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Post-surgical contributors to persistent knee pain following knee replacement: The Multicenter Osteoarthritis Study (MOST)

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ABSTRACT

Objective: Pain persistence following knee replacement (KR) occurs in ~20–30% of patients. Although several studies have identified preoperative risk factors for persistent post-KR pain, few have focused on post-KR contributing factors. We sought to determine whether altered nociceptive signaling and other peripheral nociceptive drivers present post-operatively contribute to post-KR pain.

Design: We included participants from the Multicenter Osteoarthritis Study who were evaluated ~12 months after KR. We evaluated the relation of measures of pain sensitivity [pressure pain threshold (PPT), temporal summation (TS), and conditioned pain modulation (CPM)] and the number of painful body sites to post-KR WOMAC knee pain, and of the number of painful sites to altered nociceptive signaling using linear or logistic regression models, as appropriate.

Results: 171 participants (mean age 69 years, 62% female) were included. TS was associated with worse WOMAC pain post-KR ($\beta = 0.77$ 95% CI:0.19–1.35) and reduced odds of achieving patient acceptable symptom state (aOR = 0.54 95%CI:0.34–0.88). Inefficient CPM was also associated with worse WOMAC pain post-KR ($\beta = 1.43$ 95% CI:0.15–2.71). In contrast, PPT was not associated with these outcomes. The number of painful body sites present post-KR was associated with TS ($\beta = 0.05$, 95% CI:0.01, 0.05).

Conclusions: Post-KR presence of central sensitization and inefficient descending pain modulation was associated with post-KR pain. We also noted that presence of other painful body sites contributes to altered nociceptive signaling, and this may thus also contribute to the experience of knee pain post-KR. Our findings provide novel insights into central pain mechanisms and other peripheral pain sources contributing to post-KR persistent knee pain.

1. Introduction

Knee osteoarthritis (OA) is the most common form of arthritis worldwide, affecting over 500 million people worldwide and 34 million people in the United States [1,2]. There are no treatments available that prevent its progression [3], and recommended pharmacological treatments (e.g., NSAIDs) and other treatments (e.g., exercise, weight loss) have either small-to-moderate effects or short-term effects [3]. As such, knee replacement (KR) is considered one of few therapies that can considerably improve pain and function in patients with severe, end-stage knee OA [4]. KR is among the most common orthopedic procedures in the US and continues to rise, with an estimated 3.5 million procedures expected per year by 2030 [5]. While a majority of patients experience marked improvement in pain after KR, approximately 20–30% of patients continue to experience knee pain post-KR [6,7]. Given the substantial number of KRs performed presently, the number of

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patients that continue to experience post-KR pain is substantial and will grow with the ongoing increase in procedures performed [5].

Why pain persists post-KR is not well-understood. Because the majority of patients do well when much of the pathologic tissue presumably contributing to symptoms related to OA is removed, pain persistence post-KR suggests that other factors are likely at play [6,8]. Increasing attention is being paid to alterations in nociceptive signaling for its possible role in pain persistence post-KR [8–13]. Altered nociceptive processing, such as hyperexcitability in ascending nociceptive signaling in the peripheral (i.e., peripheral sensitization) or central nervous system (i.e., central sensitization) or inefficient descending pain inhibition can negatively influence the pain experience [14,15]. These alterations can be assessed with quantitative sensory testing (QST). Studies to date regarding QST modalities and post-KR pain persistence have focused primarily on pre-operative QST measures predicting post-KR persistent knee pain [8–11,16–20]. For example, preoperative facilitated temporal summation (TS) [8,11] and lower pressure pain threshold (PPT) [9–11, 17], indicating greater sensitization, have been associated with risk of developing persistent post-KR pain.

However, few studies have focused on factors present post-operatively that may explain persistent knee pain. Kosek et al. demonstrated normalization of descending pain modulation assessed with conditioned pain modulation (CPM) on average 9 months after hip replacement, suggesting reversibility of neurobiological mechanisms with surgical removal of pathologic tissue [21]. Normalization of descending inhibitory modulation was also demonstrated to occur when assessed up to 7 months post-KR [22]. However, these were small samples in which all subjects had pain improvement (i.e., no pain or low pain) post-joint replacement. A few studies have investigated post-KR QST measures in study samples that included those with persistent knee pain post-KR with conflicting results [11,23,24]. Lower PPT values (i.e., greater pain sensitivity) in those with post-KR pain than those without pain have been reported in two studies [23,24], while another study did not find a difference between groups characterized by pain status [11]. Further, the studies that additionally investigated post-KR CPM report conflicting results: one study found that the post-KR none-to-mild pain had more efficient CPM than the moderate-to-high pain group [24], while another study found that the post-KR high pain group exhibited more efficient CPM than the post-KR low pain group [11], which is also contrary to what may be expected and what has been reported by Kosek [21] and Graven-Nielsen [22].

These prior studies have also not addressed why altered nociceptive signaling may be present despite removal of the pathologic tissue. A recent review regarding altered nociceptive signaling after healing of the original injury noted the absence of data regarding other potential peripheral pain generators as potentially contributing to persistence of central sensitization [25]. Multiple painful body sites are predictive of being a KR non-responder [26], and has been associated with altered nociceptive signaling in the central nervous system in patients with knee OA, but whether this holds true in the post-surgical setting when the predominant source of nociceptive input from the osteoarthritic joint has been removed is not known [27]. Thus, whether other painful body sites (i.e., unrelated to the joint that was replaced) may act as ongoing peripheral sources of nociceptive input contributing to pain persistence post-KR merits evaluation.

We therefore sought to determine whether post-KR abnormalities in nociceptive signaling (i.e., peripheral and central sensitization, inefficient descending pain inhibition) and presence of post-KR painful body sites contribute to pain 12 months after KR, a time when pain and function should have stabilized.

2. Methods

2.1. Study sample

The Multicenter Osteoarthritis (MOST) Study is a National Institutes of Health-funded longitudinal cohort study of 3026 older adults aged between 50 and 79 years with or at risk of knee OA in which the primary goal was to identify risk factors for incident and progressive knee OA. MOST study participants were recruited from Birmingham, Alabama, and Iowa City, Iowa, between 2003 and 2005. Details of the study cohort have been published previously [28,29]. For this cross-sectional study, we evaluated a subset of MOST participants who underwent KR and then were invited to return for a follow-up visit 12-months post-KR. Those who had bilateral primary KR surgeries, KR revision, rheumatoid arthritis, other inflammatory arthritis, or peripheral neuropathy were excluded from this study.

The study protocol was approved by the institutional review boards at the Boston University Medical Campus (data analysis center), University of Alabama at Birmingham, University of Iowa (both participant recruitment and data collection sites), and University of California at San Francisco (data coordinating center), and written informed consent was obtained from all participants.

2.2. Measures

All participants underwent pain assessments with self-reported pain questionnaires and QST evaluations that included PPT, TS, and CPM 12 months post-KR, as described below.

2.2.1. Exposures: quantitative sensory testing

2.2.1.1. Pressure pain threshold (PPT). PPT is a reliable measure of pain sensitization evoked by mechanical nociceptive stimulation using a pressure algometer [30,31]. We measured PPT at the patella of the replaced knee and the right distal radioulnar joint (the wrist) [30,31]. PPT at a diseased site (e.g., knee) is thought to reflect peripheral±central sensitization, while PPT at a distant non-diseased body site (e.g., wrist) is thought to reflect central sensitization [30,31]. PPT was assessed using a handheld pressure algometer (1 cm^2 rubber tip; Wagner FDIX25) applied at a constant rate of 0.5 kg/s on the anatomic site being tested. PPT was defined as the point at which the participant verbally indicated that the pressure first changed to slight pain. The PPT at each anatomic site was calculated by averaging 3 trials and was analyzed as a continuous exposure. Lower PPT indicates greater pain sensitivity.

2.2.1.2. Temporal summation (TS). TS, an augmented response to repetitive mechanical stimulation, is a sensitive and valid measure of amplified central pain processing, which is a feature of central sensitization, including in knee OA [30,31]. We assessed TS using a weighed 60 g von Frey monofilament (Aalborg University, Denmark) at the right distal radioulnar joint (the wrist) [30,31]. Subjects first provided a numerical pain rating (0–10 pain scale) for an initial trial of 4 stimulations. Subsequently, the weighted monofilament was applied repeatedly over the skin of the same site at a frequency of 1 Hz for 30 s. Subjects provided a pain rating at the completion of the train of 30 stimulations and 15 s post-stimulation ("after-sensations"). TS was considered as being present when the highest pain rating post-stimulation was higher than the initial pain rating [30,31]. The difference between the post-stimulation and the initial pain ratings was analyzed as a continuous exposure.

2.2.1.3. Conditioned pain modulation (CPM). CPM evaluates the adequacy of the descending pain modulation pathway, following the pain inhibits pain paradigm [21]. We used PPT as the test stimulus at the patella of the replaced knee (mean of 3 trials), before and after forearm ischemia pain as the conditioning stimulus. Specifically, we inflated a blood pressure cuff to 10 mm Hg above systolic on the upper arm contralateral to the replaced knee and had the participant perform hand exercises until pain in the forearm reached ≥4/10, or 2 min had passed. At that point, PPT was reassessed at the replaced knee's patella (mean of 3 trials) prior to deflating the cuff. CPM was computed as the ratio of the

post-conditioning stimulus PPT to the pre-conditioning stimulus PPT (i.e., PPT2/PPT1), and analyzed as a continuous exposure as previously recommended [32,33]. Additionally, we computed CPM as a binary measure, with PPT2/PPT1 ≤ 1 indicating inefficient CPM [34].

2.2.1.4. The number of painful body sites. We assessed the number of painful body sites using a standardized body homunculus [30]. The homunculus depicts 21 body sites in which the participant indicates whether they have had pain, aching, or stiffness on most days of the prior 30 days, and included joints and axial locations. Each hand and foot was counted as a single site if more than a joint in a given hand or foot was identified as being painful. The number of painful body sites was analyzed as a continuous exposure.

2.2.2. Outcome

The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (0–20 score) was used to assess knee-specific pain severity post-KR [35]. We also assessed the patient acceptable symptom state (PASS) defined as a WOMAC pain score $\leq$25/100 post-KR [36]. PASS is considered to be a threshold reflecting the level below which patients on average report that symptoms are acceptable in response to a treatment; this particular threshold is specific for KR.

3. Statistical analysis

To determine the relation of post-KR QST measures to post-KR knee pain, we separately evaluated the relation of post-KR PPT (continuous exposure), TS (continuous exposure), CPM (continuous and binary exposures), and the number of painful body sites (continuous exposure) to post-KR WOMAC pain and achievement of the PASS using linear (WOMAC pain) or logistic regression (PASS).

We analyzed the QST exposures in the direction that would indicate more pain sensitivity, and standardized each by their standard deviation (SD) units to allow for comparisons across the exposures. That is, we analyzed PPT and CPM per SD unit decrease while TS was analyzed per SD unit increase. Thus, for each of these analyses, beta estimates (from linear regression models) and the odds ratios (from logistic regression models) reflect the effect of each unit increase in the QST measure reflecting greater pain sensitivity.

Because WOMAC pain values post-KR can be skewed, we performed a sensitivity analysis using Tobit regression [37].

In addition, we explored the potential for other peripheral drivers as contributing to altered nociceptive signaling post-KR. Specifically, we examined the relation of the number of painful body sites post-KR to alterations in nociceptive signaling for post-KR QST measures that we found to be associated with post-KR pain.

All analyses were adjusted for potential confounders including age, sex, BMI, race, clinic site, depressive symptoms (defined as $\geq$16 on the Center for Epidemiologic Studies Depression Scale [38]), pain catastrophizing (defined based on a single item from the Coping Strategies Questionnaire [39]), and time of assessment relative to KR date. Statistical analysis was conducted using SAS version 9.4.

4. Results

One hundred seventy-one participants were included in this study. The mean age of participants was 69 years. The majority were female (62%) and obese (Table 1). Depressive symptoms and pain catastrophizing were present in 9% and 57% of participants, respectively, and the majority had total (vs. unicompartmental) KR (98%). The median WOMAC pain score was 1/20 at a median of 12 months post-KR. 144 (84%) participants achieved the PASS, meaning that 27 (16%) did not achieve satisfactory pain improvement following KR. Participants reported a mean of 4 painful body sites post-KR and common painful body sides other than the knee were lower back, shoulder, hip and hand.

Table 1
Participant characteristics.

Characteristics	N = 171
Age (years), mean (SD)	69.0 ± 7.8
Women, n (%)	106 (62)
White, n (%)	150 (88)
Body mass index (kg/m^2), mean (SD)	32.6 ± 6.9
Depressive symptoms, n (%)	15 [9]
Pain Catastrophizing, n (%)	91 (57)
Post-KR WOMAC pain (0–20), median (IQR)	1 (0–3)
% Post-KR WOMAC pain = 0, n (%)	67 [39]
Post-KR Patient Acceptable Symptom State, n (%)	144 (84)
Median time from KR to Post-KR visit, months (IQR)	12 [12–14]
Total knee replacement, n (%)	167 (97.7)
Post-KR number of painful body sites, mean (SD)	3.94 (3.65)
Post-KR distribution of other painful body sites, n	
Low back pain	101
Shoulder	82
Hip	70
Hand	61
Foot	48
Neck pain	47
Wrist	40
Ankle	38
Mid back pain	30
Elbow	19
Upper back pain	15
Buttocks	12

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. KR, knee replacement, IQR: interquartile range.

Post-KR mean (SD) patellar PPT and wrist PPT were 4.01 (1.95) kgf and 3.40 (1.54) kgf, respectively. For post-KR TS, the mean increase in pain (0–10 scale) with repeated stimulation was 0.67 (0.88). The mean CPM ratio was 1.17 (0.33) and 31% exhibited inefficient CPM.

4.1. Relation of post-KR QST measures and the number of painful sites to post-KR WOMAC pain

Post-KR TS was significantly associated with worse WOMAC knee pain scores post-KR (Fig. 1; numeric values are provided in supplementary table 1). Specifically, each standard deviation (SD) unit increase in TS pain rating was associated with a 0.77 higher (i.e., worse) WOMAC pain score (adjusted standardized β = 0.77 [95% CI: 0.19, 1.35]). However, post-KR PPT at the patella and the wrist were not associated with WOMAC pain post-KR (PPT patella: adjusted standardized β = 0.47 [95% CI: 0.20, 1.13]; PPT wrist: adjusted standardized β = 0.48 [95% CI: 0.24, 1.19]). While continuous CPM was not associated with post-KR WOMAC pain (adjusted standardized β = 0.34 [95% CI: 0.26, 0.94]), those with inefficient CPM had significantly worse post-KR WOMAC pain compared with those with efficient CPM (adjusted standardized β = 1.43 [95% CI:0.15, 2.71])

Each additional painful body site present post-KR was significantly associated with a 0.28 unit higher WOMAC pain score (adjusted standardized β = 0.28 [95% CI: 0.16, 0.41]).

Sensitivity analysis using Tobit regression to account for non-normally distributed outcome WOMAC data resulted in similar findings: PPT patella (adjusted standardized β = 0.66, 95% CI: 0.36, 1.67); PPT wrist (adjusted standardized β = 0.71, 95% CI: 0.37, 1.80); TS (adjusted standardized β = 1.01, 95% CI: 0.15, 1.87); continuous CPM (adjusted standardized β = 1.89 95% CI: 3.83, 0.04); inefficient CPM (adjusted standardized β = 1.80 95% CI: 0.16, 3.77); the number of panful sites (adjusted standardized β = 0.43 95% CI: 0.24, 0.62).

4.2. Relation of post-KR QST measures and the number of painful sites to PASS post-KR

Post-KR TS was significantly associated with 46% lower odds of achieving the PASS (aOR 0.54, 95% CI 0.34, 0.88) (Fig. 2). In contrast,

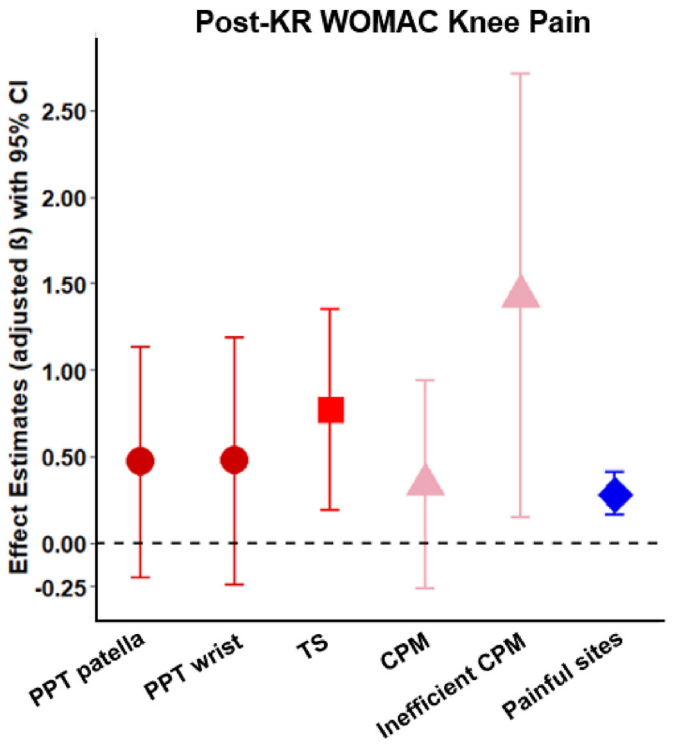

Fig. 1. Post-KR relations of altered nociceptive signaling and the number of painful sites to WOMAC pain.

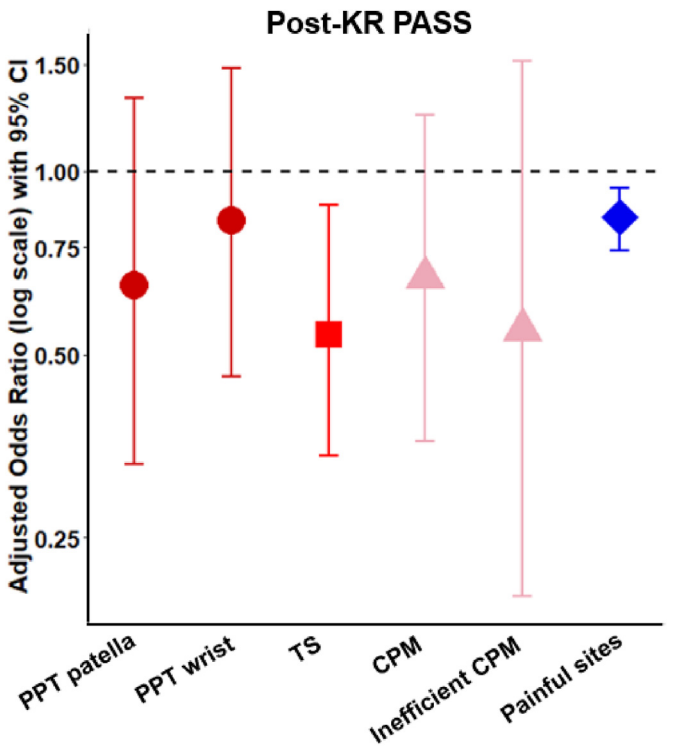

Fig. 2. Post-KR relations of altered nociceptive signaling and the number of painful sites to WOMAC pain.

PPT patella (aOR 0.65, 95% CI 0.33, 1.32), PPT wrist (aOR 0.83 95% CI 0.46, 1.48), and both continuous and binary CPM (aOR 0.67 95% CI 0.36, 1.24 and aOR 0.55, 95% CI 0.20, 1.52, respectively) were not statistically significantly associated with achieving the PASS post-KR.

Each additional painful body site present post-KR was significantly associated with 16% lower odds of achieving PASS (aOR 0.84 95% CI 0.74, 0.94).

4.3. Relation of number of painful body sites to post-KR TS and inefficient CPM

We also examined whether other potential peripheral drivers may account for altered nociceptive signaling post-KR, using number of painful body sites as an indicator of such a potential peripheral driver. Since TS and inefficient CPM were both associated with WOMAC pain severity post-KR, we examined the relation of the number of painful body sites to degree of post-KR TS and to presence of post-KR inefficient CPM. We found each additional painful body site present post-KR was significantly associated with a 0.05 higher pain rating (indicating greater TS facilitation) (adjusted standardized $\beta = 0.05$, 95% CI: 0.01, 0.05, $p = 0.022$), but not with presence of post-KR inefficient CPM (aOR = 1.01, 95% CI: 0.92, 1.13, $p = 0.856$).

5. Discussion

We evaluated whether altered nociceptive signaling present post-operatively was associated with persistent knee pain in a cohort that included participants both with and without pain improvement post-KR. We found that greater post-KR TS and inefficient CPM were associated with worse knee pain post-KR. Post-KR TS was also associated with lower likelihood of achieving the PASS 12 months after surgery. However, post-KR measures of PPT at the knee and wrist were not statistically significantly associated with post-KR pain. These findings raise the possibility that there may be different mechanisms that drive altered neural nociceptive processing contributing to persistent pain following KR. This may include the possibility that neuroplasticity, in both ascending and descending central nociceptive signaling, in some patients may still exist even after much of the pathologic tissue is removed. We also found that the number of painful body sites present 12 months post-KR was associated with worse knee pain, lower likelihood of achieving the PASS, and facilitated TS. This suggests that other peripheral drivers may also contribute to central alterations in nociceptive signaling post-KR and pain persistence post-KR.

Our findings of an association of post-KR facilitated TS with worse post-KR knee pain are in line with two prior studies that also observed greater facilitated TS 12 months post-KR in people with moderate-to-severe pain compared with mild pain [11,24]. The authors concluded that those with more intense pain 12 months post-KR "showed ongoing sensitization without a return of the pain processing to a normal state" [11]. In contrast, two prior small studies that demonstrated normalization of descending modulation through assessment of CPM after knee or hip replacement have been interpreted to demonstrate that inefficient CPM due to peripheral pathology can be reversed by removing the pathologic tissue [21,22]. Our study with a larger sample and variation in pain improvement post-KR demonstrated that inefficient CPM present post-KR was associated with worse pain post-KR. Our findings thus suggest that the reversibility of neurobiological abnormalities post-KR may not always occur, and this may be reflected by inefficient CPM or presence of TS. While peripheral sensitization and early stages of central sensitization are generally thought to be reversible once the active source of nociceptive input subsides [40], it may be that once central sensitization is established, the original peripheral nociceptive drivers are no longer needed to maintain this abnormal signaling in the central nervous system [15,40,41]. Moreover, recent neuroimaging data have shown that people with post-KR persistent pain presented with distinct alterations in neuronal activities in brain regions related to pain processing [42]. This finding supports the potential that pain can persist after pathological tissue has been removed due to central pain mechanisms. It is possible that the duration of knee pain and/or duration of altered nociceptive

signaling before KR may be a determining factor for the surgical outcome.

We were not, however, able to assess QST measures pre-operatively, and therefore cannot comment based on these data regarding the potential for ongoing central sensitization no longer being reversible versus these findings reflecting primarily other peripheral nociceptive drivers being present. We found that having multiple painful body sites was associated with worse post-KR knee pain. Number of painful body sites was also associated with a greater degree of facilitated TS, but not with inefficient CPM post-KR. This finding supports the possibility that multiple painful sites may play a role in persistence of the pain experience by maintaining central alterations in nociceptive signaling potentially through central sensitization (i.e., ascending facilitation), but not through descending modulatory pathways. Thus, addressing other pain contributors may be needed to optimize post-KR pain management. There is also a possibility that some remaining tissue in the knee joint, such as inflamed synovial tissue [24,43], may contribute to altered nociceptive signaling and/or persistent knee pain post-KR; we were unable to evaluate this possibility due to inability to perform MRIs post-KR in these participants.

In contrast to our TS findings, we noted that post-KR PPT at the wrist, another QST measure also thought to reflect central sensitization, was not associated with post-KR knee pain. Our findings for TS and PPT are consistent with a prior study [11] and raises the possibility that wrist PPT reflects different pain processing pathways than TS-assessed ascending pain facilitation/disinhibition. We also did not find an association between PPT at the replaced knee and post-KR pain, similar to the study by Petersen et al. [11], but in contrast to the study by Wright et al. [44]. Notwithstanding the discussion above about the possibility of remaining tissue in the knee joint, this finding suggests that peripheral mechanisms at the replaced knee may not be driving pain persistence post-KR, and perhaps that any potentially remaining tissues that were not entirely surgically removed may not be playing a major role as a driver of peripheral nociceptive input.

Our results also highlight a role for of the presence of post-KR inefficient CPM being associated with the persistent knee pain. The original concept of CPM, also known as diffuse noxious inhibitory controls, was to distinguish people with normal descending endogenous inhibitory control from those without, with the premise that pain sensitivity after application of a conditioning stimulus in those with normal (efficient) CPM will be reduced [34,45,46]. However, when assessing the degree of CPM efficiency, much of the range of values are within the realm of 'efficient' CPM; in our sample, 31% exhibited inefficient CPM. Whether the degree of the efficiency of CPM (i.e., analyzing CPM as a continuous measure), even in the 'efficient' range has a linear relationship with pain severity remains unknown; our findings may point to a non-linear relationship, with CPM in the inefficient range likely being more relevant.

Our results need to be considered in light of several limitations. Our effect estimates are small, suggesting central sensitization, inefficient CPM, and the number of painful body sites may not play a large role individually in post-KR knee pain. Given the multifactorial nature of pain, it is reasonable that these mechanisms may not have a large individual association [6,8]. Nonetheless, these findings provide insights into these mechanisms as at least contributing in part to pain persistence post-KR. We also cannot make definite inferences about the underlying etiology of the abnormalities identified by the QST measures and the number of painful body sites. Even so, the presence of central sensitization, inefficient CPM, or multiple joint pain, regardless of etiology, were associated with the post-KR pain experience. Another limitation, as for all observational studies, is that the potential for residual confounding remains despite controlling for relevant potential confounders.

In conclusion, post-KR presence of central sensitization, as reflected by TS, the presence of inefficient descending modulation, as reflected by inefficient CPM, and the number of painful body sites play a role in pain persistence post-KR. These results suggest the potential importance of identifying central pain mechanisms and other peripheral pain sources of nociceptive input postoperatively that may be contributing to post-KR pain persistence. Our study highlights the need for pain phenotyping to guide mechanism-based treatment approaches for managing post-KR persistent pain.

Author contributions

TN, LFL, LC, KA were involved in conception and design of the study. TN, CEL, MN, LFL were involved in acquisition of data. TN, KA, NW were involved in data analyses. All authors were fully involved in interpretation of the data. KA drafted the article. All authors were fully involved in critical revision of the article for important intellectual content and final approval of the article.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100335.

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