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Magnetic Resonance Imaging–Defined Osteoarthritis Features and Anterior Knee Pain in Individuals With, or at Risk for, Knee Osteoarthritis: A Multicenter Study on Osteoarthritis

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Objective. The lack of strong association between knee osteoarthritis (OA) structural features and pain continues to perplex researchers and clinicians. Evaluating the patellofemoral joint in addition to the tibiofemoral joint alone has contributed to explaining this structure–pain discordance, hence justifying a more comprehensive evaluation of whole-knee OA and pain. The present study, therefore, was undertaken to evaluate the association between patellofemoral and tibiofemoral OA features with localized anterior knee pain (AKP) using 2 study designs.

Methods. Using cross-sectional data from the Multicenter Osteoarthritis Study, our first approach was a within-person, knee-matched design in which we identified participants with unilateral AKP. We then assessed magnetic resonance imaging (MRI)–derived OA features (cartilage damage, bone marrow lesions [BMLs], osteophytes, and inflammation) in both knees and evaluated the association of patellofemoral and tibiofemoral OA features to unilateral AKP. In our second approach, MRIs from 1 knee per person were scored, and we evaluated the association of OA features to AKP in participants with AKP and participants with no frequent knee pain.

Results. Using the first approach (n = 71, 66% women, mean ± SD age 69 ± 8 years), lateral patellofemoral osteophytes (odds ratio [OR] 5.0 [95% confidence interval (95% CI) 1.7–14.6]), whole-knee joint effusion-synovitis (OR 4.7 [95% CI 1.3–16.2]), and infrapatellar synovitis (OR 2.8 [95% CI 1.0–7.8]) were associated with AKP. Using the second approach (n = 882, 59% women, mean ± SD age 69 ± 7 years), lateral and medial patellofemoral cartilage damage (prevalence ratio [PR] 2.3 [95% CI 1.3–4.0] and PR 1.9 [95% CI 1.1–3.3], respectively) and lateral patellofemoral BMLs (PR 2.6 [95% CI 1.5–4.7]) were associated with AKP.

Conclusion. Patellofemoral but not tibiofemoral joint OA features and inflammation were associated with AKP.

INTRODUCTION

Pain is a key feature of knee osteoarthritis (OA) that limits function and quality of life (1). However, despite the assumption that structural features of OA are directly associated with knee pain, imaging studies have revealed a discordance (i.e., lack of a strong association or conflicting findings) between knee OA structural features and pain (2,3). While early studies focused exclusively on the tibiofemoral joint, later studies demonstrated that including patellofemoral joint images reduced this apparent discordance (2,4–9). Patellofemoral osteoarthritis (PFOA) is prevalent in ~40–50% of individuals with knee symptoms (10,11), and

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SIGNIFICANCE & INNOVATIONS

- Patellofemoral joint–related structural damage is believed to cause localized anterior knee pain (AKP); however, this association has not been evaluated in patellofemoral osteoarthritis (OA).
- We used 2 different study designs within the same study to robustly evaluate the cross-sectional association between OA features and AKP: a within-person matched knee analysis, and a more traditional between-group analysis.
- Both approaches demonstrated that patellofemoral OA features (low-to-moderate effect sizes), but not tibiofemoral OA features, were associated with AKP.
- The specific OA features associated with AKP differed between the 2 designs. This may reflect that the within-person matched knee design more strongly controls for confounding, but it is not an appropriate design when evaluating exposure variables that are not strongly unilateral. OA features were commonly bilateral in our sample, supporting growing evidence that OA features may develop bilaterally and symmetrically, even in individuals in whom only 1 knee is symptomatic.

in addition to pain, it is associated with decreased function and lower quality of life (9,12). Importantly, PFOA is often the first manifestation of early knee OA, with subsequent progression to involve the tibiofemoral joint (13–15). A deeper investigation into the relationship between PFOA and pain could refine our understanding of this discordance phenomenon but also provide insights into earlier manifestations of knee OA that could inform future trial design. Better understanding this relationship is particularly important because knee OA treatments are often prescribed on the basis that they address underlying structural damage or inflammation that is believed to cause the pain (16,17).

To improve our understanding of the relationship between structure and pain in PFOA, we highlight 3 limitations in the literature that we aimed to address in the present study. First, the literature to date has typically evaluated this relationship using generalized knee pain as an outcome. However, it is generally held that patellofemoral joint–related structural damage specifically leads to localized anterior knee pain (AKP) (18–20). Despite this, the association of OA-related patellofemoral joint structural damage and AKP has not yet been thoroughly investigated (21).

A second limitation in identifying determinants of pain relates to the high interpersonal variability in pain perception. In addition to knee-level structural features influencing pain, person-level features (e.g., psychosocial features, central nervous system mechanisms, obesity, etc.) may also influence the perception or severity of pain (22–24). These factors introduce confounding that may be difficult to account for using traditional regression methods. A unique approach has been employed that involves within-person comparison of a painful knee directly to the contralateral pain-free knee (25–28). This approach accounts for all person-level factors that presumably affect both knees identically within an individual, leaving only knee-level factors that could explain the unilateral pain. Using this approach, we previously showed that radiographic PFOA (but not radiographic tibiofemoral OA) was associated with AKP (25).

Finally, many studies have relied on radiographs to evaluate the association between PFOA-related structure and pain (2,6–9). Magnetic resonance imaging (MRI) offers the advantage of directly visualizing all joint tissues including cartilage, bone marrow, as well as joint inflammation (e.g., effusion and synovitis). Some of these features are pain sensitive but cannot be well visualized on plain radiographs (3,29,30). Moreover, MRI allows these OA features to be distinguished between the medial or lateral part of the patellofemoral joint. The relationship between lateral patellofemoral joint features may be more strongly associated with symptoms, but this can be statistically masked by evaluating the whole patellofemoral joint (31,32). Thus, our previous results using radiographs (25) warrant further investigation by MRI to determine whether specific features that cannot be seen on radiographs, including their mediolateral location, might be differentially associated with AKP.

Thus, in the present study, we evaluated the relation of MRI-based patellofemoral and tibiofemoral OA–related features to AKP using 2 methodologic approaches: a within-person between-knee comparison, and a more traditional between-group comparison. The first approach uses within-person matching to strongly control between-person confounding at the expense of only including participants with unilateral AKP. The second provides weaker confounding control through statistical adjustment but allows more participants to be included, and this may be more generalizable. Using both approaches together in one study provides a more thorough and robust approach to answering our study question.

PATIENTS AND METHODS

Study design. The Multicenter Osteoarthritis Study (MOST) is a cohort of individuals with, or at risk for, knee OA (n = 3,026) (33). Participants were age 50–79 years at enrollment and were eligible if they were either overweight or obese, had knee pain, aching, or stiffness for most of the previous 30 days, or had a previous knee injury or surgery (33). Details of the study sample have been published previously (30). For the present study, we excluded knees with total knee arthroplasty.

Anterior knee pain. In the present study, we operationalized AKP as frequent isolated AKP, using 2 steps. First, at the in-person clinic visit, we identified knees with frequent knee pain. We defined "frequent knee pain" as a response of "yes" to the question, "During the past 30 days, have you had pain, aching,

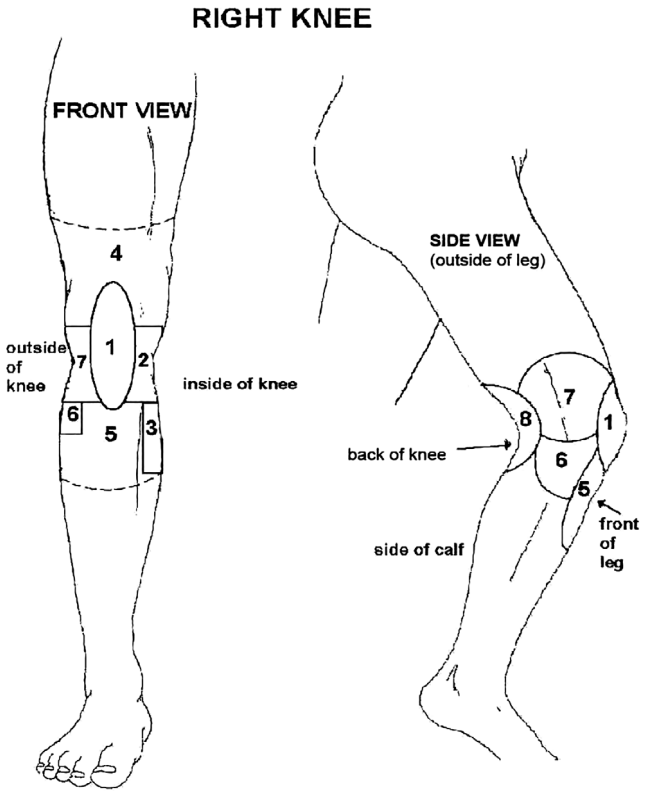

Figure 1. Knee pain map. Isolated anterior knee pain defined as pain in region 1 only.

or stiffness in your knee on most days?" This question was answered for each knee separately. Next, in knees with frequent knee pain, we evaluated the participants' knee pain maps to identify knees where pain was reported to be isolated to the anterior knee region (Figure 1). This 2-step process thus led to identifying knees with frequent isolated AKP. Knee pain maps were completed at the 60-month and 84-month visits.

MRI-defined OA features. MRIs were acquired using a 1.0T OrthOne MRI system (ONI Medical Systems) using axial and sagittal plane fat-suppressed fast spin–echo proton density–weighted and coronal short tau inversion recovery sequences. MRIs were scored by musculoskeletal radiologists semiquantitatively using a modified Whole-Organ MRI Score (WORMS) method (34). For the present study, we analyzed cartilage morphology, bone marrow lesions (BMLs), osteophytes, whole knee effusion-synovitis, and 3 specific subregions of synovitis (infrapatellar synovitis, superolateral Hoffa-synovitis, and intercondylar synovitis) (35).

We defined each OA feature as being present or not by dichotomizing WORMS OA scores. For cartilage morphology, we defined the presence of full-thickness cartilage damage as WORMS grade 2.5, 5, or 6. We defined presence of BMLs, osteophytes, whole-knee effusion-synovitis, and subregional synovitis all as WORMS grade ≥2. In the event that prevalence of a given feature, when using these cut points, resulted in empty cells and subsequent breakdown of the statistical model, we recategorized the feature using a higher or lower cut point of WORMS score as appropriate.

Within-person, knee-matched analyses. Our first methodologic approach was a within-person, knee-matched analysis. We identified participants with unilateral AKP, meaning that they had frequent isolated AKP in 1 knee and did not have frequent knee pain in the contralateral knee. We excluded participants with knee arthroplasty in either knee. We included participants who were eligible at either the 60-month or 84-month clinic visit. If participants had unilateral AKP at both visits, we only used their 60-month visit in our analyses. A single musculoskeletal radiologist (MJ) independently read and scored the MRI images of both knees in this subsample, paired but blinded to pain status.

Between-group analyses. Our second methodologic approach was a more traditional regression analysis. For these analyses, we used data from the 60-month visit only and used WORMS scores from readings of the parent MOST study (30). Images were read by 2 musculoskeletal radiologists (AG and FR) and graded in 1 randomly selected knee per participant. From this sample, we identified participants with frequent isolated AKP in the MRI knee, and for comparison we identified participants who did not have frequent knee pain in the MRI knee. We excluded individuals who had frequent knee pain that was not isolated to the anterior knee region.

Statistical analyses. We analyzed the following OA features as exposure variables: cartilage morphology, BMLs, osteophytes, whole-knee effusion-synovitis, and 3 synovitis subregions (infrapatellar synovitis, superolateral Hoffa-synovitis, and intercondylar synovitis). We analyzed cartilage morphology, BMLs, and osteophytes in 4 distinct knee compartments: the medial and lateral patellofemoral joint, and the medial and lateral tibiofemoral compartments. To do so, we defined a compartment as having a given MRI feature present if at least 1 subregion within that compartment met the definition of having that MRI feature.

For the within-person, knee-matched analyses, we evaluated the relation of each OA feature to the presence of frequent isolated AKP using conditional logistic regression. Each participant's knees were evaluated as a matched pair. On account of this approach, age, sex, and body mass index (BMI) were matched in each pair, and therefore we did not need to adjust for covariates. To adjust for possible sparse data bias, we added an exact statement to any model where the initial model resulted in an odds ratio (OR) >5 (36).

For the between-group analyses, we evaluated the relation of each OA feature to the presence of frequent isolated AKP with logistic regression (distribution: Poisson; link: log with robust variance estimation) (37). We calculated prevalence ratios (PRs)

adjusting for age, BMI, and sex. In sensitivity analyses, we additionally adjusted for depressive symptoms (score at least 16 of 57 on the Center for Epidemiologic Studies Depression Scale) (38) and pain catastrophizing (Coping Strategies Questionnaire catastrophizing subscale, item 4) (39). All statistical analyses were done using SAS, version 9.4.

RESULTS

The full MOST cohort (n = 3,026) at the 60-month visit had a mean ± SD age of 70.0 ± 8.2 years, a mean ± SD BMI of 30.9 ± 6.1 kg/m^2, and consisted of 1,820 (60.2%) women. Among the full sample, 789 (26.1%) left knees were reported to have frequent knee pain, and 818 (27.0%) right knees.

Within-person, knee-matched analyses. We identified 71 individuals who met our criteria for having unilateral frequent isolated AKP and who had bilateral MRI images. The mean ± SD age was 69 ± 8 years; the mean ± SD BMI was 30.2 ± 5.3 kg/m^2, and approximately two-thirds were women (Table 1).

The prevalence of most OA features was symmetrical between knees in the within-person comparison (Table 2). The odds of having AKP was higher in knees with osteophytes in the lateral patellofemoral joint (OR 5.0 [95% confidence interval (95% CI) 1.7–14.6]). Whole-knee effusion-synovitis was also associated with AKP (OR 4.7 [95% CI 1.3–16.2]). Regarding the 3 subregions of synovitis, only infrapatellar synovitis was associated with AKP; however, there were no knees with AKP with a score of at least grade 2, so this association was only detected by lowering the threshold of defining prevalent infrapatellar synovitis to grade 1 (OR 2.8 [95% CI 1.0–7.8]). Other features with notable ORs included lateral patellofemoral BMLs, lateral tibiofemoral BMLs, and superolateral Hoffa–synovitis, although confidence intervals were wide, and they were not significant.

Between-group analyses. In the parent MOST study, 1,174 participants had complete MRI images scored in 1 knee. Fifty-eight participants had frequent isolated AKP (mean ± SD age 69 ± 7 years, mean ± SD BMI 29.2 ± 4.9 kg/m^2, 67% women), and 824 participants did not have frequent knee pain (mean ± SD age 67 ± 8 years, mean ± SD BMI 29.3 ± 4.8 kg/m^2, 59% women) (Table 1).

Results of the between-group analyses differed from the within-person comparisons. The odds of having AKP were not associated with patellofemoral joint osteophytes, effusion-synovitis, or localized synovitis (Table 3). Rather, full thickness cartilage damage of the patellofemoral joint and BMLs of the patellofemoral joint were associated with AKP, with the strongest associations in the lateral patellofemoral joint (PR 2.3 [95% CI 1.3–4.0] and PR 2.6 [95% CI 1.5–4.7], respectively). No tibiofemoral features were associated with AKP. Results did not change when depression and pain catastrophizing were added as covariates to each model (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24604).

DISCUSSION

Using 2 different study designs, we identified several OA-related tissue changes that may be associated with AKP in individuals with, or at risk of, knee OA. The common finding between the 2 approaches was that patellofemoral OA features, but not tibiofemoral OA features, were associated with AKP. The divergent finding was that the specific features identified differed between the 2 approaches. The within-person matched-knee analyses identified lateral patellofemoral osteophytes, whole-knee joint effusion-synovitis, and at least mild infrapatellar synovitis as being associated with AKP. The between-group analysis revealed lateral and medial full-thickness patellofemoral cartilage damage and lateral BMLs as being associated with AKP. Regardless of approach, effect sizes were of low-to-moderate magnitude, with the mean within-person ORs ranging from 2.8 to 5.0, and mean between-group PRs ranging from 1.9 to 2.6.

A strength of the within-person matched-knee analyses is that all person-level factors are inherently adjusted for, leaving only knee-specific features to analyze. In cases where an exposure is strongly unilateral (e.g., traumatic knee injury), this can be a powerful approach for evaluating an exposure–outcome relationship. We found a moderate association of lateral patellofemoral osteophytes with AKP in the present study. This is similar to our previous radiographic study in this same sample (25) and can also be compared to a previous study using the same approach, where radiographic tibiofemoral OA was strongly associated with knee pain (26). We also found an association of

Table 1. Participant characteristics*

Characteristic	Within-person matched-knee analyses (both knees, n = 71)†	Between-group analyses (single knee, n = 882)	
		Frequent isolated AKP (n = 58)	No frequent knee pain (n = 824)
Age, years	69.4 ± 7.7	69.0 ± 6.9	66.9 ± 7.6
BMI, kg/m^2	30.2 ± 5.3	29.9 ± 4.9	29.3 ± 4.8
Women, no. (%)	47 (66)	39 (67)	486 (59)

* Values are the mean ± SD unless indicated otherwise. AKP = anterior knee pain; BMI = body mass index.
† Unilateral frequent isolated AKP.

Table 2. Within-person matched-knee analyses (association between osteoarthritis features and frequent isolated anterior knee pain; n = 71)*

	Painful knee prevalence	Contralateral knee prevalence	OR (95% CI)	*P*
PF joint				
Full thickness PF cartilage damage				
Medial	28/71 (39)	28/71 (39)	1.0 (0.5–2.2)	1.00
Lateral	26/71 (37)	26/71 (37)	1.0 (0.4–2.9)	1.00
PF joint	36/71 (51)	39/71 (55)	0.7 (0.3–1.8)	0.49
PF BMLs				
Medial	10/71 (14)	13/71 (18)	0.7 (0.2–1.9)	0.44
Lateral	18/71 (25)	11/71 (15)	2.8 (0.9–8.6)	0.08
PF joint	26/71 (37)	20/71 (28)	1.8 (0.7–4.2)	0.21
PF osteophytes				
Medial	35/71 (49)	31/71 (44)	1.4 (0.6–3.2)	0.42
Lateral	35/71 (49)	19/71 (27)	5.0 (1.7–14.6)†	<0.01‡
PF joint	45/71 (63)	37/71 (52)	2.3 (0.9–6.1)	0.08
TF joint				
Full thickness TF cartilage damage				
Medial	23/71 (32)	19/71 (27)	1.4 (0.6–3.4)	0.40
Lateral	26/71 (37)	20/71 (28)	2.0 (0.8–5.3)	0.17
TF BMLs				
Medial	9/71 (13)	6/71 (8)	1.8 (0.5–6.0)	0.37
Lateral	8/71 (11)	4/71 (6)	3.0 (0.6–14.9)	0.18
TF osteophytes				
Medial	57/71 (80)	54/71 (76)	1.5 (0.5–4.2)	0.44
Lateral	33/71 (46)	33/70 (47)	0.9 (0.4–2.1)	0.83
Knee inflammation				
Whole knee effusion-synovitis	20/71 (28)	9/71 (13)	4.7 (1.3–16.2)‡	0.02‡
Synovitis, infrapatellar§	21/69 (30)	12/71 (17)	2.8 (1.0–7.8)‡	0.05‡
Synovitis, superolateral Hoffa	12/67 (18)	9/69 (13)	2.7 (0.7–10.1)	0.15
Synovitis, intercondylar	9/69 (13)	9/71 (13)	1.0 (0.4–2.9)	1.00

* Values are the no./total no. (%) unless indicated otherwise. 95% CI = 95% confidence interval; BMLs = bone marrow lesions; OR = odds ratio; PF = patellofemoral; TF = tibiofemoral.
† $P \leq 0.05$. For definite lateral osteophytes, adjusting for sparse data did not alter results (OR 5.0 [95% CI 1.7–20.1], $P < 0.01$).
‡ $P \leq 0.05$.
§ No knees with anterior knee pain had grade 2 infrapatellar synovitis, so the cut point was adjusted to a score of grade ≥1.

whole–knee effusion-synovitis and infrapatellar synovitis with AKP. This could represent a localized inflammatory reaction to the presence of structural OA features and may further explain the unilateral AKP in our sample.

Within-person matched-knee analyses may be problematic, however, in cases where the exposure is potentially bilateral. Individuals with knee OA commonly have bilateral involvement or progress from unilateral to bilateral OA over time (40,41). Thus, individuals with unilateral pain may still present with bilateral OA features that remain preclinical, or asymptomatic, in the contralateral side, or they may be at risk for developing bilateral OA features. Consequently, these individuals would be at risk for developing bilateral pain. A cross-sectional study design cannot capture the temporal trajectory of bilateral pain and OA features, and thus a study design like this may represent overmatching. Our data support the possibility of overmatching for some OA features. For example, the prevalence of cartilage damage was symmetrical between knees in our within-person analyses (~40% in both knees, medial and lateral patellofemoral joints), but overall, the prevalence of cartilage damage was higher in knees without frequent knee pain in the within-person sample compared to knees without frequent knee pain in the between-group sample (19–24%). This suggests that our within-person sample, while presenting with unilateral AKP, may in fact have a higher prevalence of bilateral OA features. This possible overmatching limits the generalizability of our findings that patellofemoral cartilage was not associated with AKP using this first approach.

The between-group approach does not consider contralateral knees, and this allows for a larger sample that meets eligibility criteria. This approach may be more generalizable to individuals at different stages of unilateral or bilateral OA and those with unilateral or bilateral pain. However, confounders are adjusted statistically, which is a weaker approach to controlling for confounding than the within-person matched-knee design. While person-level confounders cannot be eliminated using this approach, there may be less selection bias, which is particularly relevant for OA features that tend to present bilaterally. With this approach, cartilage damage and BMLs were associated with AKP. Importantly, cartilage is aneural, so this positive finding likely reflects that

Table 3. Between-group analyses (association between osteoarthritis features and frequent isolated AKP)*

	Individuals with frequent isolated AKP (n = 58)	Individuals without frequent knee pain (n = 824)	Prevalence ratio (95% CI)	*P*
PF joint				
Full-thickness PF cartilage damage				
Medial	22 (41)	185 (24)	1.9 (1.1–3.3)†	0.02†
Lateral	21 (39)	149 (19)	2.3 (1.3–4.0)†	<0.01†
PF joint	30 (55)	267 (34)	2.1 (1.2–3.5)†	<0.01†
PF BMLs				
Medial	9 (17)	78 (10)	1.7 (0.8–3.4)	0.16
Lateral	17 (31)	109 (14)	2.6 (1.5–4.7)†	<0.01†
PF joint	22 (40)	164 (21)	2.3 (1.4–4.0)†	<0.01†
PF osteophytes				
Medial PF joint	32 (57)	361 (45)	1.5 (0.9–2.5)	0.16
Lateral PF joint	22 (39)	243 (30)	1.3 (0.8–2.3)	0.31
PF joint	36 (63)	402 (50)	1.6 (0.9–2.7)	0.11
TF joint				
Full-thickness TF cartilage damage				
Medial	11 (19)	170 (21)	0.8 (0.4–1.6)	0.61
Lateral	5 (9)	120 (15)	0.5 (0.2–1.3)	0.17
TF BMLs				
Medial	3 (5)	76 (9)	0.5 (0.2–1.7)	0.29
Lateral‡	6 (10)	134 (16)	0.6 (0.3–1.4)	0.24
TF osteophytes				
Medial	44 (76)	541 (66)	1.5 (0.8–2.7)	0.21
Lateral	22 (38)	273 (33)	1.1 (0.7–2.0)	0.62
Knee inflammation				
Whole knee effusion-synovitis	11 (19)	113 (14)	1.4 (0.7–2.6)	0.36
Synovitis, infrapatellar	2 (4)	32 (4)	1.0 (0.2–4.0)	0.96
Synovitis, superolateral Hoffa‡	8 (14)	109 (13)	1.1 (0.5–2.4)	0.72
Synovitis, intercondylar	9 (16)	97 (12)	1.3 (0.6–2.7)	0.47

* Values are the number (%) unless indicated otherwise. Age, sex, and body mass index included as covariates in all models. 95% CI = 95% confidence interval; AKP = anterior knee pain; BMLs = bone marrow lesions; PF = patellofemoral; TF = tibiofemoral.
† $P \leq 0.05$.
‡ No knees with AKP had grade 2 lateral tibiofemoral BMLs or superolateral Hoffa-synovitis, so cut point was adjusted to scores of grade ≥1 for both variables.

cartilage damage is a surrogate marker for a different pain-generating feature, in this case possibly BMLs. A mediation analysis in a larger cohort could confirm this.

The overall prevalence of osteophytes based on MRI was higher in the present study compared to our previous radiographic OA study of the same sample, reflecting higher sensitivity of MRI to identifying lesions (25). The present study adds to our previous work in that MRI scores were read for both the medial and lateral patellofemoral joint separately, allowing a more specific analysis in the present study. The prevalence of MRI-defined patellofemoral osteophytes was similar using both within-person and between-group approaches (63% for painful knees, 50–52% for comparison knees). However, looking only at the lateral patellofemoral joint, a higher proportion of painful knees had osteophytes in the within-person knees (49% versus 27% in contralateral pain-free knee) compared to the between-group knees (39% versus 30% in pain-free group). This resulted in significant findings for the first approach but not the second; yet, wide confidence intervals for the within-person matched-knee approach warrant acknowledgement.

A previous MRI study found patellofemoral osteophytes (OR 2.3 [99% CI 1.1–4.8]) and moderate-to-large effusion (OR 10.0 [99% CI 1.3–149.0]) were associated with general knee pain (4). We extend these findings specifically to isolated AKP and add the possible association of patellofemoral cartilage damage and BMLs to this relationship, which the previous study did not find when evaluating general knee pain (4). In addition, a previous systematic review reported that radiographic OA was prevalent in 15–76% of painful knees (2). Our MRI findings fit within this large range, with individual patellofemoral OA features present in 37–

63% of knees with isolated AKP, individual tibiofemoral OA features in 10–80%, and individual measures of inflammation (localized synovitis or whole-knee effusion-synovitis) in 4–30%. We add that, in knees without frequent knee pain, individual patellofemoral OA features were present in 21–55% of knees, individual tibiofemoral OA features in 8–76%, and individual measures of inflammation in 4–17% of knees. These findings highlight the importance of considering that OA features are commonly present in asymptomatic knees when interpreting the clinical relevance of structural features (42,43).

One of the limitations to the present study is that participants in the MOST cohort represent an enriched sample of individuals who have, or are at risk of having, OA. Knees without frequent knee pain (our defined comparator) may still have had occasional knee symptoms, including AKP, or have had other risk factors for OA. Thus, our study does not include a true control group of asymptomatic, low-risk individuals. While MRI features are prevalent in asymptomatic knees (42,43), features have been shown to be more prevalent in knees with chronic patellofemoral pain or OA compared to asymptomatic knees (4,44). In addition to not including true controls, the MRI images read and scored in the parent MOST study were only read in individuals who did not go on to require a knee arthroplasty. This may have resulted in individuals with more severe OA features or worse symptoms being excluded from the analyses. Both of these factors (not having a true control group, and not reading MRIs in individuals who later required arthroplasty) may have resulted in conservative estimates in the present study.

Another limitation is that we defined pain based on prevalence at a single time point. Pain is subjective and highly variable in severity, pattern of fluctuation, and subjective quality (e.g., dull ache, burning). Our definition of pain may not adequately characterize pain, and thus may have influenced our results. However, a strength of our study is that we used a pain map to localize pain to the anterior knee region. This contributes to the literature given that most studies have measured knee pain without consideration for specific location.

A final limitation is that we defined OA features on prevalence and did not consider OA severity. A previous radiographic study found that increased OA severity was associated with increased knee pain severity (7). Our sample was not large enough, given the limited number of participants with isolated AKP and the limited distribution of OA feature scores, to consider such analyses. Based on a preliminary (but underpowered) look at our data, we would hypothesize that subgroup analyses would reveal a stronger association of AKP with more severe PFOA features; however, this requires a larger study sample to confirm.

In conclusion, while structural features of OA remain an imprecise marker for knee pain, our study shows that MRI-defined OA features in the patellofemoral joint, as well as inflammation, are more highly associated with AKP than OA features in the tibiofemoral joint.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Stefanik had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ADDITIONAL DISCLOSURES

Author Guermazi is an employee of Boston Imaging Core Lab.

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