Predicting pain after standard pain therapy for knee osteoarthritis - the first steps towards personalized mechanistic-based pain medicine in osteoarthritis

Petersen, Kristian Kjær-Staal

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Topical Review

Kristian Kjær-Staal Petersen*

Predicting pain after standard pain therapy for knee osteoarthritis – the first steps towards personalized mechanistic-based pain medicine in osteoarthritis

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Abstract

Objectives: The prevalence of osteoarthritis (OA) is rising, and pain is the hallmark symptom of OA. Pain in OA is complicated and can be influenced by multiple joint-related factors and factors related to, e.g., physiological, epigenetic, and pain sensory profiles. Increasing evidence suggests that a subset of patients with OA are pain sensitive. This can be assessed using quantitative sensory testing (QST). Common treatments of OA are total knee arthroplasty (TKA) and administration of 3-weeks of non-steroidal anti-inflammatory drugs (NSAIDs), which provide pain relief to many patients with OA. However, approx. 20% of patients experience chronic postoperative pain after TKA, whereas NSAIDs provide an average pain relief of approx. 25%. The current topical review focuses on the emerging evidence linking pretreatment QST to the treatment response of TKA and NSAID treatments.

Content: MEDLINE was systematically searched for all studies from 2000 to 2022 on pretreatment QST, TKA, and NSAIDs. Pre-clinical studies, reviews, and meta-analyses were excluded.

Summary: Currently, 14 studies on TKA and four studies on NSAIDs have been published with the aim to attempt prediction of the treatment response. The QST methodologies in the studies are inconsistent, but 11/14 (79%) studies on TKA and 4/4 (100%) studies on NSAIDs report statistically significant associations between pretreatment QST and chronic postoperative pain after TKA or analgesic effect after NSAID treatment. The strength of the associations remains low-to-moderate. The most consistent pretreatment QST predictors are pressure pain thresholds, temporal summation of pain, and conditioned pain modulation.

Outlook: The use of QST as predictors of standard OA treatment is interesting, but the predictive strength remains low-to-moderate. A transition of QST from a research-based setting and into the clinic is not advised until the predictive strength has been improved and the methodology has been standardized.

Keywords: mechanistic pain profiling; NSAIDs; osteoarthritis; quantitative sensory testing; total knee arthroplasty.

Introduction

Osteoarthritis (OA) is characterized by cartilage degeneration and associated with decreased function, lowered quality of life, and pain. Studies have found that the assessment of cartilage degeneration does not explain the pain reported in OA [1–3], suggesting that other factors must be responsible for the pain in OA. Pain in OA is complex and it has been shown that cognitive factors [4], inflammation [5, 6], and pain sensitivity [7] are among the factors being associated with clinical pain in OA, see Figure 1.

The Osteoarthritis Research International (OARSI) organization provides clinical guidelines for the treatment of pain in OA. Some of the most utilized treatments are non-steroidal anti-inflammatory drugs (NSAIDs) plus paracetamol and total knee arthroplasty (TKA) [8, 9].

***Corresponding author: Associate Professor Kristian Kjær-Staal Petersen**, Dr.Med.Sci., PhD, MSc, Center for Neuroplasticity and Pain, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7 D3, DK-9220 Aalborg, Denmark; and Center for Mathematical Modelling of Knee Osteoarthritis, Department of Materials and Production, Aalborg University, Aalborg, Denmark, Phone: +45 9940 7529, Fax: +45 9815 4008, E-mail: KKP@hst.aau.dk

Standard pain treatment for osteoarthritis

Treatment of OA is focused on alleviating pain, improving joint function, and increasing quality of life. Based on this, the OARSI provides recommendations for the treatment of OA, which are divided into non-surgical [8] and surgical [9] therapies.

Pharmacological and non-pharmacological options are available [8, 10, 11]. Hence, the 2019 OARSI guidelines strongly endorse the use of topical NSAIDs and conditionally (with high consensus) recommend oral non-selective NSAIDs and COX-2 inhibitors [8]. The analgesic effect of NSAIDs has been widely documented [12, 13], but the underlying pain-relieving mechanisms remain largely unclear [14]. NSAIDs (and paracetamol) inhibit the synthesis of prostaglandins through modulation of cyclooxygenase (COX). Animal studies document that non-selective NSAIDs and paracetamol increase the activity of the cannabinoid system [15] and that the effect of NSAIDs and selective COX-2 inhibitors depends on an intact serotonin system [14]. Clinical studies suggest that COX-2 inhibitors can modulate widespread hyperalgesia [16–18], which further suggests that COX-2 inhibitors act on the central pain mechanisms. The long-term use of NSAIDs is harmful [17], and a study has found that 1 g of paracetamol and 400 mg of Ibuprofen three times daily (a total of 3 g of paracetamol and 1.2 g of ibuprofen daily) for a 3-week period provide analgesia with limited side-effects [19]. The analgesic effect of topical and oral NSAIDs is similar [20], and the average analgesic effect is approx. 20–35% [19].

Surgical treatment options for OA include arthroscopic surgery and total knee arthroplasty (TKA) [9], with TKA focusing on pain relief. TKA is considered the end-stage treatment of OA and is frequently performed [21]. After TKA, the majority of patients will improve in pain, function, and quality of life when comparing with non-surgical treatments [22]. However, it is evident that 10–20% of the patients experience chronic postoperative pain after TKA [23], which is a major issue since the number of TKAs is increasing world-wide [24–29].

It is evident that both NSAIDs and TKA provide pain relief to patients with OA. However, some patients might respond better than others to these treatments and identifying these patients prior to treatment is needed to advance the concept of "personalized pain medicine".

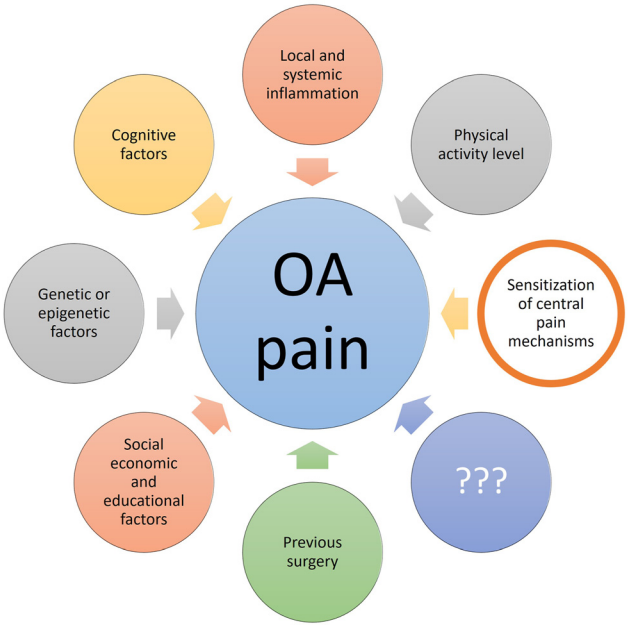

Figure 1: Factors associated with pain in osteoarthritis (OA). The current review focuses on the contribution of sensitization of central pain mechanisms, and it is important to mention that this is one of many factors associated with OA pain. The figure has been copied with permission from the doctoral thesis by Kristian K. Petersen, 2021, Aalborg University, Denmark (link: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://vbn.aau.dk/ws/portalfiles/portal/450213713/1061952_thesis_mechanistic_pain_profiling_of_patients_with_osteoarthritis_kkp.pdf).

Pain profiling of patients with osteoarthritis using quantitative sensory testing

"Personalized medicine" aims to provide the right treatment to the right patients, and this concept is being developed in, e.g., cancer medicine [30–33]. The concept may also be applied to pain medicine in future. Thus, the current research is focusing on (1) identifying the underlying mechanisms of pain, (2) identifying parameters which might predict treatment outcomes, and (3) developing new treatments or utilizing available treatments for new indications to target the underlying mechanisms of pain.

Quantitative sensory testing (QST) aims to assess nerve function, and QST assessments are often used to asses pain sensitivity in patients with OA [7]. Pressure pain thresholds (PPTs) assessed over the OA-affected joint mainly reflect localized pressure hyperalgesia, whereas PPTs assessed outside of the OA-affected joint indicate widespread pressure hyperalgesia [34, 35]. Both localized and widespread pressure hyperalgesia are found in patients with severe OA compared with pain-free individuals [36, 37], see Figure 2A. The wind-up process of dorsal horn neurons reflects the excitability of dorsal horn neurons [38], and temporal summation of pain (TSP), the human surrogate model for the wind-up process [34], is facilitated in patients with

severe OA compared with pain-free individuals [7], see Figure 2B. The descending pain inhibitory system originates from the brain stem and projects towards the dorsal horn. One human surrogate assessment for these systems is conditioned pain modulation (CPM) [39], which has been found impaired in patients with severe knee OA compared with healthy individuals [7], see Figure 2C. It seems evident that a certain subset of patients with OA are more pain sensitive than other patients [40, 41]. Studies suggest that sleep deprivation [42, 43], pain catastrophizing thoughts [44], and low-grade inflammation [45] could be factors that impact the degree of pain sensitivity.

Studies on patients undergoing abdominal [46] and thorax [47] surgery have indicated an association between preoperative pain sensitivity and chronic postoperative pain. Further, a recent systematic review found that this might apply to a range of surgical procedures [48]. Similarly, pretreatment QST has been associated with analgesic effects of opioid pain relief [49], duloxetine [50], or pregabalin [51]. The current topical review will present the current evidence for QST as a predictor of NSAID and TKA treatment of pain in OA.

Methods

This topical review is based on a systematic literature search, which was conducted in May 2022 in the MEDLINE database. Studies focusing on patients with knee OA, pre-treatment QST, and treatment responses to NSAIDs and TKA surgery were included. Reviews, meta-analyses, and preclinical studies were excluded.

Mechanistic pain profiling using quantitative sensory testing of patients with osteoarthritis

Currently, 14 studies on TKA [52–65] and four studies on NSAIDs [18, 66–68] have been published utilizing pre-treatment QST aiming to predict the treatment response.

The methodologies in the TKA and NSAID studies differ with, e.g., sample size ranging from n=14 [58] to n=288 patients [62], the number of QST modalities tested ranging from one [56, 60, 65] to six [63], and outcome measures ranging from the Western Ontario and McMaster

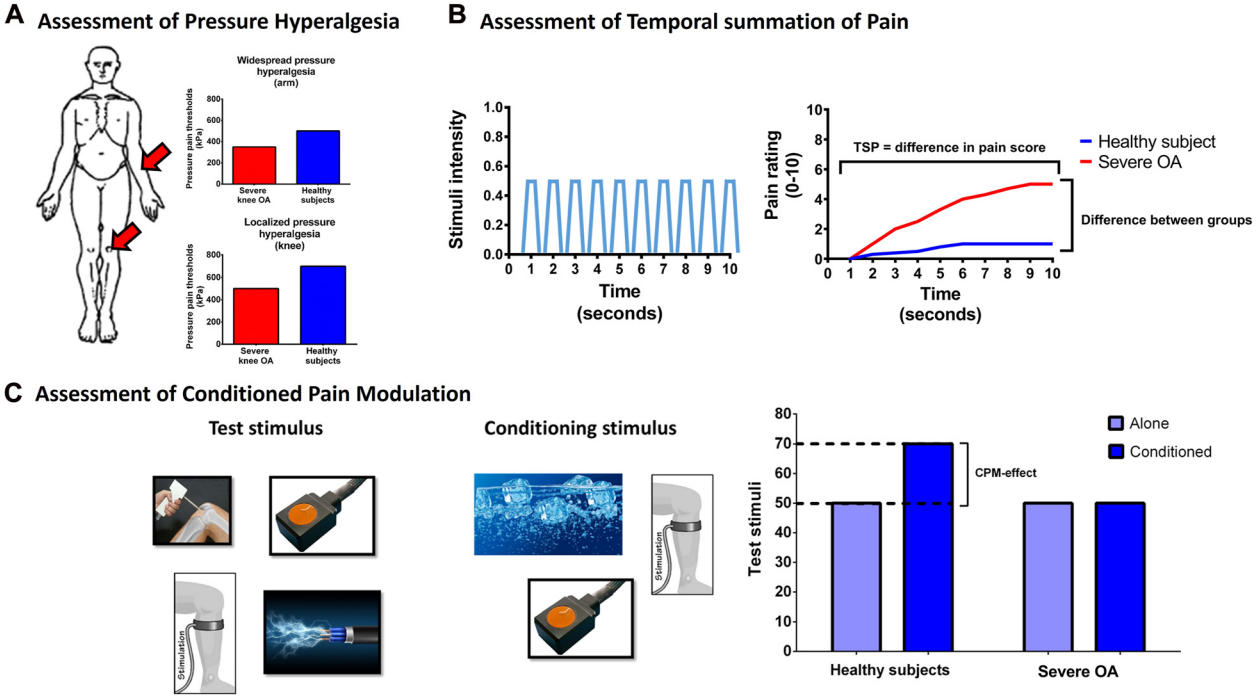

Figure 2: Illustrations of assessments and outcomes of (A) pressure hyperalgesia, (B) temporal summation of pain (TSP), and (C) conditioned pain modulation (CPM) of patients with severe knee osteoarthritis (OA) when compared with healthy pain-free individuals.
(A) Assessments of pressure pain thresholds (PPTs) at the knee (assessment of localized hyperalgesia) and at the arm (assessment of widespread hyperalgesia). (B) TSP relies on continuously fast stimuli with the same intensity and is calculated as the pain score to these painful stimuli over time. (C) Assessment of CPM requires a test stimulus and a conditioning stimulus, and multiple paradigms of test and conditioning stimuli have been utilized. In general, patients with severe OA demonstrate localized and widespread hyperalgesia, facilitated TSP and impaired CPM when compared with pain-free healthy individuals. The figure has been copied and modified with permission from the doctoral thesis by Kristian K. Petersen, 2021, Aalborg University, Denmark (link: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://vbn.aau.dk/ws/portalfiles/portal/450213713/1061952_thesis_mechanistic_pain_profiling_of_patients_with_osteoarthritis_kkp.pdf).

Universities Osteoarthritis Index (WOMAC) [53, 56, 59, 62], visual analogue scale (VAS) scores [18, 52, 55, 57, 60, 61, 63, 64, 66, 67], numerical rating scale (NRS) scores [54, 58, 65] to change in average daily pain intensity [68].

A total of eleven (out of fourteen) studies (79%) found associations between preoperative QST and chronic postoperative pain. Likewise, four (out of four) studies (100%) found associations between pretreatment QST and analgesic response to NSAIDs. A full overview of the studies can be found in the supplementary material (https://vbn.aau.dk/da/publications/mechanistic-pain-profiling-of-patients-with-osteoarthritis-curren).

Stimulation modalities for the prediction models

Multiple modalities were utilized to assess QST prior to TKA and NSAID therapies. The predictive strength of the models varied from low to moderate and the stimuli modalities might impact the predictive strength.

Preoperative assessment prior to total knee arthroplasty

A single study [52] utilized electrical stimuli and found lower electrical detection and pain thresholds to predict higher chronic postoperative pain after TKA (100%). Pressure stimuli were assessed in 10 studies [53–58, 60, 62–64], and lower pressure pain and tolerance thresholds were found to predict higher chronic postoperative pain after TKA in four studies (40%) [53, 57, 60, 63]. Thermal stimuli were assessed in three studies [53, 54, 61], and lower warm detection thresholds and lower heat pain thresholds were found predict higher chronic postoperative pain in one study (33%) [61]. TSP was assessed in six studies [55, 57, 59, 61–63], and facilitated TSP was found to predict higher chronic postoperative pain in four studies (67%) [55, 61–63]. CPM was assessed in eight studies [55, 57–59, 62–65], and impaired CPM was found to predict higher chronic postoperative pain in three studies (38%) [58, 64, 65]. Finally, one study [58] assessed exercise-induced hypoalgesia and found that lower exercise-induced hypoalgesia predicted higher chronic postoperative pain (100%).

Pre-treatment assessments prior to non-steroidal anti-inflammatory drugs treatments

Pressure stimuli were reported in three studies [18, 67, 68] and were found predictive for analgesic effect of NSAIDs in none of the studies (0%). TSP was reported in three studies [18, 67, 68], and facilitated TSP was found to be predictive of a poor analgesic effect of NSAIDs in two studies (67%) [18, 67]. CPM was reported in two studies [66, 68], and impaired CPM was found to be predictive of a poor analgesic effect of NSAIDs in both studies (100%). Offset analgesia was assessed in one study [66] and not found predictive of the analgesic effect of NSAIDs (0%).

Discussion

The current topical review highlights that the majority of studies demonstrate that pain sensitive patients with knee osteoarthritis are more likely to report chronic postoperative pain after total knee arthroplasty. Further, they also report a poor analgesic response to non-steroidal anti-inflammatory drugs. Pressure pain thresholds, temporal summation of pain, and conditioned pain modulation are the most frequently assessed modalities and are most often found as pre-treatment predictors. The strength of the associations between pretreatment pain sensory profiles and treatment responses to total knee arthroplasty and non-steroidal anti-inflammatory drugs is low-to-moderate.

Predicting treatment responses in patients with osteoarthritis

The current topical review focuses on the predictive value of QST for treatment responses to TKA and NSAIDs in patients with knee OA. The results highlight that the predictive value is low-to-moderate. It is well-known that factors such as psychological factors [44], inflammation [69], and sleep [42, 70] can influence QST parameters. Studies have found that high levels of preoperative pain catastrophizing [4], high levels of preoperative inflammation, dysregulated epigenetic profiles [5, 71, 72], and poor preoperative sleep quality [73] are directly or indirectly associated with chronic postoperative pain after TKA. Larsen et al. 2021 [64] found that the combination of preoperative CPM and pain catastrophizing predicted chronic postoperative pain after TKA better than each of the factors alone, suggesting that combining known pretreatment assessments is likely to improve future predictive models.

The current review focuses on TKA and NSAID treatment of pain in OA, but OARSI also recommends exercise-based therapy as a treatment of pain in OA [8]. Studies have found that long-term exercise programs provide approx. 25% pain relief in patients with OA [74, 75]. Four studies utilized QST to predict the pain relief following long-term exercise programs in OA with two studies finding associations [76, 77] and two studies finding no

associations [60, 78] between pre-treatment QST and pain-relief following exercise-based therapy. The studies which did find associations between pre-treatment QST and treatment response utilized assessments of central pain mechanisms (i.e., TSP, exercise-induced hypoalgesia, widespread pressure hyperalgesia) [76, 77], whereas the studies which did not find associations mainly used pressure pain thresholds [60, 78]. Future large-scale studies should be conducted utilizing assessments of central pain mechanisms to understand if QST can predict the response to exercise-based therapy.

Finally, the 2019 OARSI recommendations added duloxetine as a treatment option for patients with knee OA, depression, and/or widespread pain [8]. Studies have found that duloxetine provides an analgesic effect when compared with placebo [79, 80]. In a placebo-controlled trial, Petersen et al. 2022 [81] demonstrated that a combination of pre-treatment QST, psychological factors, and clinical pain could predict the analgesic effect of 14 weeks' treatment of duloxetine and that the strength was much stronger for the prediction of duloxetine than for the prediction of the placebo response.

Methodological considerations

QST as an assessment tool is associated with substantial inter-person variability and CPM has been discussed in recent years [82]. CPM can be assessed using a range of different tools in combination, and it is evident that combining these assessment tools will affect the reliability [83]. In 2015, Yarnitsky and colleagues [84] published the first CPM recommendations aiming to standardize the assessment of CPM, but it is still evident that CPM assessments are different across studies [82] which limits the generalizability of the results.

This topical review highlights associations between pre-treatment QST and treatment responses to TKA and NSAIDs but also highlights that there is inconsistency of QST assessments which are found as predictors. Pre-treatment PPTs were found as a predictor in 40% of TKA [53, 57, 60, 63] and 0% of NSAID studies, TSP was found as a predictor in 67% of TKA [55, 61–63] and 67% of NSAID studies [18, 67], and CPM was found as a predictor in 38% of TKA [58, 64, 65] and 100% of NSAID studies [66, 68]. Based on this, one could argue that TSP seems to be the most consistent predictor of OA treatment responses. However, large-scale studies specifically designed to investigate the predictive value of TSP are needed to confirm this hypothesis.

Targeting pain sensitivity

It is still widely unknown why some patients are more pain sensitive than others. It seems evident that some healthy individuals are more pain sensitive than others [85, 86]. A recent study on young pain-free individuals demonstrated that sleep deprivation could lead to an impairment of CPM and facilitation of TSP [87]. Sleep deprivation has also been linked to increased pain sensitivity in patients with OA [43], but studies aiming to improve sleep quality and the potential effect on QST is currently lacking.

Serotonin and noradrenaline are important neurotransmitters for the descending pain inhibitory systems [88, 89], and the balance of the descending pain inhibitory system is assessed by CPM in humans [39, 90, 91]. Duloxetine is an anti-depressant serotonin-noradrenalin re-uptake inhibitory and studies on patients with diabetic neuropathy [50] and migraine [92] suggest that duloxetine might provide an analgesic effect in pain sensitive patients. A recent small study on OA demonstrated that pain sensitive patients are more likely to gain an analgesic effect of duloxetine than non-pain sensitive patients, but the study also found many adverse events to the duloxetine treatment [81]. Pre- and postoperative administration of duloxetine to pain sensitive patients scheduled for TKA seems to decrease postoperative pain [93] although contradicting results exist [94]. These findings may suggest that duloxetine could potentially be a treatment option for pain sensitive OA patients and may be used as an add-on treatment prior to TKA. However, larger trials need to confirm this hypothesis. Additionally, studies should investigate if short-term administration of duloxetine is sufficient to provide analgesic effects in pain sensitive patients since a life-long administration of duloxetine is unwanted due to adverse events.

The N-methyl-D-aspartate (NMDA) receptors are involved in TSP [38], and a study on patients with fibromyalgia found that ketamine (an NMDA-antagonist) attenuates TSP when compared with placebo [95]. Other studies suggest that perioperative administration of ketamine reduces acute postoperative pain after TKA [96, 97]. However, a small study investigating the effect of 48-h postoperative infusion of ketamine or placebo did not find any differences in pain scores 12 months after TKA when comparing ketamine with placebo [98]. The direct use of ketamine in the treatment of OA pain and especially as an add-on treatment in relation to TKA is interesting but needs further investigations.

Conclusions

This topical review highlights that pretreatment assessments of quantitative sensory testing can be linked with treatment responses to total knee arthroplasty and NSAIDs in patients with osteoarthritis. The predictive value of quantitative sensory testing for treatment responses remains low-to-moderate. The use of quantitative sensory testing as a prognostic tool for patients with osteoarthritis is promising, but a transition from a research-based setting and into the clinic is not advised before the predictive strength has been improved and the methodology has been standardized.

Side note: This work is based on the doctoral thesis by Kristian K. Petersen to obtain the higher doctorate degree of Doctor Medicinae (D.M.Sc.). The thesis was defended on September 10th, 2021, at Aalborg University, Denmark. See supplementary material for the full thesis work.

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Author contributions: KKP conceptualized the idea, KKP conducted the review, and KKP wrote the first draft and KKP submitted the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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