Title

Association of Joint Inflammation With Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study

Journal

Arthritis & Rheumatology, 68(3)

ISSN

2326-5191

Authors

Neogi, Tuhina
Guermazi, Ali
Roemer, Frank
et al.

Publication Date

2016-03-01

DOI

10.1002/art.39488

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Arthritis Rheumatol. 2016 March ; 68(3): 654–661. doi:10.1002/art.39488.

Association of Joint Inflammation With Pain Sensitization in Knee Osteoarthritis:

The Multicenter Osteoarthritis Study

Tuhina Neogi, MD, PhD, FRCPC[1], **Ali Guermazi, MD**[1], **Frank Roemer, MD**[1], **Michael C. Nevitt, PhD**[2], **Joachim Scholz, MD**[3], **Lars Arendt-Nielsen, DrMedSci, PhD**[4], **Clifford Woolf, MB, BCh, PhD**[5], **Jingbo Niu, DSc**[1], **Laurence A. Bradley, PhD**[6], **Emily Quinn, BSc**[1], and **Laura Frey Law, MPT, MS, PhD**[7]

[1]Boston University, Boston, Massachusetts

[2]University of California, San Francisco

[3]Columbia University College of Physicians and Surgeons, New York, New York

[4]Aalborg University, Aalborg, Denmark

[5]Boston Children's Hospital, Boston, Massachusetts

[6]University of Alabama at Birmingham

[7]University of Iowa Carver College of Medicine, Iowa City.

Abstract

Objective—Pain sensitization is associated with pain severity in knee osteoarthritis (OA), but its cause in humans is not well understood. We examined whether inflammation, assessed as synovitis and effusion on magnetic resonance imaging (MRI), or mechanical load, assessed as bone marrow lesions (BMLs), was associated with sensitization in knee OA.

Methods—Subjects in the Multicenter Osteoarthritis Study, a National Institutes of Health–funded cohort of persons with or at risk of knee OA, underwent radiography and MRI of the knee, and standardized quantitative sensory testing (temporal summation and pressure pain threshold [PPT]) of the wrist and patellae at baseline and 2 years later. We examined the relation of

Address correspondence to Tuhina Neogi, MD, PhD, FRCPC, Boston University School of Medicine, Clinical Epidemiology Research and Training Unit, 650 Albany Street, X Building, Suite 200, Boston, MA 02118. tneogi@bu.edu..

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 published. Dr. Neogi 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.

Study conception and design. Neogi, Nevitt, Scholz, Arendt-Nielsen, Woolf.

Acquisition of data. Neogi, Guermazi, Roemer, Nevitt.

Analysis and interpretation of data. Neogi, Guermazi, Roemer, Nevitt, Scholz, Arendt-Nielsen, Woolf, Niu, Bradley, Quinn, Frey Law.

Dr. Guermazi has received consulting fees from TissueGene and OrthoTrophix (less than $10,000 each) and from Genzyme and Merck Serono (more than $10,000 each) and owns stock or stock options in Boston Imaging Core Lab, LLC. Dr. Roemer is CMO of and owns stock or stock options in Boston Imaging Core Lab, LLC. Dr. Woolf has received consulting fees from Abide Therapeutics (less than $10,000) and research grants from GlaxoSmithKline and is founder of Quartet Medicine and Ferrumax.

synovitis, effusion, and BMLs to temporal summation and PPT cross-sectionally and longitudinally.

Results—There were 1,111 subjects in the study sample (mean age 67 years, mean body mass index 30 kg/m^2, 62% female). Synovitis was associated with a significant decrease in PPT at the patella (i.e., more sensitized) over 2 years (adjusted β −0.30 [95% confidence interval (95% CI) −0.52, −0.08]). Effusion was similarly associated with a decrease in PPT at the wrist (adjusted β −0.24 [95% CI −0.41, −0.08]) and with risk of incident temporal summation at the patella (adjusted OR 1.54 [95% CI 1.01, 2.36]). BMLs were not associated with either quantitative sensory testing measure.

Conclusion—Inflammation, as evidenced by synovitis or effusion, is associated with pain sensitization in knee OA. In contrast, BMLs do not appear to contribute to sensitization in knee OA. Early targeting of inflammation is a reasonable strategy to test for prevention of sensitization and through this, reduction of pain severity, in knee OA.

Pain remains the primary symptomatic complaint of patients with knee osteoarthritis (OA), the most common form of arthritis in the US (1), yet the determinants of this pain remain poorly understood. Identification of key factors leading to pain is critical to improving management of the symptoms of knee OA and preventing the emergence of such symptoms.

Alteration in the neurologic processing of nociceptive signaling leading to enhanced pain facilitation has been increasingly recognized as one mechanism by which pain in knee OA may become chronic and persistent (2). Specifically, an increased responsiveness (sensitization) of peripheral or central nociceptive neurons appears to contribute to the pain experience in knee OA. Sensitization leads to heightened pain sensitivity, thereby contributing to a more severe pain experience. Pain sensitization, as assessed by quantitative sensory testing, has been associated with painful knee OA when compared with pain-free controls (3–10), and with pain severity independent of knee OA severity (11–13). While such sensitization may be a promising target for ameliorating pain severity in knee OA, the mechanisms by which this sensory sensitization occurs in humans are incompletely understood. Addressing this knowledge gap would identify a potentially novel therapeutic strategy for prevention of the typically inevitable progression of pain worsening in knee OA. In animal models, sustained inflammatory stimuli or mechanical tissue injury can lead to peripheral and central sensitization (14–22). Whether the same types of stimuli are important in the development of sensitization in humans is not known, however. There is some suggestion that sensitization may in fact be influenced by genetic predisposition, with generalized lower pain thresholds that may become manifest once nociceptive input from the OA joint is received (13).

However, it is possible that only certain pathologic features of OA, such as those that are inflammatory or those that reflect mechanical injury of the bone, which is richly innervated with nociceptors, lead to sensitization. While knee OA is traditionally considered a systemically noninflammatory arthritis, contemporary studies using magnetic resonance imaging (MRI) have demonstrated local inflammation as evidenced by synovitis and effusion; the latter is also often evident clinically. In contrast, bone marrow lesions (BMLs) are considered to be predominantly (micro)traumatic lesions related to excessive mechanical

load or remodeling related to tissue injury. Inflammatory lesions (i.e., synovitis and effusion) and BMLs are the primary pathologic lesions that have been consistently associated with pain in knee OA (23–25), but the mechanism by which they contribute to pain has not been elucidated. Given the development of sensitization in animal models related to inflammatory stimuli and/or tissue injury, we sought to determine whether inflammatory and mechanical lesions in knee OA are associated with pain sensitization in humans. If either of these types of lesions were to lead to sensitization, they would be attractive as early therapeutic targets to prevent the occurrence of sensitization, with the expectation that this would in turn prevent the eventual development of chronic and/or more severe pain in knee OA.

PATIENTS AND METHODS

Study sample

The Multicenter Osteoarthritis Study (MOST) is a National Institutes of Health–funded longitudinal cohort of older adults with or at risk of knee OA. At baseline, there were 3,026 subjects, ages 50–79, who were recruited from Birmingham, Alabama and Iowa City, Iowa. Details of the cohort have been published elsewhere (26). Briefly, subjects were assessed at baseline, 30 months, 60 months, and 84 months using imaging, standardized questionnaires, and objective measures of relevance to knee OA. The institutional review boards at the University of Alabama at Birmingham, University of Iowa at Iowa City, University of California at San Francisco, and Boston University Medical Center approved the study protocol.

The present study sample comprised subjects who attended the 60-month and 84-month study visits; these were the first visits at which standardized quantitative sensory testing, i.e., measures of sensitization, were obtained. Eighty-eight subjects who screened positive for possible peripheral neuropathy (27) were excluded from this analysis. For the purposes of this study, the 60-month visit was considered the baseline visit, and the 84-month visit was considered the followup visit.

MRI acquisition and assessment

MRIs of both knees were obtained on a 1.0T dedicated extremity unit (ONI MSK Extreme 1.0T; GE Healthcare) with a circumferential extremity coil using fat-suppressed fast spin-echo intermediate-weighted sequences in 2 planes, sagittal (repetition time [TR] 4,800 msec, echo time [TE] 35 msec, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288 × 192 matrix, number of excitations [NEX] 2, field of view [FOV] 140 × 140 mm, and echo train length [ETL] 8) and axial (TR 4,680 msec, TE 13 msec, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288 × 192 matrix, NEX 2, FOV 140 × 140 mm, and ETL 8), and a STIR sequence in the coronal plane (TR 6,650 msec, TE 15 msec, inversion time 100 msec, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256 × 192 matrix, NEX 2, FOV × 140 mm, and ETL 8). Examinations were performed at the University of Alabama at Birmingham and at the University of Iowa at Iowa City using the same MRI unit at baseline and followup. Although non–contrast-enhanced sequences were used, both synovitis and effusion assessments have been validated using this approach (28–32), and synovitis on

non–contrast-enhanced MRI has been correlated with macroscopic and microscopic evidence of inflammation (33).

Bilateral knee MRIs were obtained in all subjects in the MOST study who attended the 60- and 84-month study visits unless there were contraindications or end-stage OA was present (i.e., Kellgren/Lawrence grade 4) (34). For each subject, one knee with acceptable quality MRIs at both time points was selected for longitudinal reading; if both knees were eligible for readings, one was randomly selected. The MRIs were read and scored by 4 experienced musculoskeletal radiologists, who were blinded with regard to clinical and radiographic data, using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (35). Synovitis was scored 0–3 in the intercondylar region and infrapatellar fat pad (Hoffa's fat pad), which represents a surrogate for true synovitis (29), and is known as Hoffa-synovitis (28). Effusion was scored 0–3 in the suprapatellar pouch, often referred to as effusionsynovitis because it reflects a composite of effusion and synovitis on non–contrast enhanced MRIs (28,31). BMLs were scored 0–3 in all 14 WORMS subregions of the knee, and excluded tibial spine BMLs since this region is not subchondral. Examples of each grade of each MRI lesion are provided in Figure 1. The ranges of weighted kappa statistics for inter-reader reliability among all 4 readers for presence versus absence of each feature were 0.80–0.89 for BMLs, 0.16–0.60 for synovitis, and 0.57–0.86 for effusion.

Quantitative sensory testing

Pressure pain threshold (PPT), a measure of sensitivity to pain evoked by mechanical stimulation of nociceptors (36–38), can be reliably assessed in knee OA with pressure algometry (4–7,9,13). We obtained PPT at baseline and followup 24 months later at both patellae and at the wrist, as previously described (13). Briefly, PPT assessed at a diseased site (e.g., a knee with OA) is thought to reflect peripheral sensitization, while when assessed at a distant, normal site (e.g., the wrist), it is thought to reflect central sensitization, or a generalized level of pain sensitivity. PPT was assessed by applying an algometer (1 cm^2 rubber tip) (FDIX25; Wagner) at a rate of 0.5 kg/second and determining the point at which participants verbally indicated the pressure first changed to slight pain. The PPT at each anatomic site was calculated by averaging 3 trials; the position of the algometer was slightly altered with each trial to avoid sensitization at the test site. Lower PPT represents a greater degree of sensitization or pain sensitivity.

Mechanical temporal summation, an augmented response to repetitive mechanical stimulation, is a sensitive and valid measure of central pain amplification, a feature of central sensitization, in knee OA (9,11,13). Mechanical temporal summation was assessed at baseline and followup 24 months later using a weighted 60-gm monofilament (Aalborg University) at the patellae and wrist, as previously described (13). Briefly, subjects provided a numerical pain rating (0–10) in response to an initial trial of 4 stimulations, followed by a pain rating at the end of a train of 30 stimulations applied at a frequency of 1 Hz, and again 15 seconds poststimulation (“after sensations”). Temporal summation was defined as being present when, compared with the initial trial, the subject reported increased pain following the repeated mechanical stimulation at the site being tested.

Assessors were blinded with regard to clinical and imaging data. Fourteen-day test–retest reliability for PPT was 0.85–0.90 (intraclass coefficients) and for temporal summation was 0.61 (kappa statistic).

We refer to these measures as “sensitization” hereafter, but acknowledge that they may also reflect heightened pain sensitivity.

Potential confounders

Potential confounders included age, sex, body mass index (BMI), race, study site, radiographic OA severity (Kellgren/Lawrence grade for the tibiofemoral joint, and presence of patellofemoral OA), depressive symptoms (Center for Epidemiologic Studies Depression Scale [39]), catastrophizing (from the Coping Strategies Questionnaire [40]), widespread pain, assessed using a validated standard homunculus (41), and use of analgesics (nonsteroidal antiinflammatory drugs, cyclooxygenase 2 inhibitors, opiates, and acetaminophen).

Statistical analysis

We defined each MRI feature of interest (i.e., synovitis, effusion, and BMLs) as being present if the WORMS score was ≥1. For BMLs, we additionally evaluated a “BML burden” as a sum of the BML scores across all of the subregions.

To examine the relation of these MRI features to the presence of pain sensitization at baseline, to the change in pain sensitization (assessed as change in PPT) over 2 years, and to the development of new pain sensitization (assessed as development of temporal summation) over 2 years, we performed the following. Among all subjects, we evaluated the relation of each MRI feature at baseline in separate models to baseline PPT and to change in PPT over 2 years using linear regression (change in PPT at both the patella and at the wrist was normally distributed). We evaluated the relation of each of the MRI features at baseline to baseline presence of temporal summation and to incident temporal summation (i.e., new development of summation) over 2 years among subjects who were free of temporal summation at baseline using logistic regression. In exploratory analyses, we examined the relation of persistence and resolution of the MRI features compared with their absence at both time points to change in PPT over 2 years using linear regression. To address the same question for temporal summation, which is a binary outcome, we used a self-matched case–control study, in which data on subjects who exhibited temporal summation in one visit, but not the other, were analyzed using conditional logistic regression.

For all analyses, the MRI features were examined in relation to the quantitative sensory testing measurement in the ipsilateral patella and at the wrist in separate models. All analyses were adjusted for the potential confounders listed above. Statistical analysis was conducted using SAS version 9.3.

RESULTS

Of the 1,185 subjects whose knee MRIs were read at baseline and followup, 1,111 had quantitative sensory testing at both the patella and the wrist at baseline and followup 24

months later; these subjects were included in the evaluation of the relation of the MRI feature to baseline quantitative sensory measurement and to change in PPT. Of these subjects, 716 were eligible for the evaluation of the relation of MRI features to incident temporal summation (i.e., 716 were free of temporal summation at baseline). The mean ± SD age of the whole study sample was 66.9 ± 7.5 years, and the mean ± SD BMI was 29.7 ± 4.8 kg/m^2; 62% were women (Table 1). Thirty-eight percent had radiographic knee OA at baseline, the mean ± SD Western Ontario and McMaster Universities Osteoarthritis Index pain score was 2.2 ± 2.9, and 21% reported frequent knee pain at baseline. The range of the change in PPT over 24 months at the patella was −7.35 to 7.15 kg/cm^2; for the wrist, the range was −6.20 to 7.28 kg/cm^2.

At baseline, there was synovitis in 60% of knees, effusion in 66%, and BMLs in 79% on MRI among the whole study sample (n = 1,111). When evaluating the relation of these MRI lesions to the quantitative sensory testing measurements at the patella, we found the following. Among the whole study sample, those with synovitis at baseline had a significantly lower PPT at baseline (adjusted β −0.42 [95% confidence interval (95% CI) −0.67, −0.18]) and a significant decrease in PPT at the patella 24 months later, indicating that they had become more sensitized (adjusted β −0.30 [95% CI −0.52, −0.08]). However, synovitis was not associated with temporal summation at baseline. Baseline effusion and BMLs were not associated with baseline PPT, baseline temporal summation, or change in PPT at the patella over 24 months (Table 2). Among those who were free of temporal summation at baseline (n = 716), 22.6% exhibited temporal summation at the patella 24 months later. In this sample, 62% had synovitis, 67% had effusion, and 79% had BMLs on MRI at baseline. Knees with synovitis did not have an increased risk of developing incident temporal summation at the patella (adjusted odds ratio [OR] 1.12 [95% CI 0.75, 1.66], P = 0.6), but those with effusion at baseline had a 54% increased risk of incident temporal summation (adjusted OR 1.54 [95% CI 1.01, 2.36], P = 0.04). BML presence and BML burden were not associated with risk of incident temporal summation (Table 3).

The relation of the MRI features to the sensory testing measurements at the wrist were as follows. Baseline presence of synovitis was associated with lower PPT at baseline (adjusted β −0.19 [95% CI −0.35, −0.03]), but not with change in PPT at the wrist. In contrast, the presence of effusion was significantly associated with base-line PPT (adjusted β −0.24 [95% CI −0.40, −0.07]) and with decreased PPT (greater sensitivity) at the wrist over 2 years (adjusted β −0.24 [95% CI −0.41, −0.08]) (both P = 0.004) (Table 2). BML presence and burden were not associated with baseline PPT or change in PPT at the wrist, consistent with the findings at the patella. Neither synovitis, effusion, nor BMLs were associated with incident temporal summation at the wrist (Table 3).

Finally, in exploratory analyses, persistence of synovitis over the 2 time points was associated with a decrease in PPT over the same time period at both the patella and wrist, although the change was not significant at the patella (for the patella, adjusted β −0.24 [95% CI −0.54, 0.06], and for the wrist, adjusted β −0.26 [−0.48, −0.03]). In contrast, resolution of synovitis was not associated with a change in PPT. Similarly, persistence of effusion was associated with a decrease in PPT over 2 years (adjusted β −0.27 [95% CI −0.46, −0.09]), but its resolution was not associated with change in PPT. Persistence or resolution of BMLs

was not associated with change in PPT. There were no significant associations for change in any MRI feature with change in temporal summation in the self-matched case–control study (data not shown).

DISCUSSION

This is the first study to examine the relation of inflammatory lesions (synovitis and effusion) and BMLs, which are thought to be largely reflective of mechanical injury, to concurrent and longitudinal change in pain sensitization in a large, well-characterized cohort. Consistent with animal models of sensitization (14–22), our findings support the potential relevance of inflammation in the development and heightening of sensitization in knee OA in humans. We found that synovitis was associated with a lower PPT and a decrease in PPT at the patella over time, indicating increased pain sensitization or sensitivity. Effusion was associated with the development of new temporal summation at the patella and with a decrease in PPT at the wrist, a site distant to the site of pathology; both findings suggest the involvement of central sensitization. Thus, inflammation appears to influence the development of and perhaps amplification of sensitization.

In addition, in our exploratory analyses, we found that persistence of synovitis and persistence of effusion were associated with a decrease in PPT over time, primarily at the wrist, suggesting spreading sensitization over time. In contrast, resolution of these inflammatory features on MRI did not result in a significant change in PPT, suggesting that perhaps once sensitization or heightened sensitivity has occurred, removal of the inflammatory stimulus may not be sufficient to alter the sensitization. This may also explain why we found no change in temporal summation with change in these MRI features. In contrast, BML presence and burden were not associated with either measure of sensitization. This would imply that in human knee OA, tissue injury per se may not influence sensitization. Thus, BMLs appear to contribute to the pain experience through mechanisms that are not directly related to sensitization.

The differences we observed in the relations of synovitis and of effusion to our measures of sensitization, and in the findings at the patella and at the wrist merit discussion. Inflammation of the synovium manifests as activation of the synovial membrane, i.e., synovial thickening, or joint effusion. In the present study, synovitis was assessed using the surrogate imaging marker of Hoffa-synovitis (i.e., assessed as hyperintensity in the infrapatellar [Hoffa's] fat pad on fluid-sensitive fat-suppressed sequences). This is a sensitive but nonspecific marker of synovial inflammation and cannot distinguish inflamed synovium from other entities such as mechanical impingement of the fat pad or hypervascularity for other reasons (33,42). Thus Hoffasynovitis may reflect local effects of inflamed synovium and/or fatty tissue that may lead to local elaboration of adipokines that could influence local pain sensitivity (43,44). Effusion was assessed as effusion-synovitis, which is defined by the presence of fluid-equivalent signal in the joint cavity. Differences in inflammatory mediators that may be relevant in effusion versus Hoffa's fat pad synovitis are not well understood presently. Distension of the suprapatellar pouch may result in effects on local pain sensitivity. Additionally, the lack of a blood–synovial barrier may potentially implicate factors in the systemic circulation. Nonetheless, with non–contrast-enhanced MRIs, we

cannot truly differentiate synovitis from effusion, and acknowledge that the signal changes within Hoffa's fat pad are nonspecific given that the fat pad is an extrasynovial structure (45).

While BMLs are thought to primarily reflect mechanical injury and reparative attempts, we also recognize that BMLs may have a mixed pathology, including findings consistent with localized remodeling processes, such as microtrauma, fibrosis, and foci of necrosis that may have an additional inflammatory component (46,47). Nonetheless, unlike in rheumatoid arthritis, inflammatory cell infiltrate does not appear to be a major feature in knee OA (47). Further, the results were consistently close to the null for the relation of BMLs with each of the measures of sensitization at both the patella and the wrist.

Since it is hypothesized that prolonged exposure to inflammation or tissue injury can induce sensitization, it is possible that the time exposed to the pathologies is an important factor. It may be that in some (or even many) individuals, the MRI features were present for quite some time, either persistently or in a fluctuating manner, and this could have a bearing on our findings, particularly for temporal summation. Further, our assessment of temporal summation may not be sufficiently sensitive, since the initial pain ratings were relatively low. Indeed, temporal summation is most frequently observed with higher initial intensity nociceptive stimuli. Nonetheless, the differences between the two indirect measures of sensitization may also suggest that multiple types of assessments may be needed to fully characterize different aspects of sensitization.

Investigation of the combined effects of coexisting MRI lesions may provide additional insights. However, this was beyond the scope of the present study. Additionally, there may be pathology in other joints that we did not assess that could have contributed to pain sensitization, thereby contributing to exposure misclassification in our study. We also acknowledge that our findings indicate small effects. Because factors contributing to pain sensitization are likely multifactorial, this is not unexpected. In addition, 2 years is a relatively short timeframe to measure change in pain in the broader context of knee OA, a condition that individuals often live with for decades (48). We did not measure conditioned pain modulation in our study, which may provide additional insights regarding descending inhibition of pain. However, we were primarily interested in enhanced pain facilitation because of the hypothesized effects of inflammation and/or injury on causing sensitization.

In conclusion, inflammation within the knee, as related to synovitis and effusion, may drive peripheral and central sensitization in knee OA, consistent with findings from animal models of OA. Since sensitization is associated with pain severity in knee OA, and may potentially contribute to the transition from acute to chronic, persistent pain in knee OA, preventing sensitization from developing would be a potentially effective and novel means of preventing worsening of pain in knee OA. Early targeting of inflammation in knee OA may therefore be a reasonable strategy to test for prevention of sensitization, and thereby reduction of pain severity.

Acknowledgments

Dr. Neogi's work was supported by NIH grants P60-AR-47785 and R01-AR-062506. The Multicenter Osteoarthritis Study is supported by NIH grants U01-AG-18820, U01-AG-18832, U01-AG-18947, and U01-AG-19079.

REFERENCES

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. Arthritis Rheum. 2008; 58:26–35. [PubMed: 18163497]
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013; 21:1145–53.
3. Bajaj P, Bajaj P, Graven-Nielsen T, Arendt-Nielsen L. Osteoarthritis and its association with muscle hyperalgesia: an experimental controlled study. Pain. 2001; 93:107–14. [PubMed: 11427321]
4. Bradley LA, Kersh BC, DeBerry JJ, Deutsch G, Alarcon GA, McLain DA. Lessons from fibromyalgia: abnormal pain sensitivity in knee osteoarthritis. Novartis Found Symp. 2004; 260:258–70. [PubMed: 15283455]
5. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum. 2008; 59:1424–31. [PubMed: 18821657]
6. Lee YC, Lu B, Bathon JM, Haythornthwaite JA, Smith MT, Page GG, et al. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res (Hoboken). 2011; 63:320–7.
7. Wessel J. The reliability and validity of pain threshold measurements in osteoarthritis of the knee. Scand J Rheumatol. 1995; 24:238–42. [PubMed: 7481589]
8. King CD, Sibille KT, Goodin BR, Cruz-Almeida Y, Glover TL, Bartley E, et al. Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis [published erratum appears in Osteoarthritis Cartilage 2013;21: 1811]. Osteoarthritis Cartilage. 2013; 21:1243–52. [PubMed: 23973137]
9. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. Pain. 2010; 149:573–81. [PubMed: 20418016]
10. Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, et al. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain. 2015; 19:1406–17. [PubMed: 25545011]
11. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum. 2013; 65:363–72. [PubMed: 22961435]
12. Goode AP, Shi XA, Gracely RH, Renner JB, Jordan JM. Associations between pressure–pain threshold, symptoms, and radio-graphic knee and hip osteoarthritis. Arthritis Care Res (Hoboken). 2014; 66:1513–9. [PubMed: 24643946]
13. Neogi T, Frey-Law L, Scholz J, Niu J, Arendt-Nielsen L, Woolf C, et al. the Multicenter Osteoarthritis (MOST) Study. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Ann Rheum Dis. 2015; 74:682–8. [PubMed: 24351516]
14. Sharif Naeini R, Cahill CM, Ribeiro-da-Silva A, Menard HA, Henry JL. Remodelling of spinal nociceptive mechanisms in an animal model of monoarthritis. Eur J Neurosci. 2005; 22:2005–15. [PubMed: 16262639]
15. Schaible HG, Schmidt RF, Willis WD. Responses of spinal cord neurones to stimulation of articular afferent fibres in the cat. J Physiol. 1986; 372:575–93. [PubMed: 3723420]
16. Schepelmann K, Messlinger K, Schaible HG, Schmidt RF. Inflammatory mediators and nociception in the joint: excitation and sensitization of slowly conducting afferent fibers of cat's knee by prostaglandin I2. Neuroscience. 1992; 50:237–47. [PubMed: 1407558]
17. Schaible HG, Schmidt RF. Effects of an experimental arthritis on the sensory properties of fine articular afferent units. J Neurophysiol. 1985; 54:1109–22. [PubMed: 4078610]

18. Grigg P, Schaible HG, Schmidt RF. Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. J Neurophysiol. 1986; 55:635–43. [PubMed: 3701397]
19. Schaible HG, Schmidt RF. Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. J Neurophysiol. 1988; 60:2180–95. [PubMed: 3236065]
20. Schaible HG, Schmidt RF. Excitation and sensitization of fine articular afferents from cat's knee joint by prostaglandin E_2. J Physiol. 1988; 403:91–104. [PubMed: 3253427]
21. Schuelert N, McDougall JJ. Grading of monosodium iodoacetate-induced osteoarthritis reveals a concentration-dependent sensitization of nociceptors in the knee joint of the rat. Neurosci Lett. 2009; 465:184–8. [PubMed: 19716399]
22. Richter F, Natura G, Loser S, Schmidt K, Viisanen H, Schaible HG. Tumor necrosis factor causes persistent sensitization of joint nociceptors to mechanical stimuli in rats. Arthritis Rheum. 2010; 62:3806–14. [PubMed: 20722011]
23. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis. 2011; 70:60–7. [PubMed: 20829200]
24. Hunter DJ, Zhang W, Conaghan PG, Hirko K, Menashe L, Li L, et al. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. Osteoarthritis Cartilage. 2011; 19:557–88. [PubMed: 21396463]
25. Hunter DJ, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. Osteoarthritis Cartilage. 2013; 21:1170–8. [PubMed: 23973127]
26. Englund M, Felson DT, Guermazi A, Roemer FW, Wang K, Crema MD, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. Ann Rheum Dis. 2011; 70:1733–9. [PubMed: 21646417]
27. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care. 2001; 24:250–6. [PubMed: 11213874]
28. Hayashi D, Roemer FW, Katur A, Felson DT, Yang SO, Alomran F, et al. Imaging of synovitis in osteoarthritis: current status and outlook. Semin Arthritis Rheum. 2011; 41:116–30. [PubMed: 21295331]
29. Roemer FW, Guermazi A, Zhang Y, Yang M, Hunter DJ, Crema MD, et al. Hoffa's fat pad: evaluation on unenhanced MR images as a measure of patellofemoral synovitis in osteoarthritis. AJR Am J Roentgenol. 2009; 192:1696–700. [PubMed: 19457837]
30. Roemer FW, Hunter DJ, Guermazi A. Semiquantitative assessment of synovitis in osteoarthritis on non contrast-enhanced MRI. Osteoarthritis Cartilage. 2009; 17:820–1. [PubMed: 19070515]
31. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis. 2011; 70:1804–9. [PubMed: 21791448]
32. Rhodes LA, Grainger AJ, Keenan AM, Thomas C, Emery P, Conaghan PG. The validation of simple scoring methods for evaluating compartment-specific synovitis detected by MRI in knee osteoarthritis. Rheumatology (Oxford). 2005; 44:1569–73. [PubMed: 16188949]
33. Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson Imaging. 1995; 13:177–83. [PubMed: 7739358]
34. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis. 1957; 16:494–502. [PubMed: 13498604]
35. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004; 12:177–90. [PubMed: 14972335]
36. Slugg RM, Meyer RA, Campbell JN. Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. J Neurophysiol. 2000; 83:2179–91. [PubMed: 10758127]
37. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. Brain. 2001; 124:1754–64. [PubMed: 11522578]

38. Woolf CJ, Decosterd I. Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. Pain. 1999; (Suppl 6):S141–7. [PubMed: 10491983]

39. Radloff LS. The CES-D scale: a self report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.

40. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. Pain. 2003; 104:453–69. [PubMed: 12927618]

41. Leveille SG, Zhang Y, McMullen W, Kelly-Hayes M, Felson DT. Sex differences in musculoskeletal pain in older adults. Pain. 2005; 116:332–8. [PubMed: 15982814]

42. Loeuille D, Chary-Valckenaere I, Champigneulle J, Rat AC, Toussaint F, Pinzano-Watrin A, et al. Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: correlating magnetic resonance imaging findings with disease severity. Arthritis Rheum. 2005; 52:3492–501. [PubMed: 16255041]

43. Bas S, Finckh A, Puskas GJ, Suva D, Hoffmeyer P, Gabay C, et al. Adipokines correlate with pain in lower limb osteoarthritis: different associations in hip and knee. Int Orthop. 2014; 38:2577–83. [PubMed: 25005460]

44. Gandhi R, Takahashi M, Smith H, Rizek R, Mahomed NN. The synovial fluid adiponectin-leptin ratio predicts pain with knee osteoarthritis. Clin Rheumatol. 2010; 29:1223–8. [PubMed: 20349258]

45. Roemer FW, Kassim Javaid M, Guermazi A, Thomas M, Kiran A, Keen R, et al. Anatomical distribution of synovitis in knee osteoarthritis and its association with joint effusion assessed on non-enhanced and contrast-enhanced MRI. Osteoarthritis Cartilage. 2010; 18:1269–74. [PubMed: 20691796]

46. Hunter DJ, Gerstenfeld L, Bishop G, Davis AD, Mason ZD, Einhorn TA, et al. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. Arthritis Res Ther. 2009; 11:R11. [PubMed: 19171047]

47. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology. 2000; 215:835–40. [PubMed: 10831707]

48. Losina E, Weinstein AM, Reichmann WM, Burbine SA, Solomon DH, Daigle ME, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res (Hoboken). 2013; 65:703–11. [PubMed: 23203864]

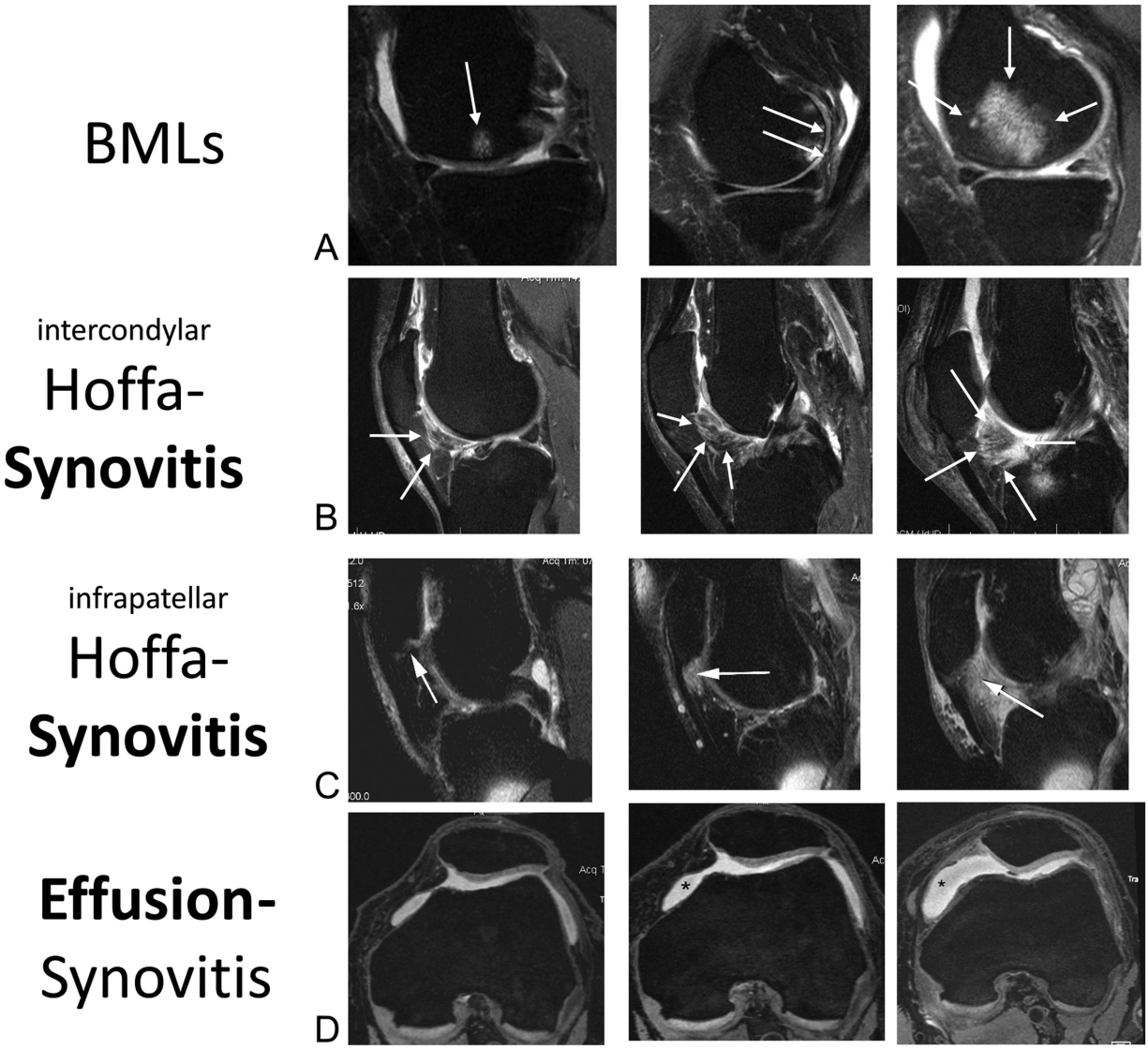

Figure 1.

Examples of magnetic resonance imaging (MRI) lesion grading. **A**, Bone marrow lesions (BMLs). **B** and **C**, Hoffa-synovitis in the intercondylar (**B**) and infrapatellar (**C**) regions. **D**, Effusion-synovitis on non–contrast-enhanced MRI. Note that BMLs were assessed on a persubregion basis, summing all BMLs in the subregion with regard to the percent involved, while Hoffa-synovitis and effusion-synovitis were assessed on a per-knee basis. The left column shows grade 1 lesions, the middle column shows grade 2 lesions, and the right column shows grade 3 lesions. **Arrows** indicate synovitis; **asterisks** indicate effusion.

Table 1

Baseline characteristics of the study participants*

	All subjects (n = 1,111)	Subjects without temporal summation at baseline (n = 716)
Age, mean ± SD years	66.9 ± 7.5	66.3 ± 7.4
% female	62	61
BMI, mean ± SD kg/m^2	29.7 ± 4.8	29.7 ± 4.8
% with radiographic knee OA	38	37
% with frequent knee pain	21	20
WOMAC pain score (range 0–20), mean ± SD	2.2 ± 2.9	1.8 ± 2.7

*BMI = body mass index; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2

Relation of MRI lesions to baseline PPT and change in PPT over 24 months *

MRI lesion at baseline (n = 1,111)	Prevalence, %	Patella				Wrist			
		Baseline PPT	*P*	Change in PPT	*P*	Baseline PPT	*P*	Change in PPT	*P*
Synovitis	60	–0.42 (–0.67, –0.18)	0.0007	–0.30 (–0.52, –0.08)	0.01	–0.19 (–0.35, –0.03)	0.02	–0.10 (–0.26, 0.06)	0.2
Effusion	66	0.23 (–0.03, 0.49)	0.08	–0.04 (–0.28, 0.19)	0.7	–0.24 (–0.40, –0.07)	0.004	–0.24 (–0.41, –0.08)	0.004
BMLs	79	0.14 (–0.16, 0.44)	0.4	0.03 (–0.25, 0.31)	0.8	0.05 (–0.14, 0.25)	0.6	–0.10 (–0.29, 0.10)	0.3
Sum of BMLs (“BML burden”) (range 0–19)	–	0.03 (–0.01, 0.08)	0.2	–0.01 (–0.05, 0.04)	0.8	0.00 (–0.03, 0.03)	0.9	0.00 (–0.03, 0.03)	1.0

* Except where indicated otherwise, values are the adjusted β (95% confidence interval), adjusted for age, sex, body mass index, race, study site, radiographic osteoarthritis severity, depressive symptoms, catastrophizing, widespread pain, and analgesic use. MRI = magnetic resonance imaging; PPT = pressure pain threshold; BMLs = bone marrow lesions.

Table 3

Relation of MRI lesions to baseline temporal summation and incident temporal summation over 24 months *

		Patella				Wrist			
MRI lesion at baseline	**Prevalence, %**	**Baseline temporal summation (n = 1,111)**	***P***	**Incident temporal summation (n = 716)**	***P***	**Baseline temporal summation (n = 1,111)**	***P***	**Incident temporal summation (n = 716)**	***P***
Synovitis	62	0.83 (0.63, 1.08)	0.2	1.12 (0.75, 1.66)	0.6	0.84 (0.64, 1.10)	0.2	1.22 (0.85, 1.75)	0.2
Effusion	67	0.89 (0.67, 1.18)	0.4	1.54 (1.01, 2.36)	0.04	1.13 (0.85, 1.51)	0.4	0.94 (0.66, 1.35)	0.7
BMLs	79	0.95 (0.68, 1.32)	0.8	0.92 (0.56, 1.49)	0.7	1.04 (0.74, 1.45)	0.8	1.05 (0.68, 1.62)	0.8
Sum of BMLs (“BML burden”) (range 0–19)		0.98 (0.93, 1.03)	0.4	1.00 (0.92, 1.07)	0.9	0.98 (0.93, 1.04)	0.5	1.00 (0.94, 1.07)	1.0

* Except where indicated otherwise, values are the adjusted odds ratio (95% confidence interval), adjusted for age, sex, body mass index, race, study site, radiographic osteoarthritis severity, depressive symptoms, catastrophizing, widespread pain, and analgesic use. MRI = magnetic resonance imaging; BMLs = bone marrow lesions.