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Original Article

Neuropathic Pain in Knee Osteoarthritis: A Narrative Review

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Abstract

Pain secondary to knee osteoarthritis (OA) is the most common cause of medical consultation in patients 55 years old and above. Knee OA pain is complex and involves both nociceptive and neuropathic pain. Recent management options have been focused on targeting the nerves of the knee, and to effectively investigate the mechanism and effect of these procedures, it is important to review the types of pain associated with knee OA, specifically neuropathic pain (NP). This article specifically focuses on the available evidence on NP, its prevalence in patients with knee osteoarthritis, outcome measures to determine the presence of NP, and their impact on the present and future management of knee OA pain. The information from this narrative review may potentially help clinicians identify the presence of NP in their patients and further guide them in providing a more appropriate and comprehensive management plan. The outcome measures presented in this review may also be used in future research exploring the management of knee OA pain.

***Key Words**: Knee Osteoarthritis, Neuropathic Pain, Pain Sensitization*

INTRODUCTION

Pain secondary to OA is among the most common reasons for medical consultation in patients 55 years and older. With a prevalence of 365 million, the knee is the most commonly affected joint, followed by the hip and the hand.[1] The current management of knee osteoarthritis includes pain relievers, exercise, lifestyle adaptation, and activity modification. When these options fail, surgical management, such as total knee arthroplasty, is considered.[5,6] However, due to the potentially harmful effects of long-term medication use, patients' fear of and high cost of surgery, as well as reports of persistence of pain, even after arthroplasty [7,8], minimally-invasive pain management options have emerged.

Initially, alternative procedures targeted the joint and consisted of intraarticular injection of steroids or hyaluronic acid. However, the limited and transient effects of these procedures enthused studies directed at targeting the nerves that supply the knee for pain relief.[9] In order to effectively investigate the mechanism and effect of procedures that target the nerves for pain relief, it is important to review the types of pain associated with knee OA, specifically NP.

This narrative review aims to summarize the available evidence on NP in knee osteoarthritis, its prevalence in patients with knee osteoarthritis, outcome measures to determine the presence of NP, and their impact on the management of knee OA pain.

English-language peer-reviewed journal articles that focused on NP in knee OA were searched from January 1, 2003, to August 13, 2023. The thirty articles used for this paper were identified via a search of PubMed and ScienceDirect using the keywords ["neuropathic pain" AND "knee osteoarthritis"]. Primary research, clinical trials, systematic reviews, meta-analyses, short reports, and literature reviews with available free full-text versions were included. Book chapters, encyclopedia entries, and grey literature were excluded. A literature review on the types of pain in knee OA was published in 2018.[10] Our review and the search strategy focused on papers exploring NP prevalence, outcome measures used for screening, and possible implications for knee OA management. Reference lists from identified articles were also searched for additional studies. All information in the selected articles relevant to this review was extracted and used for the review.

Types of Pain in Knee Osteoarthritis

Knee OA pain can be generally categorized as either nociceptive or neuropathic. Nociceptive pain occurs in response to injury and reflects the activation of nociceptors. These nociceptors are a subset of sensory neurons in the body that function as the primary unit of pain. When a noxious stimulus activates an ion channel on a nociceptor, depolarization of the nociceptors occurs. The receptor potential produced is then processed in the spinal cord, brainstem, and thalamocortical system, producing nociceptive pain. On the other hand, NP occurs in the presence of nerve injury or a lesion of the somatosensory system.[11–13]

The main pathology in knee OA is cartilage degradation. The type of pain in knee osteoarthritis has long been considered nociceptive pain related to structural changes in the subchondral bone and synovium.[14] Historically, knee OA was considered a non-inflammatory condition. However, the advent of more sensitive imaging modalities uncovered the role of synovitis and other inflammatory processes involved in OA. Synovitis triggers a cascade of events driven by inflammatory mediators, leading to enhanced cartilage turnover and matrix degradation. The inflammation enhances pain sensitivity, which may stimulate further inflammatory responses. Knee OA is now regarded as a disease of the whole joint where structures such as the synovial membrane, joint capsule, subchondral bone, periosteum, periarticular ligaments, menisci, and muscles are accepted as sources of nociceptive pain.[10,12,15–17]

Pain in knee OA was traditionally thought of as purely nociceptive, but recent studies have shown that a neuropathic component may also be present.[14–16,18–20] Since cartilage is an aneural and avascular tissue, the mechanism of pain is likely more complex than previously thought of and is affected by the pathology of other structures, such as the synovium, bone, and surrounding soft tissue. NP theoretically requires that pain is perceived in a neuroanatomically plausible distribution. In OA, the destruction of the subchondral bone leads to joint damage and alteration of the sensory nerves innervating the knee. Osteophytic changes alter the course of surrounding nerves and become points of friction and neuropathy. Soft tissue degeneration and alteration in biomechanics also result in decreased movement of nerves, and areas of tendinosis contribute to further sensitization.[21] Considering the joint destruction and sensory nerve alteration that occur in knee OA, joint pain becomes a neuroanatomically plausible sign that pain is neuropathic.[20]

Changes observed at more central levels also occur parallel to more peripheral events. Pain sensitization, a process of abnormal pain modulation due to hyperexcitability in the central nervous system, has also been

linked to OA pain.[14] Like other chronic conditions, central sensitization from chronic nociceptor stimulation and subsequent modification of central pain-transmitting neurons further contribute to knee OA pain.[22,23] Exaggerated responses to normal stimuli, together with the expansion of receptive field size, occur at the spinal level, resulting in tenderness and referred pain in areas away from the site of injury. The consequences of central sensitization remain unclear but may produce a state of hyperexcitability and other general phenomena observed in patients with chronic pain.[13]

Prevalence of Neuropathic Pain and Correlation to Other Factors

There is growing evidence suggesting the presence of a neuropathic component of knee OA. Several studies have reported the prevalence of neuropathic pain to be 5.4 – 66.7% in knee OA.[23–29] The prevalence of neuropathic-like pain and/or pain sensitization in knee OA was similar, regardless of whether the self-report questionnaire was used or the population examined.[14] A study on patients waiting for and after total knee replacement/total knee arthroplasty (TKA) also reported prevalence of possible and likely NP was 17.5% and 2.5% in the pre-TKA group compared to 3.4% and 0.4% in the outpatient group and 1.4% and 0.5% in the post-TKA group, respectively.[30]

A cross-sectional study that used the Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANSS) questionnaire and the Douleur Neuropathique 4 questionnaire (DN4) for screening showed that neuropathic pain was present in 38.6% of patients. The most frequently described NP characteristic was a sensation of electric shock (48.7%) based on DN4 and pins and needles tingling or pricking (35.7%) followed by burning pain (34.3%) according to the LANSS scale. On physical examination, 30% had touch hypoesthesis based on DN4, while 24.3 % had numbness or tenderness felt when pressing the painful area based on the LANSS scale.[29] This study also showed that according to the DN4 score, higher Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) pain, higher WOMAC physical function, and higher total WOMAC were significant risk factors for NP. According to LANSS, longer symptom duration and higher WOMAC stiffness were significant risk factors for NP.[29]

There is inconsistency regarding the correlation between NP scores and the Kellgren-Lawrence (KL) grade, with studies reporting that NP tended to be seen in KL grades of late stages of OA, while some state that there is no correlation.[23,26]

A study showed a significant positive correlation between the visual analog scale for pain and the painDETECT score but no statistically significant difference in gender, age, waist circumference, and body mass index among the different participant groups (NP likely, NP possible, and NP unlikely groups). However, the authors recommended further studies to explore the correlation more accurately due to the relatively small number of patients.[15]

Tests to Determine the Presence of Neuropathic Pain in Patients with Knee OA

The identification of NP is clinical, based on history, physical examination, and sometimes ancillary tests. History taking and physical examination are essential in determining the subjective and objective complaints of the patients. The use of validated screening tools and questionnaires is also helpful in distinguishing between nociceptive and neuropathic pain.[14,22] The following are the most commonly used tools to determine the presence of neuropathic

pain in patients with knee osteoarthritis:

Neuropathic Pain Descriptors. Central sensitization may present as several clinical features characteristic of NP conditions. Cumulative studies have reported that patients present with neuropathic-like pain associated with central sensitization and have described their pain using NP descriptors such as burning, numbness, pricking, itching, electric shock feeling, pins and needles, tingling, and sensitivity to heat, cold, touch, or pressure, even though no consistent somatosensory nervous system abnormality has been identified in OA.[10,15,16,20,22,23,29,31,32] History taking in patients with OA pain should take particular care in recognizing these pain descriptors to determine the presence of neuropathic or neuropathic-like pain.

Quantitative Sensory Testing (QST). The QST is a psychosocial test method used to investigate the functional state of the somatosensory system, and it utilizes a battery of tests using calibrated stimuli and subjective perception thresholds. The test requires trained investigators and precise oral instructions given to test subjects for each test to be performed.[33] The most common modalities used are pressure, thermal, or electrical stimulation, with pain threshold being the most common outcome measure. Several studies have used it to attempt to identify neuropathic pain in OA but with varying modalities and test protocols.[14,34–37] Due to the complexity of performing and interpreting QST, many studies use questionnaires that are simple to administer and interpret.

PainDETECT Questionnaire (PDQ). The painDETECT is a patient-based questionnaire that discriminates between nociceptive and neuropathic pain. It was originally developed for chronic low back pain, but its original and adapted forms (modified PainDETECT) are used for OA. The tool consists of questions about pain-affected sensory symptoms, including burning pain, paresthesia, mechanical allodynia, spontaneous pain attacks, thermal hyperalgesia, numbness, and pressure hyperalgesia. It also includes questions describing pain features, including frequency and radiation. Each type of pain is classified as none (0), hardly noticed (1), slightly (2), moderately (3), strongly (4), and very strongly (5). Scores range from 0 – 35, with ≥13 representing 'possible' neuropathic-like pain and > 18 representing 'probable' neuropathic-like pain. [14,15,30,38] The sensitivity of PDQ was reported at 85%, with a specificity of 80% and a probability of correct assignment at 83%.[38]

Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANSS) questionnaire. The LANSS scale is a 7-item tool with five self-report binary questions on symptom items and two self-examination clinical items. It comprises the following domains: tingling, change of skin color, sensitivity to touch, electric shocks, burning, self-examination to elicit pain, rubbing, or pressure. Subjects are categorized into two groups based on their summative score: pain is not predominantly neuropathic in origin (score <12), and pain is of a predominantly neuropathic origin (score ≥12).[14,39] The sensitivity of the LANSS ranged from 74-78%, with a specificity of 76-80%, depending on the cutoff score used.[40] A study confirmed the internal consistency (Cronbach α of 0.76 when unaided and α = 0.81 when completed at interview), convergent validity, and discriminant validity of LANSS. Compared with the gold standard (clinical examination), the LANSS correctly identified 73% and 75% of pain types when used unaided and between 79% and 80% when used in an interview format.[40]

Douleur Neuropathique 4 questions (DN4 questionnaire) The DN4 is a French screening questionnaire translated into 15

languages, developed to assess sensory descriptors and signs related to NP. It consists of 10 questions answerable by "yes" or "no." Seven self-report domains assess pain quality and include burning, painful cold sensations, electric shocks, tingling, pins and needles, numbness, and itching, while the other three relate to the bedside sensory examination to detect the presence or absence of sensory allodynia and touch needle hypoesthesia. A score ≥ 4/10 represents the presence of neuropathic pain.[29,41,42] The sensitivity and specificity of the DN4 were reported to be 75% and 76%, respectively.[43] The English version of the DN4 questionnaire had excellent sort- and long-term test-retest reliability with an almost perfect agreement for the 7-item DN4 total score between T0-T1 (baseline-immediately after) measurements (weighted *k*: 0.891, CI: 0.758-1.024) and T0-T2 (baseline-one week after) measurements (weighted *k*: 0.850, CI: 0.657 – 1.043).[44]

Implication to Knee OA Management and Research

Osteoarthritic pain is complex, consisting not only of nociceptive pain but also of NP. It is then reasonable to consider the addition of tests that determine the presence of NP during the assessment of patients with knee OA in addition to the traditional pain scoring tools such as the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS). This additional information will provide a more comprehensive profile of the patient's pain. Future research may also explore the correlation of NP with pain severity, risk factors, disease progression, and even response to management.

Due to the emerging evidence of nerve-related pain in knee OA, more studies are being done to explore management options that target knee innervation. The genicular nerves, particularly the superomedial, inferomedial, and superolateral genicular nerves, are targeted to manage pain secondary to knee OA.[45] These procedures include radiofrequency ablation (RFA), cryoablation, alcohol/chemodenervation, and genicular nerve block. Though systematic reviews and meta-analyses have initially shown the effectiveness of RFA, it is difficult to conclude its value due to the variability of protocols and parameters used.[2,4,46–48] There is also conflicting evidence regarding the effectiveness of other procedures that target the genicular nerves due to the paucity of clinical trials.[49,50]

The pain mechanisms of knee OA are heterogeneous, explaining the variability of response to different treatments. Knowing that knee OA pain involves nociceptive and neuropathic pain mechanisms, the addition of screening tools to detect the presence of NP can provide additional information that can be helpful in genuinely determining the effectiveness of procedures that target the nerves. Patients with neuropathic-like pain may respond differently to a certain management option compared to patients without this mechanism of pain.[14] Determining the pain phenotype in knee OA patients will help clinicians plan the best therapeutic strategy that is most appropriate and effective for their patients.[51]

This study presented the commonly used tests to differentiate neuropathic from non-neuropathic pain. Many of the available screening tools are composed of self-assessment questions. However, the only tools with objective significance are the LANSS and DN4 since they include self-assessment questions and sensory examination.[29] This may be worth noting when determining the most appropriate tool or outcome measure to use for future studies.

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CONCLUSION

The presence of NP has been demonstrated by different studies and populations of patients with knee OA. However, further studies should be done to determine the correlation of NP with pain severity, risk factors, disease progression, and response to management. Given that a subset of patients may have a neuropathic component to their pain, studies exploring the effectiveness of pain management options for knee OA patients should consider determining the presence of NP or neuropathic-like pain for a more complete and holistic interpretation of results. History taking should focus on identifying neuropathic pain descriptors, and examination should include screening tools such as the LANSS and DN4 questionnaires. Further research is likewise needed to support the findings of this review.

Individual author's contributions

All the authors were involved in the conceptualization, interpretation of data, drafting, reviewing, and final approval of the manuscript submitted to the journal.

Disclosure statement

This study is part of the principal author's dissertation as a scholar of the Department of Science and Technology – Philippine Council for Health Research and Development (PCHRD-DOST) under the program Ph. D. in Health Research of the University of Santo Tomas Hospital.

Conflicts of interest

MMBB and SM is a reviewer of PJAHS. CS is part of the editorial board of PJAHS.

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