Short running title: Synovitis and osteoarthritis pain experiences

Full title: Synovitis is associated with constant pain in knee osteoarthritis: a cross-sectional study of OMERACT knee ultrasound scores

Holly T. Philpott, MSc[1,2] (ORCID ID: 0000-0002-6146-0241)
Trevor B. Birmingham, PT, PhD[1,2] (ORCID ID: 0000-0002-3300-7677)
Ryan Pinto, MSc[1,2]
Codie A. Primeau, MSc[1,2] (ORCID ID: 0000-0002-2986-2216)
Dominique Arsenault, MSc[3]
Brent Lanting, MD, MSc[2,3,4] (ORCID ID: 0000-0001-8176-3824)
Yayuan Zhu, PhD[5] (ORCID ID: 0000-0003-1349-3038)
C. Thomas Appleton, MD, PhD[2,6] (ORCID ID: 0000-0001-7148-0767)

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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, University of Western Ontario, London, ON, Canada; [2]H.T. Philpott, MSc, T.B. Birmingham, PT, PhD, R. Pinto, MSc, C.A. Primeau, MSc, B. Lanting, MD, MSc, C.T. Appleton, MD, PhD, Bone and Joint Institute, University of Western Ontario, London, ON, Canada; [3]D. Arsenault, MSc, B. Lanting, MD, MSc, London Health Sciences Centre, University Hospital, London, ON, Canada; [4]B. Lanting, MD, MSc, Department of Surgery, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada; [5]Y. Zhu, PhD, Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada; [6]C.T. Appleton, MD, PhD, Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada, on behalf of the WOREO Knee Study group.

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Corresponding author:
Tom Appleton MD PhD FRCPC
SJHC Rheumatology Centre
268 Grosvenor St., London, ON, Canada, N6A 4V2
t. (519) 646-6319 (clinic office)
r. (519) 661-3768 (research office)
e. tom.appleton@sjhc.london.on.ca

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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- (KL ≤ 2) and late-stage (KL ≥ 3) disease and frequent symptoms underwent musculoskeletal US measures of inflammation using the OMERACT knee US scoring system. Pain experiences were captured using the Intermittent and Constant OA 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, body mass index (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, 8.80] 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 identified for synovitis in those with late radiographic OA.

Conclusions: 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.

INTRODUCTION

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 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Recently, using the Intermittent and Constant Osteoarthritis Pain (ICOAP) tool, it was shown that intermittent versus 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[6-9]. Clinical imaging measures of knee inflammation are associated with worse clinical outcomes in people with knee OA[8,10-14], 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, rapidly increasing use of ultrasound (US) due to its feasibility and low-cost relative to MRI, led to the development of knee osteoarthritis US measures by the OMERACT US Working Group[15]. Multiple groups have since reported that knee inflammation (*e.g.* synovitis, effusion, hyperplasia, Power Doppler) can be reliably measured using musculoskeletal ultrasound (US)[16-18]. 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 there is a clear association between imaging measures of inflammation and pain overall; whether inflammation is associated with the risk or level of different pain experiences, such as intermittent and constant pain, has not been investigated. Furthermore, given recent interest in defining earlier stages of OA to prevent disease progression (including in clinical trials[19]), it is important 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 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.

MATERIALS AND METHODS

Study Population

Participants were recruited as part of the ongoing Western Ontario Registry for Early Osteoarthritis (WOREO) Knee Study, a prospective, single-centre, multi-clinic (St. Joseph's Rheumatology clinic, Fowler Kennedy Sports Medicine Clinic, and Rorabeck Bourne Joint Replacement Clinic) cohort with 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 orthopaedic surgeon for assessment of knee OA were invited to participate in initial screening. Eligibility criteria included patients over the age of 18 with a diagnosis of knee OA based on clinical assessment by a rheumatologist or orthopaedic 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 anti-rheumatic drug (DMARD) 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- 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 impact the experience of pain[21]. Therefore, a total of 453 knees were included in the primary analysis. To detect a Cohen's f^2 of 0.02 or greater (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 (KL) grading[23]. Radiographs were read by 1 of 3 raters (a rheumatologist (TA) and

doctoral trainees (RP or HP)). Trainee raters were trained by and calibrated to rheumatologist (TA) via formal instruction, followed by radiograph training and calibration image decks. Raters had substantial-to-excellent intra-rater reliability (κ = 0.69 to 0.95) and substantial inter-rater reliability[24] (κ = 0.75) for KL grading.

Musculoskeletal ultrasound

Bilateral knee US scans were completed using a linear 3-12 MHz probe (GE LOGIQ, Boston, MA) in accordance with OMERACT knee US protocol[15]. Each participant was supine with knees semi-flexed to 30-degrees. Longitudinal axis views were acquired in three standardized suprapatellar windows defined by the midline, lateral, and medial patellar poles. A standard imaging pre-set available from GE Healthcare was applied by a technician (probe frequency = 10 MHz; Power Doppler frequency = 6.3 MHz; pulse repetition frequency = 0.8; wall filter = 124). Machine parameters such as depth, focal depth, and gain were adjusted as needed by US operator. Optimal power Doppler 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 0-3, and Power Doppler (PD), 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 three windows and used for these analyses. A quantitative measure of effusion, "maximal effusion depth in millimetres" (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. US scans were completed by 1 of 3 operators certified in musculoskeletal US by the Canadian Rheumatology Ultrasound Society with at least 1-year musculoskeletal US experience. Raters had excellent intra-rater reliability (κ = 0.81 to 0.96) and substantial to excellent inter-rater reliability[24] for (κ = 0.62 to 0.95) for semi-quantitative measures of synovitis, PD, hyperplasia, and effusion. Inter-rater reliability for the maximal effusion depth measure was moderate[25] (ICC > 0.75).

Patient-reported measures of pain

Participants completed the ICOAP questionnaire for each knee separately during baseline assessment, consisting of two 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]. (2020), were defined as: 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 Knee Injury and Osteoarthritis Outcome Score (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[26-28].

Covariates and potential confounders

Variables included age, sex, body mass index (BMI), and OA stage defined by Kellgren-Lawrence (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 homoskedasticity. 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). 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 (KL ≤ 2 early-stage; KL ≥ 3 late-stage) 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 (KL ≤ 2 = early-stage; KL ≥ 3 late-stage).

To test model assumptions, we visually inspected residuals plots for linearity, kernel density plots for normality of residuals, and used White's test for homoskedasticity. Variance inflation factor (VIF) was used to assess multicollinearity, and all variables had a VIF of <5. Data were linear with non-normally distributed and heteroskedastic residuals. In all analyses robust sandwich estimators were used to adjust for non-normal and heteroskedastic residuals, and for the variance for clustering at the patient level to ensure appropriate type 1 error rates. Bayesian Information Criterion (BIC: lowest value preferred) was used to assess model fit. All analyses were completed using Stata/SE 15.1 (StataCorp, College Station, Texas, USA). For linear regression, we reported results as unstandardized beta (ß) coefficients with 95% confidence intervals (CIs). For logistic regression, we reported odds ratios (OR) with 95% CIs. For multinomial logistic regression, we reported relative risk ratios (RRR) with 95% CIs.

RESULTS

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

Table 1 here.

Ultrasound 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, though 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).

Table 2 here.

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.

Table 3 here.

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 (Tables 3 & 4).

Table 4 here.

Other ultrasound 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).

Ultrasound measures of inflammation and ICOAP-defined pain patterns

The presence of synovitis conferred 4.73 times the relative risk 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 1.16 times the relative risk 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 + constant pain pattern groups (Table 5).

Table 5 here.

Ultrasound 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, -5.38]) compared to no synovitis, while controlling for age, sex, BMI, and radiographic stage (Supplementary Table 6). 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, -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, -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 due to 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, summarized in Figure 1.

Figure 1 here.

The semi-quantitative synovitis and quantitative effusion depth measures were associated with likelihood and level of constant pain, whereas dichotomous measures of effusion, hyperplasia, and power Doppler 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 power Doppler could be due to 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 especially germane 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 relative risk 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 be experiencing more severe disease activity, regardless of radiographic stage. Furthermore, our data raises the possibility that moderate-to-severe synovitis underlies a transition to constant pain, especially in early-stage OA, which 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 due to multiple mechanisms, dysfunctional signaling[31,32], or moderators such as depressive symptoms or pain catastrophizing[37]. 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 due to attention bias, where some patients may under-report 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[33,34] and potentially confounds the detection of an association between some pain experiences and synovial inflammation due to 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 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[16,17,35,36] 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 score between those with early- vs late-stage knee OA. This further highlights the importance of using the ICOAP questionnaire to capture

different pain experiences in people with early- vs late-stage knee OA, which the KOOS pain questionnaire may not appropriately capture.

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[15-18] 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[37].

In conclusion, simple 2D 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 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 manuscript.

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FIGURE LEGENDS

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.

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 (years), mean ± SD [range]	64.2 ± 9.5 [32 to 85]	61.2 ± 10.3 [32 to 83]	66.2 ± 8.1 [43 to 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), mean ± SD [range]	31.9 ± 7.0 [17.7 to 58.2]	29.34 ± 6.4 [17.7 to 56.5]	34.2 ± 7.0 [21.2 to 58.2]
KL grade, n knees (%)			
Early (KL ≤ 2)	214 (47.2%)	214 (100%)	----------
Late (KL ≥ 3)	239 (52.8%)	----------	239 (100%)
KOOS Pain Subscale, mean ± SD [range]	54.2 ± 18.2 [0 to 100]	72.4 ± 21.9 [19 to 100]	56.6 ± 20.9 [0 to 100]
Intermittent Pain Score, mean ± SD [range]	41.0 ± 26.4 [0 to 100]	29.0 ± 25.8 [0 to 88]	36.0 ± 28.3 [0 to 100]
Constant Pain Score, mean ± SD [range]	31.0 ± 31.9 [0 to 100]	15.0 ± 25.8 [0 to 85]	29.0 ± 32.2 [0 to 100]
US-Synovitis Grade, n knees (%)			
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), mean ± SD [range]	4.3 ± 3.4 [0 to 13.7]	3.4 ± 3.1 [0 to 13.3]	5.0 ± 3.5 [0 to 13.7]
Power Doppler, n knees (%)			
Absent	352 (77.7%)	173 (80.9%)	179 (74.9%)
Present	101 (22.3%)	41 (19.1%)	60 (25.1%)
Hyperplasia, n knees (%)			
Absent	127 (28.0%)	78 (36.5%)	49 (20.5%)
Present	326 (72.0%)	136 (63.5%)	190 (79.5%)
Effusion, knees (%)			
Absent	118 (26.0%)	67 (31.3%)	51 (21.3%)
Present	335 (74.0%)	147 (68.7%)	188 (78.7%)
ICOAP Pain Patterns, n knees (%)			
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%)

BMI, body mass index; CI, confidence interval; ICOAP, Intermittent and Constant Osteoarthritis Pain; KL, Kellgren-Lawrence; kg, kilogram; KOOS, Knee Injury and Osteoarthritis Outcomes Score; mm, millimetre; n, number; SD, standard deviation; US, ultrasound

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

Variable	Odds Ratios	Robust Standard Errors	95% CIs
Logistic Model 1: Intermittent pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.75	0.20	0.45 to 1.25
Moderate/Severe	1.19	0.36	0.66 to 2.15
Maximal Effusion Depth (mm)	1.00	0.03	0.94 to 1.06
Logistic Model 2: Constant pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	1.07	0.27	0.65 to 1.76
Moderate/Severe	1.69	0.48	0.97 to 2.93
Maximal effusion depth (mm)	**1.09***	**0.03**	**1.03 to 1.16**

Variable	β coefficient	Robust Standard Error	95% CIs
Linear Model 1: Intermittent pain subscale score			
Synovitis Grade			
None	Reference	Reference	Reference
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	Reference	Reference	Reference
Mild	2.77	3.32	-3.76 to 9.30
Moderate/Severe	**8.05***	**3.76**	**0.67 to 15.43**
Maximal effusion depth (mm)	**1.34***	**0.44**	**0.47 to 2.21**

Adjusting for age, sex, BMI, and radiographic stage (early/late)
*Indicates significance at the 5% level
CI, confidence interval; mm, millimetre; n, number

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

Early-stage OA (KL ≤ 2) (n=214 knees)

Variable	Odds Ratio	Robust Standard Error	95% CIs
Model 1: Intermittent pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.83	0.28	0.42 to 1.61
Moderate/Severe	**2.70***	**1.32**	**1.04 to 7.02**
Maximal effusion depth (mm)	1.06	0.05	0.96 to 1.17
Model 2: Constant pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	1.38	0.53	0.65 to 2.95
Moderate/Severe	**3.28***	**1.39**	**1.43 to 7.52**
Maximal effusion depth (mm)	**1.19***	**0.06**	**1.08 to 1.32**

Late-stage OA (KL ≥ 3) (n=239 knees)

Variable	Odds Ratio	Robust Standard Error	95% CIs
Model 1: Intermittent pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.53	0.23	0.23 to 1.25
Moderate/Severe	0.51	0.23	0.21 to 1.24
Maximal effusion depth (mm)	0.93	0.04	0.86 to 1.02
Model 2: Constant pain (No/Yes)			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.81	0.30	0.39 to 1.67
Moderate/Severe	1.02	0.40	0.48 to 2.18
Maximal effusion depth (mm)	1.04	0.04	0.96 to 1.12

Adjusting for age, sex, and BMI

*Indicates significance at the 5% level

CI, confidence interval; KL, Kellgren-Lawrence grade; mm, millimetre; n, number; OA, osteoarthritis

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

Early-stage OA (KL ≤ 2) (n=214 knees)			
Variable	**β coefficient**	**Robust Standard Error**	**95% CIs**
Model 1: Intermittent pain subscale score			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	-3.07	4.09	-11.13 to 5.00
Moderate/Severe	**10.47***	**4.79**	**1.03 to 19.91**
Maximal effusion depth (mm)	0.96	0.61	-0.24 to 2.16
Model 2: Constant pain subscale score			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	3.85	3.90	-3.83 to 11.54
Moderate/Severe	**12.62***	**4.87**	**3.02 to 22.23**
Maximal effusion depth (mm)	**2.04***	**0.59**	**0.89 to 3.20**

Late-stage OA (KL ≥ 3) (n=239 knees)			
Variable	**β coefficient**	**Robust Standard Error**	**95% CIs**
Model 1: Intermittent pain subscale score			
Synovitis Grade			
None	Reference	Reference	Reference
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	Reference	Reference	Reference
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

Adjusting for age, sex, and BMI

*Indicates significance at the 5% level

CI, confidence interval; KL, Kellgren-Lawrence grade; millimetre; n, number; OA, osteoarthritis

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

Variable	Relative Risk Ratio	Robust Standard Errors	95% CIs
No Pain	(base outcome)		
Intermittent Pain Only			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.80	0.27	0.42 to 1.53
Moderate/Severe	1.42	0.57	0.65 to 3.10
Maximal effusion depth (mm)	1.00	0.04	0.92 to 1.09
Constant Pain Only			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	2.44	1.42	0.78 to 7.64
Moderate/Severe	**4.73***	**3.09**	**1.31 to 17.00**
Maximal effusion depth (mm)	**1.16***	**0.07**	**1.03 to 1.30**
Intermittent + Constant Pain			
Synovitis Grade			
None	Reference	Reference	Reference
Mild	0.75	0.27	0.36 to 1.53
Moderate/Severe	1.97	0.83	0.86 to 4.48
Maximal effusion depth (mm)	1.07	0.05	0.98 to 1.17

Adjusting for age, sex, BMI, and radiographic stage (early/late)

*Indicates significance at the 5% level

CI, confidence intervals; ICOAP, Intermittent and Constant Osteoarthritis Pain; mm, millimetre; n, number

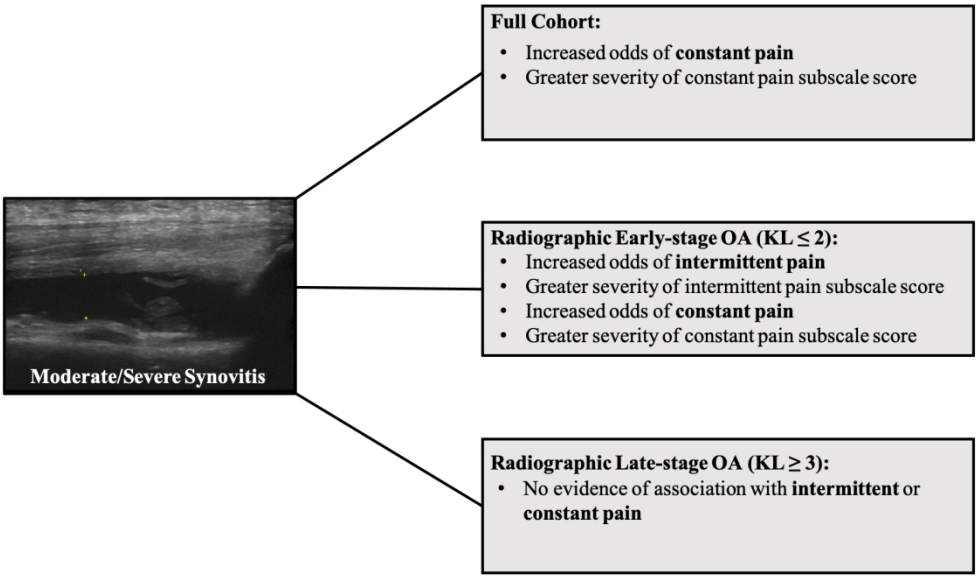

Figure 1. The association between US-synovitis and intermittent and constant pain experiences in knee OA. Summary of findings demonstrating inflammation may play context-specific roles in pain experiences, especially in earlier radiographic stages of knee OA.

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