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The relationship between sacroiliac joint MRI scores and central sensitization in axial spondyloarthritis: A cross-sectional study

Feyza Nur YUCEL[1], Halise Hande GEZER[2], Mehmet Tuncay DURUOZ[2]

[1] Department of Physical Medicine and Rehabilitation, University of Health Sciences, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey.
[2] Division of Rheumatology, Deaprtment of Physical Medicine and Rehabilitation, School of Medicine, Marmara University, Istanbul, Turkey.

Corresponding Author: Feyza Nur YUCEL
E-mail: dr.fny28@gmail.com

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ABSTRACT

Objective: To investigate the relationship between sacroiliac joint (SIJ) involvement and central sensitization (CS) in patients with axial spondyloarthritis (axSpA).

Patients and Methods: Twenty-four patients with axSpA were included in this study. CS was investigated via pressure pain threshold (PPT), temporal summation (TS), conditional pain modulation (CPM), and the central sensitization inventory (CSI). Sacroiliac joint involvement was assessed using the magnetic resonance imaging (MRI)-based Canadian Spondyloarthritis Research Consortium (SPARCC) scoring system. CS-related parameters and SPARCC score correlations were analyzed.

Results: The median (IQR) sacroiliac PPT score for the right SIJ was calculated as 17.47 (4.43) and 17.67 (4.57) for the left SIJ. In the TS measurement, the right SIJ TS median (IQR) value was calculated as 4.0 (3.5) and 4.0 (2.75) for the left side. The median (IQR) value was 149.67 (107.5) for CPM and 45.0 (27.75) for CSI. The median (IQR) sacroiliac inflammation score was calculated as 3.0 (8.75), and the median (IQR) structural score was calculated as 7.0 (11.5). No correlation was found between SPARCC scores and PPT, TS, CPM, and CSI values.

Conclusion: In axSpA patients, there was no association observed between pain sensitivity measures and sacroiliac involvement. Further comprehensive studies are required, taking into account the complex nature of CS.

Keywords: Axial spondyloarthritis, Central sensitization, Quantitative sensory testing, Central sensitization inventory, SPARCC.

1. INTRODUCTION

Pain is the main symptom that shapes the treatment in axial spondyloarthritis (axSpA) patients, as in most musculoskeletal diseases. As per classical knowledge, chronic inflammatory low back pain is the typical presentation of the disease and when supported by imaging, the patient is diagnosed with axSpA [1]. In addition to being diagnostic, imaging determines the subgroup of the disease and the severity of the involvement, and can be used to evaluate the treatment response. The use of magnetic resonance imaging (MRI) for this purpose has now been established, and the spondyloarthritis (SpA)-related lesions have been described in detail by the Assessment of Spondyloarthritis International Society (ASAS). The presence of bone marrow edema (BME)/osteitis is essential for the definition of active sacroiliitis, and SpA related lesions are grouped under two main headings: sacroiliac joint (SIJ) lesions showing disease activity or structural damage [2]. These lesions are directly related to the patient's symptoms, and it has been reported that the presence of BME is significantly associated with night pain and morning stiffness in SpA [3]. Among the structural lesions, SIJ fat metaplasia was associated with insidious onset and SIJ sclerosis with night pain [4]. It has also been shown that disease activation parameters, particularly the Ankylosing Spondylitis Disease Activity Score (ASDAS), are longitudinally related to SIJ inflammatory lesions in male axSpA patients [5]. Although, inflammation and associated lesions are accepted as the main source of pain in these patients, current data reveal that more complex mechanisms play a role in the pain process in SpA than we thought. Here, peripheral and central sensitization occur as a result of the complex interaction between the immune system and the nervous system [6]. The process, which is defined as peripheral sensitization and starts with increasing responsiveness of nociceptors via inflammatory mediators, turns into central sensitization (CS) by affecting the central nervous system with the continuation of these maladaptive changes [7]. Quantitative

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Sensory Testing (QST) is the most commonly used method in the diagnosis of CS, and thermal, pressure, and mechanical pain threshold, temporal summation (TS), and conditional pain modulation are frequently preferred for this purpose. In recent years, the Central Sensitization Inventory (CSI) has been used as an alternative to QST in the investigation of CS due to its more practical and low cost. The prevalence of CS detected by CSI in axSpA patients was reported as 45%, and a strong correlation was found between CS and disease activation parameters Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASDAS-CRP [8]. Although, the CS-disease activation relationship has been demonstrated by frequently used clinical instruments, these evaluations based on the patient's complaints should be supported by more objective methods. It is important to understand this link because increased inflammatory burden in the axSpA may trigger pain sensitization or CS may mimic disease activation by increasing pain sensitivity. The correlation of SIJ MRI findings, which are also associated with the pain patterns of the patients and accepted as a semi-objective finding of inflammation, with CS may be a guide in understanding this connection. The Canadian Spondyloarthritis Research Consortium (SPARCC) scoring system is based on the scoring of SIJ lesions in these patients, allowing for easier assessment of disease involvement [9]. With this index, sacroiliitis activation and structural damage are scored as two discrete points according to the severity and extent of the lesions. In this study, it was aimed at investigating the relationship between SIJ involvement, which was evaluated by the SPARCC score, and CS in axSpA.

2. PATIENTS and METHODS

Design and Study Population

The study was performed cross-sectionally with 24 axSpA patients. The patients aged 18-75 years diagnosed with axSpA were recruited from a rheumatology outpatient clinic of a training hospital. Patients with sacroiliac MRI images taken within the last three months were included in this study. The exclusion criteria were the presence of other 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) [10]. This study was approved by the Marmara University, School of Medicine Clinical Research Ethics Commmittee (date:08.01.2021, approval number: 09.2021.64) and written informed consent was obtained from all patients. In addition, the study has been registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT05021783).

Clinical Variables

Demographic variables including age, gender, body mass index (BMI), and clinical variables including subtype of axSpA (radiographic-axSpA/non-radiographic-axSpA), duration of disease, diagnosis time, duration of morning stiffness (min), and plasma levels of C-reactive protein (CRP) were obtained. As disease activity measures, global pain scores on a 0-10 visual analog scale (VAS) and BASDAI were performed.

Pain Centralization Assessment

Central Sensitization Inventory (CSI)

The CSI is used to detect CS in a patient with chronic pain and consists of two parts, A and B. The part A consists of 25 questions about CS-related symptoms, and a score of 40 and above indicates the presence of CS. It is also accepted that the severity of CS increases with higher scores [11]. In part B, CS-related diseases are questioned, and only part A of the scale was used in this study. 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].

Quantitative Sensory Testing (QST)

Pressure Pain Threshold

Sacroiliac PPT measurements were applied bilaterally at four points by a trained assessor (FNY) using a manual pain pressure algometer; the first point was located 1 cm medially and caudally from the spina iliaca posterior superior (SIPS) and 3 more laterally, medially, and cranially. The reliability of the measured points varied between ICC 0.60 and 0.82 [13]. A demonstration was performed on the left forearm volar side to ensure that patients understood the steps correctly before the test. On the patient lying in the prone position, a 1 cm2 algometer probe was placed vertically at each selected point, pressure was applied in a 1 kg/sec increment, and the probe was supported manually by the assessor at the bone surfaces to avoid translocation. The application was terminated once the patient reported pain, and this value was recorded as a PPT. The left trapezius muscle was used to evaluate the distant control point [14]. The PPT value of each point was calculated by averaging two applications 30 seconds apart. Low PPT scores were considered signs of peripheral sensitization, while low PPT values in the distant point were interpreted in favor of CS [15].

Temporal Summation

Temporal summation was evaluated over the trapezius muscle and sacroiliac joint with a manual algometer. It has been shown that TS can be detected with a manual algometer, and this method has acceptable reliability (test-retest ICC ranges of 0.77 and 0.94) [16]. For the measurement of sacroiliac joint TS, the point located 1 cm medial and caudally from the SIPS was preferred, and as with PPT, the left trapezius muscle was used to evaluate the distant control point. High TS scores were associated with pain sensitization.

Conditioned Pain Modulation (CPM)

In the CPM test, dysfunction of descending inhibitory pathways was investigated through the effect of the conditioned stimulus on the test stimulus [17]. A test stimulus was applied to the trapezius with pressure-inducing 4-point pain intensity on VAS. Then, as a conditioned stimulus, the patients were asked to

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keep their right hand in water at 7 C for 20 seconds. After the conditioned stimulus, the patients were asked to rate their pain by applying a retest stimulus at the same intensity as the first stimulus to the trapezius. In patients who could not keep their hands in water for 20 seconds, the retest stimulus was applied immediately after the patients took their hands out of the water. The ratio between the first and second VAS values multiplied by 100 was defined as the CPM score, and higher scores indicated better descending pain inhibition [18].

Sacroiliac MRI Scoring

The Spondyloarthritis Research Consortium of Canada (SPARCC) method was used in the sacroiliac magnetic resonance imaging (MRI) evaluation of the patients. In the assessment of sacroiliac joint (SIJ) inflammation, a signal increase consistent with bone marrow edema was scored in the T2-weighted STIR sequences, and the ICC for this method had been reported as 0.90-0.98 [9]. According to this system, in semicoronal 1.5 Tesla sacroiliac MRI sections, the SIJ was divided into sacral and iliac four quadrants. By examining six consecutive coronal slices, the increase in signal was scored as 0=normal signal and 1=increased signal. Therefore, the maximum total score for two SIJ in one section was 8, while an additional one point per joint is added for sections with intense signal increase and continuous signal increase located 1 cm or more from the articular surface. In this scoring, the maximum score in a single coronal section was 12, and the total was 72.

In the SIJ structural score, five consecutive coronal sections were examined in the T1 sequence, which included the cartilaginous part of the sacroiliac joint. The section where the cartilaginous part of the joint was first seen, which is called the transitional section, was determined, and it was investigated whether there were fat metaplasia, erosion, backfill, and ankylosis in the four quadrants of the SIJ. Of these, fat metaplasia and erosion were investigated in four quadrants, in the iliac and sacral sides, in a total of 8 regions, while backfill and ankylosis were evaluated in a total of 4 regions in the upper and lower half of the joint. In this way, fat metaplasia and erosion were scored between 0 and 40, and backfill and ankylosis were scored between 0 and 20 in five consecutive slices. All assessments were performed by two experienced rheumatologists who were trained in sacroiliac MRI reporting and completed the calibration modules developed for the SPARCC scoring system.

Statistical Analysis

Nonparametric tests were used in all analyses since the data did not show a normal distribution according to normality tests. Continuous data are presented as median and interquartile range (IQR) in accordance with a non-parametric distribution. The relationship between sacroiliac PPT, TS, CPM, CSI, and SPARCC scores was investigated by Spearman rank correlation. The Intraclass correlation coefficient (ICC) analysis was used to assess inter-rater reliability in SPARCC scoring. $P < 0.05$ was considered statistically significant, and all data were analyzed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

3. RESULTS

Twenty-four axSpA patients were included in this study. The median (IQR) age was 41.0 (15) in patients, and the rate of female patients was 67%. A comparison of patient characteristics according to CS is summarized in Table I.

Table I. *Comparison of patient characteristics according to CS*

	AxSpA patients (n:24)		
	CS positive (n: 14)	*CS negative (n: 10)*	*Diff. Sig. between CS+ and CS- P-value*
Age, years	42.5 (13.75)	38.5 (18.25)	0.472
Female (%)	11 (45.8)	5 (20.8)	0.204
BMI (kg/m^2)	26.55 (5.46)	28.24 (11.94)	0.841
R-AxSpA (%)	41.7 (10)	25.0 (6)	0.439
Disease duration, years	5.0 (7.69)	3.5 (9.0)	0.508
Morning stiffness (min.)	30.0 (120.0)	30.0 (67.75)	0.752
VAS pain (0-10)	7.5 (2.0)	6.5 (3.25)	0.437
CRP (mg/L)	3.0 (5.13)	4.5 (10.4)	0.585
BASDAI	5.75 (3.48)	5.15 (2.3)	0.709

Data are presented as median (IQR) or n (%), SD: Standard Deviation, BMI: Body mass index, VAS: visual analogue scale, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

The median (IQR) sacroiliac PPT score, which is the sum of the PPT values of four points for the right SIJ, was calculated as 17.47 (4.43) and 17.67 (4.57) for the left SIJ. The median (IQR) PPT value of the trapezius, which is the distant point, was 3.60 (1.75). In the TS measurement, the right SIJ TS value was calculated as 4.0 (3.30) and 4.0 (2.75) for the left side. The median (IQR) value was 149.67 (107.5) for CPM and 45.0 (27.75) for CSI. All QST data are shown in Table II.

Table II. *QST and CSI values of the patients*

	Median (IQR)
Sacroiliac-R PPT	17.47 (4.43)
Sacroiliac-L PPT	17.67 (4.57)
Trapezius PPT	3.6 (1.75)
Sacroiliac-R TS	4.0 (3.5)
Sacroiliac-L TS	4.0 (2.75)
Trapezius TS	4.0 (3.0)
CPM	149.67 (107.5)
CSI	45.0 (27.75)

CSI: Central Sensitization Inventory PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, CI: Confidence interval; R: right; L: left,

In the scoring of two different observers, the median (IQR) sacroiliac inflammation score was calculated as 3.0 (8.75), while the median (IQR) structural score was calculated as 7.0 (11.50). All values, including the sub-components of the structural score, are shown in Table III. The ICC was found to be 0.75 (CI:

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0.50-0.88) for the structural score, and 0.75 (CI: 0.51-0.89) for the sacroiliac inflammation score and these values indicates good reliability (p<0.001) (Table IV).

Table III. *Median values of SPARCC scores*

	Median (IQR)
SPARCC	
Structural score (total)	7.0 (11.5)
Fat metaplasia	6.75 (11.63)
Erosion	5.75 (6.0)
Backfill	0 (0.75)
Ankylosis	0 (0)
Inflammation score	3.0 (8.75)
Total SPARCC score	4.0 (9.25)

SPARCC: Spondyloarthritis Research Consortium of Canada

Table IV. *Inter-rater reliability of SPARCC structural and sacroiliitis scores*

	ICC (95% CI)	*P value*
SPARCC		
Structural score (total)	0.75 (0.50-0.88)	<0.001*
Fat metaplasia	0.87 (0.73-0.94)	<0.001*
Erosion	0.04 (-0.36-0.42)	0.435
Backfill	-0.04 (-0.43-0.36)	0.569
Ankylosis	0.98 (0.96-0.99)	<0.001*
Inflammation score	0.75 (0.51-0.89)	<0.001*

SPARCC: Spondyloarthritis Research Consortium of Canada;ICC: Interclass Coefficient; CI: Confidence interval

There was no significant correlation between sacroiliac PPT, TS, CPM, and CSI and SPARCC scores. The r values calculated in the correlation analysis of the structural score with the right and left sacroiliac joint PPT values were 0.046 and 0.044, respectively; for the sacroiliac inflammation score they were 0.054 and 0.063 (p>0.05). All correlation coefficients are shown in Table V.

Table V. *Correlations between SPARCC scores, QST and CSI*

	PPT		*TS*		*CPM*	*CSI*
	R-SIJ	L-SIJ	R-SIJ	L-SIJ		
SPARCC						
Structural score, r(p)	0.046 (0.832)	0.044 (0.837)	0.018 (0.935)	0.023 (0.914)	-0.126 (0.557)	0.133 (0.534)
Inflammation score, r(p)	0.054 (0.803)	0.063 (0.770)	0.081 (0.708)	-0.094 (0.662)	0.138 (0.519)	-0.068 (0.751)
Total score r(p)	0.123 (0.567)	0.022 (0.920)	0.097 (0.653)	0.053 (0.806)	0.021 (0.923)	-0.004 (0.986)

SPARCC: Spondyloarthritis Research Consortium of Canada, PPT: pressure pain threshold, TS: temporal summation, CPM: conditioned pain modulation, CSI: Central Sensitization Inventory, R: right; L: left, SIJ: Sacroiliac joint

When the patients were classified according to the presence of CS and their SPARCC scores were compared, no significant difference was found between the groups (Table VI).

Table VI. *Comparison of SPARCC scores according to CS*

	AxSpA patients (n:24)		
	CS positive (n: 14)	*CS negative (n: 10)*	*Diff. Sig. between CS+ and CS- P-value*
Structural score	10.75 (15.0)	12.0 (12.13)	0.709
Inflammation score	3.0 (6.5)	3.0 (16.25)	0.931
Total SPARCC score	34.83 (8.84)	36.08 (11.86)	0.886

Data are presented as median (IQR), CS: Central Sensitization; SPARCC: Spondyloarthritis Research Consortium of Canada

4. DISCUSSION

Taking into consideration the effect of CS on the clinical appearance of axSpA, this study investigated the relationship between inflammatory changes in the SIJ and quantitative parameters of pain sensitization.

We conclude that there was no association observed between pain sensitivity measures and sacroiliac involvement in axSpA patients. Subchondral bone marrow edema (BME) in the SIJ is the main pathological change responsible for disease activation and pain in SpA, as indicated by the ASAS MRI working group [19]. In cases where the pattern of osteitis is not evident, other active inflammatory lesions such as enthesitis, synovitis, and capsulitis are supportive. Radiologically, structural lesions such as sclerosis, erosion, fat infiltration, and new bone formation, in addition to active inflammatory lesions should also be assessed in patients with axSpA [20]. These inflammation-related lesions were gathered under two headings with SPARCC scoring, and their relationship with QST results was investigated; no significant correlation was found between QST, CSI, and SPARCC scores in axSpA patients. Although, there is a large body of research on the relationship between radiological findings and measures of pain sensitization in osteoarthritis (OA), there is a lack of available data on this topic in rheumatological diseases. Different studies have reported that the presence of synovitis and effusion on MRI is correlated with QST results in OA patients experiencing severe pain, but the identical connection with bone marrow lesions (BMLs) has not been shown [21, 22]. It has been reported that synovitis and effusion, among these OA-related lesions, are inflammatory in nature, while BMLs are mechanical lesions that occur as a result of microtrauma [23]. Similarly, in patients with hand osteoarthritis, local PPT values were found to be associated with radiographic findings of structural damage and the degree of synovitis detected on ultrasonography. Nevertheless, in this patient population, there was no correlation established between TS and radiological joint findings [24]. Considering the links between inflammation and pain sensitization in degenerative diseases like OA, it seems plausible that axSpA will exhibit a similar relationship. However, the heterogeneity of the radiological and QST methods used in the studies and the fact that the inflammation burden in spondyloarthritis is higher than in osteoarthritis, make it difficult to directly translate these results to axSpA patients.

The main mechanism in this regard is that inflammation-induced structural changes lead to an increase in nociceptor sensitization, first peripherally and then centrally [24].

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Accordingly, a causal and linear relationship can be expected between PPT and TS and the presence of inflammatory lesions in our patients, as in OA. Another theory is that, rather than being directly related to an increase in nociceptive input, CS in these patients may be brought on by circulating substances like cytokines [25]. It will be more challenging to demonstrate a direct correlation between QST and SIJ lesions in cases of CS that arise from systemic inflammatory mediators rather than from regional nociceptor sensitization. Considering that the main feature that distinguishes axSpA from OA is systemic inflammation, it is possible that a similar difference affects the pain sensitization process. In any case, CS can occur in axSpA in both ways, and the predominant mechanism and QST results may vary depending on the characteristics of local and systemic inflammation.

The process of assessing the endogenous analgesic mechanisms that contribute to the development of CS is known as conditioned pain modulation, or CPM. Apart from decreased CPM function, patients with CS are reported to have higher pain and increased BASDAI scores as compared to axSpA patients without CS [8]. Similarly, less effective CPM in patients with high disease activity at baseline has been demonstrated to be a major predictor of high disease activity continuing despite therapy in rheumatoid arthritis [26]. On the other hand, in a study examining the relationship between CPM and chronic rheumatic pain, it was found that although, CPM impairment was associated with pain severity, it was not associated with disease activity or other clinical parameters [27]. While there is compelling evidence connecting CPM to pain in different chronic musculoskeletal disorders, the findings in rheumatism appear to be inconsistent. In contrast to PPT and TS, which are regarded as clinical signs of pain sensitization, CPM represents the effectiveness of the endogenous analgesic system. Therefore, determining the effect of inflammatory lesions on this circuit will be more challenging than demonstrating its relationship with pain.

In similar studies, the effect of the simultaneous presence of acute and chronic lesions on pain sensitization and related parameters is unknown. As mentioned above, although, acute lesions seem to be more important in terms of activation of nociceptive pathways and circulating cytokines in the development of CS, structural lesions are also likely to affect the sensitization process in the subacute or chronic period. In this context, one of the possible reasons for this discrepancy between SPARCC scores and QST is the simultaneous presence of various inflammatory and structural lesions in many patients. Nencini et al., emphasized that the nociceptor mechanical response in an animal model changes with age and chronicity; this means that pain sensitization parameters may differ in the course of the disease depending on the structural changes [28]. In addition, it is accepted that disease activity and systemic inflammatory burden in the chronic period are relatively reduced in most patients under treatment. An association between SPARCC scores and QST results may have been obscured by the simultaneous presence of acute and chronic lesions in a significant portion of the participants in the study.

When interpreting all these results, it is useful to remember the complex nature of pain sensitization. Whether local or systemic, the sensitization process brought on by inflammation-mediated nociception takes on a unique clinical appearance when biopsychosocial variables are involved. The fact that not every patient with rheumatism develops sensitization indicates the restricted effect of inflammation in CS and the importance of defined individual characteristics such as gender, pain behavior, and self-efficacy. This multifactorial structure of the CS makes it difficult to reveal the role of specific components in this system, especially with limited patients.

The limitations of the study are the small number of patients, the lack of evaluation of spinal QST, and the inability to calculate the interobserver and intraobserver consistency for the QST because it was performed by a single practitioner. The inability to perform patient assessment and sacroiliac imaging simultaneously can be considered another limitation of this study.

The study's strengths include being the first to investigate the connection between CS and SIJ involvement in spondyloarthritis and its comprehensive assessment of pain sensitization, which takes into account PPT, TS, CPM, and CSI.

Conclusion

Whether rheumatic or not, inflammation is recognized to play a role in the process of pain sensitization. This relationship becomes even more significant in chronic pain on the basis of systemic inflammation. As the sacroiliac joint is the main site of involvement in patients with axSpA, it can be thought of as the primary focus where pain sensitization develops. This study did not show an association between QST and SPARCC scores, but the extent to which CS is influenced by underlying disease or biopsychosocial factors remains unclear. Comprehensive studies are required to examine how these elements interact with CS settings and one another.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Marmara University, School of Medicine Clinical Research Ethics Commmittee (date:08.01.2021, approval number: 09.2021.64) and written informed consent was obtained from all patients. In addition, the study has been registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT05021783). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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