
Any Tear (n=183)	116(63)	17(9)	34(19)	16(9)	1.19(0.79,1.79)	1.19(0.76,1.87)
Maceration: Number of Regions Affected[**]						
0 (n=309)	227(73)	17(6)	43(14)	22(7)	Reference	Reference
1 (n=37)	17(46)	8(22)	8(22)	4(11)	**2.58(1.37,4.87)**[#]	**2.29(1.17,4.47)**
2 (n=22)	6(27)	4(18)	10(45)	2(9)	**4.49(2.12,9.53)**[#]	**3.28(1.45,7.43)**
3 and above (n=18)	3(17)	5(28)	6(33)	4(22)	**6.40(2.719,14.68)**[#]	**6.62(2.72,16.13)**

OR = odds ratio, 95% CI = 95% confidence interval, BML = bone marrow lesion, PASE = physical activity scale for the elderly

[a] No BML at both times: BML volume below 1.00 cm^3 at baseline and follow-up

[b] Regression of BMLs: BML volume change lowest quartile: BML volume > 1.00 cm^3 at both times & BML volume change ≤−0.75 cm^3

[c] No Change in BMLs: BML volume change middle 2 quartile: BML volume > 1.00 cm^3 at both times & BML volume change >−0.75 cm^3≤1.00 cm^3

[d] Progression of BMLs: BML volume change highest quartile: BML volume > 1.00 cm^3 at both times & BML volume change >1.00 cm^3

[*] Ordinal logistic regression models were used and adjusted for age, gender and BMI

[**] Types of pathology were further adjusted for each other in multivariable analysis

[#] Analyses failed to meet the proportional odds assumptions for ordinal logistic regression. Bold denotes statistical significance at p<0.05

All multivariable models remained statistically significant after further adjustments for injury or surgery and PASE

Table 3

Association between different types of meniscal pathology and total WOMAC knee pain at baseline (24-month OAI visit).

Menisci (n = 463)	No-Little Pain[a] n(%)	Mild Pain[b] n(%)	Moderate to Severe Pain[c] n(%)	Univariable OR (95% CI)	Multivariable[*] OR (95% CI)
Type of Pathology [**]					
Intrameniscal Signal (n=259)	100(39)	57(22)	102(39)	1.10(0.79,1.55)	1.12(0.79,1.60)
Morphological Deformity/extrusion (n=142)	48(34)	34(24)	62(42)	1.34(0.93,1.93)	1.13(0.78,1.67)
Maceration (n=100)	23(23)	24(24)	53(53)	**2.35(1.54,3.58)**	**2.82(1.79,4.43)**
Any Tear (n=222)	86(39)	51(23)	85(38)	1.02(0.73,1.44)	1.30(0.91,1.86)
Maceration: Number of Regions Affected [**]					
0 (n=363)	154(42)	89(24)	121(33)	Reference	Reference
1 (n=49)	11(22)	9(18)	29(59)	**2.83(1.58,5.08)**	**2.99(1.65,5.42)**
2 (n =27)	7(26)	7(26)	13(48)	1.97 (0.94, 4.11)	**2.55(1.20, 5.34)** [d]
3 and above (n=51)	5(21)	8(33)	11(46)	2.03(0.93,4.42)	**2.54(1.15,5.60)** [d]

OR = odds ratio, 95% CI = 95% confidence interval, OAI= Osteoarthritis Initiative, BML = bone marrow lesion, PASE = physical activity scale for the elderly

[a]No-Little Pain: total WOMAC pain score ≤1

[b]Mild Pain: total WOMAC pain score 2 or 3

[c]Moderate to Severe Pain: total WOMAC pain score >3

[*]Ordinal logistic regression models were used and adjusted for age, gender and BMI

[**]Types of pathology were further adjusted for each other

Bold denotes statistical significance at p<0.05

[d]All multivariable models remained statistically significant after further adjustments for injury or surgery, BML and PASE except

Table 4

Association between types of meniscal pathology at baseline and total WOMAC knee pain change over 2 years.

Menisci (n = 463)	No pain or Decreased pain n(%)	Pain but no Change n(%)	Increase in pain n(%)	Univariable OR (95% CI)	Multivariable* OR (95% CI)
Type of Pathology**					
Intrameniscal Signal (n=259)	114(44)	61(24)	84(32)	1.19(0.84,1.67)	1.24(0.87,1.76)
Morphological Deformity/extrusion (n=142)	54(38)	39(27)	49(35)	**1.44(1.00,2.08)**	1.44 (0.99,2.09)
Maceration (n=100)	41(41)	30(30)	29(29)	1.10(0.73,1.66)	1.02(0.66,1.57)
Any Tear (n=222)	105(47)	56(25)	61(27)	0.82(0.58,1.15)	0.82(0.58,1.17)
Maceration: Number of Regions Affected**					
0 (n=363)	166(46)	89(25)	108(30)	Reference	Reference
1 (n=49)	24(49)	13(27)	12(24)	0.84(0.48,1.47)	0.84(0.47,1.47)
2 (n=27)	8(30)	10(37)	9(33)	1.53 (0.74,3.14)	1.57(0.75,3.27)
3 and above (n=24)	9(38)	7(29)	8(33)	1.30(0.61,2.79)	1.32(0.61,2.85)

OR = odds ratio, 95% CI = 95% confidence interval, BML = bone marrow lesion, PASE = physical activity scale for the elderly Decrease or increase in pain: total WOMAC pain absolute change of 2 or relative change of 40%

*Ordinal logistic regression models were used and adjusted for age, gender and BMI

**Types of pathology were further adjusted for each other in multivariable analysis

Bold denotes statistical significance at $p<0.05$

All multivariable models remained statistically significant after further adjustments for injury or surgery, BML and PASE

Table 5

Association between different types of meniscal pathology at baseline and prevalence of end-stage knee osteoarthritis at 1 year and 2 year follow-up (36 and 48 month OAI visits) using an Osteoarthritis Initiative adapted version of Escobar[23] algorithm.

	End-stage KOA[a]			
Menisci (n = 461)	**Absent n(%)**	**Present n(%)**	**Univariable OR (95% CI)**	**Multivariable[*] OR (95% CI)**
Type of Pathology[**]				
Intrameniscal Signal (n=258)	213 (83)	45 (16)	1.14 (0.69, 1.87)	1.21 (0.69, 2.12)
Morphological Deformity/extrusion (n=142)	107 (75)	35 (25)	**2.15 (1.31, 3.56)**	1.57 (0.90, 2.76)
Maceration (n=99)	55 (56)	44 (44)	**7.98 (4.67, 13.60)**	**7.53 (4.25, 13.31)**
Any Tear (n=221)	186 (85)	35 (15)	0.89 (0.54, 1.45)	1.17 (0.67, 2.03)
Maceration: Number of Regions Affected[**]				
0 (n=362)	329 (91)	33 (9)	Reference	Reference
1 (n=48)	30 (63)	18 (38)	**5.98 (3.01, 11.87)**	**5.64 (2.81, 11.35)**
2 (n=27)	13 (48)	14 (52)	**10.74 (4.66, 24.76)**	**10.80 (4.52, 25.77)**
3 and above (n=24)	12 (50)	12 (50)	**9.97 (4.15, 23.95)**	**10.61 (4.34, 25.91)**

KOA: knee osteoarthritis, OR = odds ratio, 95% CI = 95% confidence interval, OAI= Osteoarthritis Initiative, BML = bone marrow lesion, PASE = physical activity scale for the elderly

[a]Proxy for end-stage KOA: a proxy measure for prediction of end-stage KOA based on adapted Escobar algorithm

[*]Binary logistic regression models were used and adjusted for age, gender and BMI

[**]Types of pathology were further adjusted for each other in multivariable analysis

Bold denotes statistical significance at p<0.05

All multivariable models remained statistically significant after further adjustments for injury or surgery, BML and PASE