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ORIGINAL RESEARCH

Association Between Central Sensitization and Increasing Prevalence of Nocturnal Knee Pain in the General Population with Osteoarthritis from the Iwaki Cohort Study

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Purpose: Knee pain is associated with osteoarthritis (OA) and increases during this condition; however, its correlation with central sensitization (CS) in arthritis patients requires greater understanding. The present cross-sectional cohort study to explore the prevalence of knee OA, nocturnal knee pain and disability in general population and to examine the association of CS with sleep quality in Japanese general population.

Patients and Methods: From among 1056 community-dowelling volunteers, 942 were enrolled as participants in this study. Bilateral weight-bearing anterior-posterior knee radiographs were classified by the Kellgren–Lawrence grade. Nocturnal knee pain and disability were assessed with self-reported questionnaires. Using the CS inventory with nine items (CSI-9), CS was defined as 10 points or higher. Sleep quality was scored using the Pittsburgh Sleep Quality Index (PSQI). Linear regression analysis, adjusted by age, sex, body mass index, Kellgren-Lawrence grade, nocturnal knee pain, and lifestyle habits, was performed to investigate the association of CS with PSQI.

Results: The prevalence of OA, nocturnal knee pain, and disability was 37.9%, 7.6%, and 6.2%, respectively. The mean CSI-9 score was 4.9 ± 4.4, with a CS prevalence of 14.0%. The mean PSQI score was 3.9 ± 2.4, which was correlated with the CSI-9 value. CS was not correlated with OA severity; however, nocturnal knee pain prevalence increased from 13.3% to 25.5% in knee OA patients with CS. The CSI-9 value correlated with PSQI total score and subscales.

Conclusion: Knee OA severity correlated with nocturnal pain and disability; however, its association with CS was unproven. The combined effect of knee OA and CS elevated nocturnal pain and disability, resulting in diminished sleep quality.

Keywords: central sensitization, epidemiology, knee osteoarthritis, nocturnal knee pain, sleep quality

Introduction

Knee osteoarthritis (OA) typically causes chronic pain and disability in the elderly.[1] The radiographic prevalence of knee OA among adults aged >40 years has been reported to be approximately 42.0% in men and 62.4% in women.[2] The progression of knee OA leads to irreversible structural changes, high treatment costs for joint replacement, reduced productivity, and absence from work; therefore, it contributes to a growing substantial burden on the society.[3] Knee pain with OA is related to multiple confounders,[4] and it is known that a weak association exists between the

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degree of joint damage and the presence and intensity of clinical pain.[5,6] This constitutes one of the reliable predictors of knee OA-associated disability.[7–9] Nocturnal pain and disability are typical symptoms of knee OA; which diminish satisfaction over the knee condition and quality of life (QOL).[10–13] As chronic pain or nocturnal knee symptoms have considerable effects on the QOL, appropriate understanding and evaluation of chronic pain are critical for its management and control. The etiology and epidemiological background need to be evaluated further.

Recently, central sensitization (CS) has received attention as one of the key factors for recognizing chronic pain in knee OA patients.[14,15] Previous studies have revealed that CS induces hyperalgesia and widespread pain in OA patients.[14,15] According to the International Association for the Study of Pain, CS is defined as the enhanced responsiveness of nociceptors in the central nervous system to typical, non-noxious, or subthreshold afferent stimulation input.[16] This results in hypersensitivity and increased pain response outside the area of injury, ie, an expanded receptive field.[17,18] The intrinsic risk of CS in OA patients at the terminal stage was estimated to be approximately 20%;[19] this potentially led to subsequent impairments in the QOL.[20] Indeed, certain OA patients present a psychological background, such as catastrophizing or depressive conditions, for chronic pain and nocturnal knee symptoms.[21] CS may be related to nocturnal pain;[22] nonetheless, the association of CS with such symptoms in knee OA is yet to be evinced from a large-sample epidemiological study. In addition, the correlation of CS with radiographic knee OA severity remains unclear.

Therefore, this cross-sectional epidemiological study aimed to explore the prevalence of knee OA, nocturnal knee pain and disability in the general population and to examine the association of CS with sleep quality. The epidemiological nature of the study made evaluating these associations possible because a large general population with or without any stage of OA and symptoms could be included. We hypothesized that the prevalence of CS increases with radiographic knee OA severity, similar to that of nocturnal symptoms, with a concomitant decrease in sleep quality.

Materials and Methods

Participants

Held since 2008, the Iwaki Health Promotion Project is an annual community-based preventive medicine program that aims to improve average life expectancy.[9,10,23] Of approximately 10,000 people in the general population living in the Iwaki area of Hirosaki, located in western Aomori Prefecture, Japan, 1056 volunteers participating in the general health check-ups of the Iwaki Health Promotion Project from June 26 to July 4, 2018 were recruited through mass media advertisements and by public health nurses, and were screened for inclusion in this study. Individuals were excluded if they were postoperative for total knee arthroplasty or arthrodesis; received treatment for rheumatoid arthritis or psychological disorders; had malignant tumors; or had incomplete or unavailable data. For anthropometric evaluation, height and weight were measured and recorded to calculate the body mass index (BMI). In addition, the summed skeletal muscle volume of the trunk, lower extremity, and upper extremity was measured using a body composition analyzer (Tanita MC-190; Tanita Corp., Tokyo, Japan). Skeletal muscle index (SMI) was calculated as follows: SMI (kg/m^2) = skeletal muscle mass (kg)/$height^2$ (meters). This study was performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the ethics committee of the Hirosaki University Graduate School of Medicine. Written informed consent was obtained from all participants.

Radiographic Evaluation

Radiographic examination of both knees was performed using the CXDI-40EG digital radiography system (Canon Inc., Tokyo, Japan).[23] Experienced radiologic technicians and orthopedic surgeons obtained weight-bearing anterior-posterior radiographs at maximum extension with foot map positioning. The beam was placed parallel to the floor and aimed at the joint space; the sequencing was set at 60 kV, 50 mA, and 80 ms. Images obtained were converted into the joint photographic experts group (.jpeg) file format. OA severity was evaluated as Kellgren–Lawrence (KL) grades (from 0 to 4) using the KL radiographic atlas; this was performed by two trained orthopedic surgeons (D.C. and S.O.).[24] Participants rated with a KL grade of 2 and above were categorized into the OA group, while those rated with a KL grade of 0 and 1 were categorized into the non-OA group. Furthermore, based on the radiographic knee OA severity of their worse knee, participants were classified into the normal (KL grade = 0 or 1), moderate (KL grade = 2), and severe (KL grade = 3 or 4) groups.[25] Regarding the interclass correlation coefficient (ICC) between the two surgeons, the ICC (2,1) was 0.815. Surgeons were blinded to the

sequence of radiograph acquisition and the clinical status of the participants.

Central Sensitization

CS was evaluated using the central sensitization inventory A (CSI) with self-reported questionnaires.[26] CSI displays satisfactory psychometric strength, clinical utility, and initial construct validity. The completed version comprises 25 items; however, the shorter version was locally available and consists of nine items (CSI-9). Scores were assigned from 0 to 4, and calculated to 100 points in CSI full version and 36 points in CSI-9, with a higher score indicating a more severe CS condition. The CSI-9 was validated using the Spearman correlation coefficient (r = 0.91) using the full version of CSI.[27] Based on this previous report,[27] we categorized patients into the CS group if they had a score of 10 points or higher.

Knee Osteoarthritis Symptoms and Nocturnal Pain

Knee OA symptoms were evaluated using a patient-based tool (Knee Injury and Osteoarthritis Outcome Score [KOOS]) and considered under five subscales (pain, symptoms, activities of daily living, sports/recreation, and QOL).[28,29] Nocturnal knee pain was evaluated using the question: "At night, while in bed, how much knee pain did you experience during the last week?" Similarly, nocturnal disability during movement as part of activities of daily living was assessed using the question: "Last week, while lying in bed, how much difficulty did you experience while turning over or maintaining the knee position?" In these questionnaires, the participants selected the most suitable option among "none", "mild", "moderate", "severe", and "extreme"; if they chose the mild, moderate, severe, and extreme options, they were defined to have nocturnal knee pain or disability. The prevalence of such symptoms was calculated for all participants and for those with knee OA.

Sleep Quality

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), which is a valid and reliable index for patients with arthritis.[30] The PSQI consists of seven subscales for sleep evaluation: quality, latency, duration, habitual efficiency, disturbance, use of medication, and daytime dysfunction.[31,32]

Statistical Analysis

Demographic data of the non-CS and CS groups were expressed as means ± standard deviations. Comparisons were performed using the chi-square test for categorical variables and the Mann–Whitney *U*-test for continuous variables. The prevalence of CS was calculated among the following age-specific groups (years): 18–39 (106 men and 141 women), 40–49 (81 men and 89 women), 50–59 (66 men and 109 women), 60–69 (90 men and 131 women), and ≥70 (51 men and 75 women). Spearman correlation coefficients (r) were estimated between age-specific groups and prevalence of CS. Additionally, nocturnal knee pain and disability among the three categories of OA (KL grades 0/1, 2, and 3/4) were compared using the chi-square test. The chi-square test was also performed to investigate the prevalence of nocturnal knee pain and disability in those with or without knee OA or CS, and the influence of CS on the prevalence of nocturnal knee symptoms, between non-CS and CS groups in those with knee OA. The Spearman correlation coefficients between the PSQI and the CSI-9 scores were estimated. To investigate the factors related to nocturnal symptoms in the non-OA and OA groups, crude and adjusted logistic regression analyses were performed. The adjusted logistic regression model included age, sex, BMI, KL grade, CS, and lifestyle habits as covariates. Furthermore, to reveal the association of CS with sleep quality, linear regression analysis was performed with the seven subscales and aggregate score of the PSQI as the dependent variables and the CSI-9 value as the independent variable in all participants and in those with OA. Each subscale was adjusted for age, sex, BMI, KL grade, nocturnal knee pain, and lifestyle habits. Ultimately, to estimate the cut-off PSQI score for the determination of the presence of CS, receiver operating characteristic (ROC) analysis was performed with the total PSQI score as the testing variable and the presence of CS as the diseased condition. The area under the curve (AUC) was calculated; the cut-off value was defined as Youden's index based on the sensitivity and specificity. Data input and analysis were performed using SPSS version 25.0 J (SPSS Inc., Chicago, IL, USA). A p-value (p) < 0.05 was considered statistically significant.

Results

Of the 1056 participants screened, 114 were excluded because they received rheumatoid arthritis treatment (13), underwent postoperative total knee arthroplasty and

arthrodesis (9), were treated for psychological disorders (10), had malignant tumors (36), and had incomplete or unavailable data (46). Consequently, 942 participants (394 men and 548 women) were included, and their data were collected for statistical analysis. Knee OA, nocturnal knee pain, and disability were observed in 357 (37.9%), 72 (7.6%), and 58 (6.2%) participants, respectively. Furthermore, the overall mean CSI-9 score was 4.9 ± 4.4 points (range: 0–31 points) and the overall CS prevalence was 14.0%. With aging, the prevalence of CS increased in men ($r = 0.894$, $p = 0.041$) but decreased in women ($r = -0.872$, $p = 0.054$) (Figure 1). The mean PSQI score was 3.9 ± 2.4 points (range: 0–18 points) and was positively correlated with the CSI-9 score ($r = 0.390$, $p < 0.001$). Participants with a positive CSI-9 score had a lower SMI with depleted KOOS subscales ($p = 0.015$ and $p < 0.001$, respectively) and a higher PSQI score ($p < 0.001$) (Table 1).

With respect to radiographic severity, 62.1%, 32.2%, and 5.7% of the participants had KL grades of 0/1, 2, and 3/4, respectively. The prevalence of nocturnal pain ($p < 0.001$) and disability ($p < 0.001$) increased with knee OA severity; however, similar changes did not occur with CS ($p = 0.537$) (Table 2).

With knee OA, the prevalence of nocturnal pain and disability increased up to 25.5% (9.1 times, $p = 0.021$) and 21.8% (18.2 times, $p = 0.033$), respectively (Figure 2). The adjusted logistic regression analysis revealed that CS was significantly correlated with nocturnal knee pain in the OA group ($p = 0.008$, odds ratio: 2.73, 95% confidence interval [CI]: 1.30–5.72) (Tables 3 and 4). Furthermore, CS was significantly correlated with nocturnal disability in the OA group ($p = 0.009$, odds ratio: 2.94, 95% CI: 1.31–6.57) and non-OA ($p = 0.001$, odds ratio: 11.24, 95% CI: 2.84–44.73) groups.

In the OA group, the CSI-9 score was associated with the aggregate PSQI score ($p \leq 0.001$) and with the subscales of sleep quality ($p \leq 0.001$), sleep latency ($p \leq 0.001$), sleep disturbance ($p = 0.003$), use of sleeping medication ($p = 0.002$), and daytime dysfunction ($p \leq 0.001$) (Table 5). The ROC analysis showed that PSQI moderately reflected the presence of CS ($p \leq 0.001$, AUC: 0.750, 95% CI: 0.713–0.801), and indicated a PSQI score of 4 as the cut-off value based on a sensitivity of 0.833 and specificity of 0.553 (Odds ratio: 4.43) (Figure 3).

Table 1 Demographic Data of the Study Participants

	Non-CS	CS	p-value
Sample Number	**810**	**132**	
Age (y.o.)	52.27 ± 15.5	51.1 ± 15.3	0.462
Females (%)	456 (56.3%)	92 (69.7%)	0.004
Fat (%)	25.5 ± 8.0	26.7 ± 8.5	0.119
Skeletal muscle index (kg/m2)	16.0 ± 2.1	15.5 ± 1.8	0.015
Body mass index (kg/m2)	22.9 ± 3.5	22.7 ± 3.8	0.375
KOOS Symptom	91.9 ± 12.6	87.6 ± 13.9	<0.001
KOOS Pain	93.6 ± 12.7	89.4 ± 15.2	<0.001
KOOS ADL	96.8 ± 8.7	92.7 ± 13.1	<0.001
KOOS Sports	91.7 ± 18.5	84.4 ± 22.4	<0.001
KOOS QOL	86.6 ± 19.9	78.2 ± 22.7	<0.001
PSQI	3.6 ± 2.1	6.0 ± 2.9	<0.001
Central sensitization inventory full	7.4 ± 5.9	26.0 ± 8.3	<0.001
Central sensitization inventory 9	3.6 ± 2.8	13.0 ± 3.3	<0.001
Smoking habit (%)	136 (16.8%)	24 (18.2%)	0.708
Drinking habit (%)	383 (47.3%)	52 (39.4%)	0.109
Fitness habit (%)	143 (17.7%)	20 (15.2%)	0.536

Notes: Continuous variables are expressed as means ± standard deviations and compared using the Mann–Whitney *U*-test. Categorical variables were compared between the non-CS and CS groups using the Chi-square test.

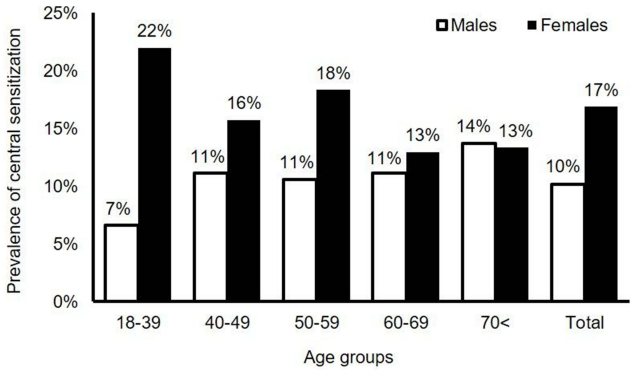

Figure 1 Prevalence of central sensitization (CS) according to age-specific groups. This was defined using CS inventory 9 (CSI-9). A score of 10 points or higher was regarded as positive.

Discussion

The most significant finding of the present study was that the prevalence of CS did not increase with increasing

Table 2 Prevalence of Nocturnal Symptoms and Central Sensitization (CS) in Terms of Radiographic Knee Osteoarthritis (OA) Severity

	KL 0/1	KL 2	KL3/4	p-value
Sample	**585**	**303**	**54**	
Central sensitization	77 (13.2%)	48 (15.8%)	7 (13.2%)	0.537
Nocturnal knee pain	18 (3.1%)	37 (12.2%)	17 (31.5%)	<0.001
Nocturnal disability	12 (2.1%)	30 (9.9%)	16 (29.6%)	<0.001

Notes: The prevalence of CS, nocturnal knee pain, and disability with respect to knee OA severity were compared using the chi-square test.

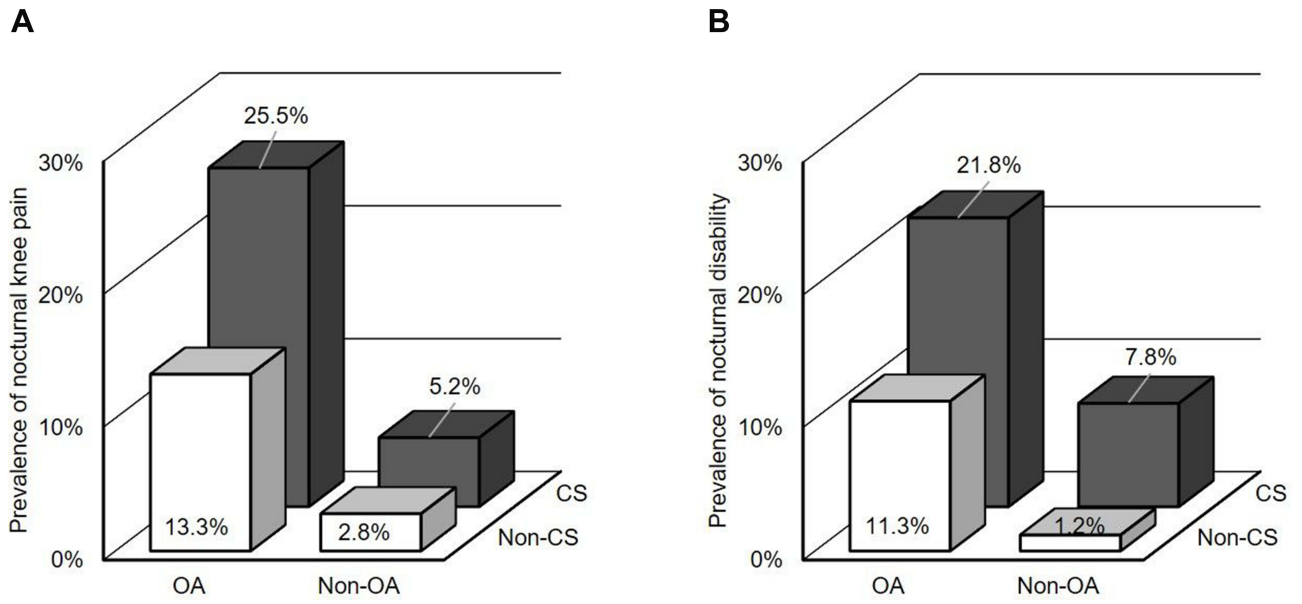

Figure 2 Prevalence of nocturnal knee pain (**A**) and disability (**B**) in the central sensitization (CS) and knee osteoarthritis (OA) groups.
Abbreviations: CS, central sensitization; OA, osteoarthritis.

radiographic knee OA severity; however, the presence of CS was correlated with an additional high prevalence of nocturnal knee symptoms in individuals with knee OA. Furthermore, the presence of CS was also associated with lower sleep quality. ROC analysis revealed that a PSQI score of 4 points or higher was a significant risk factor for potential CS. Irrespective of the radiographic knee OA severity, orthopedic surgeons should carefully evaluate the potential presence of CS, as it is related to postoperative poor outcomes.[19,33,34]

Nocturnal symptoms such as pain due to knee OA immensely impact the QOL.[10] This was the ninth-most frequently reported complaint in knee OA patients; the pain itself was infrequent and did not bother these patients.[11] In another study, the majority of hip and knee OA patients reported experiencing nocturnal pain through an interview-style investigation.[12] A large-sample cohort study featuring 118,336 subjects with arthritis reported that 17% of adults ≥18 years of age were usually experiencing some level of knee pain, which was related to

Table 3 Factors Related to the Presence of Nocturnal Knee Pain

	Non-OA				OA			
	B	**p-value**	**Odds**	**95% CI**	**B**	**p-value**	**Odds**	**95% CI**
Crude								
Central sensitization	0.66	0.256	1.93	0.62–6.03	0.81	<0.001	2.24	1.12–4.47
Adjusted								
Age	0.03	0.103	1.03	0.99–1.07	0.04	0.005	1.04	1.01–1.07
Females	−0.96	0.142	0.38	0.11–1.38	0.10	0.799	1.10	0.53–2.30
BMI	0.01	0.862	1.01	0.86–1.19	0.04	0.377	1.04	0.95–1.13
KL grade	0.51	0.376	1.67	0.54–5.19	0.52	0.129	1.68	0.86–3.28
Central sensitization	0.96	0.118	2.62	0.78–8.75	1.00	0.008	2.73	1.30–5.72
Smoking habit	−0.08	0.906	0.92	0.24–3.60	0.33	0.562	1.38	0.46–4.15
Drinking habit	−0.96	0.099	0.38	0.12–1.20	0.14	0.703	1.14	0.57–2.29
Fitness habit	0.59	0.333	1.80	0.55–5.97	−0.79	0.094	0.46	0.18–1.14

Notes: Crude and adjusted logistic regression analyses were performed with nocturnal knee pain as the dependent variable and age, sex, body mass index (BMI), Kellgren–Lawrence (KL) grade, central sensitization (CS), and lifestyle habits as the independent variables in the non-OA (n = 585) and OA (n = 357) groups.
Abbreviation: 95% CI, 95% confidence interval.

Table 4 Factors Related to the Presence of Nocturnal Disability

	Non-OA				OA			
	B	p-value	Odds	95% CI	B	p-value	Odds	95% CI
Crude								
Central sensitization	1.96	<0.001	7.07	2.22–22.52	0.79	0.035	2.20	1.06–4.58
Adjusted								
Age	0.09	0.004	1.09	1.03–1.16	0.06	<0.001	1.06	1.03–1.09
Females	−0.16	0.869	0.86	0.14–5.41	0.09	0.830	1.09	0.48–2.47
BMI	0.05	0.727	1.05	0.81–1.36	0.05	0.308	1.05	0.96–1.16
KL grade	−0.70	0.351	0.50	0.12–2.16	0.48	0.184	1.61	0.80–3.25
Central sensitization	2.42	0.001	11.24	2.84–44.73	1.08	0.009	2.94	1.31–6.57
Smoking habit	−0.06	0.971	0.00	0.14–6.34	0.52	0.622	0.70	0.50–5.71
Drinking habit	−1.01	0.858	1.39	0.07–1.96	−0.19	0.401	0.22	0.38–1.82
Fitness habit	0.18	0.837	1.20	0.21–6.81	−0.85	0.097	0.43	0.16–1.17

Notes: Crude and adjusted logistic regression analyses were performed with nocturnal disability as the dependent variable and age, sex, body mass index (BMI), Kellgren–Lawrence (KL) grade, central sensitization (CS), and lifestyle habits as the independent variables in the non-OA (n = 585) and OA (n = 357) groups.
Abbreviation: 95% CI, 95% confidence interval.

Table 5 Influence of Central Sensitization (CS) on Sleep Quality

Dependent Variables	Overall			OA		
	β	p-value	Adjusted R^2	β	p-value	Adjusted R^2
Sleep quality	0.36	<0.001	0.14	0.23	<0.001	0.11
Sleep latency	0.24	<0.001	0.06	0.20	<0.001	0.05
Sleep duration	0.13	<0.001	0.05	0.07	0.174	0.05
Habitual sleep efficiency	0.01	0.85	0.01	0.05	0.381	−0.01
Sleep disturbance	0.28	<0.001	0.1	0.16	0.003	0.05
Use of sleeping medication	0.22	<0.001	0.06	0.16	0.002	0.04
Daytime dysfunction	0.38	<0.001	0.15	0.34	<0.001	0.12
PSQI total	0.41	<0.001	0.19	0.32	<0.001	0.11

Notes: Linear regression analysis was performed with the seven subscales and the aggregate Pittsburgh Sleep Quality Index (PSQI) score as the dependent variables and with the CSI-9 score as the independent variable in all participants (n = 942) and in those with OA (n = 357). Each subscale was adjusted for age, sex, body mass index (BMI), Kellgren–Lawrence (KL) grade, nocturnal knee pain, drinking, smoking, and fitness habits. β indicates the standardized partial regression coefficients.

insomnia symptoms.[13] In addition, a previous study showed that the prevalence of nocturnal pain increased with radiographic knee OA severity.[10] In the present study, the combination of CS with radiographic knee OA was shown to increase the prevalence of nocturnal knee pain and disability in comparison with OA patients without CS. This result suggests that the CS on radiographic knee OA additionally increases the prevalence of nocturnal knee pain, while OA severity correlates to an increased prevalence of nocturnal knee pain. Furthermore, this study revealed that the combination of OA and CS diminished sleep quality. Only one-third of the participants with radiographic knee OA have previously reported symptoms;[6] their severity was considered to be influenced by CS and radiographic knee OA. In the clinical settings, persistent intense nocturnal knee pain is regarded as an indication for total arthroplasty[35,36] for providing relief.[37] In addition, reports that duloxetine administration to hip and knee OA patients reduced nocturnal pain indirectly support our results.[38,39] These findings suggest that the presence of CS is consistently associated with increasing nocturnal knee symptoms, regardless of radiographic severity, resulting in a diminished sleep quality.

In patients with nocturnal knee symptoms, the overriding concern with CS is pain sensitization, which induces signs of localized and widespread stimulation.[5,40] However, the association of radiographic knee OA severity with CS is currently controversial, because there are few large-sample cohort studies on the general population that clarify this association. The prevalence of pain

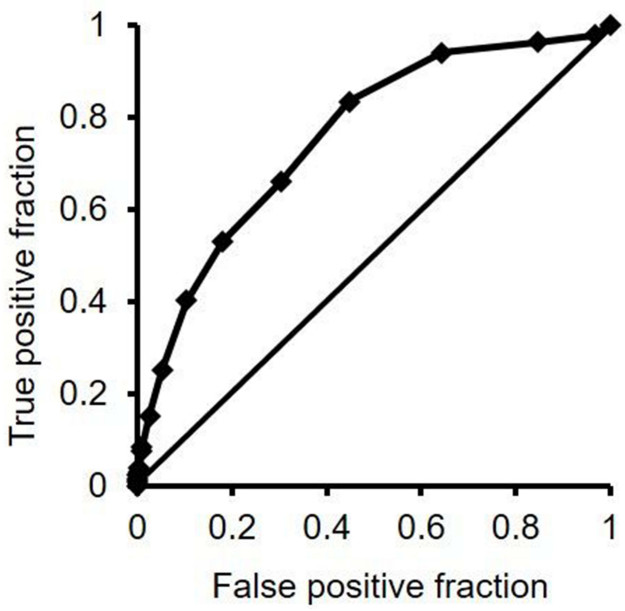

Figure 3 The receiver operating characteristic (ROC) curve of the PSQI score for detecting the presence of central sensitization (CS). To estimate the cut-off value of the PSQI score for determining the presence of CS, ROC analysis was performed with the PSQI total score as the testing variable and the presence of CS as the diseased condition. The area under the curve was 0.750 (95% confidence interval: 0.713–0.801, $p < 0.001$). The cut-off point was defined as the nearest point to the true positive, estimated as 5 points with an odds ratio of 4.43.

sensitization has been reported to be higher in terminal OA patients than in asymptomatic controls,[41] and it was shown to be associated with radiographic OA severity.[41] In contrast, the CHECK study with 2126 subjects revealed that the pressure pain threshold and temporal summation were associated with OA-related pain, but not with radiographic OA.[43] In addition, a reduced CS or a decrease in the pain threshold level was indicated by diminished intensity and not by radiographic severity.[44] Moreover, a weak association has been propounded between the degree of joint damage and the clinical pain intensity; however, sensitization has performed a significant role in the experience of chronic joint pain by OA patients.[5] In the present study, hyperalgesia around the knee joint seems to be the reason for the increased prevalence of nocturnal knee pain via sensitization in participants with CS.

A direct association between CS and radiographic knee OA severity was unproven in the present study. The descending pain inhibitory pathway was regarded as a potential cause for the chronic pain in knee OA;[45] additionally, 28% of the terminal arthritis patients displayed CS with a diminished QOL.[20] The association between knee OA severity and the comorbidity of CS is presently controversial. In patients, the degree of sensitization was noted to correlate with the clinical pain reports, but not with the radiographic findings.[46] In addition, increased sensitivity was observed to occur during elevated pain and low-grade knee OA; this suggests the apparent role of CS in elevated pain, regardless of the evidence of pathological OA changes.[44] Previous studies support our results that the prevalence of CS did not increase with the KL grade in the general population; however, the nocturnal knee symptoms escalated through pain sensitization. In contrast, the prevalence of nocturnal knee pain and disability with respect to knee OA severity was previously demonstrated.[10] The finding that the prevalence of CS is weakly dependent on age in men, but not the severity of radiographic knee OA, would be considered as influenced by the other musculoskeletal or psychiatry diseases.

In the present study, the cut-off value of the PSQI score for detecting the presence of CS was 4 points. Typically, this is set at 6 for sleep disturbance; therefore, this study finding is worthy of further evaluation. For the purpose of knee surgery, it is critical to evaluate the sleep quality and nocturnal symptoms. Based on previous clinical studies, the presence of preoperative CS would remain a potential risk for chronic post-surgical pain following total knee arthroplasty.[19,33,34] Preoperative evaluations and interventions for CS or nocturnal symptoms are necessary for satisfactory clinical outcomes, regardless of the radiographic knee OA severity. Preoperative administration of duloxetine was reported to reduce the risk of chronic post-surgical pain.[47] The present study demonstrated CS-diminished sleep quality, as evaluated by PSQI; this may be an indicator for CS.

The present study contains several limitations. First, the study sample comprised the Japanese general population; data regarding the patients' background characteristics and confounding factors were unavailable. Second, the evaluation of CS was conducted exclusively by self-administered questionnaires. The power of the CSI-9 is likely to be relatively weak in comparison with available physical examinations for pain stimulation and evaluation, such as temporal summation, pressure pain thresholds, quantitative sensory testing, mild pain detection, and pressure tolerance thresholds, and the visual analog scale.[5,40,42] However, performing these is difficult in a large-sample cohort study such as ours. Third, the psychological condition of the patients was required to be examined as some OA patients may display

a catastrophizing or depressive background for chronic pain.[21] Fourth, the imaging examination was limited to radiography; however, magnetic resonance imaging or ultrasound sonography is advantageous in detecting minute structural changes. Therefore, detailed etiology related to CS or nocturnal knee symptoms may be underestimated. Fifth, owing to the small number of patients with a KL grade 4, a positive ratio of CSI-9 was not considered for the statistical accuracy, and hence KL grade was summarized as the knee OA severity. This limitation is attributed to the epidemiological nature of the study targeting the general population whereas a clinical study would feature confirmed patients. Finally, due to the cross-sectional nature of the study, we could not identify the causal relationship between CS and nocturnal knee symptoms in participants with OA; future longitudinal studies are required.

Conclusion

Radiographic knee OA severity was correlated with an increase in nocturnal knee pain and disability; however, its association with the prevalence of CS was unproven. The combination of knee OA and CS enhanced the occurrence of nocturnal knee symptoms and diminished sleep quality. A PSQI score > 4 points could detect a significant risk of potential CS and hence be an effective screening tool.

Abbreviations

CS, central sensitization; CSI, central sensitization inventory A; ICC, interclass correlation coefficient; KL, Kellgren–Lawrence; KOOS, knee injury and osteoarthritis outcome score; OA, osteoarthritis; PSQI, Pittsburgh sleep quality index; QOL, quality of life; SMI, skeletal muscle index.

Data Sharing Statement

The study protocol, statistical analysis, and data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was performed in agreement with the 1964 Helsinki Declaration and later amendments or comparable ethical standards. Approval was obtained from the ethics committee of the Hirosaki University Graduate School of Medicine. Written informed consent was obtained from all participants.

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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 declare that they have no competing interests.

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