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Prevalence of the neuropathic pain component in rheumatoid arthritis patients and its relationship to disease activity: a cross-sectional study

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ABSTRACT

Aims: The purpose of this study is to examine the prevalence of the neuropathic pain (NP) component in patients with rheumatoid arthritis (RA) and its effects on disease activity, functional status, and quality of life.

Methods: The sample of the study consisted of 120 individuals, including 60 patients diagnosed with RA and 60 age- and sex-matched controls. The disease activity score-28 (DAS-28) for disease activity, the Visual Analog Scale (VAS) for pain, the painDETECT questionnaire (PDQ) for NP, the Rheumatoid Arthritis Quality of Life Questionnaire (RA-QoL) for quality of life, and the Health Assessment Questionnaire (HAQ) for functional status were used to collect data.

Results: The prevalence of NP was 63.3% (n=38) in the patient group and 6.7% (n=4) in the control group, and the difference between the two groups was statistically significant ($p<0.001$). The patient group was divided based on their PDQ scores into two subgroups consisting of those with unclear or likely NP symptoms (PDQ≥13) and those without NP symptoms (PDQ<13). The VAS-pain, DAS-28, HAQ, and RA-QoL scores of the subgroups with and without symptoms showed statistically significant differences ($p<0.001$). The PDQ scores of the patients were positively correlated with their DAS-28, VAS-pain, RA-QoL, and HAQ scores ($p<0.001$).

Conclusion: In addition to nociceptive pain, RA patients also have non-negligible rates of NP. NP is associated with high disease activity, low quality of life, and limited functional capacity.

Keywords: Rheumatoid arthritis, neuropathic pain, pain-DETECT questionnaire, HAQ

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, and inflammatory disease that starts in synovial tissue and leads to damage in the joints at later stages.[1] In RA cases, keeping the disease under control and in remission requires strict follow-up and management.[2] In most patients, inflammation can be effectively managed using disease modifying anti-rheumatic drugs (DMARDs) and the latest generation of agents.[1,3] However, in some patients, pain may persist despite objective signs such as a decrease in acute phase reactant levels and the number of swollen joints.[4] In addition to this, pain scores of some patients decline after starting treatment but plateau at a certain point.[5] Both situations indicate the presence of different pain mechanisms other than the nociceptive pain that develops due to synovial inflammation.[1,3] Recent studies have provided evidence of the possibility of a neuropathic component of pain in rheumatic diseases.[6]

Neuropathic pain (NP) is a form of pain caused by a dysfunction in the somatosensory nervous system due to a lesion or disease. While describing NP, patients report symptoms such as burning, stabbing, tingling, and numbness.[6] In recent studies, it was reported that pain could have a neuropathic component in some rheumatic diseases including RA.[7,8] The underlying factors of the etiology of NP in rheumatic diseases have not yet been identified completely.[9] Some researchers stated that in RA, NP could be caused by central sensitization.[4,6] Moreover, in electroneuromyography examinations of RA patients with NP conducted in a previous study, neuropathies were identified in 48.5% of the patients, and it was concluded that peripheral mechanisms could be effective in the etiology of NP.[8] Considering that pain persists even in RA patients with completely suppressed inflammation and halted joint damage, central or peripheral mechanisms may contribute to this pain.[4,10]

In this study, we aimed to determine the prevalence of the NP component of pain in patients diagnosed with RA using the painDETECT questionnaire (PDQ) and examine the relationships between NP and disease activity, functional status, and quality of life.

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METHODS

Participants

Approval to conduct the study was obtained from the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 11.04.2025, Decision No: 2025/117). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was planned with a cross-sectional design in which the data of patients diagnosed with RA were obtained from their patient files. Patients who had been diagnosed with RA according to the ACR/EULAR 2010 classification criteria and were being followed up as outpatients at the Physical Medicine and Rehabilitation Clinics between January 2023 and March 2025 were included in the study.[11] Disease duration, sex, age, swollen joint count (SJC), tender joint count (TJC), complete blood count results, erythrocyte sedimentation rate (ESR) values, and C-reactive protein (CRP) values were recorded.

Inclusion and exclusion criteria: Patients who had a follow-up duration of at least one year with the diagnosis of RA and were 18-65 years old were included. The sample of the study excluded those with diabetes mellitus, thyroid disease, peripheral or central nervous system diseases or lesions, or psychiatric disorders and those who were using antidepressant or antiepileptic drugs. The control group included individuals who were 18-65 years old, did not have any health problems, were not using any medication, and agreed to participate in the study.

II. Clinical Assessments

Disease activity score in 28 joints (DAS-28): DAS-28 was used to evaluate disease activity in the patient group. DAS-28 scores are calculated based on the number of tender and swollen joints, CRP or ESR values, and the global self-assessment of the patient.[12]

Pain DETECT Questionnaire (PDQ): Neuropathic symptoms were evaluated using PDQ. The questionnaire consists of seven sensory items reflecting the characteristics of pain, one item reflecting the course of the pain, and one item reflecting the direction of the pain. PDQ scores vary from -1 to 38. Scores are categorized as unlikely NP for <13, uncertain NP for 13-18, and likely NP for >18.[13] The severity of pain was evaluated based on a 10-cm version of the Visual Analog Scale (VAS).

Health Assessment Questionnaire (HAQ): The functional statuses of the patients were evaluated using HAQ. The scale consists of 20 items and the following categories; dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Its maximum score is 60, and higher scores indicate poorer functional status.[14]

Rheumatoid Arthritis Quality of Life (RA-QoL) Questionnaire: This disease-specific scale was used to identify the quality of life of the patients. RA-QoL consists of 30 questions with the response options of yes (1) and no (0). Scores range from 0 to 30, with higher scores indicating a poorer quality of life for the patient.[15]

Statistical Analysis

The sample size was determined based on the literature on the prevalence of NP and associated factors in patients with RA. With 90% power, a type I error rate (α) of 0.05, and a large effect size (1.07) according to Cohen's criteria, the estimated sample size was 25 participants per group.

All statistical analyses were carried out using the SPSS (20.0, Inc., Chicago, Illinois, USA) program. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Mean and standard deviation values were calculated. The Mann-Whitney U test for the non-normally distributed data and student's T test for the normally distributed data were used to compare two independent groups of variables. Chi-squared tests were used to compare categorical variables. Relationships between variables were analyzed using Spearman's correlation analysis. p-values of <0.05 were accepted as statistically significant.

RESULTS

The patient group consisted of 50 women (83.3%) and 10 men (16.7%), while the control group consisted of 47 women (78.3%) and 13 (21.7%) men. There was no statistically significant difference between the patient and control groups in terms of their sex distributions (p=0.487). The mean ages of the participants were 45.82±12.66 (19-65) in the patient group and 42.02±12.20 (22-65) in the control group, and the groups did not differ significantly from each other in terms of age (p=0.097). While 38 of the 60 patients (63.3%) were found to have NP, 4 participants in the control group (6.7%) had NP. The difference between the groups was significant (p<0.001). There was also a significant difference between the VAS-pain scores of the patient and control groups (p<0.001). The characteristics and scale scores of the patient and control groups are shown in Table 1. The demographic and disease-related characteristics of the participants are presented in Table 2.

Table 1. Descriptive characteristics and scale scores of the participants

	Patient group	Control group	p
Age (years)	45.82±12.66	42.02±12.20	0.487
Sex (F/M)	50/10	47/13	0.097
VAS-pain score	4.85±2.82	1.32±1.77	<0.001
PDQ score	14.32±8.64	3.10±4.22	<0.001
NP rate	63.3%	6.7%	<0.001

F/M: Female/male, VAS: Visual Analog Scale, PDQ: Pain-DETECT Questionnaire, NP: Neuropathic pain

The patient group was divided into two subgroups consisting of those with unclear or likely NP symptoms (PDQ≥13) and those without NP symptoms (PDQ<13), and there was no statistically significant difference between the two subgroups in terms of their age, sex, or disease duration (respectively, p=0.096, p=0.539, p=0.872). Primary-middle school graduates constituted 63.2% of the patients with NP. The rate of high school graduates was higher among those without NP. The difference between the two subgroups based on their education levels was significant (p=0.034). The VAS-

Table 2. Characteristics of patients with RA (n=60)	
Sex (F/M)	50/10
Age (years)	45.82±12.66
Disease duration (years)	9.97±7.69
Education level, n (%)	
Primary-middle school	51.7 (31)
High school	33.3 (20)
University	15.0 (9)
RA medication, n (%)	
DMARD	53.3 (32)
Biologics	21.7 (13)
DMARD+biologics	25.0 (15)
Prednisolone dose (mg/day)	3.95±3.09
DAS-28	3.61±1.28
VAS-pain	4.85±2.82
SJC	1.62±2.26
TJC	2.43±3.12
PDQ	14.32±8.64
HAQ	8.3±7.57
RA-QoL	12.08±8.24

RA: Rheumatoid arthritis, F/M: Female/male, DMARD: Disease-modifying antirheumatic drug, DAS-28: Disease activity score, VAS: Visual Analog Scale, SJC: Swollen joint count, TJC: Tender joint count, PDQ: Pain-DETECT Questionnaire, HAQ: Health Assessment Questionnaire, RA-QoL: Rheumatoid Arthritis Quality of Life- Questionnaire

Table 3. Comparison of descriptive characteristics and scale scores of the patient subgroups with uncertain or likely NP and with unlikely NP				
		PDQ≥13 (n=38)	PDQ<13 (n=22)	p
Age (years)		48.03±11.37	42.00±14.08	0.096
Sex (F/M)		32/6	18/4	0.539
Disease duration (years)		10.05±7.82	9.82±7.63	0.872
Education level n (%)	Primary-middle school	24 (63.2%)	7 (31.8%)	0.034
	High school	11 (28.9%)	9 (40.9%)	
	University	3 (7.9%)	6 (27.3%)	
RA medication n (%)	DMARD	17 (44.7%)	15 (68.2%)	0.004
	Biologic	9 (23.7%)	4 (18.2%)	
	DMARD+biologics	12 (31.6%)	3 (13.6%)	
Prednisolone dose (mg/day)		4.27±3.28	3.40±2.73	0.453
SJC		2.24±2.51	0.55±1.14	0.451
TJC		3.08±3.15	1.32±2.80	0.013
VAS-pain		6.34±2.13	2.27±1.85	<0.001
DAS-28		4.14±1.12	2.68±0.99	<0.001
HAQ		11.18±7.80	3.32±3.59	<0.001
RA-QoL		15.11±7.99	6.86±5.74	<0.001

NP: Neuropathic pain, PDQ: Pain-DETECT Questionnaire, F/M: Female/male, RA: Rheumatoid arthritis, DMARD: Disease-modifying antirheumatic drug, SJC: Swollen joint count, TJC: Tender joint count, VAS: Visual Analog Scale, DAS-28: Disease activity score, HAQ: Health Assessment Questionnaire, RA-QoL: Rheumatoid Arthritis Quality of Life Questionnaire

pain, DAS-28, HAQ, and RA-QoL scores of the subgroups with and without symptoms showed statistically significant differences (all p<0.001). In the subgroup with NP, the patients receiving a combination of biologic agents and DMARDs were significantly more prevalent than those receiving monotherapy (p=0.004). No significant difference was observed between the groups in terms of their prednisolone dosages (p=0.453). While no significant difference was found between the subgroups in terms of SJC (p=0.451), there was a significant difference in terms of TJC (p=0.013). The results of the analyses of the scale scores and subgroups of the patient group are shown in Table 3.

The PDQ scores of the patients had positive correlations with their DAS-28 (p<0.001), VAS-pain (p<0.001), RA-QoL (p<0.001), and HAQ (p<0.001) scores, while there was no significant correlation between their PDQ scores and disease durations (p=0.613). The degrees of relationships between the PDQ scores of the patients and their clinical parameters, as well as correlation coefficients, are given in Table 4.

Table 4. Relationships between PDQ scores and clinical parameters in the patient group			
	r	p	
DAS-28	0.582	<0.001	Moderate
VAS-pain	0.735	<0.001	Strong
Disease duration (years)	-0.067	0.613	No correlation
HAQ	0.650	<0.001	Strong
RA-QoL	0.620	<0.001	Strong

PDQ: Pain-DETECT Questionnaire, DAS-28: Disease activity score, VAS: Visual Analog Scale, HAQ: Health Assessment Questionnaire, RA-QoL: Rheumatoid Arthritis Quality of Life Questionnaire, r: Spearman's rank correlation coefficient

DISCUSSION

In this study, we showed that the pain experienced by RA patients had a neuropathic component. The presence of NP in the patients was also associated with high disease activity, low quality of life, and poor functional status. The prevalence of NP in RA patients was reported by Koca et al.[1] as 60.3%. The authors concluded that both central sensitization and NP were associated with disease activity. In our study, in agreement with the literature, the prevalence of NP in RA patients was found to be 63.3%, and this rate was much higher than the rate in the control group. In a recent study, the presence of NP in RA and osteoarthritis patients was investigated, and it was seen that there was an NP component in both patient groups.[9] On the other hand, while some studies showed NP presence in RA cases, these rates were reported to be low. These varying results may have originated from differences in the racial or regional characteristics of participants. Such that, as opposed to the case in Turkish patients demonstrated in this study, studies conducted with Japanese patients revealed low rates of NP.[6,16] The most important problem of RA patients is chronic pain. The International Association for the Study of Pain categorizes pain as nociceptive, neuropathic, and nociplastic pain. This classification aims to increase the likelihood of success in treatment by performing the appropriate treatment for patients with chronic pain.[17] In RA cases, nociceptive pain is caused by inflammation and/or varying degrees of damage in the joint. In addition to this, damage in nociceptive nerve endings may lead to NP by affecting the central or peripheral nervous system.[18]

The results of our study demonstrated that factors such as disease duration, sex, and age in RA cases were not associated with the NP component. This result was compatible with the literature.[6,16] On the other hand, in our study, pain levels assessed using VAS-pain and disease activity levels assessed using DAS-28 were significantly higher in the subgroup of RA patients with NP in comparison to those in the subgroup of RA patients without NP. In a previous study that included RA patients with DAS-28 scores greater than 5.1, VAS-pain, PDQ, and quantitative sensory testing were applied respectively to evaluate potential nociceptive, neuropathic, and nociplastic pain components, and it was concluded that different pain components could be seen simultaneously in RA cases.[2] A prospective study of 567 patients revealed that although there was a decrease in the disease activity levels of patients measured based on DAS-28 scores following DMARD treatment, the VAS-pain scores of 22.6% of the patients were still high. It was argued that this result could be associated with the presence of an NP component. NP prevents patients from meeting remission criteria by affecting their global self-assessments.[18] The potential presence of NP should be considered in cases of high DAS-28 scores caused by the poor subjective global self-assessments of RA patients despite their low levels of inflammatory markers. Consistent with previous studies, our results showed no significant association between the NP component and SJC, whereas TJC, which is another subjective measure reported by the patient, was significantly higher in the NP subgroup.[6,19,20] This suggested that patients with NP may perceive joint tenderness more intensely. It is well known that TJC directly influences DAS-28 scores, similar to the global self-assessment of the patient. With treatments provided to alleviate or resolve NP, high disease activity can be prevented, and there may no longer be a need for a change or dose increase in the treatments of patients for nociceptive pain. Thus, the chance of treatment success can be increased by identifying the type of pain and providing the appropriate treatment accordingly in RA patients.[5]

In line with the literature, in our study, we observed significantly higher NP scores among RA patients with lower education levels.[19] This indicated that education levels may influence the experience of pain through factors such as pain perception and treatment adherence. Considering that psychosocial factors like stress and anxiety may be more prevalent in this group, these elements could further affect pain perception. Therefore, in managing NP among RA patients, it may be beneficial to develop individualized approaches and supportive educational programs that take education levels into account.

The quality of life of RA patients is lower compared to healthy individuals, and this situation is closely related to disease activity, pain intensity, and physical functions.[21] Noda et al.[6] evaluated health-related quality of life and physical functions in RA patients and reported that NP symptoms affected both variables negatively. In a recent study by Büyük et al.,[22] NP was assessed using multiple NP questionnaires, and high NP scores in RA patients were discovered to be associated with RA-QoL and HAQ scores. In our study, we evaluated the quality of life of the patients using RA-QoL and their functional status using HAQ. Similarly, we showed that the NP component of pain in RA patients affected both parameters negatively. Pain is the main complaint of RA patients. Patients may suffer from pain that is felt in the form of multiple attacks in a month or even a day. The inconsistence of pain in RA may affect the quality of life and daily activities of RA patients to a substantial extent.[5]

In our study, NP was more prevalent among patients receiving combined treatment with biologic agents and DMARDs. This may be due to chronic pain being misclassified as nociceptive pain, leading to escalation to combination therapy. Indeed, it was stated that even when disease activity is controlled in RA patients undergoing DMARD dose adjustments or combination therapy including biologics, chronic pain may persist.[19] NP has been identified as a potential cause of such treatment-resistant pain.[18,19,23] Treatments used in RA are costly and carry significant side effects. Moreover, these therapies are designed to suppress inflammation responsible for nociceptive pain and have no place in NP management.[20] A detailed evaluation of nociceptive and NP components, the development of patient-specific treatment strategies, and perhaps a combined approach targeting both types of pain may enhance patient satisfaction and quality of life while reducing functional limitations.[23,24]

Limitations

First, while no patients in the sample had a previous diagnosis of fibromyalgia or a history of antiepileptic or antidepressant drug use, no specific assessment of fibromyalgia was made in the study. Fibromyalgia symptoms may present similarly to NP symptoms. Second, because our study was cross-sectional, we could not make assessments of NP at the time of RA diagnosis or before the initiation of RA treatment. We believe that assessments to be made at the time of first diagnosis would help us identify the presence of NP in addition to nociceptive pain.

CONCLUSION

NP accompanies nociceptive pain in a significant proportion of RA patients. This neuropathic component is associated with high disease activity, low quality of life, and poor functional status. In our opinion, in cases where pain cannot be managed, evaluating the neuropathic component of pain before increasing or changing the treatment provided for nociceptive pain will be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 11.04.2025, Decision No: 2025/117).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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