



Effect of central sensitization inventory on the number of painful sites and pain severity in a Japanese regional population cohort

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1 Abstract

2 **Background:** To investigate the association between the central sensitization inventory (CSI),
3 a screening tool for central sensitization, and the number of painful sites and the severity of
4 pain in locomotive organs in an epidemiological study in the elderly.

5 **Methods:** A total of 379 individuals who underwent musculoskeletal disease screening were
6 enrolled in this study. The CSI was used to assess symptoms of central sensitization. The
7 number and location of painful sites and the severity of pain were evaluated using pain
8 mapping and a numerical rating scale (NRS) at 37 sites. We investigated the association
9 between the number of painful sites and CSI score, and the association between the severity
10 of low back pain or knee pain and CSI score.

11 **Results:** There was a positive correlation between CSI score and the number of painful sites.

12 The CSI score was significantly higher in those with significant low back pain than in those
13 without pain, and the high-CSI group tended to have a greater number of painful sites.

14 Comparison of CSI scores between participants with low back pain alone and those with low
15 back pain and posterior lower leg pain showed that the latter group had a significantly higher
16 CSI score than the former group. The CSI score in participants with radiographic evidence
17 of knee osteoarthritis was significantly higher in those with knee pain than in those without
18 pain.

19 **Conclusions:** The results of this study suggest that participants with significant low back
20 pain and a higher number of painful sites are more susceptible to the influence of central
21 sensitization. In addition, CSI score was higher in participants with low back pain and
22 posterior lower leg pain than in those with low back pain alone, suggesting that the spread
23 of pain may be due to central sensitization.

24

25

26 **Introduction**

27 Japan is a super-aged society. Pain is the most common complaint among elderly people.
28 It is reported that 25–50% of elderly people experience some kinds of pain [1]. In Japan,
29 low back pain is the most common chronic musculoskeletal pain, followed by neck pain,
30 shoulder joint pain, and pain around the knee [2]. It has been increasingly recognized that
31 central sensitization is an important mechanism involved in chronic pain and its location and
32 severity. Central sensitization is a neurophysiological phenomenon characterized by
33 hyperexcitability in the central nervous system. It is defined as an amplification of neural
34 signaling within the central nervous system that elicits pain hypersensitivity [3]. Individuals
35 with central sensitization exhibit hypersensitivity to both nociceptive and non-nociceptive
36 stimuli [4], and present with pain hypersensitivity, tactile allodynia, and facilitated temporal
37 summation of pain [5,6]. Among patients complaining of chronic pain, some complain of
38 multiple symptoms, including fatigue, sleep disorder, headache, anxiety, and depression, that
39 cannot be explained by organic pathology [7]. It has been suggested that these symptoms
40 are related to central sensitization, and the unifying concept of central sensitivity syndromes
41 (CSSs) has been proposed [8,9].

42 Recently, the central sensitization inventory (CSI) was developed as a comprehensive
43 screening tool for central sensitization. The CSI comprises 25 health-related items identifying

44 symptoms associated with central sensitization, and has been shown to have satisfactory
45 reliability and consistency [4,10]. Studies have reported that patients undergoing total knee
46 arthroplasty (TKA) with a higher preoperative CSI score had a poorer outcome 3 months
47 after TKA [11], and that patients with a history of disease (such as depression) associated
48 with CSS had a higher CSI score [12], suggesting the usefulness of CSI as a screening tool.
49 However, no studies have specifically investigated the association between the CSI and the
50 number of painful sites and the severity of pain in the elderly. Since 2012, we have conducted
51 a community-based health checkup along with a musculoskeletal disease screening program
52 every 2 years in a hilly and mountainous area (Toei town) of approximately 3000 people,
53 through which we have conducted an epidemiological study of musculoskeletal diseases in
54 the elderly [13-17]. The objective of this study was to investigate the association between
55 the CSI, a screening tool for central sensitization, and the number of painful sites and the
56 severity of pain in the elderly in an epidemiological study of musculoskeletal diseases in the
57 elderly.

58 **Materials and Methods**

59 **Subjects**

60 A total of 395 individuals who lived in a hilly and mountainous area (Toei town) of
61 approximately 3000 people and underwent musculoskeletal disease screening in 2018 were

62 enrolled in this study. The purpose of this study was explained to all participants, and
63 informed consent was obtained. The inclusion criteria were men and women aged 50 years
64 or older who underwent whole spine X-ray imaging and whole lower-limb X-ray imaging and
65 agreed to participate in this study. Individuals who were unable to complete the questionnaire
66 by themselves were excluded. A total of 379 individuals were included in the analysis.

67 Measurements

68 The background characteristics included age, sex, height, weight, and body mass index
69 (BMI). The CSI was used to assess symptoms of central sensitization. The Japanese version
70 of CSI was developed from the original version by Mayer et al [10], and its validity and
71 consistency have been verified [18]. The questionnaire of original version was shown in
72 Table 1. The best responses to each statement such as 0=never, 1=rarely, 2=sometimes,
73 3=often, and 4=always were selected. Participants were asked to complete the
74 questionnaire by themselves, and the total scores ranging from 0 to 100 were calculated.
75 The location and severity of pain were evaluated using pain mapping and numerical rating
76 scale (NRS) at 37 sites with reference to the study by Nakamura et al. [2], and an NRS score
77 of 4 or higher indicates the presence of pain at the site (Figure 1). We investigated the
78 association between the number of painful sites and CSI score. We also investigated the
79 association between the severity of low back pain and the CSI score in participants with low

80 back pain, which is the most common complaint in Japanese individuals. Low back pain was
81 defined as pain in any of regions 23, 26, 27, or 28 on the pain map with an NRS score of 4
82 or higher. In addition, comparison of the CSI scores was performed between participants with
83 low back pain alone and those with low back pain and posterior lower leg pain. Posterior
84 lower leg pain was defined as pain in any of regions 30, 31, 32, 33, 34, and 35 on the pain
85 map with an NRS score of 4 or higher. Furthermore, the severity of knee osteoarthritis was
86 evaluated using the Kellgren-Lawrence (KL) grade based on the frontal X-ray view of the
87 whole length of the weighted lower limb, and radiographic knee osteoarthritis was defined as
88 a KL grade of ≥ 2 . The KL grade was evaluated by two orthopedic surgeons. If there was a
89 disagreement, reevaluation was performed jointly by the two orthopedic surgeons so that a
90 consensus could be reached. Participants with a KL grade of ≥ 2 and an NRS score of ≥ 4
91 were classified into group A, those with a KL grade of ≥ 2 and without significant knee joint
92 pain (NRS of ≤ 3) were classified into group B, and those with a KL grade of ≤ 1 and without
93 significant knee joint pain (NRS of ≤ 3) were classified into group C, and the CSI scores were
94 compared between the three groups. Knee joint pain was defined as pain in any of regions
95 12, 13, 32, or 33 on the pain map with an NRS score of ≥ 4 .

96 All procedures performed in studies involving human participants were in accordance with
97 the ethical standards of the institutional and/or national research committee and with the

98 1964 Helsinki declaration and its later amendments or comparable ethical standards. This
99 research has been approved by the IRB of the authors' affiliated institutions. Informed
100 consent was obtained from all individual participants included in the study.

101 Statistics

102 Statistical analysis was performed using SPSS for Windows version 22.0 (IBM Japan,
103 Tokyo, Japan). Demographic data were analyzed using the unpaired t test. The correlation
104 of the number of painful sites and severity of low back pain with CSI scores was analyzed
105 using the Spearman rank correlation coefficient. The other two-group comparisons were
106 performed using the Mann-Whitney U test. Three-group comparisons were performed using
107 the Kruskal-Wallis test with post-hoc Bonferroni correction. Statistical significance was set at
108 $p < 0.05$.

109 Results

110 Table 2 shows the demographic data of the participants. Although there was no significant
111 difference in age between sexes, height, weight, and BMI were significantly higher in men
112 than in women, and the CSI score was significantly higher in women than in men. Therefore,
113 we performed analysis separately for men and women. Table 3 shows frequency
114 distribution of CSI score according to the classification by Neblett R [12]. Most subjects
115 were classified as subclinical status. Overall, the CSI scores in this study tended to be lower

116 than those reported by Neblett R [12]. Frequency distributions of significant pain at each
117 pain site reflected front side and back side in Figure 1 were shown in Figure 2a and Figure
118 2b, respectively. Most frequent pain site was knee site reflected by region 12 and 13, and the
119 second frequent pain site was lumbar site reflected by region 23, 26, 27, and 28 in men,
120 women and total subjects.

121 There was a weak positive significant correlation between the number of painful sites on
122 the pain map and the CSI scores in both men and women (Table 4). The correlation between
123 the maximum rating for low back pain and the CSI score in participants with significant low
124 back pain was not significant in men but moderately significant in women. Participants were
125 divided into two groups with a cut-off of 30 for the CSI score; those with a CSI score of ≥ 30
126 were classified as the high-CSI group and those with a CSI score of < 30 were classified as
127 the low-CSI group. Comparison of the number of painful sites showed that for men, there
128 was no significant difference between the two groups, while for women, the number of painful
129 sites was significantly higher in the high-CSI group than in the low-CSI group (Table 5).
130 Comparison of the CSI scores between participants with and without low back pain showed
131 that the CSI score was significantly higher in those with significant low back pain than in
132 those without pain in both men and women (Table 6). Comparison of the CSI scores between
133 participants with low back pain alone and those with low back pain and posterior lower leg

134 pain showed that the latter group had a significantly higher CSI score than the former group
135 in both men and women (Table 7). Participants were divided into three groups according to
136 the presence or absence of radiographic evidence of knee osteoarthritis and the presence
137 or absence of symptoms. Comparison of the CSI scores between the three groups showed
138 that the CSI score was significantly higher in group A (presence of radiographic evidence of
139 knee osteoarthritis and its symptoms) than in groups B and C (absence of significant pain
140 irrespective of radiographic evidence of knee osteoarthritis) (Table 8).

141 **Discussion**

142 This study showed that sexual difference might be an important contributor to central
143 sensitization in elderly subjects. Several studies suggested that women had a higher
144 propensity to develop chronic pain due to central sensitization [19, 20]. Central sensitization
145 is characterized by a decreased pain threshold and expansion of the painful area [21]. A
146 study reported that 75% or more of patients with chronic low back pain had multiple painful
147 sites and that duloxetine (a drug that is effective in treating dysfunction of the descending
148 pain inhibitory system) was more effective in patients with multiple painful sites than in those
149 with isolated chronic low back pain [22]. Another study reported that there was a significant
150 association between the painful area and the degree of central sensitization in patients with
151 knee osteoarthritis [23]. In the present study, there was also a significant correlation

152 between the number of painful sites on the pain map and the CSI score in both men and
153 women, suggesting an association between the degree of central sensitization and number
154 of painful sites. In addition, the correlation between the maximum rating for low back pain
155 and the CSI score in patients with low back pain was not significant in men but moderately
156 significant in women. This result suggests that for men, the degree of low back pain reflects
157 organic disease and is not significantly associated with central sensitization, while for women,
158 the degree of low back pain may be influenced by central sensitization to some extent.

159 Participants were divided into two groups with a cut-off point of 30 on the CSI score; those
160 with a CSI score of ≥ 30 were classified as the high-CSI group and those with a CSI score of
161 < 30 were classified as the low-CSI group. The number of painful sites was compared
162 between the two groups. The rationale for using this cut-off point is based on the study by
163 Nevlett et al. where patients were divided into three groups according to the CSI score:
164 subclinical = 0 to 29, mild = 30 to 39, and moderate = 40 to 49 [12]. The cut-off point in the
165 present study was set at 30 to select patients with at least mild symptoms. It was difficult to
166 set the cut-off point higher than 30 because only 8% of participants in the present study had
167 a CSI of ≥ 30 . In contrast, in the study by Nevlett et al. [12], subjects with a CSI score of ≥ 40
168 accounted for 63% of the no-CSS patient group. In the present study, there was no significant
169 difference in the number of painful sites between the two groups, while for women, the

170 number of painful sites tended to be higher in the high-CSI group than in the low-CSI group.
171 This result suggests that for men, the number of painful sites reflects organic disease and is
172 not significantly associated with central sensitization, while for women, the number of painful
173 sites may be influenced by central sensitization to some extent.

174 A study showed that among patients with musculoskeletal pain, patients who were likely
175 to experience pain associated with central sensitization had a significantly higher degree of
176 pain, longer duration of pain, higher number of painful sites, and larger areas of pain than
177 those with other nociceptive pain or peripheral neuropathic pain [23]. Comparison of the
178 CSI scores between participants with and without significant low back pain showed that the
179 CSI score was significantly higher in those with low back pain than in those without in both
180 men and women. Central sensitization is a likely reason for the chronification of widespread
181 pain conditions [24]. The central sensitization results in more trigger points, which might
182 generate larger widespread pain area [25,26]. In this study, we considered the radiating
183 pain in the lower extremities in subjects with low back pain as widespread pain condition
184 related to central sensitization. Comparison of the CSI scores between participants with
185 low back pain alone and those with low back pain and posterior lower leg pain in the
186 subpopulation with low back pain showed that the latter group had a significantly higher CSI
187 score than the former group in both men and women. In other words, the CSI score was

188 higher in participants with low back pain and posterior lower limb pain than in those with low
189 back pain alone, suggesting that the distribution of pain might be related to central
190 sensitization.

191 It was reported that pain sensitization is also associated with the severity of pain in patients
192 with knee osteoarthritis [27]. In addition, a study investigated the discordance between
193 radiographic severity and pain in knee osteoarthritis and their associations with pain at other
194 sites, and showed that the pain threshold for the trapezius zone was significantly lower in
195 patients with high pain and low radiographic severity than in those with low pain and high
196 radiographic severity, indicating that the former group was susceptible to pain [28]. In the
197 present study, participants were divided according to the presence or absence of
198 radiographic evidence of knee osteoarthritis and the presence or absence of symptoms;
199 comparison of the CSI scores between them showed that the CSI score was significantly
200 higher in the group with significant pain and radiographic evidence of knee osteoarthritis than
201 in the group without significant pain irrespective of radiographic evidence of knee
202 osteoarthritis. Therefore, it is possible that the presence or absence of pain is influenced by
203 central sensitization, irrespective of radiographic evidence of knee osteoarthritis.

204 The limitations of this study are as follows. First, the participants were restricted to local
205 residents who were mainly involved in agriculture in a hilly and mountainous area, and they

206 may not be representative of the general Japanese population. Second, the participants were
207 residents who underwent musculoskeletal disease screening and were not a clinical
208 population with musculoskeletal disease, and this may have affected the distribution of the
209 CSI to a lesser degree. In fact, the distribution of the CSI scores in the present study was
210 substantially different from that of the study by Neblett et al. [12], and the background, such
211 as race and disease, was also different from that in their study. Third, we did not take into
212 account the etiology of pain at each site, duration of pain, or the presence or absence of
213 treatment.

214 In conclusion, we conducted an epidemiological study of musculoskeletal diseases that
215 aimed to investigate the association between CSI, a screening tool for central sensitization,
216 and the number of painful sites and severity of pain in the musculoskeletal organs of the
217 elderly. The results of this study suggest that participants with significant low back pain and
218 a higher number of painful sites are more susceptible to the influence of central sensitization.

219 In addition, the CSI score was higher in participants with low back pain and posterior lower
220 leg pain than in those with low back pain alone, suggesting that the spread of pain may be
221 due to central sensitization. The analysis of the influence of knee osteoarthritis suggests that
222 the presence or absence of pain may be influenced by central sensitization, irrespective of
223 radiographic evidence of knee osteoarthritis.

224

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307

308 Figure Legends

309 Figure 1. Self-administered pain mapping. A score from 0 to 10 is assigned to each site using
310 a numerical rating scale for subjective pain.

311 Figure 2a. Frequency distribution of significant pain at each pain region reflected front side
312 in Figure 1 . Figure 2b. Frequency distribution of significant pain at each pain region reflected
313 back side in Figure 1 .Data are expressed as the percentage of total. White bar: men, black

314 bar: women, and gray bar: total subjects.