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# Synovitis Is Associated With Constant Pain in Knee Osteoarthritis: A Cross-sectional Study of OMERACT Knee Ultrasound Scores

Holly T. Philpott[1], Trevor B. Birmingham[1], Ryan Pinto[1], Codie A. Primeau[1], Dominique Arsenault[2], Brent A. Lanting[3], Yayuan Zhu[4], and C. Thomas Appleton[5], on behalf of the WOREO Knee Study Group

*ABSTRACT.* ***Objective.*** To examine the association between ultrasound (US)-detected knee inflammation and intermittent and constant pain experiences in patients with knee osteoarthritis (OA).

***Methods.*** Participants with radiographically early-stage (Kellgren-Lawrence arthritis grading scale [KL] ≤ 2) and late-stage (KL ≥ 3) disease and frequent symptoms underwent musculoskeletal US measures of inflammation using the Outcome Measures in Rheumatology (OMERACT) knee US scoring system. Pain experiences were captured using the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) tool. We assessed the association between US-synovitis and ICOAP pain experiences using a series of linear, logistic, or multinomial logistic regression models (as appropriate for each variable), while adjusting for age, sex, BMI, and radiographic stage. Secondary analyses were performed similarly by radiographic stage.

***Results.*** Pain and synovitis measures from 248 patients (453 knees) were included. Worse synovitis was associated with higher ICOAP constant pain scores (β 8.05, 95% CI 0.67–15.43), but not intermittent pain scores. Moderate-to-severe synovitis was associated with a 4.73-fold increased relative risk (95% CI 1.06–17.00) of a constant pain pattern. In secondary analyses, moderate-to-severe synovitis in early radiographic OA was associated with 2.70-higher odds (95% CI 1.04–7.02) of any constant pain, 3.28-higher odds (95% CI 1.43–7.52) of any intermittent pain, and with higher intermittent (β 10.47, 95% CI 1.03–19.91) and constant (β 12.62, 95% CI 3.02–22.23) pain scores. No associations were identified for synovitis in those with late radiographic OA.

***Conclusion.*** In patients with knee OA, moderate-to-severe synovitis is most strongly associated with constant pain. Inflammation may play context-specific roles across pain experiences, especially in earlier radiographic stages of knee OA.

*Key Indexing Terms*: osteoarthritis, pain, synovitis, ultrasound

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*[1]H.T. Philpott, MSc, T.B. Birmingham, PT, PhD, R. Pinto, MSc, C.A. Primeau, MSc, Faculty of Health Sciences, and Bone and Joint Institute, Western University; [2]D. Arsenault, MSc, London Health Sciences Centre, University Hospital; [3]B.A. Lanting, MD, Bone and Joint Institute, and Department of Surgery, Schulich School of Medicine and Dentistry, Western University, and London Health Sciences Centre, University Hospital; [4]Y. Zhu, PhD, Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, Western University; [5]C.T. Appleton, MD, PhD, Bone and Joint Institute, and Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada.*

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*Address correspondence to Dr. C.T. Appleton, St. Joseph's Health Care Rheumatology Centre, 268 Grosvenor St., London, ON N6A 4V2, Canada. Email: tom.appleton@sjhc.london.on.ca.*

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Osteoarthritis (OA)-related pain experiences are diverse, and pain presentation may vary based on several factors including anatomic location, intensity, frequency, and specific triggers, all of which may be driven by distinct pathophysiological mechanisms.[1,2] Some pain constructs may not be captured appropriately by traditional questionnaires such as the Knee Injury and Osteoarthritis Outcome Score (KOOS) or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Previously, using the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) tool, it was shown that intermittent vs constant types of pain occur separately or together in different patterns (or experiences) and are differentially associated with severity of knee pain and radiographic stage of OA.[3] Although the mechanisms underlying different pain experiences in OA are not fully elucidated, defining associations between pain experiences and other clinical features of OA may help uncover key mechanisms for investigators and clinicians.

Inflammation is involved in the pathogenesis of OA.[4,5] and is postulated to be involved in pain signaling and sensitization.[6,7,8,9] Clinical imaging measures of knee inflammation are associated with worse clinical outcomes in people with knee OA,[8,10,11,12,13,14]

including worse pain,[8,10,11] increased risk of radiographic disease progression,[12,13] and the risk of requiring a total knee arthroplasty (TKA).[14] Magnetic resonance imaging (MRI) is most commonly used for measuring OA-related inflammation; however, the rapidly increasing use of ultrasound (US), as a result of its feasibility and low cost relative to MRI, led to the development of knee OA US measures by the Outcome Measures in Rheumatology (OMERACT) US Working Group.[15] Multiple groups have since reported that knee inflammation (e.g., synovitis, effusion, hyperplasia, power Doppler [PD] signal) can be reliably measured using musculoskeletal US.[16,17,18] Also, these groups have demonstrated that US measures of inflammation are strongly correlated with MRI measures of effusion-synovitis (Spearman correlation 0.69)[17] and significantly associated with worse pain severity scores[16,17] in people with knee OA.

The reasons why certain pain experiences occur in some patients and not others are not well defined but could be related to inflammation. While we know from previous literature that there is a clear association between imaging measures of inflammation and pain overall, the association of inflammation with the risk or level of different pain experiences such as intermittent and constant pain has not been investigated. Further, given recent interest in defining earlier stages of OA to prevent disease progression (including in clinical trials[19]), it is important that any potential associations between inflammation and pain experiences be examined in the context of radiographic early- and late-stage knee OA. Understanding the clinical significance of US measures of inflammation through their relationship to different pain experiences may therefore enhance research and clinical assessment of patient status.

The main objectives of this study were as follows: (1) to investigate whether intermittent or constant pain experiences caused by knee OA are related to US measures of knee inflammation; and (2) to determine if this relationship changes in radiographically early- vs late-stage knee OA.

## METHODS

*Study population.* Participants were recruited as part of the ongoing Western Ontario Registry for Early Osteoarthritis (WOREO) Knee Study, a prospective, single-center, multiclinic (St. Joseph's Rheumatology Clinic, Fowler Kennedy Sports Medicine Clinic, and Rorabeck Bourne Joint Replacement Clinic) cohort with a 10-year follow-up designed to investigate clinical, biomechanical, and pathophysiological features of early and late stages of knee OA. All individuals referred to a rheumatologist or orthopedic surgeon for assessment of knee OA were invited to participate in initial screening. Eligibility criteria included patients over the age of 18 years with a diagnosis of knee OA based on clinical assessment by a rheumatologist or orthopedic surgeon, and frequent knee symptoms defined as pain, aching, or stiffness on most days for the last 4 weeks within the past year.[20] Exclusion criteria were any history of inflammatory arthritis (e.g., rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, enteropathic arthritis, vasculitis, systemic sclerosis, gout, calcium pyrophosphate arthropathy, and similar diagnoses), disease-modifying antirheumatic drug use, oral corticosteroid use, or any knee procedure or corticosteroid injection within 6 months prior to enrollment assessment. The first 248 subjects (496 knees) recruited consecutively, between September 2017 to December 2020, with complete demographic, radiographic, US, and pain data at enrollment visit were included in this study. Knees with previous TKA were excluded from the analyses (n = 43 out of 496; 8.7%), as TKA may affect the experience of pain.[21] Therefore, a total of 453 knees were included in the primary analysis. To detect a Cohen $f^2 \geq 0.02$ (small-to-moderate effect size) between synovitis and pain, with an $\alpha = 0.05$ and 80% power, we needed a sample of 395 knees (G*Power).[22] Participants provided written informed consent and the registry was approved by Western University's Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB #109255).

*Radiological assessment.* Standard fixed-flexion postero-anterior or antero-posterior full-limb standing hip to ankle radiographs were acquired at study enrollment and OA severity was assessed by Kellgren-Lawrence arthritis grading scale (KL).[23] Radiographs were read by 1 of 3 raters (a rheumatologist [CTA] and doctoral trainees [RP or HTP]). Trainee raters were trained by and calibrated to a rheumatologist (CTA) through formal instruction, followed by radiograph training and calibration image decks. Raters had substantial to excellent intrarater reliability ($\kappa = 0.69–0.95$) and substantial interrater reliability[24] ($\kappa = 0.75$) for KL grading.

*Musculoskeletal US.* Bilateral knee US scans were completed using a linear 3–12 MHz probe (GE LOGIQ, GE Healthcare) in accordance with OMERACT knee US protocol.[15] Each participant was supine with knees semiflexed to 30°. Longitudinal axis views were acquired in 3 standardized suprapatellar windows defined by the midline, lateral, and medial patellar poles. A standard imaging preset available from GE Healthcare was applied by a technician (probe frequency = 10 MHz; PD frequency = 6.3 MHz; pulse repetition frequency = 0.8; wall filter = 124). Machine variables such as depth, focal depth, and gain were adjusted as needed by the US operator. Optimal PD signal was acquired by increasing gain to obtain noise, then gradually decreasing gain until noise was absent. Synovitis severity was scored in each window from grade 0 to 3, and PD signal, hyperplasia, and effusion were each scored separately as absent/present (0/1) according to the OMERACT knee US protocol.[15] Peak synovitis grade was assigned as the most severe score (0–3) of the 3 windows and used for these analyses. A quantitative measure of effusion—maximal effusion depth in mm—was also acquired using calipers to measure the largest anterior-posterior diameter, perpendicular to the femur and superior to the patella, encompassing the boundaries between hypoechoic synovial lining on either side of anechoic, compressible fluid phases. Hypoechoic synovial lining tissue was excluded from caliper measurement. Representative US images can be seen in Supplementary Figure 1 (available with the online version of this article). US scans were completed by 1 of 3 operators certified in musculoskeletal US by the Canadian Rheumatology Ultrasound Society who had at least 1 year of musculoskeletal US experience. Raters had excellent intrarater reliability ($\kappa = 0.81–0.96$) and substantial to excellent interrater reliability[24] ($\kappa = 0.62–0.95$) for semiquantitative measures of synovitis, PD signal, hyperplasia, and effusion. Interrater reliability for the maximal effusion depth measure was moderate (intraclass correlation coefficient > 0.75).[25]

*Patient-reported measures of pain.* Participants completed the ICOAP questionnaire for each knee separately during baseline assessment, consisting of 2 domains: intermittent (6 items) and constant pain (5 items),[26] where higher scores (0–100) indicate more pain. The presence/absence of intermittent and/or constant pain was confirmed using specific questions, for example, "In the past week, did you have any intermittent (or constant) pain in your LEFT (or RIGHT) knee?" (yes/no). The ICOAP pain patterns, adapted from Carlesso et al,[3] were defined as follows: (1) no intermittent or constant pain; (2) intermittent pain only (any severity/frequency); (3) constant pain only (any severity); and (4) a combination of intermittent and constant pain (any severity/frequency). Participants also completed the KOOS questionnaire, and the KOOS pain subscale (9 items; 0–100) was used in this analysis. Lower scores on the KOOS indicate more severe pain symptoms. The ICOAP and KOOS questionnaires are valid and reliable for individuals with knee OA.[26,27,28]

*Covariates and potential confounders.* Variables included age, sex, BMI, and OA stage defined by KL grade (early KL ≤ 2; or late KL ≥ 3). Age, sex, and BMI are known risk factors for OA[29] and may affect the pain experience.[30]

Radiographic severity (KL grade) is associated with knee pain,[31] and ICOAP pain experiences are differentially associated with radiographic stages of OA.[3]

*Statistical analyses.* All analyses were cross-sectional. Moderate and severe US-synovitis categories were collapsed (none = 0; mild = 1; moderate–severe = 2/3) to maintain statistical power and improve homoscedasticity. For the primary analysis, we fitted a series of logistic regression models to evaluate the association of US measures of inflammation with having any intermittent pain (no/yes) or any constant pain (no/yes). Next, we fitted a series of multivariate linear regression models to evaluate the association with ICOAP intermittent and constant pain scores. All analyses were adjusted for age, sex, BMI, and KL grade. For categorical synovitis scores, synovitis grade 0 was the reference. A sensitivity analysis was performed by removing all index knees from individuals with previously excluded contralateral TKA knee (Supplementary Table 1, available with the online version of this article). We used multinomial logistic regression to evaluate the association of synovitis grade and effusion size with ICOAP pain patterns,[3] adjusting for age, sex, BMI, and radiographic stage. In secondary analyses, we separated the cohort into radiographically early- and late-stage disease and examined the association between US measures of inflammation and the risk of having intermittent (no/yes) or constant (no/yes) pain and the intermittent and constant pain scores, respectively, while adjusting for age, sex, and BMI only. To demonstrate construct validity and consistency with previous literature, we fitted multivariate linear regression to model the association of US measures of inflammation and KOOS pain score. The KOOS pain models were also run by separating the cohort into radiographically early- and late-stage disease.

To test model assumptions, we visually inspected residuals plots for linearity, kernel density plots for normality of residuals, and used White test for homoscedasticity. Variance inflation factor (VIF) was used to assess multicollinearity, and all variables had a VIF < 5. Data were linear with nonnormally distributed and heteroscedastic residuals. In all analyses, robust sandwich estimators were used to adjust for nonnormal and heteroscedastic residuals, and for the variance for clustering at the patient level to ensure appropriate Type 1 error rates. Bayesian Information Criterion (lowest value preferred) was used to assess model fit. All analyses were completed using Stata/SE 15.1 (StataCorp). For linear regression, we reported results as unstandardized ß coefficients with 95% CIs. For logistic regression, we reported ORs with 95% CIs. For multinomial logistic regression, we reported relative risks (RRs) with 95% CIs.

## RESULTS

There were 248 participants (453 knees) included. Baseline demographics and clinical characteristics for the total cohort and separated by radiographic stage are shown in Table 1.

*US measures of synovitis and effusion depth are associated with constant pain but not intermittent pain.* We first considered the absence or presence of intermittent or constant pain individually. While adjusting for age, sex, BMI, and radiographic stage, we found no evidence of an association between synovitis severity or maximal effusion depth and the odds of reporting intermittent pain (Table 2). However, every 1-mm increase in maximal effusion depth conferred 9% higher odds of having constant pain (OR 1.09, 95% CI 1.03–1.16), and moderate-to-severe synovitis conferred 69% higher odds of having constant pain, although the 95% CI included 1.0 (OR 1.69, 95% CI 0.97–2.93; Table 2). Using the intermittent and constant scores, we found that knees with moderate-to-severe synovitis on average report 8.05 (95% CI 0.67–15.43) points higher (worse pain) on the constant pain subscale than those with no synovitis (Table 2). Similarly, each 1-mm increase in maximal effusion depth was associated with a 1.34 (95% CI 0.47–2.21) point higher constant pain score (worse pain). In contrast, there was no evidence of an association between synovitis or effusion depth and intermittent pain score, with considerable imprecision around the estimates at each level of synovitis (Table 2). In a sensitivity analysis, removal of index knees from individuals with a previously excluded contralateral TKA knee did not change the associations (Supplementary Table 1; available with the online version of this article).

*Associations of synovitis and effusion depth with intermittent and constant pain in radiographically early- and late-stage knee OA.* Having detected associations between synovitis and effusion depth, and different experiences of pain in the overall cohort, we explored whether these associations differed between radiographic stages of knee OA (Table 3). While controlling for age, sex, and BMI, knees with radiographically early-stage OA (KL ≤ 2) and moderate-to-severe synovitis have 2.70 (95% CI 1.04–7.02) times the odds of having intermittent pain, and 3.28 (95% CI 1.43–7.52) times the odds of having constant pain. Similarly, every 1-mm increase in maximal effusion depth is associated with 19% (OR 1.19, 95% CI 1.08–1.32) higher odds of having constant pain.

Intermittent pain scores were 10.47 (95% CI 1.03–19.91) points higher, and constant pain scores were 12.62 (95% CI 3.02–22.23) points higher in knees with early-stage knee OA and moderate-to-severe synovitis (Table 4), compared to those with no synovitis (reference group). Similarly, for every 1-mm increase in maximal effusion depth, there is an increase of 2.04 (95% CI 0.89–3.20) points in constant pain score (Table 4), but no clear association with intermittent pain.

In the radiographically late-stage OA (KL ≥ 3) subgroup, there was insufficient evidence to suggest any associations between synovitis or maximal effusion depth and either intermittent or constant pain (Table 3 and Table 4).

*Other US measures of inflammation and intermittent and constant pain outcomes.* There was insufficient evidence to suggest any associations between PD signal, hyperplasia, and effusion (absent/present) and intermittent or constant pain in any of our analyses (Supplementary Tables 2–5, available with the online version of this article).

*US measures of inflammation and ICOAP-defined pain patterns.* The presence of synovitis conferred 4.73 times the RR of being classified in the constant pain pattern group relative to the no pain group (base outcome), while adjusting for age, sex, BMI, and OA stage (Table 5). Additionally, for every 1-mm increase in maximal effusion depth, there is a 1.16-times increase in the RR of being classified in the constant pain pattern group (Table 5). No clear association was detected for synovitis grade or effusion size and being classified in either the intermittent pain pattern, or the intermittent and constant pain pattern groups (Table 5).

*US measures of inflammation and knee pain severity measured by KOOS.* Moderate-to-severe synovitis was associated with lower KOOS pain scores indicating worse pain (β −10.54, 95% CI −15.70 to −5.38) compared to no synovitis, while controlling for age, sex, BMI, and radiographic stage

*Table 1.* Demographic, clinical, and imaging characteristics for the entire cohort and separated by radiographic stage.

| | Total Cohort, n = 248; n = 453 Knees | Early Stage (KL ≤ 2), n = 127; n = 214 Knees | Late Stage (KL ≥ 3), n = 157; n = 239 Knees |
|---|---|---|---|
| Age, yrs | 64.2 ± 9.5 (32–85) | 61.2 ± 10.3 (32–83) | 66.2 ± 8.1 (43–85) |
| Sex, n (%) | | | |
| Female | 149 (60.1) | 85 (66.9) | 88 (56.1) |
| Male | 99 (39.9) | 42 (33.1) | 69 (43.9) |
| BMI, kg/m$^2$ | 31.9 ± 7.0 (17.7–58.2) | 29.34 ± 6.4 (17.7–56.5) | 34.2 ± 7.0 (21.2–58.2) |
| KL grade | | | |
| Early (KL ≤ 2) | 214 (47.2) | 214 (100) | – |
| Late (KL ≥ 3) | 239 (52.8) | – | 239 (100) |
| KOOS pain subscale | 54.2 ± 18.2 (0–100) | 72.4 ± 21.9 (19–100) | 56.6 ± 20.9 (0–100) |
| Intermittent pain score | 41.0 ± 26.4 (0–100) | 29.0 ± 25.8 (0–88) | 36.0 ± 28.3 (0–100) |
| Constant pain score | 31.0 ± 31.9 (0–100) | 15.0 ± 25.8 (0–85) | 29.0 ± 32.2 (0–100) |
| US-synovitis grade | | | |
| None (grade 0) | 116 (25.6) | 68 (31.8) | 48 (20.1) |
| Mild (grade 1) | 190 (41.9) | 96 (44.9) | 94 (39.3) |
| Moderate (grade 2) | 120 (26.5) | 43 (20.1) | 77 (32.2) |
| Severe (grade 3) | 27 (6.0) | 7 (3.2) | 20 (8.4) |
| Maximal effusion depth, mm | 4.3 ± 3.4 (0–13.7) | 3.4 ± 3.1 (0–13.3) | 5.0 ± 3.5 (0–13.7) |
| Power Doppler | | | |
| Absent | 352 (77.7) | 173 (80.9) | 179 (74.9) |
| Present | 101 (22.3) | 41 (19.1) | 60 (25.1) |
| Hyperplasia | | | |
| Absent | 127 (28.0) | 78 (36.5) | 49 (20.5) |
| Present | 326 (72.0) | 136 (63.5) | 190 (79.5) |
| Effusion | | | |
| Absent | 118 (26.0) | 67 (31.3) | 51 (21.3) |
| Present | 335 (74.0) | 147 (68.7) | 188 (78.7) |
| ICOAP pain patterns | | | |
| No pain | 81 (17.9) | 54 (25.2) | 27 (11.3) |
| Intermittent pain only | 191 (42.2) | 99 (46.3) | 92 (38.5) |
| Constant pain only | 44 (9.7) | 6 (2.8) | 38 (15.9) |
| Both intermittent and constant pain | 137 (30.2) | 55 (25.7) | 82 (34.3) |

Values are mean ± SD (range) or n (%) of knees unless otherwise indicated. ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain; KL: Kellgren-Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score; US: ultrasound.

(Supplementary Table 6, available with the online version of this article). Similarly, for every 1-mm increase in maximal effusion depth, there was a decrease in KOOS pain score by 1.30 points (β −1.30, 95% CI −1.89 to −0.72; Supplementary Table 6). The presence of hyperplasia was also associated with worse pain measured by KOOS (β −6.07, 95% CI −10.65 to −1.49), whereas PD signal and effusion trended toward association with lower KOOS pain scores; however, the 95% CIs for these estimates included 0 (Supplementary Table 7). Additionally, synovitis or maximal effusion depth were not differentially associated with KOOS pain when separating the group by radiographically early- and late-stage disease (Supplementary Table 6).

## DISCUSSION

Pain experiences as a result of knee OA are diverse and not all types of pain can be explained by a single pathological feature. Although synovial inflammation is well recognized as an important feature generally associated with pain in knee OA, we investigated the relationship between synovial inflammation and intermittent and constant pain experiences in knee OA. We identified that US-detected synovitis and effusion size are differentially related to intermittent and constant pain constructs and disease stages, as summarized in Figure 1.

The semiquantitative synovitis and quantitative effusion depth measures were associated with the likelihood and level of constant pain, whereas dichotomous measures of effusion, hyperplasia, and PD signal were not. Since the OMERACT US-synovitis grade integrates the presence and size of both hyperplasia and effusion, this may better represent the complexity of synovial inflammation than segregated dichotomous scores. The lack of association with PD signal could be because the lack of statistical power or increased blood flow may have a different relationship to inflammation in OA than it does in other types of inflammatory arthritis.

Since pain experiences evolve during the course of knee OA, we performed secondary analyses by radiographic OA stage. Surprisingly, associations between synovitis and effusion size with both intermittent and constant pain were found in radiographically early-stage (KL ≤ 2), but not in late-stage disease (KL ≥ 3), therefore suggesting synovitis and effusion size may be

*Table 2.* Multivariate logistic and linear regression model estimates for intermittent and constant pain (n = 453 knees).

| | OR | Robust SE | 95% CI |
|---|---|---|---|
| Logistic model 1: intermittent pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.75 | 0.20 | 0.45–1.25 |
| Moderate/severe | 1.19 | 0.36 | 0.66–2.15 |
| Maximal effusion depth, mm | 1.00 | 0.03 | 0.94–1.06 |
| Logistic model 2: constant pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 1.07 | 0.27 | 0.65–1.76 |
| Moderate/severe | 1.69 | 0.48 | 0.97–2.93 |
| Maximal effusion depth, mm | **1.09** | **0.03** | **1.03–1.16** |
| | β | Robust SE | 95% CI |
| Linear model 1: intermittent pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | −2.75 | 3.15 | −8.94 to 3.44 |
| Moderate/severe | 5.57 | 3.54 | −1.38 to 12.52 |
| Maximal effusion depth, mm | 0.71 | 0.42 | −0.10 to 1.53 |
| Linear model 2: constant pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 2.77 | 3.32 | −3.76 to 9.30 |
| Moderate/severe | **8.05** | **3.76** | **0.67–15.43** |
| Maximal effusion depth, mm | **1.34** | **0.44** | **0.47–2.21** |

Adjusted for age, sex, BMI, and radiographic stage (early/late). Values in bold indicate significance at the 5% level. SE: standard error.

especially relevant to pain experiences in early radiographic knee OA. In later radiographic stages, it is likely that contributors to pain experiences increase in number and diversity. The association of constant pain with synovitis and effusion size in early radiographic knee OA is consistent with previous studies that have demonstrated an increased risk of radiographic progression in individuals with knee synovitis on MRI.[12,13] Moreover, it has been shown that constant pain is associated with an increased RR of worse outcomes in knee OA compared to intermittent pain,[32] and that individuals who had longer disease duration, had higher odds of having constant pain compared to intermittent pain.[3] Taken together, worse synovitis and greater effusion size in individuals who are experiencing constant pain may indicate that they are experiencing more severe disease activity, regardless of radiographic stage. Further, our data raises the possibility that moderate-to-severe synovitis underlies a transition to constant pain, especially in early-stage OA; this may be important for studies interested in modifying OA disease activity and/or risk of progression.

Our data also indicate that once late-stage radiographic disease is established, synovitis and effusion size may play a smaller role specifically for intermittent or constant pain experiences. Pain experiences in later stages of disease may be a result of multiple mechanisms, dysfunctional signaling,[31,32] or moderators such as depressive symptoms or pain catastrophizing.[33] Alternatively, the complexity of inflammation itself may evolve during later stages of disease in ways not captured by the US measures of inflammation used in this study. Therefore, incorporating additional measures of inflammation such as compositional imaging and/or histopathological tools may help elucidate this relationship further. The lack of association herein may also have occurred as a result of attention bias, where some patients may underreport less severe symptoms when severe symptoms are present, although Rasch analysis of the ICOAP did not uncover response dependency.[2] It is therefore likely that a more complex pain milieu exists in late-stage disease[34,35] and potentially confounds the detection of an association between some pain experiences and synovial inflammation because of factors not accounted for here (e.g., bone marrow lesions).

Inflammation is important in the pathogenesis of OA, including for pain processing and sensitization.[8,9] For example, MRI measures of synovitis and effusion are associated with quantitative measures of pain sensitization including decreased pressure pain threshold cross-sectionally, and increased risk of developing temporal summation, respectively.[8] Synovitis may lead to constant pain experiences by increasing nociceptive input, thereby contributing to sensitization of primary afferents within the knee joint and central nervous system,[9] whereas different

*Table 3.* Multivariate logistic regression model estimates for secondary analyses (early- and late-stage OA).

| | Early-stage OA (KL ≤ 2), n = 214 Knees | | |
|---|---|---|---|
| | OR | Robust SE | 95% CI |
| Model 1: intermittent pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.83 | 0.28 | 0.42–1.61 |
| Moderate/severe | **2.70** | **1.32** | **1.04–7.02** |
| Maximal effusion depth, mm | 1.06 | 0.05 | 0.96–1.17 |
| Model 2: constant pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 1.38 | 0.53 | 0.65–2.95 |
| Moderate/severe | **3.28** | **1.39** | **1.43–7.52** |
| Maximal effusion depth, mm | **1.19** | **0.06** | **1.08–1.32** |
| | Late-stage OA (KL ≥ 3), n = 239 Knees | | |
| | OR | Robust SE | 95% CI |
| Model 1: intermittent pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.53 | 0.23 | 0.23–1.25 |
| Moderate/severe | 0.51 | 0.23 | 0.21–1.24 |
| Maximal effusion depth, mm | 0.93 | 0.04 | 0.86–1.02 |
| Model 2: constant pain (no/yes) | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.81 | 0.30 | 0.39–1.67 |
| Moderate/severe | 1.02 | 0.40 | 0.48–2.18 |
| Maximal effusion depth, mm | 1.04 | 0.04 | 0.96–1.12 |

Adjusted for age, sex, and BMI. Values in bold indicate significance at the 5% level. KL: Kellgren-Lawrence; OA: osteoarthritis; SE: standard error.

mechanisms may be involved in the genesis of intermittent pain. Although we did not assess associations between US measures of synovitis or effusion size and central sensitization, it is likely the presence of knee synovitis on US is associated with similar risks of developing central sensitization as when measured by MRI.

We found US-synovitis, effusion depth, and presence of hyperplasia are associated with worse patient-reported pain (KOOS pain), confirming previous literature using both MRI-[8,10,11] and US-synovitis[16,17,36,37] measures. Unlike the intermittent and constant pain models, when the KOOS pain model was separated based on radiographic stage, there were no differential associations between synovitis and KOOS pain scores between those with early- vs late-stage knee OA. This further highlights the importance of using the ICOAP questionnaire to identify different pain experiences in people with early- vs late-stage knee OA, which the KOOS pain questionnaire may not appropriately identify.

Strengths of our study include a sample of patients with a wide range of synovitis, intermittent and constant pain scores, and radiographic severity, and deployment of a highly feasible point of care tool to measure knee inflammation on US. This was enabled by the WOREO Knee Study design as a prospective cohort with a focus on US measures of inflammation and includes patients with early-stage OA and frequent knee symptoms at baseline, regardless of radiographic damage. Consistent with other studies, our findings support the use of US in knee OA research[15,16,17,18] and confirm associations of US measures of synovitis and effusion size with KOOS pain.[16,17]

Limitations of our study include the cross-sectional design and lack of an external validation cohort. Although we demonstrated statistical significance, several of our model estimates show imprecision (wide CIs), even though our sample size requirement was exceeded for the primary analysis. We did not include psychosocial factors that may contribute to an individual's pain experience such as coping, catastrophizing, anxiety, and depression.[33]

In conclusion, simple 2-dimensional US measures of synovitis and effusion size are associated with knee-specific pain symptoms on the ICOAP and KOOS tools. Our study confirms previous work demonstrating an association between MRI and US measures of inflammation and pain outcomes and supports the use of US as a feasible bedside tool for assessing inflammation in people with knee OA. We have also identified a link between inflammation and intermittent and constant pain, including ICOAP-defined pain patterns, particularly in early-stage disease. These findings underscore the clinical significance of synovitis to

*Table 4.* Multivariate linear regression model estimates for secondary analyses (early- and late-stage OA).

| | Early-stage OA (KL ≤ 2), n = 214 Knees | | |
|---|---|---|---|
| | β | Robust SE | 95% CI |
| Model 1: intermittent pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | −3.07 | 4.09 | −11.13 to 5.00 |
| Moderate/severe | **10.47** | **4.79** | **1.03–19.91** |
| Maximal effusion depth, mm | 0.96 | 0.61 | −0.24 to 2.16 |
| Model 2: constant pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 3.85 | 3.90 | −3.83 to 11.54 |
| Moderate/severe | **12.62** | **4.87** | **3.02–22.23** |
| Maximal effusion depth, mm | **2.04** | **0.59** | **0.89–3.20** |
| | Late-stage OA (KL ≥ 3), n = 239 Knees | | |
| | β | Robust SE | 95% CI |
| Model 1: intermittent pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | −3.40 | 4.91 | −13.07 to 6.28 |
| Moderate/severe | 0.24 | 5.35 | −10.31 to 10.78 |
| Maximal effusion depth, mm | 0.34 | 0.57 | −0.79 to 1.46 |
| Model 2: constant pain subscale score | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 1.62 | 5.70 | −9.61 to 12.84 |
| Moderate/severe | 5.45 | 5.93 | −6.24 to 17.13 |
| Maximal effusion depth, mm | 1.00 | 0.65 | −0.27 to 2.28 |

Adjusted for age, sex, and BMI. Values in bold indicate significance at the 5% level. KL: Kellgren-Lawrence; OA: osteoarthritis; SE: standard error.

*Table 5.* Multinomial logistic regression model estimates for ICOAP-defined pain patterns (n = 453 knees).

| | RR | Robust SE | 95% CI |
|---|---|---|---|
| No pain | (base outcome) | | |
| Intermittent pain only | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.80 | 0.27 | 0.42–1.53 |
| Moderate/severe | 1.42 | 0.57 | 0.65–3.10 |
| Maximal effusion depth, mm | 1.00 | 0.04 | 0.92–1.09 |
| Constant pain only | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 2.44 | 1.42 | 0.78–7.64 |
| Moderate/severe | **4.73** | **3.09** | **1.31–17.00** |
| Maximal effusion depth, mm | **1.16** | **0.07** | **1.03–1.30** |
| Intermittent and constant pain | | | |
| Synovitis grade | | | |
| None | Ref. | Ref. | Ref. |
| Mild | 0.75 | 0.27 | 0.36–1.53 |
| Moderate/severe | 1.97 | 0.83 | 0.86–4.48 |
| Maximal effusion depth, mm | 1.07 | 0.05 | 0.98–1.17 |

Adjusted for age, sex, BMI, and radiographic stage (early/late). Values in bold indicate significance at the 5% level. ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain; RR: relative risk; SE: standard error.

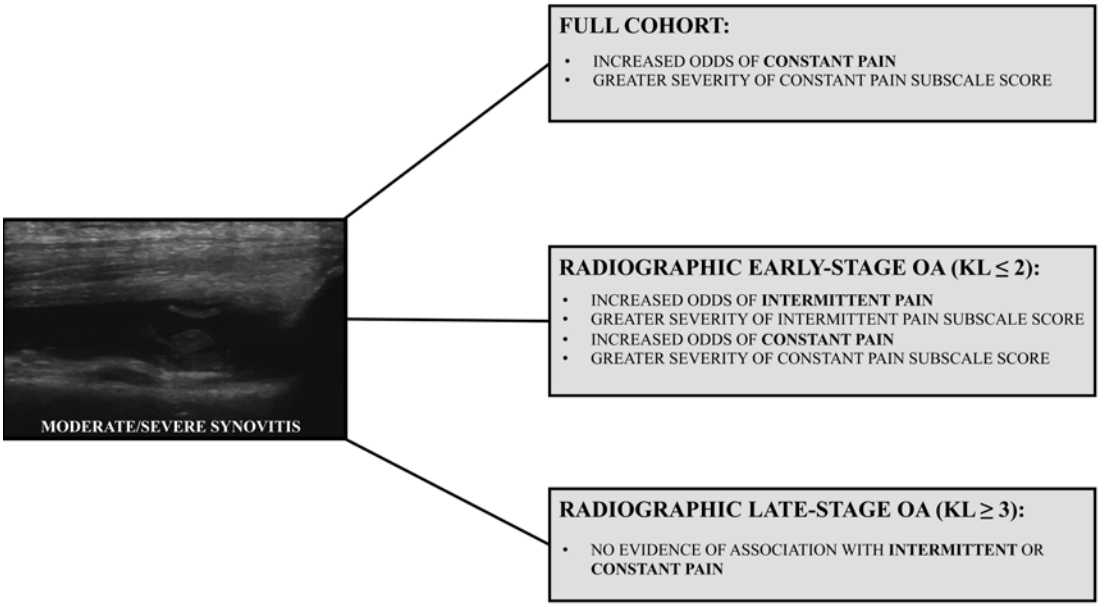


*Figure 1.* The association between US-synovitis and intermittent and constant pain experiences in knee OA. Summary of findings demonstrating inflammation may play context-specific roles in pain experiences, especially in earlier radiographic stages of knee OA. KL: Kellgren-Lawrence; OA: osteoarthritis; US: ultrasound.

different pain constructs in relation to OA disease activity, and the importance of evaluating radiographic stage-specific roles of inflammation related to the pain experiences in knee OA.


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## DATA AVAILABILITY

Data are available from the corresponding author upon reasonable request.

## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

## REFERENCES


1. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis -- an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415-22.
2. Moreton BJ, Wheeler M, Walsh DA, Lincoln NB. Rasch analysis of the intermittent and constant osteoarthritis pain (ICOAP) scale. Osteoarthritis Cartilage 2012;20:1109-15.
3. Carlesso LC, Hawker GA, Torner J, Lewis CE, Nevitt M, Neogi T, et al. Association of intermittent and constant knee pain patterns with knee pain severity, and with radiographic knee osteoarthritis duration and severity. Arthritis Care Res 2021;73:788-93.
4. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016;12:580-92.
5. Scanzello CR, Plaas A, Crow MK. Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? Curr Opin Rheumatol 2008;20:565-72.
6. Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996;384:360-4.
7. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765-9.
8. Neogi T, Guermazi A, Roemer F, Nevitt MC, Scholz J, Ardent-Nielsen L, et al. Association of joint inflammation with pain sensitization in knee osteoarthritis: the Multicenter Osteoarthritis Study. Arthritis Rheumatol 2016;68:654-61.
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.
10. Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007;66:1599-603.
11. Baker K, Grainger A, Niu J, Clancy M, Guermazi A, Crema M, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann Rheum Dis 2010;69:1779-83.
12. Felson DT, Niu J, Neogi T, Goggins J, Nevitt MC, Roemer F, et al. Synovitis and the risk of knee osteoarthritis: the MOST Study. Osteoarthritis Cartilage 2016;24:458-64.
13. 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.
14. Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Ann Rheum Dis 2010;69:644-7.
15. Bruyn GA, Naredo E, Damjanov N, Bachta A, Baudoin P, Hammer HB, et al. An OMERACT reliability exercise of inflammatory and structural abnormalities in patients with knee osteoarthritis using ultrasound assessment. Ann Rheum Dis 2016;75:842-6.
16. Yerich NV, Alvarez C, Schwartz TA, Savage-Guin S, Renner JB, Bakewell CJ, et al. A standardized, pragmatic approach to knee ultrasound for clinical research in osteoarthritis: the Johnston County Osteoarthritis Project. ACR Open Rheumatol 2020; 2:438-48.

17. Oo WM, Linklater JM, Bennell KL, Pryke D, Yu S, Fu K, et al. Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, and radiographic and magnetic resonance imaging findings? J Rheumatol 2021;48:270-8.
18. Oo WM, Linklater JM, Daniel M, Saarakkala S, Samuels J, Conaghan PG, et al. Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis. Osteoarthritis Cartilage 2018;26:601-11.
19. Luyten FP, Bierma-Zeinstra S, Dell'Accio F, Kraus VB, Nakata K, Sekiya I, et al. Toward classification criteria for early osteoarthritis of the knee. Semin Arthritis Rheum 2018;47:457-63.
20. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
21. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015;373:1597-606.
22. Cohen JE. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc; 1988.
23. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
24. Landis JR, Koch GG. Measurement of observer agreement for categorical variables. Biometrics 1977;33:159-74.
25. Portney LG, Watkins MP. Foundations of clinical research: applications to practice. New Jersey: Prentice Hall; 2000.
26. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:409-14.
27. Mehta SP, Sankar A, Venkataramanan V, Lohmander LS, Kats JN, Hawker GA, et al. Cross-cultural validation of the ICOAP and physical function short forms of the HOOS and KOOS in a multi-country study of patients with hip and knee osteoarthritis. Osteoarthritis Cartilage 2016;24:2077-81.
28. Ruyssen-Witrand A, Fernandez-Lopez CJ, Gossec L, Anract P, Courpied JP, Dougados M. Psychometric properties of the OARSI/OMERACT osteoarthritis pain and functional impairment scales: ICOAP, KOOS-PS and HOOS-PS. Clin Exp Rheumatol 2011;29:231-7.
29. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24-33.
30. Pereira D, Severo M, Ramos E, Branco J, Santos RA, Costa L, et al. Potential role of age, sex, body mass index and pain to identify patients with knee osteoarthritis. Int J Rheum Dis 2017;20:190-198.
31. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844.
32. Nevitt MC, Toistykh I, Song J, Neogi T. Risk of poor long-term outcomes of intermittent and constant knee pain: data from the osteoarthritis initiative [abstract]. Osteoarthritis Cartilage 2017;25:S182-3.
33. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthrits Cartilage 2013;21:1145-53.
34. Power JD, Perruccio AV, Gandhi R, Veillette C, Davey JR, Syed K, et al. Neuropathic pain in end-stage hip and knee osteoarthritis: differential associations with patient-reported pain at rest and pain on activity. Osteoarthrits Cartilage 2018;26:363-9.
35. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64:2907-16.
36. Hall M, Doherty S, Courtney P, Latief K, Zhang W, Doherty M. Synovial pathology detected on ultrasound correlates with the severity of radiographic knee osteoarthritis more than with symptoms. Osteoarthritis Cartilage 2014;22:1627-33.
37. Sarmanova A, Hall M, Fernandes GS, Bhattacharya A, Valdes AM, Walsh DA, et al. Association between ultrasound-detected synovitis and knee pain: a population-based case–control study with both cross-sectional and follow-up data. Arthritis Res Ther 2017;19:281.