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The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis[1]

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Summary

Introduction: Pain is the most common symptom in knee osteoarthritis (OA), a leading cause of chronic disability, and a major source of the disability attributable to OA in general. Pain severity in knee OA is variable, ranging from barely perceptible to immobilizing. The knee lesions that contribute to pain severity have received little attention.

Objective: To examine whether worse pathology of specific knee tissues – i.e. cartilage, bone (attrition, cysts, bone marrow lesions, and osteophytes), menisci (tears and subluxation), ligaments, and synovium (synovitis/effusion) – is associated with more severe knee pain.

Methods: One hundred and forty-three individuals were recruited from the community with primary (idiopathic) knee OA, with definite tibiofemoral osteophytes in at least one knee, and at least some difficulty with knee-requiring activity. Knee magnetic resonance (MR) images were acquired using coronal T1-weighted spin-echo (SE), sagittal fat-suppressed dual-echo turbo SE, and axial and coronal fat-suppressed, T1-weighted 3D-fast low angle shot (FLASH) sequences. The whole-organ magnetic resonance imaging (MRI) scoring (WORMS) method was used to score knee tissue status. Since summing tissue scores across the entire joint, including regions free of disease, may dilute the ability to detect a true relationship between that tissue and pain severity, we used the score from the worst compartment (i.e. with the poorest cartilage morphology) as our primary approach. Knee pain severity was measured using knee-specific, 100 mm visual analogue scales. In analyses to evaluate the relationship between knee pain severity and lesion score, median quantile regression was used, adjusting for age and body mass index (BMI), in which a 95% CI excluding 0 is significant.

Results: The increase in median pain from median quantile regression, adjusting for age and BMI, was significant for bone attrition (1.91, 95% confidence interval (CI) 0.68, 3.13), bone marrow lesions (3.72, 95% CI 1.76, 5.68), meniscal tears (1.99, 95% CI 0.60, 3.38), and grade 2 or 3 synovitis/effusion vs grade 0 (9.82, 95% CI 0.38, 19.27). The relationship with pain severity was of borderline significance for osteophytes and cartilage morphology and was not significant for bone cysts or meniscal subluxation. Ligament tears were too infrequent for meaningful analysis. When compared to the pain severity in knees with high scores for both bone attrition and bone marrow lesions (median pain severity 40 mm), knees with high attrition alone (30 mm) were not significantly different, but knees with high bone marrow lesion without high attrition scores (15 mm) were significantly less painful.

Conclusion: In persons with knee OA, knee pain severity was associated with subarticular bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears. The contribution of bone marrow lesions to pain severity appeared to require the presence of bone attrition.

Key words: Knee osteoarthritis, Pain.

Introduction

Knee pain is the most common symptom in knee osteoarthritis (OA), a condition that is a leading cause of chronic disability in older individuals and a major source of the disability attributable to OA in general. Severity of knee pain ranges widely in knee OA, from none or barely perceptible to immobilizing and disabling.

It is unlikely that knee pain severity in persons with OA is a simple phenomenon. As almost invariably noted in textbooks, pain in OA could arise from any of several innervated tissues. However, findings from three areas of investigation imply that OA pathology may not play a large role in pain severity: while knee pain increased with radiographic disease severity in most studies, the relationship was not strong (summarized in Ref. 1); in contrast there is a strong relationship between knee pain and psychosocial factors

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[e.g., well-being[2], low spirits[3], depression, anxiety, coping, and hypochondriasis[4,5]]; and, nociceptive pathways, depicted in Fig. 1, may be less important than persistent alteration in nociceptor sensitization especially in chronic disease[6,7].

Of note, only a few studies have used sensitive imaging methods in the examination of the disease pathology/pain severity relationship. There is insufficient information at present to make conclusions about the role of tissue pathology.

Most of what is believed about the relationship between disease and pain in persons with OA comes from studies that used radiography to assess disease. Even with superior acquisition and reading protocols, x-ray is a suboptimal technique to advance knowledge about what aspects of OA cause pain, as it cannot capture key elements of OA pathology. Unlike x-ray, magnetic resonance imaging (MRI) affords an opportunity to visualize cartilage, menisci, ligaments, synovial effusion, and bone marrow lesions. Furthermore, MRI is better than x-ray at showing bone cysts, osteophytes, and attrition. Of the studies which used MRI, most tested hypotheses dealing with knee pain presence vs absence and not pain severity.

Our goal was to examine whether worse specific knee tissue pathology – i.e. articular cartilage, subarticular bone (attrition, cysts, bone marrow lesions, and osteophytes), menisci (tears and subluxation), ligaments, and synovium (synovitis/effusion) – is associated with more severe knee pain.

Methods

Participants were recruited from the community through advertising in neighborhood periodicals, community centers, letters sent to members of the registry of the Beuhler Center on Aging at Northwestern University, and through medical center referrals. Inclusion criteria[8] were: definite tibiofemoral osteophyte presence [Kellgren/Lawrence (K/L) radiographic grade $\geq$2] in one or both knees; and Likert category of at least "a little difficulty" for two or more items in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) physical function scale[9]. Exclusion criteria were: corticosteroid injection within the previous 3 months; history of avascular necrosis, rheumatoid or other inflammatory arthritis, periarticular fracture, Paget's disease, villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, acromegaly, hemochromatosis, gout, pseudogout, or osteopetrosis; or exclusion criteria for MRI such as presence of a pacemaker, artificial heart valve, aneurysm clip or shunt, metallic stent, implanted device (e.g. pain control/nerve stimulator, defibrillator, insulin/drug pump, ear implant), or any metallic fragment in an eye.

Approval was obtained from the Office for the Protection of Research Subjects – Institutional Review Board of Northwestern University. Written consent was obtained from all participants.

MRI ACQUISITION AND READING

All participants had MRI of their right knee using a commercial knee coil and one of two whole-body scanners (1.5 T or 3 T, GE Healthcare, Milwaukee, WI). The protocol included coronal T1-weighted spin-echo (SE), sagittal fat-suppressed dual-echo turbo SE, and axial and coronal fat-suppressed, T1-weighted 3D-fast low angle shot (FLASH) sequences.

Following a detailed reading protocol including atlas representations of each grade for each tissue lesion, the knee was scored using the whole-organ MRI scoring (WORMS) method of Peterfy *et al.*[10]. Specifically, three regions (anterior, central, and posterior) of the medial and lateral femoral condyles and tibial plateaus, and two regions (medial and lateral) of the patella were each scored separately for cartilage morphology, subarticular bone marrow lesions, bone cysts, bone attrition, and osteophytes. For each lesion, each region of a compartment surface received its own score. The scores for a given tissue were then summed within each knee compartment to derive separate medial tibiofemoral, lateral tibiofemoral, and patellofemoral scores for that tissue.

At each region, cartilage morphology was scored 0–6: 0 for normal thickness and signal; 1 for normal thickness but increased signal on T2-weighted images; 2 for solitary, focal, partial or full-thickness defect $\leq$1 mm in width; 3 for multiple areas of partial-thickness loss or a grade 2 lesion $>$1 mm, with areas of preserved thickness; 4 for diffuse, $>$75%, partial-thickness loss; 5 for multiple areas of full-thickness loss, or a full-thickness lesion $>$1 mm, with areas of partial-thickness loss; and 6 for diffuse, $>$75%, full-thickness loss. Subarticular bone marrow lesions (depicted as poorly marginated areas of free water signal in the normally fatty epiphyseal marrow on T2 images) and bone cysts were each scored 0–3: 0 for normal; 1 for mild, $<$25% of region; 2 for moderate, 25–50% of region; and 3 for severe, $>$50% of region. Subchondral bone attrition (flattening and depression of the articular surfaces) was scored 0–3, for normal, mild, moderate, and severe. Osteophytes were scored 0–7: 0 if none; 1 if equivocal; 2 if small horizontal spur; 3 if moderate horizontal or small curved spur; 4 if large horizontal or moderate curved spur; 5 if moderate-large curved spur; 6 if large, exuberant spur; and 7 if very large, irregular spur.

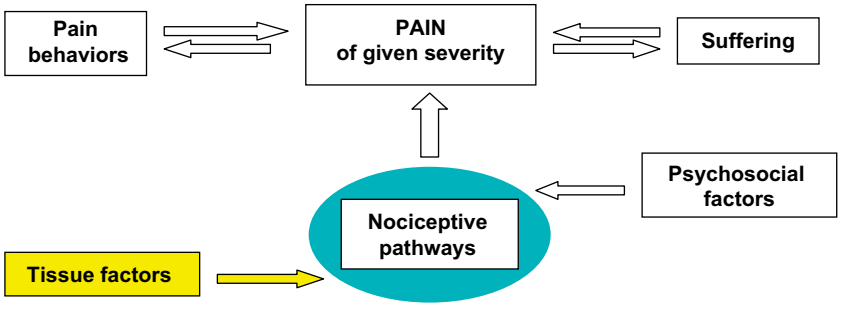

Fig. 1. The nociceptive pathway [adapted from figure by Kidd[7]].

The anterior and posterior cruciate ligaments (ACL and PCL) were scored 0 if intact or 1 if torn. The medial and lateral collateral ligaments (MCL and LCL) were scored 0 if intact, 1 if thickened, and 2 if torn. The anterior horn, posterior horn, and body of the medial and lateral meniscus were each scored 0–4: 0 for intact; 1 for minor radial or parrot-beak tear; 2 for nondisplaced tear or prior surgical repair; 3 for displaced tear, partial maceration, or partial resection; and 4 for complete maceration and destruction or complete resection. A cumulative tear grade was calculated for each meniscus[10]. Subluxation of the body segments of the medial and lateral menisci was graded (0 if none, 1 if less than half the meniscus, or 2 if greater than half) using coronal images at the level of the MCL and LCL, respectively.

Intravenous contrast was not injected in this study, which precluded distinction of synovial thickening and joint effusion. Thickening and effusion were therefore graded collectively as per the WORMS protocol from 0–3: 0 for normal; 1 for $<$33% of maximum estimated distention of the synovial cavity; 2 for 33–66% of maximum distention; and 3 for $>$66% of maximum distention.

Magnetic resonance (MR) images were read by one of three experienced readers. Inter-rater reliability for these readers applying this scoring system has been published[10]. Readers were blinded to all other data.

TISSUE SCORING FOR THE WORST COMPARTMENT

The best approach to analyze tissue lesion status as a source of pain is not clear from the literature. OA tends to involve the tibiofemoral compartments asymmetrically, and may involve the patellofemoral compartment alone or in combination with a tibiofemoral compartment. Many tissue lesions are present in more than one knee compartment. The pain from OA involvement of that tissue could come mostly from the predominantly diseased (worst) compartment or could reflect the tissue state throughout the joint. Since summing tissue scores across the entire joint, including large regions without disease, may dilute the ability to detect a real relationship between that tissue and pain severity, we used the score from the worst compartment as our primary approach. Since MRI is superior to x-ray as a tool to gauge disease severity in knee OA, and since cartilage loss is the essence of the disease, we defined the worst compartment as the one with the worst cartilage morphology score on MRI. Secondarily, we also examined the sum of a given tissue lesion score across all compartments.

MEASUREMENT OF KNEE PAIN SEVERITY

Knee pain over the past week was measured using 100 mm visual analogue scales, with separate scales for the right and left knees. The scales were anchored at 0 with ''no pain'' and at 100 with ''pain as bad as it could be'', and standardized instructions were given.

RADIOGRAPHIC ACQUISITION AND READING

All participants had AP, weight-bearing knee radiographs at baseline and 18 months in the semi-flexed position with fluoroscopic confirmation of superimposition of the anterior and posterior tibial plateau lines and centering of the tibial spines within the femoral notch. The Buckland-Wright protocol[11] was followed, which addresses knee position, criteria for beam alignment relative to knee center, radiopaque markers to account for magnification, and foot position.

To describe the knees, K/L global radiographic scores were used (0 = normal; 1 = possible osteophytes; 2 = definite osteophytes without definite joint space narrowing; 3 = definite joint space narrowing, some sclerosis, and possible attrition; and 4 = large osteophytes, marked narrowing, severe sclerosis and definite attrition)[12]. Reliability for the single reader was very good (kappa coefficient 0.85–0.86).

STATISTICAL ANALYSIS

All persons had K/L $\geq$2 OA in at least one knee. All right knees were analyzed. This approach was taken to generalize results to a *person* with OA rather than any groupings of knees within persons with OA. Also, MRI definitions of OA are not established, and including all right knees (rather than only K/L $\geq$2) increased the likelihood of analyzing a spectrum of tissue pathology by MRI. A risk of examining only knees at K/L 2 or more is a range truncated to include only moderate to severe pathology.

Since knee pain severity had a skewed distribution, median (rather than mean) pain severity was analyzed. To illustrate the relationship between knee pain severity and MRI-based tissue lesion score, median pain severity was determined for each quartile of lesion score (for continuous scores) or by lesion grade. Analyses to evaluate the relationship between median pain severity and lesion score used median quantile regression, run with Stata software[13]. Using quantile regression to model *median* pain as the dependent variable is analogous to least squares regression that models the mean outcome. Since quantile regression is robust to outliers and does not require assumptions regarding the underlying distribution of the outcome to obtain valid inference tests, the method is advantageous for modeling outcomes that are not normally distributed[14]. Results from median pain regressed on continuous scores are presented as the increase in median pain per unit of increase in the score; a 95% CI excluding zero indicates a significant relationship. Quantile regression results from discrete factors (e.g. lesion grades) are presented as the difference in median pain relative to a reference; a 95% CI excluding zero is significant. Analyses were adjusted for age (treated as a continuous variable) and body mass index (BMI) (continuous).

Results

The 143 participants (78% women) had a mean ($\pm$SD) age of 70 $\pm$ 10 years, BMI of 31 $\pm$ 6 kg/m^2, and a median knee pain severity of 20 $\pm$ 7 mm. The K/L grade was 0–2 in 64 persons, 3 in 44 persons, and 4 in 35 persons.

In the knees in which the worst compartment was the medial tibiofemoral compartment (48 knees), the cumulative cartilage morphology score was 14.3 ($\pm$11.0) for the medial compartment [vs 2.7 ($\pm$5.7) for the lateral compartment and 6.6 ($\pm$7.2) for the patellofemoral compartment]. In the knees in which the lateral tibiofemoral was the worst compartment (33 knees), the cumulative cartilage morphology scores for the lateral, medial, and patellofemoral compartments were 22.7 ($\pm$8.2), 6.7 ($\pm$7.9), and 7.8 ($\pm$5.5), respectively. In the knees in which the patellofemoral was the worst compartment (62 knees), the cumulative cartilage morphology scores for the patellofemoral, medial, and lateral compartments were 12.1 ($\pm$6.7), 4.3 ($\pm$5.1), and 1.7 ($\pm$2.9), respectively.

Median knee pain severity decreased with age (median decrease of 0.6 mm for each year over 70 years, 95% CI

0.09, 1.09) and increased with BMI (increase of 2.2 mm per unit BMI, 95% CI 1.56, 2.74), but did not differ between men and women (median pain 20 mm in both groups).

TISSUE LESION SCORES

The median score and range (for the sample) are provided in Table I(A) for bone attrition, bone marrow lesions, bone cysts, osteophytes, cartilage morphology, and meniscal tears. In Table I(B), the distribution of scores is shown for meniscal subluxation, the ligaments, and synovitis/effusion. The relationships between tissue lesions are shown in Table II.

TISSUE LESION SCORES BY PAIN GROUP

Median pain severity for knees grouped by quartile of tissue lesion score is shown for the four types of bone lesions, cartilage morphology, and meniscal tears in Fig. 2. In Fig. 3, median pain severity is shown by score of meniscal subluxation, ligament status, and synovitis/effusion.

THE RELATIONSHIP BETWEEN TISSUE LESION SCORE AND KNEE PAIN SEVERITY

As shown in Table III, bone attrition, bone marrow lesions, meniscal tears, and synovitis/effusion (grade 2 or 3 vs 0) were significantly related to knee pain severity after adjusting for age and BMI. The magnitude of the correlations between these four lesions (see Table IV) precluded analyzing them within a single statistical model. Osteophytes and cartilage morphology were weakly significant. The wide 95% CI for LCL grade very likely reflects the small number of knees with LCL pathology.

Results from similar analyses using the sum of scores from all compartments for a given lesion showed a significant relationship only for bone attrition and bone marrow lesions (results not shown).

PAIN SEVERITY IN KNEES WITH AND WITHOUT BONE MARROW ABNORMALITY AND BONE ATTRITION

To explore a question raised by Sowers *et al.*[15] of whether it is necessary for another type of bone lesion to be present for bone marrow lesions to cause pain, we examined median pain severity in four groups of knees, with: high bone marrow lesion and attrition scores; high bone marrow lesion score only; high attrition score only; and neither high bone marrow lesion nor high attrition scores. We defined high bone marrow lesion and high attrition as above the cut-off for the highest quartile. Pain was most severe when scores were high for both, as shown in Table IV. When compared to the pain severity in knees with high scores for both lesions, knees with high attrition alone were not significantly different, but knees with high bone marrow lesion scores alone were significantly less painful.

Table I
Median MRI-based tissue lesion scores (A) in the worst compartment and the percent of knees (B) at each grade

(A) Lesion	Median (range found in sample)
Bone attrition	2 (0–13)
Bone marrow lesions	2 (0–12)
Bone cysts	1 (0–10)
Osteophytes	14 (0–39)
Cartilage morphology	17 (0–30)
Meniscal tears	1 (0–6)
(B) Lesion, grades	**% of knees at each grade**
Meniscal subluxation (0,1,2)	48/34/18
MCL (0,1,2)	81/18/1
LCL (0,1,2)	95/4/1
ACL (0,1)	91/9
PCL (0,1)	99/1
Synovitis/effusion (0,1,2,3)	31/48/15/6

Discussion

In persons with knee OA, bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears were each significantly related to knee pain severity after adjusting for age and BMI. The relationship was weakly significant for osteophytes and cartilage morphology, and not significant for bone cysts and meniscal subluxation. The link between bone marrow lesions and pain severity appeared to require the presence of bone attrition.

Current knowledge of tissue sources of pain in knee OA is based upon a few studies, mostly examining knee pain presence/absence. An exception to this, the study by Link *et al.* found greater pain in patients with than without cartilage lesions[16]. Unlike our study, they did not find a relationship between pain severity and bone marrow lesions, synovitis/effusion, or meniscal tears, possibly related to use of a person- rather than knee-specific pain measure.

The importance of subarticular bone to disease progression[17–19] and as a source of pain in knee OA has been an area of interest for some time. The observation in patients with OA of a disturbance of venous drainage and intraosseus stasis in subarticular bone extends at least as far back as 1955[20]. Arnoldi *et al.* found that patients with knee pain, some with and some without knee OA, had elevated juxtaarticular intraosseus pressure[21]. Support, some indirect, that bone may be a key source of knee pain in OA also comes from scintigraphic studies[22], reports of the relationship between the adduction moment and the ratio of medial to lateral tibial bone density[23,24], a large epidemiologic literature reporting a link between pain and radiographic osteophytes, the recent report of a relationship between pain and subchondral bone sclerosis[25], and the investigations concerning bone marrow lesions (formerly labeled bone marrow edema) in knee OA.

Bone marrow edema is a term first used to describe ill-defined hyperintensities on T2-weighted MR images in patients with knee and hip pain[26]. These lesions have been reported in several painful conditions including transient painful osteoporosis, fracture, osteonecrosis, infection, and inflammatory arthropathy. In histopathologic studies, Zanetti *et al.* found that the MRI-identified edema lesion included normal tissue, some true edema (only 4% of the MRI lesion), and bone marrow necrosis and fibrosis[27]. Of note, MRI is more sensitive than histology for water, and the only source of signal on a properly fat-suppressed MR image is free water.

We found that with worse bone marrow lesion score came more severe pain, although the quartile data suggest that the main difference may be between knees with no lesions and with lesions, without much further increase by score. Our results are in keeping with the Boston Osteoarthritis Knee Study (BOKS) findings that bone marrow

Table II
Correlation matrix providing correlation coefficients (R values) for relationships between tissue lesions

	Bone attrition	Bone marrow lesions	Bone cyst	Osteophyte	Cartilage morphology	Meniscal tear	Meniscal subluxation	Synovitis/ effusion
Bone attrition	1.00	0.53	0.47	0.67	0.75	0.55	0.17	0.62
Bone marrow lesions		1.00	0.60	0.54	0.56	0.34	0.15	0.40
Bone cyst			1.00	0.53	0.48	0.24	0.08	0.23
Osteophyte				1.00	0.73	0.33	0.27	0.52
Cartilage morphology					1.00	0.48	0.15	0.57
Meniscal tear						1.00	0.08	0.51
Meniscal subluxation							1.00	0.37
Synovitis/effusion								1.00

lesions were more common in OA knees with symptoms (pain, aching, or stiffness on most days) than in knees without symptoms and the trend towards more severe pain in knees with vs without such lesions[28]. Zhai *et al.* confirmed that bone marrow lesions were associated with a greater risk of knee pain presence, and further found that the relationship was independent of chondral defects[29]. Sowers *et al.* found that large bone marrow lesions were more common in painful than painless OA knees[15]. Bone "ulceration" under cartilage defects appeared to be particularly important, and they theorized that bone marrow lesions may need to be accompanied by other bone changes to cause pain.

In our report, another bony feature associated with knee pain severity was bone attrition. Of note, Dieppe *et al.* recently reported evidence of possible link between radiographic bone attrition and night pain[30]. Our findings suggest that bone marrow lesions may require the presence of bone attrition to contribute to pain severity. Osteophytes were related to pain severity, but the relationship was only weakly significant. A radiographic literature spanning many years describes a stronger relationship between knee pain and osteophytes than other radiographic features such as narrowed joint space width. It is possible that at least part of the radiographic osteophyte/pain relationship is due to confounding by bone attrition and/or bone marrow lesions, which are not easily characterized by x-ray.

Despite the lack of intravenous contrast to highlight inflammation and distinguish effusion from synovial tissue, we found a significant relationship between the grade of synovitis/effusion, i.e. the grade of synovial cavity distention, and knee pain severity. It is a widely held clinical belief that joint inflammation increases pain in knee OA. These results are consistent with those from BOKS, in which effusion was more common in knees with vs without pain[31].

In our study, worse cartilage integrity was linked to pain severity, albeit with weak significance. This result agrees with the report of Wluka *et al.* of a modest correlation ($R = 0.28$) between worsening of symptoms of knee OA and greater tibial cartilage volume loss over 2 years[32]. Since articular cartilage is not innervated, the link between cartilage and pain severity may be due to other aspects of OA disease pathology.

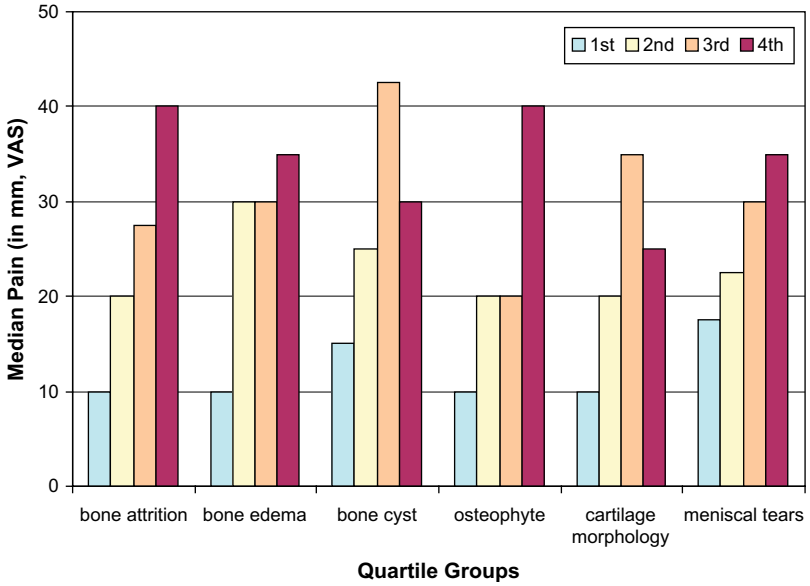

Fig. 2. Median knee pain severity (mm, visual analogue scale) by MRI-based tissue lesion score quartiles for bone lesions, cartilage morphology, and meniscal tears. In this figure, median knee pain severity (in mm by visual analogue scale) is given for each quartile of lesion score. Higher lesion scores represent more severe pathology. The quartile cut-offs were: for bone attrition, 0, $\leq$2, $\leq$4, and $>$4; for bone marrow lesions, 0, $\leq$2, $\leq$4, and $>$4; for bone cysts, 0, $\leq$1, $\leq$2, and $>$2; for osteophytes, $\leq$7.50, $\leq$14, $\leq$21, and $>$21; for cartilage morphology, $\leq$7.25, $\leq$17, $\leq$23, and $>$23; and for meniscal tears, 0, $\leq$1, $\leq$4, and $>$4.

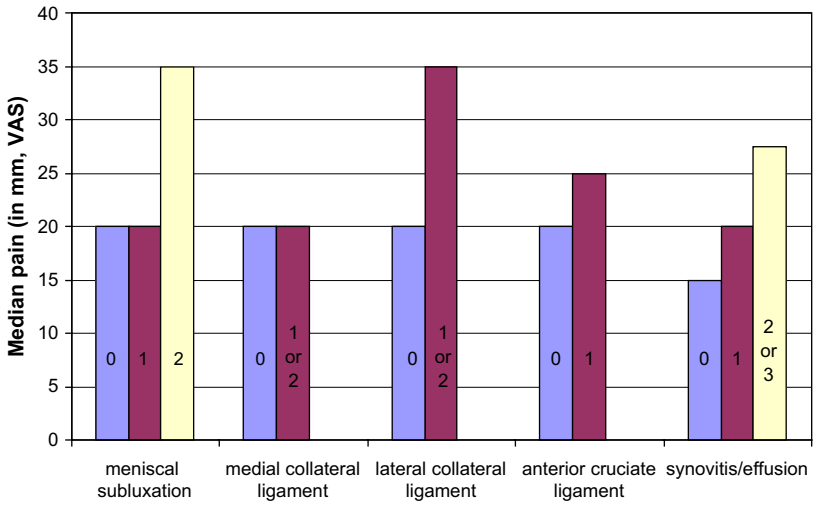

Fig. 3. Median knee pain severity (mm, visual analogue scale) by MRI-based tissue lesion score for meniscal subluxation, ligament lesions, and synovitis/effusion. In this figure, median knee pain severity (in mm by visual analogue scale) is depicted for knees with the given tissue lesion score. Higher lesion scores represent more severe pathology.

The finding that meniscal tear grade was related to knee pain severity differs from BOKS, in which there was no difference in person-specific or in knee-specific measures of pain between those with and without meniscal tears[33]. The difference between studies in this result may relate to a difference in the meniscal tear parameter analyzed, i.e. in our study, meniscal tear grade of the worst compartment, and, in BOKS, any meniscal tear presence/absence.

The greater ability to detect these relationships in our study may relate to the worst compartment approach we undertook, which minimized the dilution effect of including less diseased or nondiseased parts of the knee. It is very rare for OA to involve the three compartments of the knee equally. The value of the worst compartment approach comes not only from the effort to consider the most severely involved area but also by excluding the most spared area. Since OA generally involves focal lesions within a joint or compartment, evaluation of lesions within a worst region of interest may yield an even stronger relationship between lesion severity and pain severity, a stimulating area for future study.

It is particularly interesting that the pathologic status of bone and synovium seems to be important, both in our study and in prior studies, and, both in terms of OA progression and knee pain. Kidd *et al.* suggest that synovial- and bone-derived mediators may sensitize nociceptive neurons to everyday stimuli. Among the neuronal changes are increased production and release of neuropeptides that may act with cytokines and other mediators to contribute to ongoing tissue injury[1,2].

There are limitations to our study that must be acknowledged. Important pain constructs include not only pain severity and pain presence but also pattern of pain (night pain, rest pain, and activity-related pain). Factors predisposing to pain patterns in OA should also be identified. We have not described psychosocial correlates. In theory, psychosocial factors are unlikely to be confounders, but may modify the tissue lesion/pain severity relationship,

Table III

The coefficients from median quantile regression are provided to characterize the relationship between tissue lesion and knee pain severity. The coefficient represents the increase in median knee pain severity associated with a 1-unit increase in lesion score, among persons aged 70 and with a BMI of 30. A 95% CI excluding 0 is significant (shown in bold)

Lesion	Unadjusted coefficient (95% CI)	Coefficient, adjusted for age and BMI (95% CI)
Bone attrition	**3.33 (1.79, 4.87)**	**1.91 (0.68, 3.13)**
Bone marrow lesions	**5.00 (3.00, 7.00)**	**3.72 (1.76, 5.68)**
Bone cysts	2.50 (−0.38, 5.38)	0.82 (−0.50, 2.14)
Osteophytes	**1.18 (0.63, 1.72)**	**0.50 (0.07, 0.94)**
Cartilage morphology	**1.03 (0.56, 1.49)**	**0.53 (0.08, 0.98)**
Meniscal tears	**3.33 (0.90, 5.77)**	**1.99 (0.60, 3.38)**
Meniscal subluxation		
Grade 1 vs 0	0 (−11.88, 11.88)	−2.96 (−10.39, 4.46)
Grade 2 vs 0	15.00 (−0.32, 30.32)	2.22 (−6.89, 11.33)
MCL, grade 1 or 2 vs 0	0 (−19.81, 19.81)	−6.10 (−13.95, 1.74)
LCL, grade 1 or 2 vs 0	15.00 (−8.16, 38.16)	**29.46 (17.80, 41.12)**
ACL, grade 1 vs 0	5.00 (−12.96, 22.96)	6.79 (−5.38, 18.96)
Synovitis/effusion		
Grade 1 vs 0	5.00 (−13.69, 23.69)	1.30 (−6.57, 9.16)
Grade 2 or 3 vs 0	15.00 (−8.18, 38.18)	**9.82 (0.38, 19.27)**

Table IV
Median knee pain severity (in mm, by visual analogue scale) is shown by status of bone attrition and bone marrow lesions. High was defined as above the cut-off for the highest quartile (i.e. score >4). A 95% CI excluding 0 represents a significant difference from the reference group (knees with both high attrition and high bone marrow lesion scores)

Subarticular bone attrition and bone marrow lesion status (*n* of knees)	Median pain severity (mm)	Difference in median pain (mm) from knees with high attrition and high bone marrow lesion	95% CI of difference
Both high (14)	40.00	(Reference)	–
High attrition only (19)	30.00	−10	−32.43, 12.43
High bone marrow lesion only (13)	15.00	−25	−49.64, −0.36
Neither high (96)	20.00	−20	−38.06, −1.94

an interesting area for future study. Our sample, as is often the case with knee OA samples, has a high average BMI. The role of knee tissue status in pain severity should also be examined in persons with OA and healthy body weight. The relationship between tissue lesions precluded forcing the major correlates of pain severity into one model. Potential confounding by other tissues and lesions is an inherent problem in this area of investigation that to our knowledge has not been addressed by previous studies. The lack of findings for the cruciate and collateral ligaments may be due to the relatively crude assessment of ligaments (e.g. tear present vs absent) afforded by our MRI protocol and/or a low frequency of pathology in any ligament in our sample. A more refined or functional assessment of ligament tissue may reveal a relationship between ligament pathology and knee pain severity. The question of whether the relationship between pain severity and worst compartment tissue lesions differs according to which compartment was the worst is not something we can address given the size of our study, but is an interesting question for future study.

In sum, in persons with knee OA, knee pain severity was associated with subchondral bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears, but not with meniscal subluxation or bone cysts. The contribution of bone marrow lesions to pain severity depended upon the presence of subarticular bone attrition.

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