North Clin Istanb 2024;11(2):140–146
doi: 10.14744/nci.2023.81231

Original Article PM&R

Impact of central sensitization on clinical parameters in patients with rheumatoid arthritis

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ABSTRACT

OBJECTIVE: This study aimed to investigate the effects of central sensitization (CS) on pain sensitivity, disease activity, neuropathic symptoms and quality of life (QoL) in patients with rheumatoid arthritis (RA).

METHODS: Sixty patients diagnosed with RA according to the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) 2010 classification criteria were included in the study. Patient assessment tools included visual analog scale (VAS) for pain, algometer for pain pressure threshold (PPT), disease activity score in 28 joints (DAS-28) for disease activity (DA), central sensitization inventory (CSI) for CS and rheumatoid arthritis QoL questionnaire for QoL.

RESULTS: Central sensitization was identified in 29 (48.3%) patients. Although erythrocyte sedimentation rate (ESR), C-reactive protein and swollen joint count were comparable between patients with or without CS, higher VAS, tender joint count and DAS-28 scores were observed in patients with CS (all $p<0.05$). Pain pressure thresholds (PPT) at the wrist (PPT_W) and the trapezius muscle (PPT_T) were lower in patients with CS ($p=0.004$, $p=0.001$, respectively). It was found that neuropathic pain components increased and quality of life decreased as CSI scores increased (all $p=0.000$).

CONCLUSION: The presence of CS leads to pain sensitivity as well as overestimation of disease activity in RA patients. The presence of CS should not be overlooked in RA patients to avoid overtreatment for inflammation and to determine the treatment need for nociplastic pain.

Keywords: Central sensitization; pain threshold; rheumatoid arthritis.

Cite this article as: *Mesci N, Mesci E, Unkun Kandemir E, Geler Kulcu D, Celik T. Impact of central sensitization on clinical parameters in patients with rheumatoid arthritis. North Clin Istanb 2024;11(2):140–146.*

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by synovial inflammation. Undoubtedly, pain is the major symptom of RA. Inflammation is the primary pathology in RA, and pain is largely a consequence of inflammation. However, although improvements in objective inflammatory markers such as swollen joint count, erythrocyte sedimentation rate and CRP have been obtained with disease-modifying anti-rheumatic drugs (DMARDs), pain relief cannot be achieved. This suggests that other mechanisms may play a role in the pathogenesis of pain in RA [1]. In effect, several studies have demonstrated that objective inflammatory markers are poorly correlated with pain severity in some RA patients [2].

Central sensitization (CS) is a phenomenon of increased neuronal responsiveness and synaptic plasticity in central pain pathways following painful stimulation. CS results in increased sensitivity of the central nervous system to painful and non-painful stimuli. It is known that central pain mechanisms are

Received: February 28, 2023 *Accepted:* March 09, 2023 *Online:* April 22, 2024

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involved in the pathogenesis of pain in many rheumatic diseases, especially fibromyalgia [3]. Central sensitization has been reported in 15–40% of patients with inflammatory rheumatic diseases [4]. In previous studies, CS has been mostly discussed in the context of fibromyalgia syndrome (FMS). It was underscored that this does not necessarily mean that non-inflammatory pain occurs only in patients meeting the FMS criteria [5].

The confounding effect of CS-related pain (nociplastic pain) on the clinical markers used to evaluate inflammatory pain associated with disease activity is another topic of debate. It has been considered that discrepancies commonly observed between the results of patient global assessment (PGA) and evaluator global assessment (EGA) that are used for clinical follow-up of RA patients may be related to central sensitization [6]. There are findings that the said discordance results from overestimation of pain severity by patients due to increased pain sensitivity [2].

It has been shown that DAS-28 scores are overestimated in RA patients with concomitant FMS [7]. Lower pain pressure threshold has been associated with higher disease activity in RA patients [8]. Although the assessment of treatment needs is mostly based on these disease activity markers, such markers are largely affected by biases in subjective pain ratings of the patients, and this represents an important clinical concern. Determining the correlation between central sensitization and clinical parameters in RA patients may inform clinicians to what extent nociplastic pain should be considered during treatment planning.

In the few studies that evaluated central sensitization using the central sensitization inventory (CSI) in RA patients, there was evidence that pain is somewhat associated with increased central sensitization in these patients. We have limited information about the frequency of central sensitization in patients with RA [9]. Moreover, the relationship between neuropathic pain-like symptoms and central sensitization in patients with rheumatoid arthritis has not been clearly elucidated [10].

The aims of this study were twofold. The primary aim was to determine the frequency of central sensitization among RA patients, and the second aim was to investigate the association of the presence of central sensitization with various clinical parameters including pain sensitivity, disease activity, neuropathic symptoms and quality of life.

Highlight key points

- Rheumatoid arthritis causes central sensitization.
- Generalized pain sensitivity occurs in patients with rheumatoid arthritis developing central sensitization.
- Since patients with central sensitization tend to report their current pain as more severe than it actually is, the disease activity is overestimated.
- The neuropathic component of the pain is more prominent and quality of life is lower in RA patients with central sensitization.

MATERIALS AND METHODS

Patients (aged 18 years or older) with a diagnosis of rheumatoid arthritis who were being followed at the physical therapy and rehabilitation outpatient clinics of Haydarpasa Numune Training and Research Hospital were included in this study. The diagnosis of rheumatoid arthritis was based on the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) 2010 classification criteria [11]. Among these patients, the presence of FMS was assessed according to the 1990 ACR FMS classification criteria [12]. Approval for the study was obtained from the local ethics committee of Haydarpasa Numune Training and Research Hospital (2022/245/26.12.2022). All study procedures were conducted in accordance with the principles set forth in the Declaration of Helsinki. Prior to initiation of the study, written informed consent was signed by all participants. Patients with a neurological disorder, cognitive dysfunction (e.g., dementia), malignant disease, severe psychiatric illness or a history of orthopedic surgery and those who refused to participate by giving written consent were excluded from the study. Patients receiving treatment with antidepressants, antiepileptic drugs or any medication that could affect pain perception were also excluded. Ultimately, 60 patients were included in the study.

Demographic and clinical data of the patients were noted, including age, height, body weight and body mass index (BMI). Anti-rheumatic drugs used, disease duration and systemic comorbidities of the patients were questioned. Swollen joint count (SJC) and tender joint count (TJC) were determined during the physical examination. Pain intensity at rest (VAS_R) and on movement (VAS_M) were measured on a 10 cm visual analog scale (VAS). Current erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values of the patients were retrieved from their follow-up laboratory investigations. The following parameters were assessed for the patients included in the study.

Disease Activity Score in 28 joints (DAS-28)

Disease activity was determined by calculating DAS 28 scores. The DAS 28 is a tool that assesses 28 joints as a measure of disease activity in patients with RA. The DAS28 score is estimated using a specific formula that takes into account a number of clinical parameters including SJC, TJC, PGA and CRP level. A DAS28 score greater than 5.1 indicates high disease activity, 3.2 to 5.1 denotes moderate disease activity and 2.6 to 3.2 indicates low disease activity. A score less than 2.6 suggests disease remission [13].

Pain Pressure Threshold

Pain pressure threshold (PPT) was measured using a JTECH™ Commander algometer (JTECH, USA). Measurements were obtained from the midpoint of the dorsal aspect of the dominant wrist (PPT_W) used as the joint test site and from the midpoint of the superior trapezius muscle (PPT_T) used as the remote test site. Measurements were taken from the hand and wrist placed on a table, with the patient in a sitting position. Gradually increasing pressure was applied over the test sites using the probe (1 cm^2) of the algometer until the patient first felt pain, and this pressure value was recorded in kg/cm^2. Two measurements were done for each site at an interval of 30 seconds and average values were included in the analyses. The same evaluator performed the measurements for all patients.

PainDETECT

The presence of neuropathic pain components was assessed using the painDETECT questionnaire (PDQ). The final PDQ score is obtained by adding the scores from 7 questions to the scores from questions related to pain course pattern and radiating pain. PDQ scores are interpreted as follows: 0 to 12, the pain is unlikely to have a neuropathic pain component; 13 to 18, the pain is likely to have a neuropathic pain component; 19 to 38, the pain is most likely to have a neuropathic pain component. Reliability and validity of the Turkish version of the PainDETECT were demonstrated by Alkan et al. [14].

Central Sensitization Inventory

The Central Sensitization Inventory (CSI) consists of 25 questions. The response to each question is assigned a score between 0 and 4. Total possible score is 100. The cut-off score of the CSI is 40, and a score of ≥40 indicates the presence of central sensitization. Higher overall scores represent a higher degree of symptomatology. The reliability and validity of the Turkish version of the CSI were demonstrated by Duzce E et al. [15].

Table 1. Characteristics of the patients with rheumatoid arthritis

	Rheumatoid arthritis (n=60)
Age (years, Mean±SD)	56.8±1.1
BMI (kg/m^2, Mean±SD)	27.5±4.2
Disease duration, years	10 (1–30)[a]
TJC2	(0–21)[a]
SJC0	(0–7)[a]
VAS_R (Mean±SD)	4.4±2.2
VAS_M (Mean±SD)	4.7±2.5
ESR (mm/h)	28.5 (2–85)[a]
CRP	4.14 (0.2–28)[a]
DAS-28 ESR (Mean±SD)	3.9±1.3
DAS-28 CRP (Mean±SD)	3.2±1.1
PPT_W	33.8 (16.2–96.9)[a]
PPT_T	30.9 (16.7–86.7)[a]
CSI (Mean±SD)	38.6±19.5
PDQ	6 (0–22)[a]
RAQoL	13.5 (0–30)[a]
Treatment, n (%)	
Synthetic DMARDs	37 (61.7%)
Biological DMARDs	23 (38.3%)

a: Median (minimum–maximum); BMI: Body mass index; CRP: C-reactive protein; CSI: Central sensitization inventory; DAS-28: Disease activity score-28; DMARD: Disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; h: Hour; kg: Kilogram; m: Meter; mm: Millimeter; PDQ: PainDETECT questionnaire; PPT_T: Pain pressure threshold-trapezius; PPT_W: Pain pressure threshold-wrist; RA: Rheumatoid arthritis; RAQoL: Rheumatoid arthritis quality of life; S: Second; SD: Standard deviation; SJC: Swollen joint count; TJC: Tender joint count; VASM: Visual analog scale-movement; VASR: Visual analog scale-rest.

Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)

The RAQoL consists of thirty questions answered with a yes (1) or no (0). The scores range from 0 to 30, with high scores indicating poor quality of life. The reliability and validity of the Turkish version of the RAQoL were demonstrated by Kutlay et al. [16].

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows, version 22.0 (IBM Corp., Armonk, NY) was used

TABLE 2. Comparison of the characteristics of patients with or without central sensitization

	CS group (n=29) Mean±SD	Non-CS group (n=31) Mean±SD	p
Age (years)	56.9±13.6	56.5±7.5	0.912
BMI (kg/m^2)	27.9±4.3	27.7±4.1	0.855
Disease duration, (years)	9 (1–30)[a]	10 (1–25)[a]	0.801
ESR (mm/h)	25.8±18.0	30.8±15.9	0.260
CRP	3.3 (0.2–19.4)[a]	5 (0.4–28)[a]	0.105
SJC	0 (0–7)[a]	0 (0–4)[a]	0.416
TJC	6 (0–21)[a]	1 (0–12)[a]	0.006**
DAS-28 ESR	4.3±1.3	3.5±1.1	0.016*
DAS-28 CRP	3.6±1.1	2.9±0.9	0.012*
VAS_R	5.4±2.1	3.5±1.8	0.000**
VAS_M	6 (2–10)[a]	3 (0–9)a	0.000**
PPT_T	27.7 (16.7–78.6)[a]	46 (18.0–86.7)[a]	0.001**
PPT_W	28.1 (18.9–70.3)[a]	47 (16.2–96.9)[a]	0.004**
PDQ	10.4±5.6	4.8±2.5	0.000**
RAQoL	17 (7–30)[a]	3 (0–20)[a]	0.000**
CSI	54.8±11.1	22.1±8.1	0.000**

a: Median (minimum–maximum); *: P<0.05; **: P<0.01; BMI: Body mass index; CRP: C-reactive protein; CSI: Central sensitization inventory; DAS-28: Disease activity score-28; ESR: Erythrocyte sedimentation rate; h: Hour; kg: Kilogram; m: Meter; mm: Milimeter; PDQ: Pain detect questionnaire; PPT_T: Pain pressure threshold-trapezius; PPT_W: Pain pressure threshold-wrist; RAQoL: Rheumatoid arthritis quality of life; SD: Standard deviation; SJC: Swollen joint count; TJC: Tender joint count; VASM: Visual analog scale-movement; VASR: Visual analog scale-rest.

for the statistical analysis the study findings. Descriptive statistics were summarized as mean, median, standard deviation and minimum–maximum. For between-group comparisons, Student's t-test was used for quantitative data with a normal distribution and Mann-Whitney U test for quantitative data without a normal distribution. Relationships between CSI and normally distributed variables were analyzed using Pearson correlation analysis, and correlations between non-normally distributed variables were examined with Spearman correlation analysis. The results were considered significant at the p<0.05 level with a 95% confidence interval.

TABLE 3. Correlations of central sensitization with swollen and tender joint counts and DAS28 scores

	SJC	TJC	DAS28 CRP	DAS28 ESR
CSI				
rho	0.100	0.336**	0.342**	0.342**
P value	0.446	0.009	0.007	0.008

**: Significant at the 0.01 level; CRP: C-reactive protein; CSI: Central sensitization inventory; DAS-28: Disease activity score-28; ESR: Erythrocyte sedimentation rate; SJC: Swollen joint count; TJC: Tender joint count.

RESULTS

Demographic, laboratory and clinical characteristics of the RA patients are presented in Table 1. FMS was identified in 20 of 60 patients (33.3%) included in the study (Table 1).

When the CSI responses of the patients were reviewed, 29 (48.3%) patients were identified as having central sensitization. It was observed that 20 (69%) of the patients with CS had FMS but none of the 31 patients without CS had a diagnosis of FMS. Table 2 shows the comparison of demographic and laboratory data, pain sensitivity parameters, disease activity, quality of life and neuropathic pain scores between patients with or without CS (Table 2).

Correlations of CSI scores with DAS-28 scores and swollen and tender joint counts are displayed in Table 3. It is noteworthy that the CSI scores were not correlated with swollen joint count (Table 3).

Table 4. Correlations of central sensitization scores with pain sensitivity parameters, neuropathic pain and quality of life scores

	VAS_R	VAS_M	PPT_T	PPT_W	PDQ	RAQoL
CSI						
rho	0.481**	0.499**	-0.371**	-0.324*	0.534**	0.773**
P value	0.000	0.000	0.005	0.015	0.000	0.000

*: Significant at the 0.05 level; **: Significant at the 0.01 level; CSI: Central sensitization inventory; PDQ: PainDETECT questionnaire; PPT_T: Pain pressure threshold-trapezius; PPT_W: Pain pressure threshold-wrist; RAQoL: Rheumatoid arthritis quality of life; VAS_M: Visual analog scale-movement; VAS_R: Visual analog scale-rest.

Table 4 shows the correlations of CSI scores with PainDetect and Rheumatoid Arthritis Quality of Life scores and VAS and PPT (pain sensitivity parameters) values (Table 4).

DISCUSSION

Our findings showed that despite comparable ESR, CRP and swollen joint count between patients with or without CS, VAS_R, VAS_M, tender joint count and DAS-28 scores were higher in patients with CS. Poorer quality of life and significantly higher neuropathic pain scores were found in patients with CS compared to those without CS. Both mean PPT_W values from the proximity of the joint and mean PPT_T values from the remote test site were lower in patients with CS versus those without CS. As an important finding, when all patients were evaluated as a whole, it was observed that PPT_T and PPT_W values decreased as CSI scores increased. This suggests that the presence of central sensitization is associated with generalized pain sensitivity.

In one of the few studies examining CS in pain associated with various rheumatic diseases, Guler et al. [9] found no correlation between CSI scores and disease duration, VAS pain scores or disease activity in RA patients. Likewise, our results did not show any correlation of CSI scores with patient age, disease duration, and ESR and CRP values. However, CSI scores were positively correlated with VAS_R, VAS_M and DAS-28 scores in our study. This finding was expected since it is known from the general literature that patients have increased pain perception in the presence of CS, and disease activity parameters are overestimated when patient global assessments are used. Although the duration of morning stiffness, ESR, CRP and swollen joint count were similar between RA patients with or without FMS, DAS-28, VAS pain scores and tender joint count were higher in those with FMS [7].

While the mean CSI score observed in our study is similar to that reported by Guler et al. [9], the percentage of patients identified as having CS in their study (41%) is slightly lower than what we found in this study (48.3%). In contrast, in a study using the CSI, Saitou et al. [10] identified CS in only 7.5% of the patients with RA. However, this CS frequency is considerably lower compared to the CS rates reported by other studies as well [17, 18].

In RA patients, pain associated with CS has often been discussed in the context of neuropathic pain or in relation to the coexistence of CS with FMS. However, the relationship among these clinical entities is still unclear [5, 10]. Our results showed that although the majority of the patients with CS had a diagnosis of FMS, not all of them had FMS. Looking at the literature data, it is seen that the frequency of neuropathic pain among RA patients is generally lower than that of CS [19, 20].

It was reported that low pain pressure threshold is correlated with high disease activity as determined by the clinical disease activity index (CDAI) but not with swollen joint count in RA patients. In these patients, PPT values from the remote trapezius muscle (non-joint test site) were also found to be correlated with high disease activity [8]. Our findings are in line with their results, and additionally, our study showed that increased pain sensitivity as demonstrated by the PPT values from both joint and non-joint sites were correlated with central sensitization. Also, our study found that while TJC, a parameter assessed by the patient, was affected by the presence of central sensitization, SJC was not. In a study by Jonaratham et al. [21], low PPT values from remote sites such as the tibia and sternum were found to be correlated with high DAS28 scores in RA patients. This finding was interpreted by the authors as evidence that central pain mechanisms have an important role in the development of pan sensitivity in these patients. In the same study, the components of DAS28 such as ESR and SJC, which are not patient-reported outcomes, were not correlated with low PPT values. These findings also support our results.

Our findings showed that PPT values from both the wrist and the trapezius muscle were low in patients with CS. In a study by Lee et al. [22], lower PPT values were observed in RA patients compared to healthy controls, with significantly lower PPT found at the periarticular regions.

Furthermore, impaired central pain modulation was demonstrated in RA patients using quantitative sensory testing.

The aforementioned changes in subjective pain parameters due to increased pain sensitivity in RA patients with CS, potentially resulting in overestimated disease activity, represent a major concern that needs to be addressed. This may cause unnecessary use of medications in patients. In a study by Salaffi et al. [23] using the simplified disease activity index (SDAI) criteria for remission, it was reported that the presence of FMS prevented RA patients from achieving remission criteria. They concluded that, in order to avoid overtreatment, the possibility of FMS presence should be considered in RA patients identified as having high disease activity based on disease activity scales. Central sensitization should be borne in mind in RA patients in whom persistently high disease activity is detected without objective signs of inflammatory activity, such as laboratory data. This will allow continuation of patient treatment based on their actual needs and help avoid consequences of overtreatment including potential complications and additional costs.

Another important aspect of detecting the presence of non-inflammatory pain in RA patients is that this type of pain is accompanied by symptoms of fatigue, sleep disorders as well as psychosomatic problems, and requires distinct treatment approaches. Therefore, it seems important that, when making a treatment decision between DMARDs and non-inflammatory pain management strategies in RA patients, misleading effects of patient-reported components on disease activity markers such as DAS28 need to be considered.

The strength of our study lies in the fact that we comprehensively evaluated the effects of central sensitization (as determined by CSI) in RA patients in terms of pain, PPT, inflammation, disease activity, neuropathic pain components and quality of life. However, our study is limited by a relatively small sample size and cross-sectional design.

Conclusion

The presence of central sensitization leads to increased pain sensitivity and overestimation of disease activity in RA patients. To avoid overtreatment for inflammation and identify the treatment needs for nociplastic pain, the presence of CS in these patients should not be overlooked. The CSI is a practical tool for identifying patients with CS, and the use of algometer for detecting changes in pain sensitivity will allow for objective assessment.

Ethics Committee Approval: The Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 26.12.2022, number: 2022/245).

Authorship Contributions: Concept – NM, EM, DGK, TC; Design – NM, EM, DGK, EUK; Supervision – NM, EM, DGK, EUK, TC; Fundings – NM, EM, EUK, TC; Materials – NM, EM, EUK, TC; Data collection and/or processing – NM, EM, EUK, TC; Analysis and/or interpretation – EM, NM, DGK, EUK, TC; Literature review – EM, NM, DGK, EUK, TC; Writing – EM, NM, DGK, EUK; Critical review – EM, NM, DGK, TC.

Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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