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ORIGINAL RESEARCH

Prevalence and Association of Neuropathic Pain and Central Sensitization in Participants with Knee Osteoarthritis: Establishing a Cutoff Score for the Central Sensitization Inventory

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Objective: This study examined the prevalence of Neuropathic pain (NP) and its association with central sensitization (CS) among individuals with symptomatic knee osteoarthritis (OA).

Methods: A cross-sectional study was conducted in Saudi Arabia and included participants from community service centers and hospitals who aged ≥45 years and diagnosed with knee OA according to National Institute for Health and Care Excellence (NICE) criteria. Exclusion criteria included language barriers, inability to walk or stand independently, and pregnancy. NP was measured using the Arabic version of painDETECT questionnaire, and CS was measured using the central sensitization inventory (CSI). Multivariable logistic regression was performed to examine associations between CSI scores and NP, and Receiver Operator Characteristics analysis was used to determine an optimal cutoff score for CSI that was associated with NP.

Results: This study included a total of 155 participants with knee OA, 11% (n=17) were classified as having NP. After excluding 30 participants with unclear NP classification, 125 participants were included in the final analysis. Increased CSI scores was independently associated with increased odds of NP (OR = 1.10; 95% CI: 1.05–1.15) after adjusting for age, sex, body mass index, and employment status. A cutoff score of ≥26 for CSI was identified participants with NP, with 94% sensitivity and 63% specificity.

Conclusion: CS was associated with the presence of NP in individuals with knee OA. A cutoff score of ≥26 for CSI demonstrated a high sensitivity in predicting NP in people with knee OA, suggesting its utility as an effective screening tool for guiding an appropriate intervention and measuring response to treatment in this population.

Keywords: arthritis, neuropathy, widespread pain, prediction

Introduction

Knee osteoarthritis (OA) is the most common cause of chronic pain and joint-related diseases.[1] OA is currently estimated to affect approximately 37% of individuals aged 45 years and older, and the prevalence of this condition is expected to increase as the population of older adults continues to grow.[1,2] Globally, the prevalence of OA was 7.6% ranging from 6.8% to 8.4% in 2020,[3] with an increased prevalence of knee OA by 2.9 folds in the Middle East and North Africa regions.[4] In Saudi Arabia and Gulf Cooperation Council countries, a 2021 meta-analysis found that the estimated prevalence of OA was 16.3%.[5]

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In Saudi Arabia, OA has become a public health concern and estimated that the adult prevalence of knee-OA is in the range of 13% to 41%, which is approximately one-third of the whole population, and 60.6% in the age group of 66–75 years. This pattern has direct socioeconomic implications as the estimated direct medical costs and workforce productivity losses for OA of exceed $75.7 billion.[6]

The knees, hips, hands, and spine are the most common body regions affected by OA, which is characterized by cartilage loss, osteophyte formation, and synovial inflammation. One of the primary causes of disability and the main reason to seek medical treatment for individuals with knee OA is knee pain that is considered a common feature of OA.[7]

Pain is often categorized into two main phenotypes: nociceptive pain and neuropathic pain (NP) that may determine the treatment options.[8] Nociceptive pain, often described as sharp and dull aching pain, arises from the activation of pain receptors in response to inflammation in the synovium and subchondral bone.[9] In contrast, NP results from neural system lesions or malfunction that is usually described as burning, numbness, and/or tingling which can occur in chronic conditions like-knee OA.[9] According to recent studies, the prevalence of NP among people with knee OA ranged from 19% to 28.6%[10–13] and may be higher after other potential causes of NP are excluded.[14] Treatment options differ according to pain phenotype and severity including non-pharmacological interventions (eg, physical therapy) and pharmacological interventions (eg, medications).[8] Early identification and distinction between nociceptive and neuropathic pain is crucial in clinical decision making for patient management. A recent meta-analysis of 15 studies showed that the presence of neuropathic pain and central sensitization in candidates for total knee arthroplasty is a risk factor for postoperative chronic pain.[15]

Clinically, NP can present with burning-type continuous pain, electric shock sensation, and mechanical allodynia. In addition, NP is characterized by hyperalgesia, paresthesia, and dysesthesia.[16] People with NP conditions often score higher on the CS, especially if the pain is chronic and widespread.[17]

CS is a process where the central nervous system becomes hyperresponsive to sensory input, leading to an exaggerated pain response. This amplification can significantly affect how pain is perceived in various conditions, including NP. Neurophysiological studies demonstrated that wide dynamic range neurons in the dorsal horn exhibit prolonged neuronal discharges, increased responses to non-noxious and noxious stimuli, from the joint and expansion of the receptive field. Repeated excessive nociceptive stimulation of dorsal horn neurons will lead to a state of increased excitability called windup.[18]

CS and NP have been studied recently, and they were the focus of research for participants with knee OA.[19] Thus, the identification of individuals with CS may help in explaining the weak response to treatment in people with knee OA. Previous research found that individuals with CS, as identified using the Central Sensitization Inventory (CSI), were more likely to experience adverse outcomes after knee arthroplasty.[20,21]

The CSI is an effective screening tool for identifying people with CS whose pain may be exacerbated by a higher sensitivity. Although CS and NP have some links including the involvement of the nervous system with chronic pain, limited research has examined their association in people with knee OA.[21–24] The previous studies did not determine the cutoff score of the CSI that was associated with NP. Therefore, establishing a CSI cutoff score for predicting NP will facilitates early recognition of the pain phenotypes associated with CS and thereby enable the design of a tailored treatment plan.

Understanding the association between NP and CS in individuals with knee OA is critical to establish interdisciplinary approaches for knee OA management. The usability of self-reported CSI as a screening tool for detecting NP in individuals with knee OA will help in determining the appropriate interventions and measuring response to treatment. Therefore, the primary aim of this study was to examine the prevalence of NP and its association with CS among individuals with knee OA. The Secondary aim was to establish a cutoff score for CS using CSI that predicted NP using PainDETECT in this population. We hypothesized that individuals with knee OA would exhibit a high prevalence of NP and CS would be associated with NP.

Methods

Study Design and Setting

This study was a cross-sectional observational study including participants with knee OA. A convenient sampling method used to recruit participants. Adults' community-dwellers were recruited to participate in the study according to

the inclusion/exclusion criteria. The data collection was conducted in-person by seven independent trained physiotherapy researchers (between January and April 2025) Many recruitment locations were used including community service centers, hospitals, outpatient rehabilitation clinics, and orthopedic and rheumatology departments from different regions in Saudi Arabia, including Riyadh-King Salman Social Center, Alkharj-Prince Sattam bin Abdulaziz University Hospital, Aseer-Aseer Central Hospital, and Makkah Region. We used Flyers, physician referrals, and community postings to promote recruitment. Data were collected using a standardized form designed by the research team for the purpose of the study. The form contained questions related to demographics including age, gender, and body mass index (BMI), employment and PainDetect questionnaire.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee at Prince Sattam bin Abdulaziz University (Approval No.: RHPT/024/015). All participants signed an informed consent before the enrollment in this study.

Participants

Participants were screened to meet the following inclusion criteria: Diagnosed with knee OA based on the National Institute for Health and Care Excellence (NICE) criteria (Skou et al, 2020), including age of 45 years or older, presence of activity-related joint pain, and either no morning knee stiffness or stiffness of 30 min or less. Additional eligibility criteria included the ability to stand and ambulate independently to complete functional tests and fluency in spoken and written Arabic to complete self-reported questionnaires.

Participants were excluded if they were younger than 45 or had a history of total or partial knee arthroplasty. Pregnant due to hormonal influences on pain perception and physiological changes or diagnosed with other neurological disorders affecting pain perception (eg, multiple sclerosis) were excluded.

Sample Size and Sampling Strategy

The sample size was calculated based on previous studies for the prevalence of NP using PainDetect in people with knee OA with estimated prevalence of 11% (Polat et al, 2017). Therefore, the sample size was calculated based on this formula $[n = Z^2 P(1\text{-}P)/d^2]$, where n = sample size, Z = *Z* score statistic for a level of confidence (1.96), P= the prevalence of NP (11%), and d= the degree of precision (0.05). Therefore, the sample size was estimated to be 150. However, the recruited sample was 155 participants for the current study to overcome the possibility of missing some key variables.

Assessment of Neuropathic Pain

NP was assessed using a validated Arabic version of the painDETECT questionnaire.[16] This questionnaire is a 9-items, self-administered screening tool that evaluates seven dimensions of pain quality, as well as the time course and radiation of pain. The total score ranges from −1 to 38, where a score less than 12 suggests nociceptive pain, scores between 13 and 18 suggest possible NP, and scores of ≥19 indicate a greater than 90% likelihood of NP.[25] The Arabic version used in this study demonstrated high validity, sensitivity, and specificity in distinguishing NP from non-NP cases.[16,19]

Assessment of Central Sensitization

CS was evaluated using the Arabic version of the CSI, a validated, self-reported questionnaire.[26,27] The CSI consists of two parts. Part A includes 25 items assessing CS-related symptoms, each scored on a 5-point Likert scale from 0 to 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = always), with total scores ranging from 0 to 100. Higher scores indicate greater severity of CS symptoms, and a total score of 40 or above suggests the presence of CS.[28] The severity is categorized as subclinical (0–29), mild (30–39), moderate (40–49), severe (50–59), or extreme (60–100).[24] Part B includes 10 binary (yes/no) questions regarding comorbid conditions commonly associated with CS (eg, fibromyalgia, chronic fatigue syndrome),; however, responses in Part B do not contribute to the total CSI score.[29]

Covariates

Demographic variables were collected and included as covariates in the analysis. These included age (years), sex (male or female), employment status (employed or unemployed), and body mass index (BMI). BMI was calculated following

the measurement of weight and height using a calibrated height and weight scale. BMI was computed as weight in kilograms divided by the square of height in meters (kg/m^2) and analyzed as a continuous variable.

Statistical Analysis

NP was considered as a binary dichotomous variable using PainDetect score ≥19 and non-NP for those with PainDetect score ≤12. Participants with unclear NP status with scores between 13 to 18 were excluded from the main analysis (n=30). Categorical variables were expressed as counts and percent while continuous variables were expressed as mean and standard deviation (SD). Comparisons between NP and non-NP were conducted using independent *t*-test for continuous variables and Chi-Square for categorical variables.

To investigate the association between CSI scores and NP status, multivariable binary logistic regression was conducted along with odds ratio (OR) and 95% Confidence Interval (CI). The model was controlled for age, sex, BMI, and employment status.

To determine the optimal cutoff score for CSI that was associated with NP status, receiver operator characteristics (ROC) curve and Area Under the Curve (AUC) were used to show the overall accuracy of the model in distinguishing participants with NP and those without NP. The cutoff score for the CSI was identified using the largest Youden index (sensitivity + [1 – specificity]). In addition, sensitivity and specificity were calculated to indicate true positive and true negative results, respectively. Positive and negative likelihood ratios were calculated to express the numeric value of positive classification if the NP is present and to express the numeric value of negative classification if NP is present, respectively. An alpha level of 0.05 was used and all analyses were conducted using IBM SPSS for Mac version 25.0 (SPSS Inc. Chicago, IL, USA) and STATA for Mac version 14.1 (Stata Corp, College Station, TX).

Results

This study included a total of 155 participants with knee OA. The prevalence of NP based on PainDetect scores score ≥ 19 was 11% (n= 17), and the prevalence of unclear NP with scores between 13 to 18 was 19.4% (n= 30). For further analysis, participants with unclear NP were excluded. Table 1 shows the demographics and clinical variables for all sample and after exclusion of unclear NP (n=30). Therefore, the final sample was 125 participants with NP and without NP. There was no significant difference in demographics between participants with NP when compared to participants without NP as shown in Table 1 using independent *t*-test and Chi Square for continuous and categorical variables, respectively. Only CSI was significantly higher in participants with NP compared to those without NP.

The results for the multivariable binary logistic regression examining the association between CSI was shown in Table 2. The results showed that an increase in CSI scores was significantly associated with increased odds of having NP ((Odds Ratio) (OR): 1.10, 95% Confidence Interval (95% CI): 1.05, 1.15, p<0.001) after controlling for age, sex, BMI, and employment status. Other risk factors and demographics were not associated with NP.

Table 1 Participants' Demographics and Clinical Characteristics

Factors	Total Sample n=155	NP* n=17	Non-NP* n=108	*p**
Age, years (mean±SD)	56.04±8	55.06±7	56.23±8	0.60
Sex, females, (% within NP)	141 (91.0)	16 (94.1)	1 (5.9)	0.51
BMI, Kg/m^2 (mean±SD)	32.28±6	33.07±7	31.9±5	0.46
Employment N (%)				0.83
Employed	52 (33.5)	6 (35.3)	41 (38.0)	
Unemployed	103 (66.5)	11 (64.7)	67 (62.0)	
CSI (mean±SD)	32.11±16	45.71±12	26.76±13	**<0.001**

Notes: NP: neuropathic pain category based on PainDetect score ≥ 19. *After exclusion of unclear neuropathic pain category using PainDetect scores between 13 and 18. Boldface indicates that it was statistically significant.

Abbreviations: BMI, Body Mass Index; CSI, Central Sensitization Inventory; n, number.

Table 2 Binary Logistic Regression for the Association Between CSI and NP in (n=125)

	OR [95% CI]	*p*-value
Age	0.95 [0.87, 1.04]	0.28
Sex	0.59 [0.05, 6.6]	0.66
BMI	0.96 [0.87, 1.06]	0.44
Employment	0.75 [0.17, 3.36]	0.71
CSI	1.10 [1.05, 1.15]	**<0.001**

Notes: The model was adjusted for age, sex, BMI, and employment status. Boldface indicates that it was statistically significant.
Abbreviations: n, number; OR, odds ratio; CI, confidence interval; CSI, Central Sensitization Inventory.

Table 3 Receiver Operating Characteristics Curve and Cutoff Score for CSI That Predicted NP

N=125*	AUC (95% CI)	Cutoff Score (Sensitivity, Specificity)**	Positive Likelihood Ratio	Negative Likelihood Ratio
CSI	0.85 (0.77, 0.91)	≥ 26 (94%, 63%)	2.54	0.09

Notes: *After exclusion of unclear neuropathic pain category using PainDetect scores between 13 and 18. **Selected by highest Youden index.
Abbreviations: AUC, Area Under the Curve; CSI, Central Sensitization Inventory.

The results of the optimal cutoff score for CSI that predicted NP using ROC and AUC are shown in Table 3 and Figure 1. The optimal cutoff score of CSI with 26 or more was associated with NP in people with knee OA, with a sensitivity of 94% and specificity of 63%.

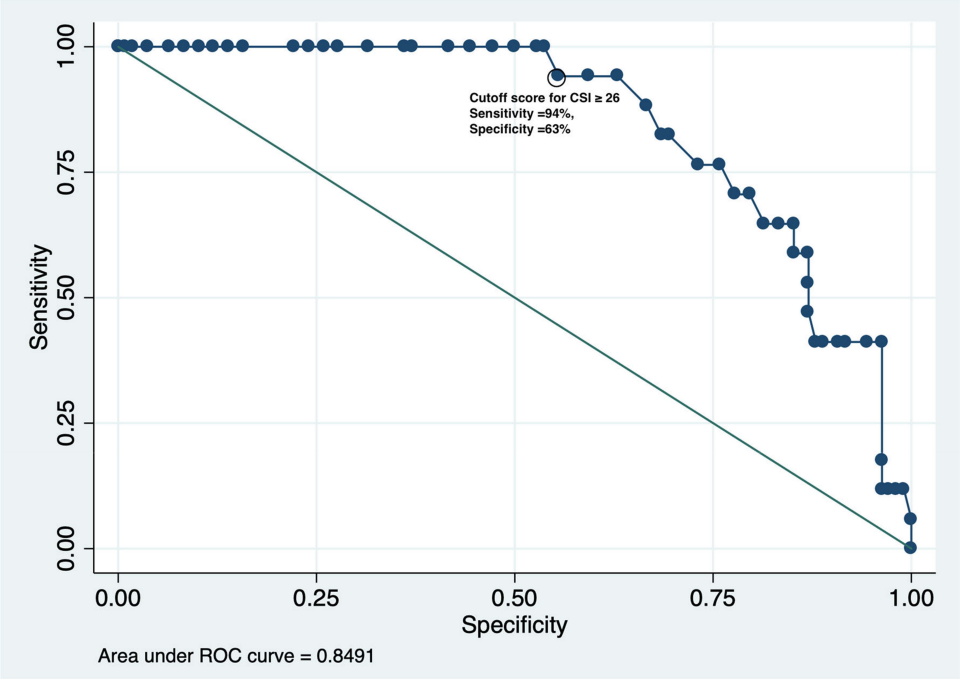

Figure 1 Receiver Operating Characteristics for CSI scores that are associated with NP.

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Discussion

This study examined the prevalence of NP and its association with CS among individuals with knee OA. The prevalence of NP was 11% in participants with knee OA. This estimate is notably lower than previously reported rates but still indicates a significant subset of the knee OA population experiencing neuropathic features. Importantly, CS, measured by the CSI, was significantly associated with NP. Participants with higher CSI scores demonstrated increased odds of having NP, even after controlling for covariates including age, sex, BMI, and employment status. Furthermore, a CSI cutoff score of 26 or higher was identified as the optimal threshold for predicting NP, with a sensitivity of 94% and specificity of 63%. These findings highlight that a CSI score ≥26 is a strong predictor of NP in people with knee OA, emphasizing the critical role of CS mechanisms in the pathogenesis of NP in this population. Clinically, these results suggest that early identification of elevated CS symptoms could be a key for targeting appropriate interventions to reduce the burden of pain in those with knee OA.

Our study findings were consistent with previous investigations examining NP and CS in individuals with knee OA. The prevalence of NP in our cohort aligns with earlier reports, which showed rates ranging from approximately 11% to over 50% depending on the population and assessment method.[24,29–31] Similar to the findings by Polat et al[31] and Mougui et al,[30] this study observed that a substantial proportion of patients exhibited neuropathic-like symptoms alongside nociceptive pain. Moreover, the recruitment of participants for the current study from community settings and multiple hospitals, and the inclusion of individuals diagnosed with symptomatic knee OA, reflect the sample characteristics described in previous studies.[10,32] Furthermore, consistent with Salaffi et al[24] and Elsehrawy et al,[22] the current study findings highlight a significant association between higher CS scores and NP that may worsen physical functions and quality of life. Collectively, these findings support the growing recognition that NP mechanisms and CS play an important role in the pain experience in individuals with knee OA. Thus, this emphasizes the need for targeted screening and tailored interventions for this subgroup of patients.

In contrast to the prevalence of NP in several previous studies,[24,30] the current study found a slightly lower prevalence of NP. This difference may be explained by participants with end-stage knee OA in previous reports compared to the current study that recruited participants from the community. The current participants in the current study may have different severity levels or less severity compared to previous research with end-stage knee OA. In end-stage knee OA, the chronicity and structural deterioration may lead to predominant nociceptive mechanisms, while neuropathic components become less distinguishable.[10,22] Additionally, severe joint destruction may mask the subtle neuropathic symptoms detectable in earlier stages.[32] Overall, while supporting the concept that NP and CS significantly impact knee OA symptoms, the current results highlight that an increase in the CSI score was significantly associated with increased odds of experiencing NP in individuals with knee OA.

The associations between CS and NP may present with features of NP characteristics, such as spontaneous, electric shock-like sensations,[11,33] Moreover both CS and NP have been linked to reduced pressure pain thresholds at both local and remote areas, which were consistent with a previous study.[34] Gervais-Hupé et al also identified widespread pain, somatization, and symptoms of anxiety and depression as significant predictors of CSI scores. In contrast, the current findings did not examine mood disorders as predictors of CS. The current study findings were in line with those of Moss et al, who reported that individuals were classified under the "positive neuropathic" category.[12]

CS symptoms involve overactivation of pain-facilitating pathways and impaired function of the brain's descending pain-inhibitory mechanisms. It may also involve sensory abnormalities detectable through quantitative sensory testing, such as mechanical hyperalgesia, increased temporal summation, and allodynia.[35,36] These factors may also play a role in sustaining CS in individuals with knee OA.[23]

CS is considered one of the key mechanisms driving the transition from acute to chronic pain and may also be involved in the structural brain changes observed in chronic pain conditions. According to the International Association for the Study of Pain, CS is defined as "an increased responsiveness of nociceptive neurons in the central nervous system to normal or sub-threshold sensory input. In contrast to peripheral sensitization, which leads to localized hypersensitivity at the site of injury, CS leads to widespread pain sensitivity that extends to unaffected areas and can continue even when there is no clear ongoing peripheral nociceptive input. This underscores the extensive and systemic influence of CS on

the nervous system. It is increasingly evident that the conventional separation between structural ("organic") and neurochemical-structural ("functional") disorders is no longer adequate, as many patients present with a combination of both types of conditions.[13]

The clinical implication of the study findings is to support the early identification and screening of patients with NP using the CSI. This facilitates timely medical referral, improves detection accuracy, and potentially aids in preventing the progression of pain by addressing CS mechanisms early in the clinical course. The findings of the current study highlight the importance of further investigating the underlying mechanisms of the CS and NP among OA individuals. Future longitudinal studies are needed to investigate whether CS either causes or aggravates NP through time in OA individuals.

This study has some limitations that should be acknowledged. Firstly, the cross-sectional design is not suitable to establish a cause-and-effect relationship between CS and NP in people with knee OA. Secondly, excluding individuals with PainDetect scores of 13–18 from the primary analysis may decrease the external validity of the results as this may include participants with borderline characteristics of NP. Thirdly, the group of participants with NP was relatively small (n=17), although this study was the first that examine the prevalence of NP and its association with CS in Saudi Arabia. The current study did not consider knee OA severity due to limited resources without radiographs for knees that may affect the generalizability of the findings. Lastly, relying on self-reported questionnaires (PainDetect and CSI), although reliable and validated, might be subjected to a possible recall bias. A future longitudinal study with a larger sample size and objective measures for neuropathic pain and pain severity with knee OA severity is recommended to establish a better causal relationship between CS and the incidence of NP among individuals with knee OA.

Conclusion

The prevalence of NP was 11% in participants with knee OA as determined by PainDetect scores. The increase in CSI was associated with the presence of NP in this population. The established cutoff score of 26 or greater with sensitivity of 94% and specificity if 63% for CSI demonstrates that the CSI may be a valuable tool in identifying individuals with NP in a population with knee OA. The relatively low prevalence of NP (n=17) in the current study might be influenced by earlier disease stages and community-based recruitment. These results emphasize the importance of incorporating the CSI into the routine assessment for participants with knee OA. Early identification facilitates timely medical referral, improves detection accuracy, guides targeted treatment strategies, and potentially aids in preventing the progression of pain by addressing CS mechanisms early in the clinical course. Furthermore, future longitudinal studies are needed to investigate the validity of the CSI cutoff score in predicting worse outcomes or responding to treatment. While the study contributes valuable findings, the current sample was drawn from limited geographical regions, which may limit the generalizability of our results, so future studies to include a more diverse sample are needed.

Data Sharing Statement

The data will be available via corresponding author based on reasonable request due to data privacy agreement.

Ethics Committee Approval Statement

This study was approved by Research Ethics Committee of Prince Sattam bin Abdulaziz University (Approval No.: RHPT/024/015).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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