

Difference in the impact of central sensitization on pain-related symptoms between patients with chronic low back pain and knee osteoarthritis

This article was published in the following Dove Press journal:
Journal of Pain Research

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Purpose: The aims of the present study were to investigate whether the association between the Central Sensitization Inventory (CSI) score, pain-related symptoms, pain-related disability, and health-related quality of life differed by disease (chronic low back pain [CLBP] vs knee osteoarthritis [KOA]), and to determine optimal cutoff scores for the CSI reflecting disease-specific characteristics.

Patients and methods: A total of 104 patients with CLBP and 50 patients with KOA were recruited. Central sensitization-related symptoms (CSI), EuroQol 5-dimension (EQ-5D), Brief Pain Inventory, widespread pain (Widespread Pain Index [WPI]), pressure pain threshold (PPT), and temporal summation (TS) were assessed and compared between the CLBP and KOA groups. Univariate correlation analysis was performed in each group. The receiver operating characteristic (ROC) curve analysis was performed to identify 1) presence/absence of central sensitization (CS), 2) presence/absence of central sensitivity syndromes (CSSs), and 3) pain intensity and pain interference in each group.

Results: The CSI and WPI scores were significantly higher in the CLBP group than in the KOA group. EQ-5D and pain interference scores significantly correlated with the CSI score in both the CLBP and KOA groups. The WPI score, PPT, and TS did not correlate with the CSI score in either the CLBP or KOA group. **The suggested cutoff scores were 28 in the CLBP group and 17 in the KOA group** to identify presence or absence of CSSs, and 34 in the CLBP group and 18–19 in the KOA group to identify pain severity.

Conclusion: The impact of CS on pain could differ between CLBP and KOA and that cutoff scores differ by each parameter we attempted to identify. Therefore, we should use the appropriate cutoff scores for the purposes and consider the difference in the impact of CS on pain by the patient group.

Keywords: central sensitization, chronic low back pain, knee osteoarthritis, cutoff score

Introduction

The International Association for the Study of Pain defines central sensitization (CS) as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input.¹ **An increasing number of studies have indicated that CS is related to the pathology of pain-related symptoms in chronic low back pain (CLBP),^{2,3} osteoarthritis (OA),^{2,4,5} shoulder pain,^{6,7} fibromyalgia (FM),^{8,9} and whiplash-associated disorders.^{10,11} Furthermore, recent systematic reviews have shown that CS is associated with the success of treatment for these musculoskeletal pain conditions.^{12–14} That is, CS could be a risk factor for**

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poor outcomes after treatment, and so it is critical to screen for to allocate and prioritize treatment.

The Central Sensitization Inventory (CSI) was developed as a screening tool to assess CS-related symptoms in patients with FM, chronic widespread pain, and CLBP.¹⁵ The CSI has been translated into numerous languages^{16–21} and widely adopted into scientific research and clinical practice. Previous studies have determined a cutoff score of 40 out of 100 to identify patients with a central sensitivity syndrome (CSS) such as FM, chronic fatigue syndrome, temporomandibular joint disorder, irritable bowel syndrome, migraine or tension headaches, multiple chemical sensitivities, and restless leg syndrome.^{22,23} Recent studies have shown the clinical utility of this cutoff score. Kim et al²⁴ found that patients with high CSI score (≥ 40) before knee arthroplasty showed more severe postsurgical pain intensity and less favorable outcome in pain relief at 1 month and 3 months postoperatively compared to patients with low CSI score (< 40). Bennett et al²⁵ also showed that preoperative pain-related disability and health-related quality of life (HRQOL) were significantly worse in patients with CSI ≥ 40 compared to patients with CSI < 40 , and the preoperative CSI score was significantly associated with higher postoperative pain-related disability and lower health-related QOL in the patients who underwent spinal fusion. These results suggest that the CSI has a role in the diagnosis of CS and prognosis of poor outcome.

A recommended cutoff score of 40 was determined to differentiate patients with and without CSSs in studies with patients diagnosed with a CSS such as myofascial pain syndrome, tension headache/migraines, FM, temporomandibular joint disorder, and complex regional pain syndrome in interdisciplinary pain clinics.^{22,23} However, considering the fact that musculoskeletal pain, such as in CLBP and knee osteoarthritis (KOA), is a complex phenomenon that involves various contributing factors (eg structural and functional abnormalities and psychosocial factors) as well as CS,^{26–29} the impact of CS on pain and pain-related disability may differ among diseases. The validity study of the CSI in people with KOA exhibiting symptoms of CS determined a lower than 40 cutoff score, which suggests that the impact of CS could differ among diseases.³⁰ In addition, previous studies have evaluated the sensitivity (Sn) and specificity (Sp) of the CSI in identifying people with signs of CS using the pressure pain threshold (PPT) and temporal summation (TS)³⁰ and diagnosed CSS.^{22,23} In clinical practice, in patients with chronic musculoskeletal pain, the goal of treatment is to improve

activity of daily living and QOL, which are impacted by persistent pain, and not CS or CSS per se. Therefore, using the CSI with a cutoff score that directly reflects the impact of CS on the severity of pain and pain-related disability may be more suitable for clinical practice.

The aims of the present study were to investigate whether the association between the CSI score, pain-related symptoms, pain-related disability, and HRQOL differed by disease (CLBP vs KOA) and to determine optimal cutoff scores for the CSI for identifying the severity of pain and pain-related disability at presentation reflecting disease-specific characteristics. We hypothesized that the CSI score and cutoff scores differed by disease reflecting the difference of impact on pain.

Patients and methods

Participants

Participants with CLBP or KOA were recruited consecutively from two orthopedic clinics in Osaka, Japan. The inclusion criteria for the CLBP group were 1) CLBP for more than 3 months and 2) age between 20 and 80 years and those for the KOA group were 1) confirmed diagnosis of KOA by orthopedic surgeons based on clinical guidelines,³¹ 2) knee pain for more than 3 months, and 3) age between 20 and 80 years. The exclusion criteria for both groups were 1) presence of a postoperative condition, 2) serious pathologies (unhealed fractures, tumors, acute trauma, or serious illness), 3) history of central nervous system disease, and 4) diagnosed psychiatric disorders (eg schizophrenia, bipolar disorder, or somatoform disorder) as diagnosed by a psychiatrist.

Ethics approval was obtained from the institutional ethics committee of Konan Women's University in Kobe, Japan. Written informed consent was obtained from all subjects prior to the study. This study was conducted in compliance with the Declaration of Helsinki.

Measures

Demographic and clinical characteristics

Demographic data (age, sex, weight, height, education level, and duration of symptoms) and clinical characteristics were assessed in all participants with CLBP or KOA using self-reported measures. The Kellgren–Lawrence (KL) score was assessed by an orthopedic surgeon in patients with KOA. The characteristics for each KL-grade can be summarized as grade I, doubtful OA with presence of minor osteophytes of doubtful importance;

grade II, minimal OA, with definite osteophytes but unimpaired joint space; grade III, moderate OA, with osteophytes and moderate diminution of joint space; and grade IV, severe OA, with greatly impaired joint space and sclerosis of subchondral bone.³²

The CSI consists of two parts: A and B.¹⁵ Part A is a 25-item self-report questionnaire designed to assess health-related symptoms that are common in CSSs. Each item is rated on a 5-point Likert-type scale (0= never and 4= always), with total scores of 0–100. Part B (which is not scored) is designed to determine whether one or more specific disorders, including seven separate CSSs, have been previously diagnosed (restless leg syndrome, chronic fatigue syndrome, FM, temporomandibular joint disorder, migraine or tension headaches, irritable bowel syndrome, multiple chemical sensitivities, neck injuries [including whiplash], anxiety or panic attacks, and depression).

Health-related QOL was measured using the EuroQOL 5-dimension (EQ-5D).³³ The EQ-5D was developed as a non-disease-specific instrument, but has been standardized and can be used as a complement to existing health-related QOL measures.^{34,35} It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of severity (“no problems, some problems, and extreme problems”), which can generate a single index value for each health state. These are numerical values on a scale with 1 denoting full health and 0 denoting death.

Pain intensity and pain interference were measured using the Brief Pain Inventory (BPI).^{36,37} It consists of four pain intensity and seven pain interference items. These items are presented on 0–10 scales, with 0= no and 10= worst (completely). From these, individual pain intensity and pain interference scores are calculated by averaging. The validation and clinical utility of the BPI has been evaluated for several disorders.³⁸ In addition, we used the Widespread Pain Index (WPI),³⁹ originally developed for patients with FM, to count the number of painful sites. The WPI results in an overall score of 0–19 points, provided by the number of up to 19 specific areas where the patient experienced pain over the previous week, including left shoulder girdle, right shoulder girdle, right upper arm, left upper arm, right lower arm, left lower arm, right hip, left hip, right upper leg, left upper leg, right lower leg, left lower leg, right jaw, left jaw, chest, abdomen, upper back, lower back, and neck.

Pressure pain threshold and temporal summation of pain

PPT and TS were assessed by five physical therapists who performed independent training without instruction based on a standardized testing protocol.⁴⁰ Both tests were carried out at the dominant side of the extensor carpi radialis longus muscle (5 cm distally to the lateral epicondyle). When assessed at a distant, normal site, it is considered to reflect systematic altered pain processing, which may be related to CS.⁴¹

PPT was assessed using a digital algometer with a 1-cm² probe (AlgoMed; Medoc Ltd., Ramat Yishai, Israel). Pressure was applied at a rate of 1 N/s until subjects verbally indicated when the sensation became painful.^{40,42} The test was repeated three times with intervals of 30 s and the mean value was calculated.

Two minutes after the PPT assessment, TS was assessed. The previously determined PPT was applied 10 times. Pressure was increased at a rate of 1 N/s to the determined PPT and maintained for 1 s before being released with a 1-s interstimulus interval.^{40,43,44} After applying 10 stimuli, the subjects reported the pain intensity of the first, fifth, and tenth stimuli using a 0–10 numeric rating scale (0= “no pain” to 10= “worst possible pain”). The value of TS was defined by subtracting the first pain rating from the 10th.

Tertiles of PPT data were created and subjects who were in the lowest tertile and had positive values of TS were classified as having CS.^{30,41,42}

Statistical analysis

Descriptive characteristics are expressed using means ± standard deviation for continuous variables and N (%) for categorical variables. The data distribution was tested for normality using the Kolmogorov–Smirnov test. As most of our data were not normally distributed and in order to avoid switching between tests, we used the less sensitive but more robust nonparametric tests in all statistical analyses. Demographic and clinical characteristics and the QST results were compared between the CLBP and KOA groups using the Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables. To examine whether the relationship of the pain-related variables and QST to the CSI differed between the CLBP and KOA groups, we performed univariate correlation analysis using Spearman’s correlation coefficients in each group. Furthermore, we performed receiver operating characteristic (ROC) curve analysis to determine the

Table 1 Demographic and clinical characteristics of participants

	CLBP (n=104)	KOA (n=50)	p-value
Age	58.4±14.2	66.7±7.7	<0.01
Gender (Female)	77 (74.0)	45 (90.0)	<0.05
Height (cm)	159.7±8.3	157.2±6.3	0.10
Weight (kg)	58.1±11.6	60.5±10.3	0.11
Education level			
College and university	54 (51.9)	23 (46.0)	
High school	43 (41.3)	23 (46.0)	
Junior high school	7 (6.7)	4 (8.0)	
Duration of symptom (weeks)	277.8±345.2	58.0±74.2	<0.001
Pain intensity score	2.7±1.7	2.7±1.7	0.75
Pain interference score	2.2±2.0	2.3±2.0	0.71
WPI score	2.1±1.5	1.7±1.1	<0.05
CSI score	25.5±12.2	17.6±10.3	<0.001
EQ-5D	0.716±0.111	0.726±0.130	0.58
K-L grade			
I	NA	5 (10.0)	
II	NA	35 (70.0)	
III	NA	10 (20.0)	
IV	NA	0 (0)	
PPT (N)	25.7±11.6	26.1±10.2	0.54
TS	1.7±2.3	1.8±2.6	0.46
Presence of CS	19 (18.3)	12 (24.0)	0.40
Presence of CSS	26 (25.0)	5 (10.0)	<0.05

Notes: Descriptive characteristics are expressed using mean ± SD for continuous variables and N (%) for categorical variables.

Abbreviations: CLBP, chronic low back pain; KOA, knee osteoarthritis; WPI, Widespread Pain Index; CSI, Central Sensitization Inventory; EQ-5D, EuroQol 5-dimension; K-L, Kellgre-Laurence; PPT, pressure pain threshold; CS, central sensitization; CSS, central sensitivity syndrome; NA, not applicable; TS, temporal summation.

Sn and Sp of the CSI to identify the 1) presence or absence of CS, 2) presence or absence of CSSs, and 3) pain intensity and pain interference in each group. The presence of CS was defined by the PPT and TS as mentioned above.³⁰ The presence of CSSs was defined as one or more CSS diagnoses (CSI part B).²² The reference standard cases for the analysis of pain intensity and pain-related disability were set by the median partitioning of the BPI-pain intensity and interference scores (“higher” vs “lower”).⁴⁵ We evaluated the area under the curve (AUC) in each analysis to assess the discriminative ability of CSI. The AUC ranges from 0.5 (for a test that shows no ability to discriminate between patients and nonpatients) to 1.0 (for a test that discriminates perfectly between patients and nonpatients). Generally, 0.7 is considered a satisfactory AUC value. The maximum Youden Index (Sn + Sp - 1) was defined as the optimal cutoff point.⁴⁶ All statistical analyses were conducted using JMP® 16 (SAS institute Inc., Cary, NC, USA). The significance level was set at $p < 0.05$ for all statistical analyses. Bonferroni’s correction was applied to correlation analyses, resulting in a significance level of $p < 0.007$.

Results

Comparisons of clinical characteristics between the CLBP and KOA groups

In this study, we recruited 104 patients with CLBP (77 female, 58.4±14.2 years old) and 50 patients with KOA (45 female, 66.7±7.7 years old). Table 1 shows the summary of measurements. Table 2 shows the number of patients with CSS and their CSI score. Regarding pain-related outcomes, there were no significant differences in pain intensity and pain interference scores between the CLBP and KOA groups (pain intensity: 2.7±1.7 for CLBP, 2.7±1.7 for KOA, $p=0.75$; pain interference: 2.2±2.0 for CLBP, 2.3±2.0 for KOA, $p=0.71$), whereas the WPI score was significantly higher in the CLBP group than in the KOA group (CLBP: 2.1±1.5, KOA: 1.7±1.1, $p < 0.05$). The CSI score was significantly higher in the CLBP group than in the KOA group (CLBP: 25.5±12.2, KOA: 17.6±10.3, $p < 0.001$). The proportion of participants who were diagnosed with one or more CSSs was higher in the CLBP group than in the KOA group

Table 2 Number of CSS and their CSI scores in CLBP and KOA

Number of CSS	CLBP (N=104)		KOA (N=50)	
	N (%)	CSI score	N (%)	CSI score
0	78 (75.0)	23.3±11.6	45 (90.0)	16.8±10.4
1	17 (16.3)	29.6±11.8	2 (4.0)	21.0±5.7
2	6 (5.8)	33.8±10.4	1 (2.0)	25.0
3	2 (1.9)	38.0±8.5	2 (4.0)	24.5±7.8
4	1 (0.1)	50.0	0 (0)	NA

Note: CSI scores are expressed using mean ± SD.

Abbreviations: CSS, central sensitivity syndrome; CSI, central sensitization inventory; CLBP, chronic low back pain; KOA, knee osteoarthritis.

(CLBP: $n=26$ [25.0%], KOA: $n=5$ [10.0%], $p<0.05$). There were no significant differences in PPT (CLBP: 25.7 ± 11.6 , KOA: 26.1 ± 10.2 , $p=0.54$), TS (CLBP: 1.7 ± 2.3 , KOA: 1.8 ± 2.6 , $p=0.46$), and the proportion of participants who were classified as having CS (CLBP: $n=19$ [18.3%], KOA: $n=12$ [24.0%], $p=0.40$).

Correlation of pain-related variables and QST with the CSI score in CLBP and KOA

Table 3 shows the correlation coefficients of pain-related variables and QST results with the CSI score in CLBP and KOA. The EQ-5D and pain interference scores significantly correlated with the CSI score in both the CLBP (EQ-5D: $r_s = -0.47$; pain interference: $r_s = 0.42$) and KOA (EQ-5D: $r_s = -0.57$, interference: $r_s = 0.53$) (all, $p<0.0001$) groups. The pain intensity score significantly correlated with the CSI score only in the CLBP group (CLBP: $r_s = 0.37$, $p<0.001$; KOA: $r_s = 0.35$, $p=0.02$). The duration of symptoms, WPI score, PPT, and TS did not correlate with the CSI score in either the CLBP or KOA group (all, $p>0.007$).

Table 3 Correlation with CSI score

	CLBP (N=104)		KOA (N=50)	
	r_s	p -value	r_s	p -value
Duration of symptom	0.02	0.84	0.23	0.11
EQ-5D	-0.47	<0.0001	-0.57	<0.0001
Pain intensity	0.37	<0.001	0.35	0.02
Pain interference	0.42	<0.0001	0.53	<0.0001
WPI score	0.25	0.01	0.27	0.06
PPT	-0.09	0.39	-0.16	0.26
TS	0.09	0.38	-0.13	0.39

Abbreviations: CLBP, chronic low back pain; KOA, knee osteoarthritis; EQ-5D, EuroQol 5-dimension; WPI, Widespread Pain Index; PPT, pressure pain threshold; TS, temporal summation.

Discriminative ability of the CSI

Table 4 summarizes the AUC and suggested cutoff points with the Sn and Sp determined by each ROC curve analysis. The AUC analysis to identify the presence of CSS was 0.698 and the suggested cutoff score was 28 in the CLBP group. In the KOA group, the AUC was 0.764 and the suggested cutoff score was 17. In the analysis to determine pain intensity as “higher” or “lower,” the AUC was 0.657 and the suggested cutoff score was 34 in the CLBP group. In the KOA group, the AUC was 0.714 and the suggested cutoff score was 19. In the analysis to determine pain interference as “higher” or “lower,” the AUC was 0.734 and the suggested cutoff score was 34.

Table 4 AUC values and sensitivity and specificity for suggested cutoff score

Dependent variable		AUC	95% CI	Cutoff score (Sn, Sp)
CS+ or CS-	CLBP	0.512	0.380–0.646	20 (73.7%, 37.7%)
	KOA	0.620	0.409–0.793	11 (50.0%, 79.0%)
CSS+ or CSS-	CLBP	0.698	0.571–0.800	28 (69.2%, 69.2%)
	KOA	0.764	0.540–0.900	17 (100%, 51.0%)
Pain intensity “higher” vs “lower” (median split value =2.72)	CLBP	0.657	0.545–0.754	34 (45.1%, 84.9%)
	KOA	0.714	0.553–0.835	19 (64.0%, 76.0%)
Pain interference “higher” or “lower” (median split value =1.71)	CLBP	0.734	0.629–0.818	34 (47.1%, 86.9%)
	KOA	0.759	0.601–0.868	18 (68.0%, 76.0%)

Abbreviations: CLBP, chronic low back pain; KOA, knee osteoarthritis; AUC, area under the curve; Sn, sensitivity; Sp, specificity; CS, central sensitization; CSS, central sensitivity syndrome.

In the KOA group, the AUC was 0.759 and the suggested cutoff score was 18. In the analysis to discriminate the presence or absence of CS, the AUC values were very low (CLBP: 0.512, KOA: 0.620).

Discussion

The aim of the current study was to investigate whether the association between the CSI, pain-related symptoms, pain-related disability, and HRQOL differs among musculoskeletal disorders. We found that patients with CLBP showed more pronounced CS-related symptoms and higher prevalence of CSSs compared to the patients with KOA, and pain-related disability and health-related QOL were associated with the CSI in both CLBP and KOA. In addition, pain intensity correlated with the CSI score only in the CLBP group. These findings suggested that although CS as diagnosed by CSI is involved in the pathology of pain in both CLBP and KOA, the impact of CS on pain and pain-related disability differs between CLBP and KOA. Among various factors contributing to pain (ie structural, psychosocial, and neurophysiological), it presently remains unclear how strong is the involvement of CS in CLBP and KOA. CS is not a yes/no or present/absent single entity or phenomenon, but it occurs over a continuum, from a minor to a great extent.⁴⁷ Therefore, as a basic characteristic of the disease, CS may be more involved in pain in CLBP than in KOA.

Conversely, our results showed that both the PPT and TS were not significantly correlated with the CSI score and there were no significant differences in the PPT and TS between patients with CLBP and patients with KOA. Both the PPT assessed at a distant site and TS are used as psychophysical tests of CS.¹⁵ That is, there was no significant difference in the psychophysical factors of CS between patients with CLBP and KOA. Regarding previous studies that investigated the correlation between the CSI score and QST, Gervais-Hupe et al³⁰ showed that the CSI scores had significant weak correlations with PPT, but not with TS, in patients with KOA. Furthermore, Coronado et al showed that the CSI score was not associated with PPT of remote sites in patients with shoulder pain.⁴⁸ Our results were consistent with those of these previous studies. However, Kregel et al reported weak correlations between the CSI score and PPT in patients with chronic CLBP.⁴⁹ Although the difference in results between the studies may be due to differences in sample size and population characteristics, the lack of consensus regarding the

correlation between the CSI and QST in the existing literature suggests that the CSI may not reflect a direct measurement of CS as a neurophysiological phenomenon that comprises an augmented response to repetitive mechanical stimulation and reduced endogenous pain inhibition, resulting from alterations in the properties of neurons in the central nervous system.

The results of the ROC curve analysis also reflected the difference in the impact of CS on pain and pain-related disability between CLBP and KOA. We performed ROC curve analysis to determine optimal cutoff scores that identify the presence/absence of CS, the presence/absence of CSS, and the severity of pain and pain-related disability. We showed that the cutoff scores differed based on each parameter we attempted to identify and were higher in CLBP than in KOA in all analyses. Furthermore, all of cutoff scores we showed in the current study were lower than the previously suggested score of 40 investigating to the patients with CSSs such as myofascial pain syndrome, tension headache/migraines, FM, temporomandibular joint disorder, and complex regional pain syndrome in interdisciplinary pain clinics.^{22,23} This result was consistent with that of the previous study reported by Gervais-Hupe.³⁰ The proportion of participants who had one or more CSS diagnoses in the study by Neblett et al was higher than that in our study (74% [range: 1–7] vs 25% for CLBP [range:1–4] and 10% for KOA [range:1–3]). Therefore, the differences in the suggested cutoff scores between the previous study and our study may also reflect the disease-specific characteristic of CS. Our findings suggest that we should use the appropriate cutoff scores for these purposes (ie to identify the presence/absence of CSS or to identify the severity of pain and pain-related disability) and consider the difference in the impact of CS on pain by the patient group. However, this finding should be replicated in the following studies because this is the first study to show differences in the cutoff score between the parameters to be identified and between patient groups and our sample size was small.

The AUC was nearly 0.7 in all analyses performed to determine the severity of pain and pain-related disability (pain intensity and pain interference), which is considered satisfactory. The suggested cutoff scores of 34 in CLBP and of 18–19 in KOA provided low to moderate Sn (45.1–68.0%) and higher Sp (76.0–86.9%). Although the lower Sn would not be sufficient as a screening tool, we showed the ability of the cutoff score to identify patients who had higher pain intensity and pain-related disability caused by CS.

We also performed ROC curve analysis to identify patients with CSS as performed in a previous study.²² The determined cutoff scores in both CLBP and KOA were lower than the initially recommended threshold of 40. A distinct difference between our study and the previous one that could explain the difference in the cutoff score is the included population; the previous study included patients diagnosed in interdisciplinary pain clinics with a CSS such as myofascial pain syndrome, tension headache/migraines, FM, temporomandibular joint disorder, and complex regional pain syndrome.^{22,23} This finding also suggests the existence of disease-specific differences in the impact of CS on pain.

Another ROC curve analysis to identify the patients with CS determined by the QST found that the AUCs were low, which indicates low detection accuracy. This result may be due to the non-significant correlation between the CSI score and QST results. Therefore, the cutoff scores suggested by this analysis would not be meaningful for clinical practice.

This study's limitations should be considered when interpreting the results. First, this study was cross-sectional; therefore, it is not possible to draw conclusions regarding causation, predictive validity, or response to intervention. Second, the average pain intensity and interference scores of our participants were low and most of the participants with KOA were at the early stage of OA. These aspects of the clinical characteristics of our patients may have influenced our results. Especially, the results of the ROC curve analysis could have been influenced in the case of patients with severe pain. Therefore, our results regarding the difference in impact between the patient groups should be replicated under various conditions including in different countries and cultures. Third, our sample characteristic may have contributed to the low to moderate Sn in the ROC curve analysis: the proportion of participants who had one or more CSS diagnosis and who had higher CSI score was low. Further longitudinal large cohort studies are required to show the discriminative and predictive ability of the CSI as a screening tool of CS and CSS.

Conclusion

We showed initial findings that the impact of CS on pain and pain-related disability could differ between CLBP and KOA and that the cutoff scores differ by each parameter we attempted to identify. Considering the findings of this

study, further studies examining the disease-specific impact of CS on pain and pain-related disability and optimal cutoff scores in each patient group are needed for various diseases.

Ethics approval and informed consent

Ethics approval was obtained from the institutional ethics committee of Konan Women's University in Kobe, Japan. Written informed consent was obtained from all subjects prior to the study.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author.

Acknowledgments

We thank Yuno Yonezaki and Aya Ishihara for assistance with data collection. Eli Lilly Japan K.K. funded this study.

Author contributions

Study design: AM, TN. Data collection: AM, KT, MM, SY. Data analysis: AM. Drafting manuscript: TN, AM. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

TN reports grants from Eli Lilly Japan K.K., during the conduct of the study. The authors report no other conflicts of interest in this work.

References

1. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. *Pain*. 2008;137:473–477. doi:10.1016/j.pain.2008.04.025
2. Staud R. Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. *Curr Rheumatol Rep*. 2011;13:513–520. doi:10.1007/s11926-011-0206-6
3. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain*. 2013;29:625–638. doi:10.1097/AJP.0b013e31826f9a71
4. Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol*. 2011;38:1546–1551. doi:10.3899/jrheum.100724
5. Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2012;20:1075–1085. doi:10.1016/j.joca.2012.06.009

6. Paul TM, Soo Hoo J, Chae J, Wilson RD. Central hypersensitivity in patients with subacromial impingement syndrome. *Arch Phys Med Rehabil*. 2012;93:2206–2209. doi:10.1016/j.apmr.2012.06.026
7. Coronado RA, Simon CB, Valencia C, George SZ. Experimental pain process support peripheral and central sensitization in patients with unilateral shoulder pain. *Clin J Pain*. 2014;30:143–151. doi:10.1097/AJP.0b013e318287a2a4
8. Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain*. 2006;124:242–263. doi:10.1016/j.pain.2006.06.001
9. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26:465–473. doi:10.1007/s10067-006-0433-9
10. Sterling M, Treleaven J, Edwards S, Jull G. Pressure pain thresholds in chronic whiplash associated disorder: further evidence of altered central pain processing. *J Musculoskel Pain*. 2002;10:69–81. doi:10.1300/J094v10n03_05
11. Herren-Gerber R, Weiss S, Arendt-Nielsen L, et al. Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. *Pain Med*. 2004;5:366–376. doi:10.1111/j.1526-4637.2004.04055.x
12. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *Eur J Pain*. 2013;17:299–312. doi:10.1002/j.1532-2149.2012.00193.x
13. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *Eur J Pain*. 2014;18:1367–1375. doi:10.1002/j.1532-2149.2014.499.x
14. Noten S, Struyf F, Lluch E, D'Hoore M, Van Looverson E, Meeus M. Central Pain Processing in Patients with Shoulder Pain: a review of the literature. *Pain Pract*. 2017;17:267–280. doi:10.1111/papr.12502
15. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract*. 2012;12:276–285. doi:10.1111/j.1533-2500.2011.00493.x
16. Caumo W, Antunes LC, Elkfury JL, et al. The Central Sensitization Inventory validated and adapted for a Brazilian population: psychometric properties and its relationship with brain-derived neurotrophic factor. *J Pain Res*. 2017;10:2109–2122. doi:10.2147/JPR.S131479
17. Kregel J, Vuijk PJ, Descheemaeker F, et al. The Dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. *Clin J Pain*. 2016;32:624–630. doi:10.1097/AJP.0000000000000306
18. Cuesta-Vargas AI, Roldan-Jimenez C, Neblett R, Gatchel RJ. Cross-cultural adaptation and validity of the Spanish central sensitization inventory. *Springerplus*. 2016;5:1837. doi:10.1186/s40064-016-3515-4
19. Knezevic A, Neblett R, Jeremic-Knezevic M, et al. Cross-cultural adaptation and psychometric validation of the Spanish version of the central sensitization inventory. *Pain Pract*. 2018;18:463–472. doi:10.1111/papr.12618
20. Pittance L, Piroux E, Lannoy B, et al. Cross cultural adaptation, reliability and validity of the French version of the central sensitization inventory. *Man Ther*. 2016;25:e83–e84. doi:10.1016/j.math.2016.05.139
21. Tanaka K, Nishigami T, Mibu A, et al. Validation of the Japanese version of the Central Sensitization Inventory in patients with musculoskeletal disorders. *PLoS One*. 2017;12:e0188719. doi:10.1371/journal.pone.0188719
22. Neblett R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain*. 2013;14:438–445. doi:10.1016/j.jpain.2012.11.012
23. Neblett R, Hartzell MM, Cohen H, et al. Ability of the central sensitization inventory to identify central sensitivity syndromes in an outpatient chronic pain sample. *Clin J Pain*. 2015;31:323–332. doi:10.1097/AJP.0000000000000113
24. Kim SH, Yoon KB, Yoon DM, Yoo JH, Ahn KR. Influence of centrally mediated symptoms on postoperative pain in osteoarthritis patients undergoing total knee arthroplasty: a prospective observational evaluation. *Pain Pract*. 2015;15:E46–E53. doi:10.1111/papr.2015.15.issue-6
25. Bennett EE, Walsh KM, Thompson NR, Krishnaney AA. Central sensitization inventory as a predictor of worse quality of life measures and increased length of stay following spinal fusion. *World Neurosurg*. 2017;104:594–600. doi:10.1016/j.wneu.2017.04.166
26. Verbunt JA, Smeets RJ, Wittink HM. Cause or effect? Deconditioning and chronic low back pain. *Pain*. 2010;149:428–430. doi:10.1016/j.pain.2010.01.020
27. Nordeman L, Gunnarsson R, Mannekorpi K. Prevalence and characteristics of widespread pain in female primary health care patients with chronic low back pain. *Clin J Pain*. 2012;28:65–72. doi:10.1097/AJP.0b013e318223622c
28. Urquhart DM, Phymaung PP, Dubowitz J, et al. Are cognitive and behavioural factors associated with knee pain? A systematic review. *Semin Arthritis Rheum*. 2015;44:445–455. doi:10.1016/j.semarthrit.2014.07.005
29. Fingleton C, Smart K, Moloney N, Fullen BM, Dooby C. Pain sensitization in people with osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2015;23:1043–1056. doi:10.1016/j.joca.2015.02.163
30. Gervais-Hupe J, Pollice J, Sadi J, Carlesso LC. Validity of the central sensitization inventory with measures of sensitization in people with osteoarthritis. *Clin Rheumatol*. 2018;37:3125–3132. doi:10.1007/s10067-018-4279-8
31. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the Knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*. 1986;29:1039–1049.
32. Link TM, Steinbach LS, Ghosh S, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology*. 2003;226:373–381. doi:10.1148/radiol.2262012190
33. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.
34. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med*. 2001;33:337–343.
35. Tsuchiya A, Ikeda S, Ikegami N, et al. Estimating an EQ-5D population value set: the case of Japan. *Health Econ*. 2002;11:341–353. doi:10.1002/hec.673
36. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23:129–138.
37. Uki J, Mendoza T, Cleeland CS, Nakamura Y, Takeda F. A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory-BPJ-J. *J Pain Symptom Manage*. 1998;16:364–373.
38. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121. doi:10.1016/j.jpain.2007.09.005
39. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology Preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62:500–610. doi:10.1002/acr.20140
40. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference value. *Pain*. 2006;123:231–243. doi:10.1016/j.pain.2006.01.041
41. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitization in relation to pain severity in knee osteoarthritis: trait or state? *Ann Rheum Dis*. 2015;74:682–688. doi:10.1136/annrheumdis-2013-204191
42. Neogi T, Guermazi A, Roemer F, et al. Association of joint inflammation with pain sensitization in knee osteoarthritis: the multicenter osteoarthritis study. *Arthritis Rheumatol*. 2016;68:654–661. doi:10.1002/art.39488

43. Goubert D, Danneels L, Graven-Nielsen T, Descheemaeker F, Meeus M. Differences in pain processing between patients with chronic low back pain, recurrent low back pain, and fibromyalgia. *Pain Physician*. 2017;20:307–318.
44. Lluch Girbes E, Duenas L, Barbero M, et al. Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis. *Phys Ther*. 2016;96:1196–1207. doi:10.2522/ptj.20150492
45. Keegan PE, Matthews JN, Lunec J, Neal DE. Statistical problems with ‘optimal’ thresholds in studies of new prognostic factors in urology. *BJU Int*. 2000;85:392–397.
46. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic test. *Prev Vet Med*. 2000;45:23–41.
47. Lluch E, Nijs J, Countney CA, et al. Clinical descriptors for the recognition of central sensitization pain in patients with knee osteoarthritis. *Disabil Rehabil*. 2018;40:2836–2845. doi:10.1080/09638288.2017.1358770
48. Coronado RA, George SZ. The Central Sensitization Inventory and Pain Sensitivity Questionnaire: an exploration of construct validity and associations with widespread pain sensitivity among individuals with shoulder pain. *Musculoskeletal Sci Pract*. 2018;36:61–67. doi:10.1016/j.msksp.2018.04.009
49. Kregel J, Schumacher C, Dolphens M, et al. Convergent validity of the dutch central sensitization inventory: associations with psychophysical pain measures, quality of life, disability, and pain cognitions in patients with chronic spinal pain. *Pain Pract*. 2018;18:777–787. doi:10.1111/papr.12672

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