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**Original Article**

# Central Sensıtızatıon ın Axıal Spondyloarthrıtıs: An Exploratıve Study wıth Quantıtatıve Sensory Testıng and Clınıcal Scales

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**ABSTRACT**

**Objective:** To evaluate the central sensitization (CS) and the related parameters in patients with axial spondyloarthritis (axSpA).

**Methods:** Quantitative sensory testing (QST) which consists of pressure pain threshold (PPT), temporal summation (TS), and conditioned pain modulation (CPM) were applied to the participants. Disease activity, functional status, sleep quality, pain, depression, and fatigue were assessed. Patients were divided as the ones with and without CS according to the central sensitization inventory (CSI) and the results were compared.

**Results:** One hundred patients and fifty controls were recruited. Sixty axSpA patients had CS. When QST results were compared between the patient and control groups, all PPT scores were found lower ($p<0.05$) in patients. Regarding the comparison of the patients with and without CS, sacroiliac, and trapezius PPT scores were found lower in the patients with CS ($p<0.05$). On the other hand, there was no significant difference in the mean TS scores ($p>0.05$) between patients and controls, and in patients with and without CS. All investigated

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comorbidities were found to be significantly more frequent ($p<0.001$) in the patients with CS. In regression analysis female gender, morning stiffness duration, CPM, depression, and fatigue were detected as related parameters with CSI scores.

**Conclusion:** CS and related comorbidities were found to be increased in axSpA patients. This increase should be taken into consideration in the management of these patients.

**Keywords:** Axial spondyloarthritis, central sensitization, central sensitization inventory, quantitative sensory testing

## INTRODUCTION

The cardinal symptoms of inflammation are known as pain, swelling, redness, and warmth, and pain is considered a disease activation marker and used as a main clinical parameter in treatment planning [1, 2]. It is accepted that pain in axSpA is mostly caused by increased inflammatory burden and structural changes [3]. Treatment strategies in these patients are based on reducing the patient's pain and preventing structural damage by suppressing inflammation. However, the failure to provide adequate analgesia in the patients whose inflammation is suppressed with treatment diverts clinicians from the assumption that pain equals inflammation. Central sensitization (CS) is accepted as one of the main mechanisms disrupting this equality, and the evidence for this clinical entity is constantly increasing. Although there are many definitions of CS in the literature, it is commonly defined as the increase in the response of nociceptive neurons in the central nervous system to normal or subthreshold stimuli [4]. The inflammatory response causing changes in the peripheral and central nervous system results in chronic pain and continuation of local inflammatory changes in the nervous system presents as neuroinflammation [5]. Kaplan et al. emphasized that peripheral inflammation in rheumatic diseases can cause subtle changes in the CNS and lead to complex comorbid symptoms [6]. CS is located at the junction of all these mechanisms and it can accompany many painful conditions. The lack of standardized criteria in the diagnosis of CS makes the diagnosis difficult, however, it is possible to detect the sensitization in most patients with clinical features and quantitative sensory testing (QST). With QST, information can be obtained about the tendency of pain to become chronic, individual pain sensitivity and potential underlying mechanisms [7]. CS can be evaluated from various aspects such as pain threshold, provoked hyperalgesia/allodynia, temporal summation, descending pain modulation vb. via QST [8]. Although it is reliable, the time-consuming, costly and experienced

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practitioner requirement of QST limits its use [9]. Central sensitization inventory (CSI) is preferred by some researchers to investigate pain sensitization through CS-related symptoms, related comorbidity and it can help determine the severity of CS [10]. In addition to the pros and cons of present methods, the diversity of protocols in the literature complicates the choice of diagnostic method.

Awareness about CS is increasing in rheumatology clinics, however, studies on this subject focus on RA and the data on CS in patients with axSpA, one of the most common rheumatological diseases, are still quite limited. Therefore, we aimed to investigate the frequency of patients with axSpA with CS and to make a detailed clinical profile of these patients by exploring related factors. Moreover, in this study, it was aimed to investigate the feasibility and relationship of the methods used in the diagnosis of CS in these patients. We hypothesized that CS and related conditions are common in axSpA.

## MATERIAL AND METHODS

### Design and study population

The study was performed cross-sectional, case-controlled with 100 patients of axSpA and 50 age and gender similar healthy groups. The patients aged 18-75 years diagnosed with axSpA according to the ASAS criteria were recruited from a Rheumatology outpatient clinic of a training hospital. Patients were excluded if they had another systemic inflammatory rheumatic diseases, peripheral vascular diseases, peripheral neuropathy, and spine diseases (e.g., symptomatic herniated disc, spinal stenosis), using centrally acting pain medications (e.g., pregabalin, duloxetine, opioids) or glucocorticoids (>10 mg prednisone or its equivalent) [11]. The study is approved by the local medical ethics committee and registered to Clinical Trials.gov (ClinicalTrials.gov identifier: NCT04485078). The written consent is obtained from all participants.

### Pain Centralization Assessment

### Central Sensitization Inventory (CSI)

Central sensitization was evaluated by Central Sensitization Inventory (CSI). Patients were divided into two groups as those with and without CS. The CSI has been developed to detect CS in a patient with chronic pain and consists of two parts, A and B. In scoring only part A is used and 40 points out of 100 indicate the presence of CS. This scale has been demonstrated to be a reliable and valid tool in the Turkish population with chronic pain (test-retest reliability = 0.92, Cronbach's alpha = 0.93) [12]. We didn't determine the presence of CS with QST in this study due to the high number of measurement sites and lack of evidence about the usefulness of

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these regions in axSpA. We classified the patients according to CSI as with and without CS. In this way, we aimed to determine the regions where QST changes can be shown, as well as confirming each other of the tests used in these patients.

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**Quantitative Sensory Testing (QST)**

While the patients were administered QST consisting of pressure pain threshold (PPT), temporal summation (TS), and conditioned pain modulation (CPM), the control group's test included PPT and TS. All measurements were applied by a trained assessor (FNY) using a manual pain pressure algometer.

**1. Pressure Pain Thresholds (PPTs)**

The spinal hyperalgesia was evaluated from C3 and C7 (cervical); T6 and T2 (thoracic); L3 and L5 (lumbar) levels. The PPT assessments of these levels were performed over the spinous process and 2 cm right and left side of the corresponding spinous process. The regional PPT scores were composed of the sum of all PPT values for related segments at the spine. The sacroiliac PPT scores were obtained bilaterally from four measurement points; the first point was located 1 cm medially and caudally from Spina iliaca posterior superior (SIPS) and others are 2 cm lateral, medial, and caudal of this point (the reliability of the measured points varied between ICC 0.60 and 0.82) [13]. The left trapezius muscle was used to evaluate the distant control point [14]. Before beginning the procedure, a demonstration was performed at the left forearm volar side to make sure patients understand the test correctly. The 1 cm2 algometer probe was placed vertically in each selected point and the pressure was increased by 1 kg/sc until the participant reporting pressure became painful. When the patient reported pain, the pressure was terminated and this value was recorded as PPT. The PPT value for each point was recorded as an average of two applications with an interval of 30 seconds. The probe was supported manually by the assessor at the bone surfaces to avoid translocation. While the cervical region and trapezius measurements were performed as patient sitting, the others were done prone position. Low PPT scores were accepted in favor of peripheral sensitization; besides that low PPT values at the distant site indicate CS [15].

**2. Temporal Summation (TS)**

TS was evaluated over the trapezius muscle, sacroiliac joints, C7, T6, and L3 levels at the spine with a manual algometer. Middlebrook et al. have been reported that TS can be elicited with a manual algometer at the spine and this method has acceptable reliability (test-retest ICC range 0.77 and 0.94) [16]. TS scores were calculated

for each spine level as the sum of three values measured over the spinous process and 2 cm right and left side of the corresponding level. In the evaluation of TS, a pressure as much the PPT value of each point was applied with pain pressure algometer ten times with a 1-second interstimulus interval. Patients were asked to rate their pain using a 0 to 10 visual analog scale (VAS) after first, fifth and tenth stimulus. TS was calculated by subtracting the rating at first stimulus from the rating at tenth stimulus [14]. The point that was located 1 cm medially and caudally from SIPS was used for SI joint TS measurement on both sides. As with PPT, the left trapezius muscle is used to evaluate the distant control point. Higher TS scores indicate CS.

**3. Conditioned Pain Modulation (CPM)**

For the assessment of conditioned pain modulation (CPM) the protocol published by Yarnitsky et. al was followed (ICC = 0.59) [17, 18]. According to this protocol first stimulus was applied to the trapezius with the pressure that induced a pain intensity of 4 points on a 10 point VAS as called a test stimulus. After that, the right hand of the patient was immersed in 7 °C water for 20 seconds to create a conditioning stimulus. The second test stimulus with the same intensity as the first one was applied to the trapezius after the conditioning stimulus and patients were asked to rate their pain. If the patients cannot hold their hands in the water for 20 seconds, the test stimulus was applied immediately after the patients removed their hands out of water. The ratio between the first and second VAS values multiplied by 100 was defined as CPM score. The values greater than 100 were accepted normal CPM response and higher scores indicate better descending pain inhibition.

**Clinical Variables**

Demographic variables including age, gender, body mass index (BMI), and clinical variables including subtype of axSpA (r-axSpA/nr-axSpA), duration of disease, diagnosis time, HLA- B27 status, duration of morning stiffness (min), biologic disease-modifying antirheumatic drugs (DMARDs) therapy and NSAID use within a month, plasma levels of C-reactive protein (CRP), vitamin B12 and 25(OH)D were obtained.

**Measures**

As a disease activity measures global pain score on a 0 to 10 visual analog scale (VAS), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), and Bath Ankylosing Spondylitis Activity Index (BASDAI) were performed. Ankylosing Spondylitis Quality of Life (ASQoL) was used to evaluate the quality of life, and Istanbul Low Back Pain Disability Index (ILBPDI) was used in disability assessment. To investigate fatigue,

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sleep disturbance, and depression, Fatigue Severity Scale (FSS), Pittsburg Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI) were used, respectively [19-21]. The frequency of fibromyalgia, which is a well-known CS-related disease, was investigated with Fibromyalgia Rapid Screening Tool (FIRST).

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**Statistical Analysis**

The sample size calculated based on the previous study was 46 per group, to achieve an error alpha of 0.05 for a %95 confidence interval (CI) and power of 0.95 [22]. However, the 100 patients and 50 controls were taken to investigate the frequency of CS in axSpA patients at follow-up in our center. The calculation was conducted with G-power (v3.1.9.4; University of Dusseldorf, Dusseldorf, Germany).

Statistical analyses were performed using the SPSS, version 20.0 (IBM Corporation, Armonk, NY, USA). The distribution of data was assessed using skewness and kurtosis. Data with an absolute skew value < 2, an absolute kurtosis (proper) value <7 were considered to have a normal distribution [23]. According to this rule, since our data show normal distribution, parametric tests were used in all analyzes. The Student's t-test was used for the comparison of continuous variables in two groups and one-way ANOVA test was used in multiple comparisons. Bonferroni correction was applied for statistically significant comparisons. Categorical variables were analyzed with $\chi 2$ test. The Pearson correlation was used to analyze the association with CSI score and other continuous variables. Finally, to identify possible predictors of CS development, a hierarchical linear regression model was created for data with significant correlation and difference between groups. $P < 0.05$ is considered statistically significant with 95% confidence interval.

**RESULTS**

**Patient characteristics**

One hundred axSpA patients and fifty controls were included in this study. Sixty-four of axSpA patients and 32 of the control group were women and the ratio of women and men are equal in both groups ($p = 1.000$). Mean (SD) age was 42.31 (1.00) in patients and 43.64 (1.50) in the control group. There was no significant difference in baseline demographics between groups ($p>0.05$). The number of patients with and without CS according to the CSI was sixty and forty, respectively. While demographic and clinical characteristics of the patients were determined according to the presence of CS, the other variables were also reported based on CSI severity. The baseline demographics of patients and controls are summarized in Table 1.

**Clinical Variables**

When the diagnosis distribution of the patients was examined, 65% of patients with CS and 77.5% without CS were determined as radiographic axSpA and there was no significant difference between the groups (p = 0.181). Similarly, no significant difference was found between the groups in terms of duration of disease, diagnosis time, HLA-B27 status, level of CRP, vitamin B12, and 25(OH)D (p>0.05). The rates of patients receiving bDMARD treatment did not differ between the groups (with CS: 13%, without CS: 27.5%), however, NSAID use was detected significantly higher in the patients with CS (with CS: 4.16/ wk, without CS: 2.77/ wk; p = 0.017) (Table 2).

**Measures**

The disease activity parameters (VAS, duration of morning stiffness, MASES and BASDAI) were detected significantly higher in patients with CS ( respectively, p <0.001, 0.014, 0.003 and <0.001). FSS, PSQI, and BDI scores were also significantly higher in patients with CS (p<0.001). This significance continues in the comparison of CS subgroups (Figure 1). All clinical variables of the patients are summarized in Table 2.

**Pain Centralization Assessment Quantitative Sensory Testing (QST)**

**1. Pressure Pain Thresholds (PPTs)**

PPT scores for all regions were significantly lower in the patients compared to the controls (p<0.05). When PPT scores of patients with and without CS were compared, sacroiliac region and trapezius values were found to be significantly lower in the patients with CS ( Table 3). However, no significant difference was found between CS subgroups in PPT scores ( Table 4).

**2. Temporal Summation (TS)**

TS scores calculated for all regions were similar between the patient and control groups (p>0.05) ( Table 3). Similarly, no difference was observed in TS scores when the groups were compared according to the presence and severity of CS (p>0.05) ( Table 4).

**3. Conditioned Pain Modulation (CPM)**

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The mean of the CPM scores in patients with and without CS were 147.14 (SD: 81.93) and 183.09 (SD: 96.21), respectively. Although this difference was statistically significant ($p = 0.048$), it did not persist between the CS subgroups ($p>0.05$).

**Correlations**

Correlation coefficients of VAS pain ($r = 0.609$), duration of morning stiffness ($r = 0.274$), NSAID use ($r = 0.276$), BASDAI ($r = 0.697$), MASES ($r = 0.287$), ASQoL ($r = 0.666$), ILBPDI ($r = 0.423$), FIRST ($r = 0.694$), FSS ($r = 0.646$), BDI ($r = 0.600$), PSQI ($r = 0.499$) and CPM ($r = 0.012$) which are among the clinical variables examined in the correlation analysis with CSI, were detected statistically significant. There was no relationship between CSI, PPT and TS scores (Table 5).

**Regression analysis**

In multiple hierarchical regression analysis, we examined the relationship between CSI score and clinical variables which are possible risk factors for CS development. In this analysis, the full model containing variables that could affect the CSI score was found statistically significant (for Model 7: $R2 = 0.676$, $F(8,91) = 26.68$, $p<0.001$). As a result; female gender, duration of morning stiffness, CPM, BDI, and FSS scores were detected as related parameters with CSI scores (Table 5).

**DISCUSSION**

Pain diversity in rheumatic diseases and individual differences in pain perception requires a multi-dimensional assessment of pain in these patients. Centralization of pain has been common in chronic musculoskeletal diseases, which negatively affects patient functionality, quality of life and reduces treatment effectiveness. Recent studies have shown the presence of central sensitization (CS) in various rheumatic diseases, especially rheumatoid arthritis, however, data on the CS in axSpA is very limited [11, 14]. Therefore, this study aimed to investigate the frequency of CS and to disclose the clinical parameters associated with CS in axSpA. In this study, CS was detected in 60 axSpA patients. This rate was reported as 45 % in a previous studies investigating the frequency of CS with CSI in SpA [24, 25]. The higher CS rate in our study compared to other studies can be explained by the high rate of female patients included in this study. It is known that there is a difference in gene expression between the sexes, and HLA-B27 positivity in axSpA has been reported to be lower in women. This is associated with later radiological progression and delay in diagnosis and treatment in female patients [26].

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Few patients had HLA-B27 results in our study, as HLA-B27 was non-diagnostic and referred selected patients, so it is difficult to detect a possible association. In addition, the fact that non-radiographic axSpA (nr-axSpA) is more common in women than AS is another reason that may delay the diagnosis in these patients. In this study, the distribution of diagnosis, diagnosis time and duration of disease were similar among the groups, and these factors did not affect the frequency of CS in axSpA. In our opinion, the most important factor that increases the frequency of CS in female patients is that pain transmission is different in women from men due to the effect of gonadal hormones and increased pain receptors, and the results of regression analysis also support this assumption [27]. Another consequence of female dominance and high CS rate in these patients is the increased frequency of fibromyalgia (FM). It is known that the concomitant FM is increased in axSpA compared to the healthy population, and this rate has been reported as 13.8% (9.1-18.6%) for AS and 20.3% (6.5-34.1%) for nr-axSpA [28]. In our study, this rate was calculated as 41% and 53%, respectively, and no significant difference was found between the groups. Considering the data on the role of CS in the pathogenesis of FM, this result is not surprising and the strong correlation between CSI and FIRST scores confirms this relationship [29, 30]. The increased frequency of FM in these patients and the overlapping symptoms of both diseases make it difficult to distinguish whether the pain originates from the disease itself or from FM. However, CS was not considered an exclusion or classification criterion given that CS is considered the neurobiological continuum of FM and that a significant proportion of patients with CS will be in the FM group [31]. Both diseases play a role in the chronicity of pain by potentiating each other, and it does not seem possible to clearly distinguish the source of pain in these patients. It is reported that FM or CS accompanying axSpA cause a significant increase in outcome measures and negatively affect frequently used evaluation methods, especially BASDAI [31]. All symptoms, such as pain, morning stiffness and increased sensitivity, which are questioned in BASDAI, are also seen in sensitive patients and FM. Therefore, BASDAI results should be interpreted more carefully in patients with CS. It would not be correct to associate the increased BASDAI in these patients only with CS, FM or increased inflammation, there seems to be a complicated relationship between pain sensitization and disease activation in rheumatism. It is suggested that lesions such as enthesitis, capsulitis, especially bone marrow edema (BME), which are known as acute lesions of the disease in SpA, are associated with the severity of pain [32]. In animal models, mechanoreceptors in the bone marrow were activated after the increase in intraosseous pressure with saline injection, and a significant decrease in the pain threshold was observed after sensitization of these fibers with capsaicin. These results were interpreted by the authors as BME potentiating the sensitizing effect on mechanoreceptors [33]. Synovitis, another inflammation-related lesion, has also been found to be directly related

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to lower PPT and pain sensitization in patients with osteoarthritis [34]. All these data can be explained by the easier and more frequent development of pain sensitivity due to the inflammatory lesions of the patients or the increase in disease activation parameters due to CS. The correlation of all these parameters with CSI shows that CS has a significant portion in this increase. Moreover, the fact that the PPT difference is detected not in the spine but in the sacroiliac joint (SIJ) can be explained by the intensity of inflammatory lesions there. The general agreement is that prolonged disease duration is associated with the development of chronic pain and CS. The absence of time difference between the groups and the lack of correlation between CSI and disease duration indicate that the process progresses differently in axSpA patients. The age of the patients increases in parallel with the duration of the disease and in a study of patients with osteoarthritis, a decrease in PPT was observed with increasing age [35]. Also, greater fluctuation in sensitivity in response to varying levels of painful stimuli was observed in the elderly compared to younger individuals [36]. Considering all these factors, persistence of CS triggered by disease activation rather than an increase in sensitization as the disease becomes chronic may explain the lack of expected association with disease duration in axSpA.

Chronic pain is the main indicator of CS and there is increased use of analgesics in sensitized patients. Since it is the main drug in the treatment of axSpA and it is easily accessible, an increase in the use of NSAIDs is observed in these patients in relation to their higher pain scores. The use of centrally acting drugs was accepted as an exclusion criterion as it would affect the results. Therefore, the use of NSAIDs is at the forefront in this study, and since most clinicians try to treat axSpA, rather than pain sensitization, increasing the dose of NSAIDs or biologic treatments are preferred in these patients.

In this study, while investigating the factors associated with pain sensitization, the effect of vitamin D and B12 levels, which are known to be related to the nervous system and pain pathways, were also examined. In a literature review of patients with knee osteoarthritis, low vitamin D levels were found to be associated with pain sensitization and increased pain scores [37]. Besides, it is thought that vitamin D provides clinical benefit in the treatment of pain, and there are opinions that it can be used as an analgesic alone or in combination [38]. Vitamin B12 is used in peripheral nerve diseases due to its neuroprotective effect, and its role in pain sensitization is unknown. In animal models, it has been shown that systemic administration of vitamin B complex can reduce inhibitory gabaergic neuron loss and spinal sensitization [39]. Since the D and B12 vitamin follow-ups of the patient's included in the study were carried out regularly, these values are within normal limits. Therefore, a possible relationship with pain sensitization could not be demonstrated in this study.

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There is not a recommended method as the gold standard for the diagnosis of CS and the protocols used in studies vary widely [40]. Considering that a large area such as the axial skeleton, sacroiliac, and peripheral joints can be affected in axSpA, demonstrating pain sensitization with quantitative methods becomes more difficult. Therefore, we also investigate the usefulness of quantitative sensory testing (QST) and most appropriate region for the detection of CS in axSpA patients. Since the SIJ is the primary site of involvement, it is critical in the QST evaluation of these patients. In our study, the sacroiliac PPT scores of the axSpA group was lower than the controls and this difference appears to be related to disease involvement. In the comparison where the effect of CS on sacroiliac PPT scores was investigated, an additional decrease was found in the sacroiliac PPT scores of patients with CS compared to those without, and this PPT difference seems to be associated with CS. The PPT decrease observed in patients with CS in the trapezius, which was chosen as the control point, confirms this assumption. Perhaps one of the most surprising results of the study is that, unlike PPT, there was no difference between all groups in the temporal summation (TS). One of the reasons for this may be the individual differences in the pain process of the patients. TS is reported as a phenomenon that can be observed not only in patients but also in healthy individuals, and it has been reported that TS is elicited in healthy individuals through various modalities [41, 42]. Also this discrepancy seems to be related to the VAS scores in the TS measurement. In this study, TS value was calculated as the difference of VAS scores obtained after 10th and 1st stimulation. We think that especially the higher VAS scores recorded with the 1st stimulus in patients with CS mask the summation effect.

The conditioned pain modulation (CPM) paradigm is increasingly being used in the evaluation of endogenous analgesic pathways that play a role in the pathogenesis of CS [43]. CPM has been shown to be associated with pain sensitization in various diseases, and this link has been confirmed in axSpA. In this study, although the CPM values of both groups were within normal limits, it was observed that the pain inhibition system of patients without CS worked better. CS is a complex process involving many different mechanisms, and clinical findings are the result of this cumulative effect. It has been reported that the function of descending inhibitory pathways in animal models changes with inflammation, and the severity of axSpA is likely to affect these results [44]. For these reasons, this significance may have disappeared in the comparison of patients as a CS subgroup.

The strengths of our study are that it is the most comprehensive study for the investigation of CS in axSpA patients and the first study in which PPT, TS, and CPM assessments were done in these patients. Also, the comparison of patient's QST results with healthy controls increases the value of this study. We think that use of SIJ PPT assessment in CS diagnosis will guide further prospective studies in axSpA patients, where it is difficult

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to perform QST due to the involvement of the entire axial skeleton. Another important aspect of our study is the comprehensive evaluation of the clinical effects of CS. And the determination of the clinical characteristics of these patients and the factors associated with CS may help to identify patients with pain sensitization earlier. The limitations of the study are the cross-sectional design, the inability to calculate the interobserver and intraobserver consistency of these methods in axSpA patients since the QST is performed by the only practitioner, and the CPM assessment was not performed in the control group.

## CONCLUSION

Despite the high rates of remission, especially with the use of biological treatments, chronic pain in axSpa patients is a challenge for clinicians. In this study, CS was detected in 60% of patients with axSpA. In line with these data, it becomes necessary to consider CS while determining the treatment strategies of these patients. Impaired quality of life, increased disability, fatigue, sleep disturbances, and depression rates also increase in these patients in the presence of CS. Recognition of CS in axSpA patients, one of the most common patient groups of rheumatology clinics, will enable these patients to be treated more effectively.

## CONFLICT OF INTEREST

None

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**Figure legend**

**Figure 1.** Box-plot graphs of distribution of clinical scores by CSI levels. One-way ANOVA results show that there is a significant difference in clinical scores according to CSI levels. ( * p< 0.05, ** p< 0.01, *** p< 0.001, **** p< 0.0001, Bonferroni adjustment ) CSI: Central Sensitization ; ASQoL: Ankylosing Spondylitis Quality of Life; ILBPDI: Istanbul Low Back Pain Disability Index; FIRST: Fibromyalgia Rapid Screening Tool; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory; PSQI: Pittsburg Sleep Quality Index

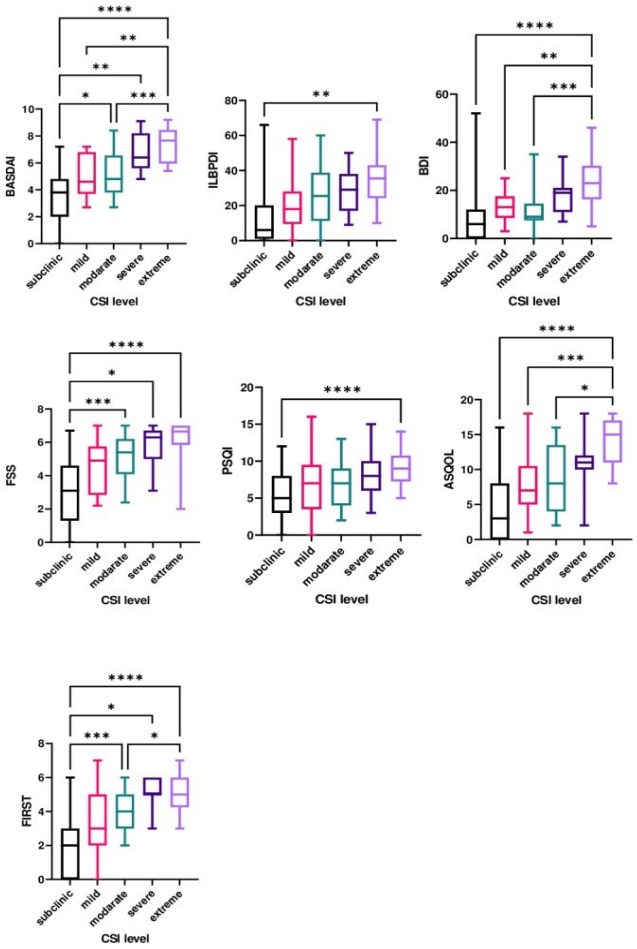


**Figure 1.** Box-plot graphs of distribution of clinical scores by CSI levels. One-way ANOVA results show that there is a significant difference in clinical scores according to CSI levels. ( * p< 0.05, ** p< 0.01, *** p< 0.001, **** p< 0.0001, Bonferroni adjustment ) CSI: Central Sensitization ; ASQoL: Ankylosing Spondylitis Quality of Life; ILBPDI: Istanbul Low Back Pain Disability Index; FIRST: Fibromyalgia Rapid Screening Tool; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory; PSQI: Pittsburg Sleep Quality Index

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**Table 1. Baseline demographics of the study population**

| | AxSpA patients (n:100) | | | Controls (n: 50) | *Diff. Sig. between AxSpA and controls p-value* |
|---|---|---|---|---|---|
| | **CS positive (n: 60)** | **CS negative (n: 40)** | ***Diff. Sig. between CS+ and CS- p-value*** | | |
| Female gender, % | 77 | 45 | <0.001* | 64 | 1.000 |
| Age (year), mean (SD) | 42.31 (9.04) | 43.75 (11.32) | 0.649 | 43.64 (1.50) | 0.452 |
| BMI (kg/m$^2$), mean (SD) | 28.57 (5.51) | 27.93 (4.78) | 0.552 | 27.79 | 0.528 |

SD: Standard deviation; BMI: body mass index; CS: central sensitization

**Table 2. Characteristics of the axSpA patients**

| | AxSpA patients (n:100) | | |
|---|---|---|---|
| | **CS positive (n: 60)** | **CS negative (n: 40)** | ***Diff. Sig. between CS+ and CS- p value*** |
| R- AxSpA, % | 65 | 77.5 | 0.181 |
| HLA-B27 positivity, % (N) | | | |
| Positive | 8 (5) | 10 (4) | |
| Negative | 15 (9) | 15 (6) | 0.959 |
| Unknown | 77 (46) | 75 (30) | |
| Disease duration (year), mean (SD) | 6.38 (4.96) | 6.86 (6.49) | 0.674 |
| Diagnosis time (year), mean (SD) | 3.52 (4.21) | 4.67 (5.27) | 0.322 |
| Psoriasis, % (N) | 6.6 (4) | 2.5 (1) | 0.148 |
| IBD, % (N) | 6.6 (4) | 5 (2) | 0.235 |
| Fibromyalgia, % | 62 | 20 | <0.001* |
| Morning stifness (min.), mean (SD) | 50.17 (54.30) | 25.87 (34.29) | 0.014* |
| VAS pain (0-10), mean (SD) | 7.75 (1.96) | 5.15 (2.37) | <0.001* |
| NSAID (day/week), mean (SD) | 4.16 (2.77) | 2.77 (2.85) | 0.017* |
| Biologic DMARD, % | 13 | 27.5 | 0.568 |
| MASES, mean (SD) | 23 (25.13) | 8.7 (15.13) | 0.003* |
| CRP (mg/L), mean (SD) | 6.65 (7.77) | 10.28 (18.51) | 0.09 |
| BASDAI, mean (SD) | 6.49 (1.69) | 4.07 (1.85) | <0.001* |
| CSI, mean (SD) | 53.28 (13.93) | 24.77 (10.62) | <0.001* |
| ASQoL, mean (SD) | 11.45 (4.81) | 5.63 (4.69) | <0.001* |
| ILBPDI, mean (SD) | 30.20 (15.72) | 16.05(18.07) | <0.001* |
| BDI, mean (SD) | 17.72 (10.13) | 9.33 (9.44) | <0.001* |
| FSS, mean (SD) | 5.76 (1.33) | 3.48 (1.80) | <0.001* |
| PSQI, mean (SD) | 8.15 (3.36) | 5.52 (3.15) | <0.001* |
| FIRST, mean (SD) | 4.75 (1.16) | 2.43 (1.96) | <0.001* |

SD: Standard deviation, CS:Central sensitization ;IBD: Inflammatory Bowel Disease, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; CSI: Central Sensitization Inventory; ASQoL: Ankylosing Spondylitis

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Quality of Life; ILBPDI: Istanbul Low Back Pain Disability Index; BDI: Beck Depression Inventory; FSS: Fatigue Severity Scale; PSQI: Pittsburg Sleep Quality Index; FIRST: Fibromyalgia Rapid Screening Tool,

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**Table 3. QST values of patients and controls**

| | AxSpA patients (n:100) | | | Controls (n: 50) | *Diff. Sig. between AxSpA and controls p-value* |
|---|---|---|---|---|---|
| | **CS positive (n: 60)** | **CS negative (n: 40)** | ***Diff. Sig. between CS+ and CS- p value*** | | |
| Cervical PPT, mean (SD) | 21.52(5.93) | 24.04(7.34) | 0.062 | 26.55(6.94) | 0.001* |
| Thoracal PPT, mean (SD) | 26.60(6.94) | 28.05(7.77) | 0.333 | 34.27(9.07) | <0.001* |
| Lumbar PPT, mean (SD) | 26.17(6.86) | 28.36(7.98) | 0.147 | 32.74(8.18) | <0.001* |
| Sacroiliac-R PPT, mean (SD) | 15.98(4.11) | 18.43(5.80) | 0.015* | 20.73(5.49) | <0.001* |
| Sacroiliac-L PPT, mean (SD) | 16.35(4.18) | 18.39(5.88) | 0.045* | 20.75(5.41) | <0.001* |
| Trapezius PPT, mean (SD) | 3.23(1.06) | 3.77(1.19) | 0.021* | 4.14(1.14) | 0.001* |
| Cervical TS, mean (SD) | 11.12 (5.55) | 10.03 (5.65) | 0.341 | 10.54(4.65) | 0.879 |
| Thoracal TS, mean (SD) | 9.31 (4.77) | 9.77 (6.02) | 0.673 | 8.90(3.65) | 0.472 |
| Lumbar TS, mean (SD) | 9.56 (4.67) | 8.80 (5.41) | 0.452 | 9.42(5.50) | 0.858 |
| Sacroiliac TS, mean (SD) | 7.45 (3.81) | 7.27 (3.49) | 0.817 | 7.82(3.46) | 0.482 |
| Trapezius TS, mean (SD) | 3.76 (2.12) | 3.40 (1.89) | 0.379 | 3.70(1.86) | 0.816 |
| CPM, mean (SD) | 147,14(81,93) | 183,09(96,21) | 0.048* | | |

SD: Standard deviation, CS:Central sensitization;, PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, ; R: right; L: left, * statistically significant

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**Table 4. QST distributions of patients according to CSI severity and comparison with controls**

| | AxSpA patients (n:100) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CS levels | | | | | *Diff. Sig. between subgroups p-value* | Controls (n: 50) | *Diff. Sig. between AxSpA and controls p-value* |
| | Subclinic (n: 27) | Mild (n: 13) | Modarate (n: 25) | Severe (n: 11) | Extreme (n: 24) | | | |
| Cervical PPT, mean (SD) | 24,41 | 22,92 | 21,99 | 19,67 | 22,09 | 0,716 | 26.55(6.94) | 0.001* |
| Thoracal PPT, mean (SD) | 28,83 | 25,65 | 26,66 | 25,54 | 27,47 | 0,563 | 34.27(9.07) | <0.001* |
| Lumbar PPT, mean (SD) | 28,77 | 26,13 | 26,81 | 24,39 | 27,08 | 0,758 | 32.74(8.18) | <0.001* |
| Sacroiliac-R PPT, mean (SD) | 18,78 | 16,60 | 16,04 | 15,96 | 16,52 | 0,233 | 20.73(5.49) | <0.001* |
| Sacroiliac-L PPT, mean (SD) | 18,96 | 16,15 | 16,35 | 16,26 | 16,97 | 0,198 | 20.75(5.41) | <0.001* |
| Trapezius PPT, mean (SD) | 3,82 | 3,53 | 3,34 | 2,97 | 3,31 | 0,253 | 4.14(1.14) | 0.001* |
| Cervical TS, mean (SD) | 10,44 | 8,61 | 10,84 | 10,64 | 11,92 | 0,562 | 10.54 (4.65) | 0.879 |
| Thoracal TS, mean (SD) | 10,33 | 8,69 | 8,96 | 8,72 | 9,92 | 0,812 | 8.90 (3.65) | 0.472 |
| Lumbar TS, mean (SD) | 9,15 | 7,92 | 9,64 | 8,45 | 10,08 | 0,734 | 9.42 (5.50) | 0.858 |
| Sacroiliac TS, mean (SD) | 7,55 | 6,38 | 6,20 | 7,63 | 8,83 | 0,112 | 7.82 (3.46) | 0.482 |
| Trapezius TS, mean (SD) | 3,25 | 3,84 | 4,12 | 2,81 | 3,75 | 0,365 | 3.70 (1.86) | 0.816 |
| CPM, mean (SD) | 190,86 | 160,29 | 169,27 | 131,81 | 134,70 | 0,514 | | |

CS: central sensitization, PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, SD: Standard deviation; R: right; L: left, * statistically significant

**Table 5. Bivariate correlation and regression analysis**

| **Correlation** | **CSI score** | |
|---|---|---|
| | **Pearson's r** | ***P value*** |
| Age, years | 0.052 | 0.607 |
| Duration of disase, years | -0.154 | 0.126 |
| VAS pain, 0-10 | 0.609 | <0.001* |
| Duration of morning stifness, min | 0.274 | 0.006* |
| NSAID use, week | 0.276 | 0.005* |
| BASDAI | 0.697 | <0.001* |
| MASES | 0.287 | 0.004* |
| CRP | -0.109 | 0.282 |

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| | | |
|---|---|---|
| ASQoL | 0.666 | <0.001* |
| ILBPDI | 0.423 | <0.001* |
| FIRST | 0.694 | <0.001* |
| FSS | 0.646 | <0.001* |
| BDI | 0.600 | <0.001* |
| PSQI | 0.499 | <0.001* |
| CPM | 0.250 | 0.012* |
| PPT score, cervical | -0.142 | 0.158 |
| PPT score, thoracal | -0.070 | 0.486 |
| PPT score, lumbar | -0.092 | 0.365 |
| PPT score, right sacroiliac | -0.161 | 0.109 |
| PPT score, left sacroiliac | -0.142 | 0.158 |
| PPT trapezius | -0.166 | 0.099 |

| **Regression** | **ß ($\Delta R^2$)** | ***P value*** |
|---|---|---|
| Gender | -0.36 (0.13) | <0.001* |
| Morning stiffness | 0.26 (0.09) | 0.001* |
| BASDAI | 0.65 (0.32) | <0.001* |
| CPM | -0.17 (0.03) | 0.02* |
| FSS | 0.33 (0.07) | <0.001* |
| PSQI | 0.12 (0.01) | 0.125 |
| BDI | 0.23 (0.03) | 0.03* |

CSI: Central Sensitization Inventory VAS: visual analogue scale; NSAID: non-steroidal anti-inflammatory drug; MASES: Maastrich Ankylosing Spondylitis Enthesitis Score; CRP: C-reactive protein; ASQoL: Ankylosing Spondylitis Quality of Life; ILBPDI: Istanbul Low Back Pain Disability Index; FIRST: Fibromyalgia Rapid Screening Tool; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory; PSQI: Pittsburg Sleep Quality Index; CPM: Conditioned Pain Modulation, PPT: pressure pain threshold

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