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MRI findings associated with development of incident knee pain over 48 months: data from the osteoarthritis initiative

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Abstract

Purpose The purpose of this nested case-control study was to identify baseline, incident, and progressive MRI findings visible on standard MRI clinical sequences that were associated with development of incident knee pain in subjects at risk for OA over a period of 48 months.

Methods We analyzed 60 case knees developing incident pain (WOMAC_{pain}=0 at baseline and WOMAC_{pain}≥5 at 48 months) and 60 control knees (WOMAC_{pain}=0 at baseline and WOMAC_{pain}=0 at 48 months) from the Osteoarthritis Initiative. 3 T knee MRIs were analyzed using a modified WOMS score (cartilage, meniscus, bone marrow) at baseline and after 48 months. Baseline and longitudinal findings were grouped into logistic regression models and compared using likelihood-ratio tests. For each model that was significant, a stepwise elimination was used to isolate significant MRI findings.

Results One baseline MRI finding and three findings that changed from baseline to 48 months were associated with the development of pain: at baseline, the severity of a cartilage lesion in the medial tibia was associated with incident pain—(odds ratio (OR) for incident pain=3.05; $P=0.030$). Longitudinally, an incident effusion (OR=9.78; $P=0.005$), a progressive cartilage lesion of the patella (OR=4.59;

$P=0.009$), and an incident medial meniscus tear (OR=4.91; $P=0.028$) were associated with the development of pain.

Conclusions Our results demonstrate that baseline abnormalities of the medial tibia cartilage as well as an incident joint effusion, progressive patella cartilage defects, and an incident medial meniscus tear over 48 months may be associated with incident knee pain. Clinically, this study helps identify MRI findings that are associated with the development of knee pain.

Keywords Osteoarthritis · Pain · MRI · Knee · Osteoarthritis initiative

Introduction

Knee pain from osteoarthritis (OA) is one of the primary causes of disability-adjusted life years in the United States [1, 2]. While knee structural changes in OA such as cartilage loss, meniscal tears, and bone marrow edema patterns have been well described [3, 4], it is unclear which particular morphologic findings are associated with prevalent and incident pain. Identifying such morphologic abnormalities could lead to treatments targeting specific pain-related structural changes, thus improving quality of life for OA patients.

The discrepancies between pain and morphologic evidence of OA have been well documented [5, 6]: there is evidence that subjects with radiographic OA may not have pain and vice-versa. For example, studies have shown that 50% of patients with radiographic OA did not have symptoms [7], and a large variation in pain scores was evident among subjects with the same radiographic score [8]. In addition, multiple studies have evaluated the relationship between MRI findings and Western Ontario and McMaster Universities (WOMAC) [9] pain scores in knee OA; however, a distinct temporal

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relationship has not been reliably demonstrated [10, 11], potentially due to intra- and inter-subject pain tolerance variability. These studies highlight the complexity and multifactorial nature of OA, and emphasize the need for longitudinal evaluation of predictors for symptomatic disease.

The purpose of this nested case-control study was to identify baseline, incident, and progressive MRI findings visible on standard MRI clinical sequences that were associated with development of incident knee pain in subjects at risk for OA over a period of 48 months. The current study design is unique from previous research, as it utilizes the Osteoarthritis Initiative database (OAI) [12] to assess longitudinal changes in knee morphology (including the cartilage, meniscus, bone marrow) in subjects that develop pain over 48 months. Evaluating the same subjects over time mitigates errors due to inter-subject variations in pain tolerance. In addition, assessing subjects from the OAI, a longitudinal database with MR images of subjects scanned annually over 8 years, facilitates identifying subjects that develop pain and evaluating their concurrent changes in knee morphology.

Methods

Subjects

Subjects were selected from the Osteoarthritis Initiative (OAI) [12], a large multicenter, longitudinal cohort study of patients either with or at risk for developing knee OA. The OAI dataset includes both MRI and radiographic images of subjects scanned annually over 8 years. This database can be used to longitudinally evaluate MRI biomarkers for the development and progression of OA. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards.

Figure 1 shows a flowchart of subject selection. Of the 4,796 subjects enrolled in the OAI study, knees with a pain increase and controls were selected based on the following 6 inclusion criteria: (1) age 45–70 years old at baseline; (2) subjects did not have symptoms at baseline, but were considered high risk for developing symptomatic knee OA due to being overweight, prior knee injury or surgery, family history of knee replacement, Heberden's nodes or frequent knee bending activity; (3) WOMAC knee pain score of 0 at baseline in the index knee, (4) complete WOMAC knee pain data at 12, 24, 36 and 48 month follow-up, (5) availability of Kellgren-Lawrence (KL) scores at baseline [13], and (6) availability and acceptable quality of baseline and 48-month follow-up MRI exams. Case knees were those that had a WOMAC pain score of ≥ 5 at 48 months. There were only 60 knees that met these criteria. Eligible control knees had a WOMAC knee pain score ≤ 2 at all follow-ups between 0 and 48 months. A WOMAC pain score threshold of ≤ 2 was chosen based on a

previous study [14], which showed that using the Visual Analogue Scale (VAS), a minimal perceptible change in pain required a 10% difference, which equates to a change greater than 2 using the Likert scale.

From the total of 885 knees eligible from the control cohort, 60 subjects were randomly selected frequency-matched for age, gender, body mass index (BMI), and knee side (left or right). The frequency matching (in addition to adjustment in the statistical analysis) was used to account for any potential confounding effects in the analysis [15, 16]. The case knees and the knees eligible for the control cohort showed an equal distribution of Kellgren-Lawrence grades; therefore, we did not frequency-match controls by this criterion. We excluded subjects with interval acute events such as trauma or infection.

WOMAC questionnaires

To assess pain severity and monitor pain progression, we used the WOMAC Osteoarthritis Index [9] which quantifies pain, stiffness, and physical function [9]. This well-established and validated questionnaire was administered in yearly intervals to all 4,796 OAI subjects in a standardized manner. As subjects with a WOMAC pain score ≥ 5 have at least one activity with moderate amounts of pain [15], we used a threshold of ≥ 5 to define significant knee pain.

Magnetic resonance imaging

Knee MRIs were obtained at 3 T at baseline and after 48 months, using identical MR scanners (Trio, Siemens, Erlangen) and standard knee coils (Siemens, Erlangen, Germany) at four different sites. Four MRI sequences from the OAI protocol [12] were analyzed, and the scanning parameters are listed in Table 1.

MR image analysis

Following standard clinical radiology practice, paired readings of baseline and 48-month MRI exams were performed on a PACS workstation (Agfa, Ridgefield Park, NJ) using the modified Whole-Organ MR Imaging Scoring (WORMS) method, which has been established for evaluating early degenerative joint disease [3, 16]. Cartilage and subchondral bone marrow edema abnormalities were assessed in six regions: patella, trochlea, medial/lateral tibia, and medial/lateral femur. Cartilage lesions were graded using the modified WORMS scale [3]. Subchondral bone marrow edema pattern was defined as poorly marginated areas of increased T2 signal intensity and graded using a modified 4-point WORMS scale (0, none; 1, diameter 0–5 mm; 2, 5–20 mm; 3, >20 mm) [19], as well as a volumetric quantification described previously [17].

Fig. 1 Patient selection from the OAI database

Meniscal lesions were graded separately in 6 regions (medial/lateral and anterior/body/posterior) using the following 4-point scale: 0, normal; 1, intrasubstance signal; 2, non-displaced tear; 3, displaced or complex tear; 4, complete destruction/maceration. As established in previous studies [16, 18], intrasubstance degeneration was added to the WORMS classification to permit the inclusion and quantification of early degenerative disease [19]. Each MRI was evaluated for the presence or absence of an effusion. An “incident effusion” was defined as absent at baseline, but present at 48 months.

Sequences were analyzed blinded to subject data. A “training period” was performed in which three radiologists (S.W.H., 3rd year radiology resident; S.L., board-certified radiologist with 1 year of MSK fellowship training; L.N., 4th year radiology resident) and a senior MSK radiologist (T.M.L., more than 20 years of experience in MSK radiology) together analyzed 30 MRI exams in order to arrive at a consensus reading and to calibrate thresholds for grading

abnormalities. The remaining studies were then reviewed independently by S.W.H., S.L., and L.N with two radiologists reading each study. In those instances where scores were not identical, consensus readings were performed with the senior MSK radiologist (T.M.L.). Regarding changes in findings between baseline and 48 months, a finding was considered incident if it was absent at baseline but present at 48 months, and was considered progressive if it was present at baseline but worse at 48 months.

Statistical analysis

Independent t-tests (for numeric variables) and chi-square tests (for categorical variables) were used to evaluate differences in subject characteristics between cases and controls. Baseline and longitudinal predictors were assessed in logical groups using logistic regression and likelihood-ratio tests. In total, ten different statistical models were employed. All

Table 1 OAI knee MRI protocol acquisition parameters, from Peterfy et al. [12]

Scan	COR IW 2D TSE	SAG 3D DESS WE	COR T1W 3D FLASH WE	SAG IW 2D TSE FS
Plane	Coronal	Sagittal	Coronal	Sagittal
Fat saturation	No	WE	WE	FS
Number of slices	35	160	80	37
FOV (mm)	140	140	160	160
Slice thickness/gap (mm/mm)	3/0	0.7/0	1.5/0	3/0
Flip angle (°)	180	25	12	180
TE/TR (ms/ms)	29/3700	4.7/16.3	7.57/20	30/3200
Bandwidth (Hz/pixel)	352	185	130	248
X-resolution (mm)	0.365	0.365	0.313	0.357
Y-resolution (mm)	0.456	0.456	0.313	0.511

models were adjusted for age, sex, and BMI. Incident pain was predicted using three different models for baseline findings and seven different models for changes in findings between baseline and 48 months. The MRI findings were grouped into statistical models according to the type of tissue the lesion affected. Three models for baseline findings included meniscal pathology, cartilage lesions, and bone marrow edema pattern. Six models for longitudinal changes included the menisci, cartilage, and bone marrow, with each type of tissue having one model for incident lesions and one model for progressive lesions. The final model evaluated an incident effusion.

The baseline models included: model 1 investigated baseline pathology of the anterior horn, body, and posterior horn of both the medial and lateral menisci; model 2 evaluated baseline pathology of the patella, trochlea, medial femoral condyle, lateral femoral condyle, medial tibia, and lateral tibia cartilage; model 3 tested baseline pathology of bone marrow edema pattern, (same compartments as model 2). All baseline models utilized the raw WOMS scores and not the binary data.

The longitudinal models included: models 4 and 5 investigated incident and progressive pathology, respectively, of the medial and lateral menisci at 48 months; models 6 and 7 evaluated incident and progressive pathology, respectively, of cartilage, with the same compartments as model 2; models 8 and 9 tested incident and progressive pathology, respectively, of bone marrow edema pattern, again with the same compartments as model 2; model 10 investigated an incident effusion. All longitudinal models utilized binary (yes/no) predictor variables representing incidence or progression.

The likelihood-ratio test was used to compare each model to a base model consisting of only age, sex, and BMI. For those models that were significantly different from the base

model, a backward-stepwise method using the likelihood ratio test was implemented to reduce the number of variables to a significant subset. This two-stage approach (first requiring a statistically significant improvement over the base model) protects against multiple testing of the individual components for each model. Thus, omnibus tests were used to control for the overall error rate before proceeding to the stepwise regressions. A final logistic regression model, which included the significant variables that remained, was used to determine the odds for developing incident pain. This model was adjusted for age, gender and BMI, and Wald tests were used for calculating *P*-values. Statistical analysis was performed using Stata/IC Version 13 (StataCorp, College Station, TX).

Results

Subject characteristics

Table 2 shows the baseline demographics and clinical characteristics of 120 knees (in 120 subjects) included in our study. The cases and controls had similar distributions of age, gender, BMI, and KL grade.

Baseline MRI findings predictive of development of incident pain

Baseline knee morphologic characteristics were considered to be associated with the development of knee pain if case knees had more frequent MRI findings than control knees, as assessed using a likelihood ratio test. The statistical models evaluating baseline MRI findings (models 1–3) are shown in Table 3.

Table 2 Baseline demographics are displayed for control and case subjects. Data are presented as mean $\pm$ SD or number of subjects (*n*), (proportion to total in percentage). *P*-values of intergroup differences were assessed using independent *t*-tests and Chi-square tests, for numerical and categorical variables, respectively. * signifies that these variables were included as part of the study design

	Case (<i>n</i> = 60)	Control (<i>n</i> = 60)	<i>P</i> -value
Gender (male)	25 (41.7%)	25 (41.7%)	*
Knee side (right)	34 (56.7%)	34 (56.7%)	*
WOMAC pain score at baseline	0 $\pm$ 0	0 $\pm$ 0	*
WOMAC pain score at 48 months	6.4 $\pm$ 1.4	0 $\pm$ 0	*
Age (mean $\pm$ SD) (years)	59.0 $\pm$ 6.8	59.2 $\pm$ 7.1	0.91
BMI (kg/m ²)	29.4 $\pm$ 4.8	28.6 $\pm$ 4.1	0.31
History of knee injury	29 (48.3%)	24 (44.4%)	0.68
History of knee surgery	11 (18.3%)	9 (16.7%)	0.82
Family history of knee replacement surgery	8 (13.3%)	5 (9.3%)	0.49
PASE ^a score at baseline	177.34 $\pm$ 87.76	175.34 $\pm$ 79.82	0.89
Change in PASE score (48 months – baseline)	–18.52 $\pm$ 81.98	–8.98 $\pm$ 94.11	0.56
Kellgren-Lawrence grade $\geq$ 2 at baseline	20 (33.3%)	15 (25.0%)	0.32
Kellgren-Lawrence grade $\geq$ 2 at 48 months	27 (45.0%)	26 (43.3%)	0.85

^a PASE physical activity scale for the elderly

Table 3 Ten statistical regression models were evaluated. Models 1–3 evaluated baseline MR findings. Models 4–10 evaluated changes in MR findings from baseline to 48 months. All 10 models were adjusted for age,sex, and BMI. *P*-values were calculated using a likelihood ratio test comparing each model to a base model. The base model consisted of only age, sex, and BMI

Model number	Model	Variables	Number of variables added to base model	<i>P</i> value
1	Baseline meniscal findings	Anterior horn, posterior horn, and body of medial and lateral meniscus	6	0.110
2	Baseline cartilage findings	Cartilage of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	0.028
3	Baseline bone marrow findings	Bone marrow of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	0.226
4	Incident meniscal tear	Medial and lateral meniscus	2	<0.0001
5	Progressive meniscal tear	Medial and lateral meniscus	2	0.121
6	Incident cartilage lesion	Cartilage of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	0.438
7	Progressive cartilage lesion	Cartilage of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	<0.0001
8	Incident bone marrow lesion	Bone marrow of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	0.034
9	Progressive bone marrow lesion	Bone marrow of patella, trochlea, medial and lateral femoral condyles, medial and lateral tibia	6	0.055
10	Incident effusion	Incident effusion	1	0.0003

Bold signifies $p < 0.05$

Model 2, which evaluated cartilage pathology, was significantly different from the base model. A backward step-wise method using the likelihood ratio test for model 2 identified a cartilage lesion of the medial tibia to be significant. At baseline, a cartilage lesion of the medial tibia was

present in 18.3% of knees in the case cohort, compared to 3.3 % of knees in the control cohort (Table 4). This finding was associated with the development of incident pain with an odds ratio (OR) of 3.05 using the likelihood ratio test ($P = 0.030$, $CI = 1.11$ – 8.36).

Table 4 A cartilage lesion in the medial tibia at baseline, the presence of an incident effusion, the presence of a progressive cartilage lesion in the patella, and the presence of an incident medial meniscus tear were associated with new knee pain at 48 months. A knee was defined as having an incident effusion if it had no effusion at baseline, but developed an effusion at 48 months. A progressive cartilage lesion was defined as a cartilage lesion at baseline, which evolved into a higher grade

and/or larger size at 48 months. A knee was defined as having an incident medial meniscus tear if it did not have a medial meniscus tear at baseline, but developed one at 48 months. Data are presented as number of subjects (proportion to total in percentage). The odds ratios were calculated using logistic regression models, adjusted for age, gender, and BMI (with Wald tests for the calculation of *P*-values)

	Case	Control
No medial tibia cartilage lesion at baseline	49 (81.7%)	58 (96.7%)
Medial tibia cartilage lesion at baseline	11 (18.3%)	2 (3.3%)
Odds ratio = 3.05, <i>P</i>-value = 0.030, CI = 1.11–8.36		
No incident effusion	45 (75.0%)	58 (96.7%)
Incident effusion	15 (25.0%)	2 (3.3%)
Odds ratio = 9.78, <i>P</i>-value = 0.005 CI: 1.99–48.08		
No progressive cartilage lesion in the patella	44 (73.3%)	55 (91.6%)
Progressive cartilage lesion in the patella	16 (26.7%)	5 (8.3%)
Odds ratio = 4.59, <i>P</i>-value = 0.009, CI = 1.46–14.43		
No incident medial meniscus tear	48 (80.0%)	57 (95.0%)
Incident medial meniscus tear	12 (20.0%)	3 (5.0%)
Odds ratio = 4.91, <i>P</i>-value = 0.028, CI = 1.18–20.33		

Bold signifies $p < 0.05$

Changes in MRI findings associated with development of incident pain

A change in an MRI finding at 48-months needed to be more frequent in case knees than in control knees to be considered associated with development of incident pain. The statistical models evaluating baseline MRI findings (models 4–10) are shown in Table 3.

Models 4, 7, 8, and 10, which evaluated incident meniscal tears, progressive cartilage lesions, incident bone marrow lesions, and an incident effusion, respectively, differed significantly from the base model. A backward-stepwise method identified an incident medial meniscus tear ($\geq$ grade 2), a progressive cartilage lesion of the patella (increase ≥ 1 grade), and an incident effusion to be significant (models 4, 7 and 10). Incident bone marrow lesions were not significant following backward-stepwise regression. Of all degenerative knee changes over 48 months, an incident effusion had the highest odds for the development of pain. An incident effusion was present in 25.0% of knees in the case cohort, compared with 3.3% of knees in the control cohort (Table 4). This finding was associated with development of incident pain with an OR of 9.78 using the likelihood ratio test ($P=0.005$, CI=1.99–48.08). Figure 2 shows an example of an incident effusion, which was associated with the development of incident pain. In addition, a progressive cartilage lesion of the patella was present in 26.7% of knees in the case cohort, compared with 8.3% of knees in the control cohort (Table 4; Fig. 2). This finding also was associated with development of incident pain, with an OR of 4.59 using the likelihood ratio test ($P=0.009$, CI=1.46–14.43). Finally, an incident medial meniscus tear was present in 20.0% of knees in the case cohort, compared with 5.0% of knees in the control cohort (Table 4; Fig. 2). This finding was associated with development of incident pain, with an OR of 4.91 using the likelihood ratio test ($P=0.028$, CI=1.18–20.33).

In addition, 54.17% of cases vs. 17.5 % of controls had at least one of the significant abnormalities (baseline medial tibial cartilage lesion, incident medial meniscal tear, incident effusion, or progressive patellar cartilage lesion), which yielded an odds ratio of 7.31 ($P<0.0001$, CI=3.05–17.22).

Discussion

In this analysis of the OAI longitudinal data set, a medial tibial cartilage lesion at baseline, an incident effusion, a progressive cartilage lesion in the patella, and an incident medial meniscus tear were associated with incident pain in subjects enrolled in the OAI. Collectively, these results may implicate the origins of pain in knee OA, and also facilitate radiologists to identify clinically relevant knee MRI findings associated with pain

and attributable to morphologic joint degeneration in OA in a clinical population.

The only baseline morphologic finding associated with the development of pain was the severity of cartilage lesions in the medial tibia. These results corroborate prior studies, which have reported an association between cartilage lesions and pain [20–22]. In addition, the results are consistent with prior knowledge that the medial compartment of the knee is the most load-bearing [23]. Furthermore, cartilage lesions in the medial tibia are signs of more substantial cartilage damage compared to other cartilage compartments, especially in early

Fig. 2 Sagittal intermediate-weighted fast spin echo images (TR 3200 ms, TE 30 ms) at baseline (a) and at 48 months (b) show an incident effusion. A finding was considered incident if it was absent at baseline, but present at 48 months. Coronal intermediate-weighted fast spin echo images (TR 3,700 ms, TE 29 ms) at baseline (c) and at 48 months (d) show an incident medial meniscal flap tear (arrow). The medial meniscus body WOMS score was 0 at baseline and 4 at 48 months. Sagittal intermediate-weighted fast spin echo images (TR 3200 ms, TE 30 ms) at baseline (e) and at 48 months (f) show a progressive patellar cartilage lesion. The patellar cartilage WOMS score was 3 (partial thickness cartilage loss) at baseline and was 5 at 48 months with incident full thickness defects (arrow)

stages of disease. The cartilage of the medial tibia is relatively thin compared to other compartments such that one of these lesions may be more likely osteochondral involving the underlying subchondral bone. Osteochondral lesions are more indicative of joint disruption and potentially able to initiate symptomatic OA (regardless of whether the lesion remains unchanged or progresses).

The MRI finding most strongly associated with development of incident knee pain was an incident effusion. This result is consistent with prior literature, as multiple studies have correlated an effusion with pain [24–26], possibly due to capsular distention [26]. While joint effusion is not generally regarded as a cause of OA, it often develops during the course of disease. Of note, one study showed that change in synovitis, assessed by synovial thickness rather than change in an effusion was associated with pain [27]. However, the same study also demonstrated poor to moderate range of inter-reader reliability on the synovial assessment of the non-contrast study. It is possible that the incident effusions are more closely associated with acute inflammatory component and synovitis than progressive or unchanged effusions at 48 months.

Another central finding in this study was that progression of cartilage lesions in the patella was associated with the development of pain. An association between cartilage degeneration and pain has been demonstrated in previous studies [28, 29]; however, a direct link between cartilage degeneration and pain may be ambiguous to identify, since cartilage is aneural and avascular. Degenerative changes in the patellar cartilage in particular may be a by-product of its unique tissue properties such as shear load bearing as well as greater thickness than the other cartilage compartments. In addition, the progression of lesions in the patella may alter the surface geometry and trochlear tracking patterns, which may lead to degenerative changes such as patellar instability, chondromalacia, and consequently anterior knee pain [30], thus corroborating the results of the current study.

The results showed that an incident medial meniscus tear was associated with the development of incident knee pain, corroborating previous studies demonstrating that meniscus abnormalities are associated with pain [26, 31]. Since one of the primary functions of the meniscus is shock absorption and load bearing in the joint, the occurrence of a meniscal tear may compromise these functions, thus increasing the contract stresses in the knee [32]. Meniscal tears not only shift the mechanical stress distributions in the surrounding tissues including the cartilage, but also alter whole joint kinematics and suggest that it is possible that the disruption to knee joint mechanics may be associated with the development of symptoms.

An incident bone marrow edema pattern in the medial tibia demonstrated a trend toward being predictive of development of pain, but was not statistically significant

(dropped out of the final stepwise regression model). Given that a cartilage lesion of the medial tibia was predictive of pain in our study, it would be reasonable for bone marrow edema pattern of the medial tibia also to be predictive. Our finding of a statistically insignificant trend is expected, as multiple studies have demonstrated a strong association [10, 11], while others have shown no association [33]. Further research is required, possibly including analysis of bone attrition, given that one prior study suggested that bone attrition is required for bone marrow edema pattern to contribute to pain severity [26].

One limitation of our study is a focus on development of incident pain without stratification of severity of pain. While analysis of pain severity is compelling, we chose to focus our study on incident knee pain in order to target early stages of symptomatic OA. Nonetheless, further investigation into which morphologic MR findings are associated with increased severity of pain is warranted. The small sample size was a limiting factor: with additional subjects, other possible knee joint parameters may have been significant. In addition, the low prevalence of abnormalities highlights that OA is a heterogeneous disease, and that there may be other possible contributing factors related to pain that imaging may not explain.

In conclusion, our study identified MRI findings, including baseline abnormalities of medial tibia cartilage, an incident effusion, progressive patella cartilage pathology, and incident medial meniscus tears, which were associated with development of incident knee pain in subjects with OA risk factors that volunteered in the OAI. The results of this study may help a radiologist and a referring clinician better understand the clinical significance of MR findings responsible for the development of pain, and may also aid to understand the evolution of symptomatic OA in a clinical population.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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