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Functional ability in knee osteoarthritis: role of neuropathic pain and central sensitization

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Abstract

Background Pain in osteoarthritis (OA) has been attributed traditionally to local tissue injury causing 'nociceptive pain'. However, recent studies suggest that neuropathic and central sensitization mechanisms may contribute to the pain experience. However, the relationship between these pain mechanisms and physical function has not been thoroughly addressed. This study aimed to assess the association of central sensitization and neuropathic pain with physical function in knee OA.

Results Participants with a positive central sensitization inventory score (CSI) (≥ 40) had a decreased total Knee injury and Osteoarthritis Outcome Score (KOOS) and its subscales ($p < 0.001$), a longer timed up and go test time ($p = 0.002$) and a higher PainDETECT questionnaire (PD-Q) and visual analogue scale ($p < 0.001$, $p = 0.026$ respectively). The severity of Kellgren-Lawrence grading (KL) ($p < 0.001$), depressive and anxiety symptoms ($p < 0.001$) increased with neuropathic pain severity. In addition, participants with a high PD-Q score (≥ 19) had a longer timed up and go test time ($p < 0.001$) and a decreased total KOOS score ($p < 0.001$). Moreover, we found that CSI score, KOOS score, and KL grading were significantly predicted the PD-Q score ($p = 0.046$, $p < 0.001$, $p = 0.007$, respectively). Regarding the physical function predictors, multivariate linear regression analysis revealed that pressure pain threshold at right elbow and right knee ($p = 0.005$, $p < 0.001$) in addition to PD-Q ($P < 0.001$) were significantly associated with KOOS score, while CSI and Hospital Anxiety Depression Scale were not.

Conclusion Knee OA patients with significant central sensitization and neuropathic pain reported increased pain, more functional impairment, more anxiety and depressive symptoms than OA patients without central sensitization and neuropathic pain. Additionally, neuropathic pain and presence of central sensitization were significant predictors for functional ability.

Keywords Knee osteoarthritis, Central sensitization, Neuropathic pain

Background

Pain is a prominent symptom for people with osteoarthritis (OA) and the main reason why people with OA seek medical help, because of its substantial burden and impact on quality of life [1]. Currently, no disease-modifying drugs are available for OA, and most patients continue to experience pain, despite multiple pharmacological and non-pharmacological interventions [2].

Pain associated with OA has traditionally been considered nociceptive, i.e. caused by damage or inflammation to joints. Nevertheless, many studies have found weak associations or discordances between OA severity and pathology [3–5]. In the last few decades, peripheral and central sensitization has been recognized as contributing factors to chronic pain experienced by OA patients [6, 7]. Central sensitization

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is defined by the International Association for the Study of Pain as the enhanced responsiveness of central nervous system nociceptors to non-noxious or subthreshold stimulation input [8]. While peripheral sensitization refers to a state of peripheral nociceptive hypersensitivity characterized by a lowered excitation threshold or hyperresponsiveness of local nociceptors to both noxious and non- noxious stimuli [9].

The Nor-Hand study of people with hand OA found a high prevalence of central pain sensitization and a link between it and severe hand pain [9]. There have also been several small studies demonstrating greater sensitization among people suffering from painful knee OA compared to people with pain-free, healthy knees [6, 7, 10, 11].

Furthermore, some individuals with knee OA may experience neuropathic pain manifesting as burning, numbness, itching and electric shocks [12]and some researchers have suggested that neuropathic pain may result from damaged sensory receptors in subcortical bone due to degenerative pathology [13, 14]. Consequently, there is a growing evidence that neuropathic mechanisms may contribute to OA pain [15].

It is unclear what determinants cause central pain sensitization in OA or neuropathic pain, and how they are related to functional status. Therefore, this cross-sectional study aimed to explore the association of central sensitization and neuropathic pain with physical function in knee OA patients.

Methods

This cross-sectional study was carried out between December 2020 and March 2022.

We recruited patients diagnosed with knee OA based on the American College of Rheumatology (ACR) criteria [16] after history taking and clinical examination.

Individuals were excluded if they had ligaments or meniscal injures, total knee arthroplasty or arthrodesis, autoimmune disease, diabetic neuropathy, knee pain referred from the back or hip joint, or psychiatric disorders. We also excluded patients with intervention e.g. PRP or Visco-supplementation and steroid injections at least 6 months before the study.

We calculated the sample size based on a percentage of patients with OA who report neuropathic pain of 21.1% [17], with 80% power and 95% confidence interval and an error margin of 5%. The minimum required sample size was calculated to be 65 patients using Open source epidemiologic statistics for public health (openEPi).

All participants were evaluated by the following measures:

Visual analogue scale (VAS)

Patients were asked to mark the severity of knee pain on a graded line "0" indicating no pain and "10" indicating the worst pain imaginable [18].

Central sensitization

Pressure pain threshold (PPT)

Tests of PPT are performed at a diseased site to measure local pain sensitivity as a surrogate for peripheral and/or central sensitization. Tests performed at distant, nonpainful sites test widespread hypersensitivity, a sign of central sensitization [19]. Using standardized instructions, we applied the pressure algometer to the following sites: the OA knee and the contralateral knee (medial joint line) as well as the elbow over the extensor carpi radialis brevis (ECRB) muscle. The average of three measurements was obtained [20].

Using a pressure algometer (PainTest™ FPN 100 Algometer (Wagner Instruments, Greenwich, USA), the first point at which a sensation of pressure changes to a sensation of pain was used. Induced pressure was applied to the previous places using a flat circular metal probe covered in a rubber cover with a surface area of 1 cm^2. The algometer was mounted vertically and the pressure was increased. As soon as patients began feeling pain, they were asked to notify the examiner. 30 s of rest was allowed between each measure. Lower PPT values indicate increased sensitivity [21].

The central sensitization inventory (CSI) [22]

As a screening tool, CSI was introduced in 2012 to determine if presenting symptoms are related to central sensitization or indicate central sensitivity [23]. Psychometric strength and clinical utility of the CSI are satisfactory, along with its initial construct validity. The completed version contains 25 items. CSI scores range from 0–4, and are calculated to 100 points. There are five levels: subclinical (0–29), mild (30–39), moderate (40–49), severe (50–59), and extreme (60–100) [24].

PainDETECT questionnaire (PD-Q) [25]

This is a screening test for neuropathic pain. It was first used to detect neuropathic pain caused by back pain, and its specificity and sensitivity were reported as 80% and 85%, respectively. This test consists of seven sensory weighted descriptive questions and two items that describe temporal and propagation characteristics of pain. The final score is between 0 and 38 probability; scores within 13 to18 indicate indeterminate points. For neuropathic pain, a score of ≤ 12 indicates low

probability; and a score of ≥ 19 indicates high probability [25].

DN4 questionnaire [26]

Douleur neuropathique 4 questionnaire was developed for the assessment of neuropathic pain. It consists of 10 items that are either answered as yes or no. Seven of these items assess pain quality and the other three items detect the presence of sensory allodynia and touch- needle hypoesthesia based on the clinical examination [26]. Each item answered as "yes" yields 1 point, and a total score at or above 4/10 is evaluated as positive. This questionnaire has 83% sensitivity and 90% specificity for chronic pain associated with a lesion in central nervous system (central or peripheral) [27].

Hospital anxiety depression scale (HADS) [28]

HADS was designed to determine the risk of anxiety and depression and assess a patient's level and the change in its intensity. It has anxiety and depression subscales. It is made up of a total of 14 items. Seven of these (odd numbered) items assess anxiety and the remaining (even numbered) items assess depression. An overall subscale score of > 8 points out of 21 indicates significant anxiety or depressive symptoms [27].

Physical function tests

Performance-based chair stand test (CST)

Using the Osteoarthritis Initiative manual as a guide, CST was performed. As the patients sat in a chair without armrests, their feet were comfortably placed on the ground and their knees were flexed slightly more than 90 degrees. Using a stopwatch, patients were asked to stand up five times as quickly as they could without using their hands. Time began at "Go" after a countdown from three and ended at the fifth stand [29]. The reference value for the CST was 8.50 s (95%CI = 7.93–9.07 s) [30].

Timed up and go

This test documents the time in seconds which a person requires rising from a standard chair, walking to a line at 3 m away, turning 180, returning to the chair and sitting down. The arms of the chair can be used as support for rising or sitting if necessary. It took two trials for the average [31]. Functional mobility has a strong correlation with this test. Healthy elderly typically complete the task in less than 10 s [32].

Knee injury and Osteoarthritis Outcome Score (KOOS) [33]

The KOOS is composed of five subscales with a total of 42 items: 1) pain, 2) other symptoms, 3) daily living (ADL), 4) sport and recreation, and 5) knee-related quality of life. The scores for each question range from 0 to 4, which are converted to a score from 0 to 100. A lower score indicates more problems [33].

Radiological imaging

The Kellgren-Lawrence (KL) classification was originally described using AP knee radiographs. Each radiograph was assigned a grade from 0 to 4, which they correlated to increasing severity of OA, with Grade 0 signifying no presence of OA and Grade 4 signifying severe OA [34].

Ethics

The study was approved by the Committee of Ethical Research, Faculty of Medicine, (date of approval: 25/3/2019, Number 3905#). The participants received oral and written information about the study and gave their written informed consent.

Statistical analysis

Data normality was tested with the shapiro wilk test. We presented continuous variables as means and standard deviations (SD) or median and interquartile range (IQR), while categorical variables were described as frequencies and percentages. Additionally, between-groups differences were tested for statistical significance using Mann–Whitney test for continuous data. We estimated Spearman correlation coefficients between measures of physical function and CSI scores. Finally, we designed several multivariate linear regression models to reveal the predictors of CS, neuropathic pain and physical function in knee OA. P value less than 0.05 was considered significant.

Results

We recruited a total of 68 patients, where 94.2% of them were females. The patients' age ranged from 29 to 71 (mean 47.12 ± 10.52) and the mean body mass index (BMI) was 30.17 ± 4.73 (range: 23 – 44.5). In addition, 36.2% of the participants had chronic illnesses and 25% had history of minor trauma as shown in Table 1.

The study participants demonstrated a wide range in PPT and neuropathic pain severity. The means of anxiety, depressive symptoms and central sensitization were 16.81 ± 5.09, 15.18 ± 5.28, and 53.16 ± 13.93 respectively. The mean of KOOS score was 29.35 ± 9.96 ranging from 11 to 70, where the lower scores indicate more impairment (Table 2).

Regarding central sensitization assessment, the overall mean CSI score was 53.16 ± 13.93 with 85.3% of the patients scored at 40 or more. While there was no correlation between CSI score and age, BMI, symptoms duration, and KL grading, there was a positive correlation with depression and anxiety scales ($r = 0.506$, $r = 0.448$,

Table 1 Distribution of the studied cases according to demographic and clinical characteristics ($n=68$)

	No. (%)
Age (/years)	
Mean ± SD	47.12 ± 10.52
Median (Min. – Max.)	45.0 (29 – 71)
Sex	
Male	4 (5.9%)
Female	64 (94.1%)
Symptoms duration (/years)	
Mean ± SD	5.26 ± 4.86
Median (Min. – Max.)	3 (0.10 – 20)
Body mass index (kg/m^2)	
Mean ± SD	30.17 ± 4.73
Median (Min. – Max.)	29 (23 – 44.5)
Education	
Illiterate	18 (26.5%)
Primary	14 (20.6%)
Bachelor	24 (35.3%)
Diploma	12 (17.6%)
Occupation	
House-wife	39 (57.4%)
Employee	14 (20.6%)
Worker	1 (1.5%)
Nurse	12 (17.6%)
Doctor	2 (2.9%)
Marital status	
Single	1 (1.5%)
Married	55 (80.9%)
Widow	6 (8.8%)
Divorced	6 (8.8%)
Residency	
Rural	36 (52.9%)
Urban	32 (47.1%)
History of Knee Trauma	17 (25%)
Chronic Illnesses	
No chronic illnesses	43 (63.2%)
HTN	18 (16.4%)
HCV	7 (10.3%)
KL Grade	
1	6 (8.8%)
2	31 (45.6%)
3	18 (26.5%)
4	13 (19.1%)

SD Standard deviation, *HTN* Hypertension, *HCV* Hepatitis C Virus, *KL* Kellgren-Lawrence grading

Table 2 Descriptive analysis of the studied cases regarding pain-related and functional variables ($n=68$)

	Min. – Max	Mean ± SD	Median (IQR)
VAS	5 – 10	8.29 ± 1.55	8.5 (8 – 10)
PPT right knee (N)	10 – 55	21.35 ± 5.96	20 (19 – 24)
PPT left knee (N)	5 – 60	19.99 ± 7.98	20 (15 – 21)
PPT right Elbow (N)	5 – 46	20.97 ± 5.67	21 (19 – 25)
CSI	24 – 87	53.16 ± 13.93	55 (46 – 60)
PainDetect	1 – 31	15.4 ± 7.9	17 (10 – 21)
DN4	0 – 9	3.28 ± 2.17	4 (1 – 5)
HAD-Depression	4 – 21	15.18 ± 5.28	16 (11 – 20)
HAD-Anxiety	4 – 30	16.81 ± 5.09	18 (15 – 20)
Timed up and go (seconds)	12 – 37	23.16 ± 5.47	23.5 (19 – 28)
CST (seconds)	13 – 50	23.81 ± 5.46	23 (21 – 25)
KOOS total	11 – 70	29.35 ± 9.96	29.5 (25 – 36)
KOOS symptoms	0 – 82	39.18 ± 15.3	39 (27 – 54)
KOOS Pain	0 – 67	29.1 ± 11.12	25 (25 – 35)
KOOS ADL	15 – 94	33.51 ± 14	30 (25 – 43)
KOOS Sports	0 – 50	9.49 ± 13.13	0 (0 – 25)
KOOS QOL	0 – 69	35.13 ± 16.38	37.5 (25 – 50)

IQR Inter quartile range, *SD* Standard deviation, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *N* newton, *CST* performance-based chair and stand test, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *ADL* activity of daily living, *QOL* quality of life

$p<0.001$ and $p<0.001$, respectively) as demonstrated in Table 3.

Participants with a high CSI score (≥ 40) had a lower total KOOS score and its subscales ($p<0.001$), a longer timed up and go test time ($p=0.002$) and a higher PainDETECT, DN4 scores, and VAS scale ($p<0.001$, $p=0.001$, $p=0.026$ respectively) (Table 4).

Additionally, a multivariate linear regression was run to assess the factors affecting central sensitization. However, no significant factors were found in this model (Table 5).

With respect to neuropathic pain, 39.7%, 22.1%, and 38.2% of the participants had painDETECT scores of low, intermediate, and high probability, respectively. The severity of KL grading ($p<0.001$), depressive and anxiety symptoms ($p<0.001$) increased with neuropathic pain severity. In addition, participants with a high painDETECT score (≥ 19) had higher BMI ($P=0.044$), a longer timed up and go test and CST time ($p<0.001$, $p=0.017$) and a decreased total KOOS score ($p<0.001$) as illustrated in Table 6. Moreover, we found that CSI score, KOOS score, and KL grading were significantly predicted higher PainDETECT score ($p=0.046$, $p<0.001$, $p=0.007$, respectively) (Table 7).

Regarding the physical function predictors, the multivariate linear regression analysis revealed that PPT at right elbow and right knee ($p=0.005$, $p<0.001$) in addition to PainDETECT and VAS ($P<0.001$, $P=0.006$) significantly predicted KOOS score, while CSI and HADS scores did not (Table 8).

Table 3 Correlation between demographic and clinical data with different measurement ($n=68$)

	Age (/years)		Symptoms duration (/years)		Body mass index (kg/m^2)		KL	
	r_s	p	r_s	p	r_s	p	r_s	p
VAS	-0.200	0.103	0.108	0.379	0.167	0.173	0.173	0.159
PPT right knee	0.015	0.900	0.223	0.067	-0.239	0.050	0.001	0.995
PPT left knee	-0.043	0.726	-0.044	0.724	-0.330*	0.006*	-0.457*	< 0.001*
PPT right Elbow	-0.120	0.328	-0.076	0.540	-0.372*	0.002*	-0.248*	0.041*
CSI	0.136	0.270	-0.046	0.711	0.169	0.168	0.228	0.062
PainDetect	0.306*	0.011*	0.141	0.251	0.227	0.062	0.542*	< 0.001*
DN4	0.271*	0.026*	0.165	0.177	0.112	0.365	0.386*	0.001*
HAD-D	0.269*	0.027*	-0.064	0.604	0.005	0.968	0.210	0.086
HAD-A	0.336*	0.005*	-0.050	0.685	-0.131	0.288	0.341*	0.004*
Timed up and go	0.398*	0.001*	0.095	0.442	0.242*	0.046*	0.457*	< 0.001*
CST	0.135	0.274	0.099	0.423	-0.138	0.261	-0.042	0.736
KOOS	-0.151	0.218	-0.209	0.088	-0.133	0.279	-0.340*	0.005*
KOOS symptoms	-0.212	0.082	-0.076	0.540	-0.383*	0.001*	-0.413*	< 0.001*
KOOS Pain	0.102	0.410	-0.221	0.070	0.108	0.379	0.019	0.881
KOOS ADL	-0.097	0.429	-0.057	0.644	-0.322*	0.007*	-0.413*	< 0.001*
KOOS Sports	0.070	0.569	-0.130	0.289	0.261*	0.032*	0.212	0.082
KOOS QOL	-0.154	0.209	-0.126	0.306	-0.112	0.365	-0.405*	0.001*

r_s: Spearman coefficient

KL Kellgren-Lawrence grading, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *CST* performance-based chair and stand test, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *ADL* activity of daily living, *QOL* quality of life

* Statistically significant at $p \leq 0.05$

Discussion

This study investigated levels of neuropathic pain, central sensitization, and physical function and their relation to each other in participants with knee OA. We found that patients with high levels of neuropathic pain and high CS demonstrated greater pain, widespread hyperalgesia, and greater functional limitations, suggesting a relation between these two types of pain and physical function in patients with knee OA.

Regarding the prevalence of central sensitization in knee OA patients, there was a significant heterogeneity among studies. Central sensitization was reported to be 48% of 941 patients by Kim et al. and in 24% of 422 by Koh et al. [35, 36]; however, it was present in 85% of our participants. A meta-analysis documented a prevalence of pain sensitization of 20% with a significant heterogeneity of results because of the diagnostic tool used [37]. This discrepancy may be due to differences in sample size and diagnostic tools.

We also found that radiographic knee OA severity was correlated with a decrease in functional ability; however, radiographic grade was not correlated with CSI and knee pain. Finan et al. [38] also reported that there was no congruence between radiological findings and perception of pain in OA. In addition, knee pain degree increased in knee OA patients with central sensitization which is also found by Sasaki et al. [39] who also revealed that participants with a positive CSI-9 score had a decreased KOOS subscales similar to our results. As a result, central sensitization appears to contribute to elevated pain and impairment, regardless of the presence of pathological OA. This indicates a possible relationship between symptom severity and sensitization, independent of radiographic severity, and supports the concept that peripheral pathology is not the only cause of painful symptoms in knee OA [21, 38]. Accordingly, central sensitization may also explain persistent pain following arthroplasty [40].

Besides, we found no association between duration of OA with sensitization either by CSI or PPT similar to other studies [41]. Similarly, Skou et al. [42] found no correlation between knee OA pain duration and pressure pain sensitivity. In light of these findings, it is believed that central sensitization is rather a "trait" than a "state", and that the hypersensitivity was present before knee OA and related to the individual's predisposition to sensitization, rather than the result of peripheral nociceptive input caused by OA [41].

Moreover, central sensitization and neuropathic pain both correlated with decreased pressure pain thresholds

Table 4 Comparison between CSI groups regarding different measurement ($n=68$)

	CSI		p
	< 40 ($n=10$)	**≥ 40 ($n=58$)**	
VAS			
Mean ± SD	7.3 ± 1.6	8.5 ± 1.5	0.026*
Median (Min. – Max.)	7.5 (5 – 10)	9 (5 – 10)	
Timed up and go			
Mean ± SD	18.4 ± 5.3	24 ± 5.1	0.002*
Median (Min. – Max.)	17 (12 – 27)	24.5 (13 – 37)	
CST			
Mean ± SD	23.8 ± 7.7	23.8 ± 5.1	0.438
Median (Min. – Max.)	22 (13 – 36)	23 (15 – 50)	
PainDetect			
Mean ± SD	5.9 ± 4.9	17 ± 7.1	< 0.001*
Median (Min. – Max.)	4 (1 – 17)	17 (1 – 31)	
DN4			
Mean ± SD	1.1 ± 1.7	3.7 ± 2	0.001*
Median (Min. – Max.)	0 (0 – 5)	4 (0 – 9)	
HAD-D			
Mean ± SD	10.4 ± 5.5	16 ± 4.8	0.005*
Median (Min. – Max.)	9 (4 – 21)	17 (6 – 21)	
HAD-A			
Mean ± SD	12.2 ± 5.6	17.6 ± 4.6	0.007*
Median (Min. – Max.)	11 (4 – 21)	18 (7 – 30)	
KOOS			
Mean ± SD	42 ± 11.3	27.2 ± 8	< 0.001*
Median (Min. – Max.)	39 (29 – 70)	26.5 (11 – 50)	
KOOS symptoms			
Mean ± SD	52.2 ± 11.6	36.9 ± 14.8	0.004*
Median (Min. – Max.)	50 (43 – 82)	36 (0 – 71)	
KOOS Pain			
Mean ± SD	42.3 ± 12.4	26.8 ± 9.2	< 0.001*
Median (Min. – Max.)	40.5 (25 – 67)	25 (0 – 50)	
KOOS ADL			
Mean ± SD	43.9 ± 19.9	31.7 ± 12.1	0.021*
Median (Min. – Max.)	43 (25 – 94)	25 (15 – 75)	
KOOS Sports			
Mean ± SD	24 ± 15.2	7 ± 11.1	0.001*
Median (Min. – Max.)	25 (0 – 50)	0 (0 – 25)	
KOOS QOL			
Mean ± SD	47.6 ± 10.7	33 ± 16.3	0.016*
Median (Min. – Max.)	50 (25 – 69)	28 (0 – 56)	

SD Standard deviation, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *CST* performance-based chair and stand test, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *ADL* activity of daily living, *QOL* quality of life

p *p* value for Relation between CSI with different measurement

* Statistically significant at $p \leq 0.05$

Table 5 Multivariate linear regression analysis for the parameters affecting CSI ($n=68$)

	p	B (LL – UL 95%C.I)
VAS	0.210	1.710 (-0.992 – 4.412)
Timed up and go	0.886	-0.060 (-0.895 – 0.775)
PainDetect	0.651	0.193 (-0.657 – 1.043)
DN4	0.347	1.108 (-1.231 – 3.447)
HAD-D	0.139	0.901 (-0.300 – 2.101)
HAD-A	0.863	-0.098 (-1.230 – 1.034)
KOOS	0.720	0.084 (-0.384 – 0.553)

B Unstandardized Coefficients, *C.I* Confidence interval, *LL* Lower limit, *UL* Upper Limit

KL Kellgren-Lawrence grading, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *CST* performance-based chair and stand test, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score

* Statistically significant at $p \leq 0.05$

locally and remotely which is consistent with a study by Gervais-Hupé et al. [43]. On the other hand, they found that wide spread pain, somatization, and anxiodepressive symptoms significantly predicted CSI scores unlike our findings where we did not find mood disorders to be significant predictors of central sensitization. This difference may be due to differences in population, since patients of OA are characteristically different from patient with wide spread pain.

In a systematic review by Zolio et al. [12].the pooled prevalence of neuropathic pain using PainDETECT was: possible neuropathic pain (score ≥ 13) 40%; probable neuropathic pain (score > 18) 20%. In other studies, the percentage of participants scoring in the "positive neuropathic" pain category ranged from 5.4% to 32% [13, 15, 44]. The findings from our study are a little more than some previous studies but nevertheless close to the previously published range.

Regarding the correlations between neuropathic pain and other variables, our results support Moss et al. who suggested that participants in the "positive neuropathic" pain category reported increased pain and decreased function relative to the remaining patients. They also exhibited slower times to complete physical tasks [20]. This further emphasizes that they were experiencing greater functional limitation associated with their pain.

In addition, participants in the "positive neuropathic" category also exhibited increased pain sensitivity at the OA knee and at the distant ECRB in the upper limb [20] which is consistent with our study where there is a significant correlation between PD-Q and PPT left knee and ECRB. Patients with higher modified PD-Q scores (> 12.0) had higher odds of having pain sensitization on

Table 6 Comparison between painDetect groups in relation to different measurement ($n=68$)

	Pain detect			p
	≤ 12 ($n=27$)	13 – 18 ($n=15$)	≥ 19 ($n=26$)	
Age (years)				
Mean ± SD	43.9 ± 11.2	46.5 ± 5.9	50.8 ± 11	0.083
Median (Min. – Max.)	43 (29 – 71)	45 (36 – 57)	51.5 (29 – 70)	
Body mass index (kg/m^2)				
Mean ± SD	28.7 ± 3.7	30.1 ± 5.2	31.8 ± 5	0.044*
Median (Min. – Max.)	28 (23 – 37)	30 (26 – 44.5)	30.5 (23 – 40)	
KL				
1, 2	23 (85.2%)	5 (33.3%)	9 (34.6%)	< 0.001*
3, 4	4 (14.8%)	10 (66.7%)	17 (65.4%)	
VAS				
Mean ± SD	7.56 ± 1.60	8.67 ± 1.84	8.85 ± 0.92	0.005*
Median (Min. – Max.)	8 (5 – 10)	10 (6 – 10)	9 (7 – 10)	
PPT right knee				
Mean ± SD	22.9 ± 7.6	21.1 ± 2.6	20 ± 5.3	0.373
Median (Min. – Max.)	22 (10 – 55)	19 (19 – 25)	20 (10 – 30)	
PPT left knee				
Mean ± SD	24 ± 8.5	18 ± 7.3	17 ± 6.2	< 0.001*
Median (Min. – Max.)	21 (12 – 60)	15 (9 – 30)	20 (5 – 30)	
PPT right Elbow				
Mean ± SD	22.6 ± 5.3	22.3 ± 3.8	18.5 ± 6.2	0.084
Median (Min. – Max.)	22 (13 – 46)	21 (15 – 30)	20 (5 – 26)	
CSI				
Mean ± SD	43.6 ± 12.1	58 ± 13.9	60.3 ± 9.7	< 0.001*
Median (Min. – Max.)	46 (24 – 69)	57 (35 – 80)	58 (48 – 87)	
Timed up and go				
Mean ± SD	18.7 ± 3.7	25.5 ± 4.5	26.4 ± 4.4	< 0.001*
Median (Min. – Max.)	18 (12 – 27)	27 (16 – 32)	25.5 (17 – 37)	
CST				
Mean ± SD	22.2 ± 4	24.6 ± 8.5	25 ± 4.2	0.017*
Median (Min. – Max.)	22 (13 – 36)	21 (15 – 50)	25 (19 – 33)	
HAD-D				
Mean ± SD	11.4 ± 5	16.7 ± 4.6	18.2 ± 3.2	< 0.001*
Median (Min. – Max.)	11 (4 – 21)	17 (11 – 21)	19.5 (10 – 21)	
HAD-A				
Mean ± SD	13 ± 5	19.1 ± 2	19.5 ± 3.8	< 0.001*
Median (Min. – Max.)	15 (4 – 21)	19 (15 – 21)	19 (13 – 30)	
KOOS				
Mean ± SD	36.6 ± 9.3	27.9 ± 3.9	22.7 ± 7.9	< 0.001*
Median (Min. – Max.)	35 (26 – 70)	29 (21 – 37)	25 (11 – 38)	

SD Standard deviation

p p value for Relation between Pain detect with different measurement

* Statistically significant at $p \leq 0.05$

KL Kellgren-Lawrence grading, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *CST* performance-based chair and stand test, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score

quantitative sensory testing (QST) measures as found by Hochman and colleagues [45]. Gwylim et al. [46] reported that participants with high PD-Q scores were more likely to have signs of central sensitization, e.g., higher ratings of sharpness and greater cerebral activity on functional magnetic resonance imaging during

Table 7 Multivariate linear regression analysis for the parameters affecting PainDetect ($n=68$)

	#Multivariate	
	p	B (LL – UL 95%C.I)
Increase in **KL**	0.007*	2.137 (0.605 – 3.668)
PPT left knee	0.639	0.050 (-0.163 – 0.264)
PPT right Elbow	0.388	-0.124 (-0.410 – 0.162)
Timed up and go	0.038*	0.291 (0.017 – 0.566)
HAD-D	0.910	-0.026 (-0.477 – 0.425)
HAD-A	0.527	0.142 (-0.304 – 0.588)
KOOS	< 0.001*	-0.373 (-0.498 – -0.247)
CSI	0.046*	0.093 (0.002 – 0.185)

B Unstandardized Coefficients

C.I Confidence interval, *LL* Lower limit, *UL* Upper Limit

* Statistically significant at $p \leq 0.05$

KL Kellgren-Lawrence grading, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *CSI* central sensitization inventory, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *KOOS* Knee Injury and Osteoarthritis Outcome Score

Table 8 Multivariate linear regression analysis for the parameters affecting KOOS ($n=68$)

	#Multivariate	
	p	B (LL – UL 95%C.I)
Increase in KL	0.447	-0.837 (-3.025 – 1.351)
VAS	0.006*	-1.561 (-2.657 – -0.465)
PPT right knee	< 0.001*	0.951 (0.551 – 1.351)
PPT left knee	0.319	-0.165 (-0.493 – 0.163)
PPT right Elbow	0.005*	-0.579 (-0.976 – -0.182)
HAD-D	0.477	-0.230 (-0.872 – 0.413)
HAD-A	0.192	0.393 (-0.203 – 0.989)
Pain detect	< 0.001*	-0.789 (-1.189 – -0.389)
CSI	0.784	0.017 (-0.109 – 0.144)

B Unstandardized Coefficients

C.I Confidence interval, *LL* Lower limit, *UL* Upper Limit

* Statistically significant at $p \leq 0.05$

KL Kellgren-Lawrence grading, *VAS* Visual Analogue Scale, *PPT* pressure pain threshold, *DN4* Douleur neuropathique 4, *HAD-A* Hospital Anxiety score, *HAD-D* Hospital Depression score, *CSI* central sensitization inventory, *KOOS* Knee Injury and Osteoarthritis Outcome Score

punctate stimulation. These findings support the hypothesis that central sensitization and neuropathic mechanisms may contribute to the pain experience in a subset of people with OA as seen in another studies [45]. While nerve damage is not a recognized feature of OA, there may be sub-clinical damage to small peripheral nerves innervating OA joints [47].

Furthermore, PD-Q and CSI scores can indicate which patients may benefit from Duloxetine, a serotonin norepinephrine reuptake inhibitor now approved for treatment of OA pain [48]. Alternatively, treatment of depression and anxiety with medications that target neuropathic pain, such as tricyclic antidepressants, may reduce the contribution of CS to OA pain, especially for individuals with higher PD-Q scores [49].

We found that there is a significant correlation between PPT and knee pain, PD-Q, and physical function. Similarly, three studies [41, 42], including one large cross-sectional study of 2,126 participants with knee OA [41] found a significant correlation between pressure pain sensitivity and symptom severity. In the adjusted regression models by Moore et al. [50], manual tender point count demonstrated strong associations with QST measures. However, in our regression model, predictors of PPT were inconsistent. Further investigation is recommended to establish this possible association.

In line with other studies [51, 52] of patients with OA, we found that participants scoring "positive neuropathic" or positive CSI had higher anxiety and depressive symptoms. Wood et al. [53] also found that people with knee OA reporting enlarged areas of pain had more persistent and severe pain and higher anxiety levels, which also was interpreted as reflecting altered central pain processing mechanisms. These findings support that the pain experience in OA is multidimensional, fitting well with the biopsychosocial model, which reflects the influence of biological, psychological, and social factors in the individual's suffering [54].

Finally, there was no relationship between BMI and CS or neuropathic pain as found by Hochman et al. [45]; however, a significant correlation was found between BMI and symptoms, activity of daily living, sports subscales of KOOS, and timed up and go test. This may indicate that BMI could affect functional ability but in a different mechanism than does CS.

Limitations

The following limitations should be acknowledged. The cross-sectional design of this study prevented us from drawing any conclusions about the temporal relationships between the measures. The majority of participants were women, which may indicate a selection bias. Further research in a larger sample is needed to confirm the findings of this study. We did not use the complete set of QST tests; however, those chosen are commonly used in the studies of this population.

Conclusion

Individuals with knee OA who have concomitant neuropathic pain and central sensitization tend to report increased pain, more functional impairment, more anxiety and depressive symptoms. Presence of high levels of neuropathic pain and central sensitization were

significant predictors for functional ability. Since neuropathic pain and pain sensitization were prevalent in people with knee OA, we need to consider them in OA management since their presence may affect response to treatment. Furthermore, targeting neuropathic pain and pain sensitization for treatment may improve outcomes. Therefore, it is imperative to conduct further research to determine whether the presence of neuropathic pain and/or CS predicts the response to knee OA treatment.

Abbreviations

ACR	American College of Rheumatology
ADL	Activity of Daily Living
BMI	Body Mass Index
CSI	Central Sensitization Inventory
CST	Performance-Based Chair Stand Test
DN4	Douleur Neuropathique 4 Questionnaire
ECRB	Extensor Carpi Radialis Brevis
OpenEpi	Open source epidemiologic statistics for public health
HADS	Hospital Anxiety Depression Scale
HAD-A	Hospital Anxiety score
HAD-D	Hospital Depression score
IQR	Interquartile Range
KL	Kellgren-Lawrence Grading System
KOOS	Knee Injury and Osteoarthritis Outcome Score
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PD-Q	PainDETECT Questionnaire
PPT	Pressure Pain Threshold
QOL	Quality of Life
QST	Quantitative Sensory Testing
SD	Standard Deviations
VAS	Visual Analogue Scale
WSP	Widespread Pain

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Authors' contributions
G.G.E., N.K.E., M.E.I., N.H.A., and M.A.H. designed the study. G.G.E. collected the clinical data. G.G.E. and M.E.I. analyzed and interpreted the patient data. N.K.E. and M.A.H. interpreted the patient data. All authors discussed the results, contributed to the final manuscript, and approved it. N.H.A. discussed the results and supervised all the research process. All authors approved the final manuscript and agreed to the published version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
The study was approved by the Committee of Ethical Research, Faculty of Medicine, Suez Canal University, (date of approval: 25/3/2019, Number 3905#). The participants received oral and written information about the study and gave their written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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