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**ORIGINAL ARTICLE /** ARAŞTIRMA YAZISI Physical Medicine and Rehabilitation / Fiziksel Tıp ve Rehabilitasyon

# Neuropathic Pain and Related Factors in Female Patients with Rheumatoid Arthritis

**Halime Kibar**[1]

[1]Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, Istanbul, Turkey

**ABSTRACT**

**Purpose:** Neuropathic pain (NP) can accompany Rheumatoid arthritis (RA) like many other diseases. The aim of our study was to investigate the frequency of NP and related factors in female patients with RA.

**Methods:** Age, disease duration, body mass index (BMI) and erythrocyte sedimentation rate (ESR) were recorded. A pain visual analog scale (VAS) was used to record pain intensity and a pain-detect questionnaire (PDQ) was used to record NP score. RA disease activity was calculated with DAS28 score. Health Assessment Questionnaire (HAQ) was used for functional status.

**Results:** NP scores of the patients were high. A significant correlation was found between PDQ and VAS, BMI and HAQ values. The correlation value between PDQ and disease duration, age, inflammation and disease activity was not significant.

**Conclusion:** All of the patient's pain may not be caused by inflammation. If this is the case, treatment can change. If the pain pattern is questioned and treated, unnecessary use of anti-inflammatory drugs can be prevented.

**Keywords:** inflammation, pain, rheumatoid arthritis

Halime KİBAR

**Romatoid Artritli Kadın Hastalarda Nöropatik Ağrı ve İlişkili Faktörler**

**ÖZET**

**Amaç:** Nöropatik ağrı (NP), diğer birçok hastalık gibi Romatoid artrite (RA) de eşlik edebilir. Çalışmamızın amacı, RA'lı kadın hastalarda NP sıklığını ve ilişkili faktörleri araştırmaktır.

**Yöntem:** Yaş, hastalık süresi, vücut kitle indeksi (VKİ) ve eritrosit sedimantasyon hızı (ESR) kaydedildi. Ağrı şiddetini kaydetmek için bir ağrı görsel analog skalası (VAS) kullanıldı ve NP skorunu kaydetmek için ağrı algılama anketi (PDQ) kullanıldı. RA hastalığı aktivitesi DAS28 skoru ile hesaplandı. Fonksiyonel durum için Sağlık Değerlendirme Anketi (HAQ) kullanıldı.

**Bulgular:** Hastaların NP skorları yüksekti. PDQ ile VAS, BMI ve HAQ değerleri arasında anlamlı bir korelasyon bulundu. PDQ ile hastalık süresi, yaş, inflamasyon, ve hastalık aktivitesi arasındaki korelasyon değeri anlamlı değildi.

**Sonuç:** RA hastalarının tamamında ağrı nedeni inflamasyon olmayabilir. Bu durumda tedavi değişebilir. Ağrı paterni sorgulanıp tedavi edilirse gereksiz antiinflamatuar ilaç kullanımının önüne geçilebilir.

**Anahtar kelimeler:** İnflamasyon, ağrı, romatoid artrit

**Correspondence:** Halime Kibar
Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, Istanbul, Turkey
**Phone:** -
**E-mail:** halimekibar22@gmail.com

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As a chronic, inflammatory condition that mostly affects the synovial joints, rheumatoid arthritis (RA) is known (1). The main complaint of patients with RA is pain. It has been reported that the improvement in pain is the most important parameter for the patient (2).

Activation of inflammatory cytokines and sensitization of peripheral nerve endings cause pain (3). Synovial inflammation causes the release of bradykinin and prostaglandins, thus, the thin C fibers in the synovium are stimulated (4,5). Because RA is an inflammatory disease, treatment is aimed at suppressing inflammation. Complaints are expected to decrease as inflammation is suppressed. However, it is difficult to fully control the pain even in RA patients who are under close follow-up. In a study, evaluating patients who were in remission for more than a year, it was concluded that 12.5% of patients had significant pain complaints. It has been reported that pain control remains inadequate even if inflammation is controlled (6).

These results brought to mind the idea that there are other pain mechanisms in the pathogenesis of pain. Questioning the character of pain has revealed that different mechanisms also cause pain in inflammatory diseases. The frequency of neuropathic pain (NP) was investigated and important results were obtained in studies conducted with female and male RA patients (7,8).

The aim of our study was to investigate the frequency of NP and related factors in female patients with RA.

## MATERIALS AND METHODS

104 patients with RA who were admitted to the outpatient clinic were included consecutively in this cross-sectional observational study. 2 patients were missing data. We performed a face to face interview and physical examination.

All patients were previously diagnosed according to the ACR 1987 or 2010 diagnostic criteria. All patients were followed up regularly.

1987 ACR Classification criteria for RA (It is necessary for the patient to have at least 4 criteria for the diagnosis of RA.)

**A.** Morning stiffness in and around joints lasting at least one hour before maximal improvement,

**B.** Soft tissue swelling of three or more joint areas observed by a physician

**C.** Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints

**D.** Symmetric joint swelling

**E.** Rheumatoid nodules

**F.** The presence of rheumatoid factor in blood tests

**G.** Radiographic erosions and periarticular osteopenia in hand or wrist joints or both

2010 ACR/EULAR Classification criteria for RA (A score of ≥ 6/10 is needed for a definite classification of a patient with RA.)

**A.** Joint involvement: Large joint 0, 2-10 large joints 1, 1-3 small joints (with or without involvement of large joints) 2, 4-10 small joints (with or without involvement of large joints) 3, >10 joints (at least one small joint) 5

**B.** Serology (at least one test result is needed for classification): Negative RF and negative ACPA 0, Low positive RF or low positive ACPA 2, High positive RF or high positive ACPA 3

**C.** Acute Phase Reactans (at least one test result is needed for classification): Normal CRP and normal ESR 0, Abnormal CRP or abnormal ESR 1

**D.** Duration of symptoms: < 6 weeks 0, ≥ 6 weeks 1

Patients with diabetes were not included in the study. Patients who were using regular nonsteroidal anti-inflammatory drugs (NSAID) were excluded from this study. It was questioned whether the patients had previously received pregabalin, gabapentin, amitriptyline, duloxetine or another medical treatment for NP. Patients who use these drugs were not included in the study. Patients with a history of NP, neurological disease, spinal surgery or a history of spinal disease were excluded.

Age, disease duration, body mass index (BMI) and medication were recorded. Tenderness and swelling in the joints were evaluated by the physiatrist. DAS28 score was calculated with an erythrocyte sedimentation rate (ESR). A patient with a DAS28 score of less than 2.6 is in remission; a score greater than or equal to 2.6 and less than 3.1 indicates low activity; a score greater than or equal to 3.1 and

<5.1 indicates moderate activity and a score of 5.1 or more indicates high activity (9).

A visual analog scale (VAS, 0-100 mm) was used for the pain assessment of the patients.

The Turkish version of the pain-detect questionnaire (PDQ) was used for the evaluation of NP (10). The severity, location, spread, course and pattern of the pain are evaluated with the PDQ. Patients are asked to rate the questions between 0-10. The score is calculated in the range of 0-38.

12 Unlikely neuropathic pain

13–18 Possible neuropathic pain

19 Likely neuropathic pain is defined.

Alkan H et al. (10) performed the Turkish validity and reliability PDQ. When the cut-off value was accepted as 19 or below, the sensitivity was 77.5 % and the specificity was 82.5%. Hallström et al. (7) determined its sensitivity as 68 % and specificity as 83%. In Hallström's study, the sensitivity of the DN4 questionnaire was 93%, and the specificity was 75%; The sensitivity of the LANSS questionnaire was 36% and the specificity was 100% (11).

Functions were measured by Health Assessment Questionnaire (HAQ). HAQ has been developed by Fries et al. (12). It has been adapted for the Turkish people (13).

The study protocol was approved by the Istanbul Kanuni Sultan Suleyman Training and Research Hospital ethics committee (KAEK/2022.12.235). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Written informed consent was obtained from the patients.

### *STATISTICS*

Utilizing the package application SPSS version 22.0, statistical analyses were performed. The four main components of descriptive statistics were number, percentage, mean, and standard deviation. Utilizing both mathematical and visual techniques (such as probability graphs and histograms), the appropriateness of variables to the normal distribution was evaluated (Shapiro-Wilk test). The Levene test was used to assess the homogeneity of the variances.

Descriptive statistics were used to show the nonparametric data, and the chi-square test was used to assess them. Both numbers (n) and percentages (%) were used to represent the categorical variables.

Pearson correlation test was used in correlation. Multiple Regression Analysing was used. In the statistical analyzes in the study, values (p) below 0.05 were considered significant.

## RESULTS

102 patients completed in the study. The characteristics of the patients are presented in Table 1. The mean age of patients was 55.01 ± 12.55 (Minimum 23, Maximum 78, Median 54.5). The mean disease duration was 10.87 ± 7.9 years (Minimum 1, Maximum 35, Median 8). The mean BMI of the patients was 28.9 ± 5.92 (Minimum 17.7, Maximum 44.4, Median 27.95). The mean VAS of the patients was 40.89 ± 22.9 (Minimum 0, Maximum 95, Median 50). The mean ESR value of the patients was 23.8± 16.8 (Minimum 3, Maximum 81, Median 21). The disease activity score was calculated by ESR value, swelling and tenderness of 28 joints and general health evaluation score of the patient with 0-100 mm, and the mean DAS28 value was 3.3 ± 1.12 (Minimum 1, Maximum 5.7, Median 3.3). The mean HAQ score was 0.94 ± 0.78 (Minimum 0, Maximum 3, Median 0.72).

The mean PDQ was 14.2 ± 7.83 (Minimum 0, Maximum 32, Median 15). PDQ evaluation results of the patients were recorded in 3 groups. Most patients were identified in the possible neuropathic pain group (40%). Possible and likely neuropathic pain was detected in 61.43% of the patients.

24.5% of patients were normal weight, 36.2% were overweight, and 39.3% were obese. 19.6% of the patients were in remission, 38.4% had low disease activity, 35% had moderate disease activity, and 7% had high disease activity.

Considering the drugs used by the patients, 47.1% were disease-modifying antirheumatic drug (DMARD) therapy (88% methotrexate, 9% leflunomide, 2% hydroxikhlorokin, 1% sulfasalazine), 25% DMARD + glucocorticoid therapy, 10.57% was only biological therapy, 8.68% was biological therapy + glucocorticoid, 8.65% was DMARD + biological therapy.

**Table 1**

| Characteristics of Patients | Mean ± SD | Min-Max | Median |
|---|---|---|---|
| Age (years) | 55.01 ± 12.55 | 23-78 | 54.5 |
| Disease duration (years) | 10.87 ± 7.9 | 1-35 | 8 |
| BMI (kg/m$^2$) | 28.9 ± 5.92 | 17.7-44.4 | 27.95 |
| VAS (0-100 mm) | 40.89 ± 22.9 | 0-95 | 50 |
| DAS28 | 3.33 ± 1.12 | 3.3-5.7 | 3,3 |
| ESR | 23.8 ± 16.8 | 3-81 | 21 |
| HAQ | 0.94 ± 0.78 | 0-3 | 0.72 |
| PDQ | 14.2 ± 7.83 | 0-32 | 15 |
| PDQ1 (%) | 38.57 | | |
| PDQ 2 (%) | 40 | | |
| PDQ3 (%) | 21.43 | | |
| Medical therapy (%) | | | |
| DMARD | 47.1 | | |
| DMARD+gc | 25 | | |
| Biological therapy | 10.57 | | |
| Biological therapy+gc | 8.68 | | |
| Biological therapy+DMARD | 8.65 | | |
| Disease activity (%) | | | |
| Remission | 19.6 | | |
| Low activity | 38.4 | | |
| Moderate acvtivity | 35 | | |
| High activity | 7 | | |

*Data are means , BMI: body mass index, VAS: visual analog scale (0-100 mm), HAQ: health assessment questionnaire , ESR: erythrocyte sedimentation rate, PDQ: painDETECT quastionnare*

**Table 2**

**Multiple Regression Analysis**

Method

Categorical predictor coding (1, 0)
Rows unused 1

Analysis of Variance

| Source | DF | Adj SS | Adj MS | F-Value | P-Value |
|---|---|---|---|---|---|
| Regression | 11 | 1069.44 | 97.222 | 2.46 | 0.010 |
| Age | 1 | 2.90 | 2.902 | 0.07 | 0.787 |
| BMI | 1 | 354.71 | 354.71 | 9.06 | 0.003 |
| Disease duration | 1 | 80.53 | 80.533 | 2.03 | 0.157 |
| ESR | 1 | 5.66 | 5.664 | 0.14 | 0.706 |
| Das28 | 1 | 32.51 | 32.511 | 0.82 | 0.367 |
| HAQ | 1 | 517.18 | 517.18 | 13.21 | <0.001 |
| VAS | 1 | 1200.41 | 1200.41 | 30.67 | <0.001 |
| Medication 1- syn DMARD 2-syn D | 4 | 55.15 | 13.787 | 0.35 | 0.845 |
| Error | 91 | 3602.52 | 39.588 | | |
| Total | 102 | 4671.96 | | | |

Model Summary

| S | R-sq | R-sq(adj) | R-sq(pred) |
|---|---|---|---|
| 6.25599 | 37.63% | 36.26% | 33.42% |

Coefficients

| Term | Coef | SE Coef | T-Value | P-Value | VIF |
|---|---|---|---|---|---|
| Constant | -1.80 | 2.72 | -0.66 | 0.509 | |
| BMI | 0.2714 | 0.0901 | 3.01 | 0.003 | 1.02 |
| HAQ | 2.648 | 0.729 | 3.64 | <0.001 | 1.14 |
| VAS | 0.1381 | 0.0249 | 5.54 | <0.001 | 1.16 |

Regression Equation

pDQ = -1.80 + 0.2714 BMI + 2.648 HAQ + 0.1381 VAS

**Table 3**

**Correlations Between Characteristics of Patients**

| | Age (p) | BMI (p) | VAS (p) | DAS28 (p) | Disease duration (p) |
|---|---|---|---|---|---|
| BMI | 0.320 | - | 0.363 | 0.986 | 0.760 |
| VAS | 0.825 | 0.363 | - | <0.001 | 0.643 |
| Disease duration | <0.001 | 0.760 | 0.643 | 0.160 | - |
| DAS28 | 0.453 | 0.986 | <0.001 | - | 0.160 |
| HAQ | 0.847 | 0.924 | 0.173 | 0.522 | 0.359 |

*Data are means , BMI: body mass index, VAS: visual analog scale (0-100 mm), HAQ: health assessment questionnaire*

The multi-regression analysis is presented in Table 2. A significant correlation was found between PDQ and VAS, BMI and HAQ values (Figure 1,2,3 respectively). The correlation value between PDQ and disease duration, age and DAS28 was not significant. There was no relationship between the drugs used by the patients and NP.Correlations between patient characteristics are presented in Table 3. The relationship between age, BMI, VAS, HAQ and disease duration was investigated. A significant correlation was found between age and disease duration. In addition, a significant correlation was found between DAS28 and VAS. There was no correlation between other parameters.

## DISCUSSION

The purpose of this study was to determine the prevalence of NP in female patients with RA and to evaluate the associations between NP and the patient's age, disease duration, disease activity, inflammation, BMI, pain intensity, functional status, and medication use.

NP unpossible was 38.57%, NP possible was 40%, and likely NP was 21.43% of the patient with RA.

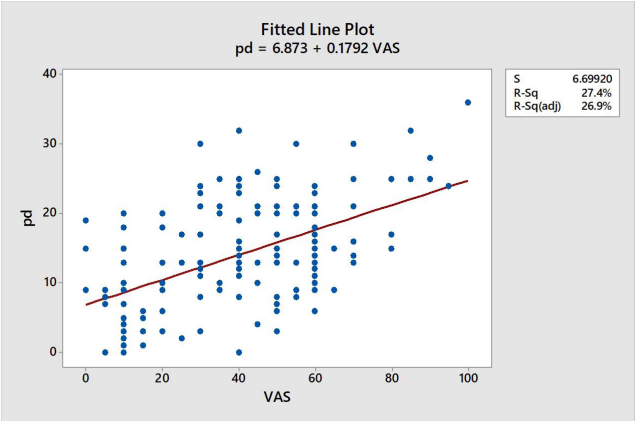


***Figure 1.*** *The Relationship Between PDQand VAS.*

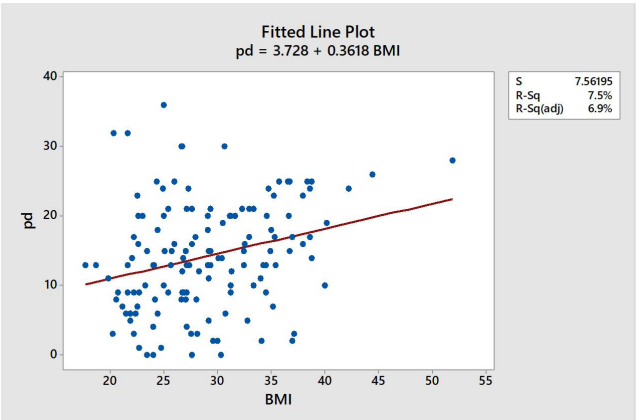


***Figure 2.*** *The relationship Between PDQ and BMI.*

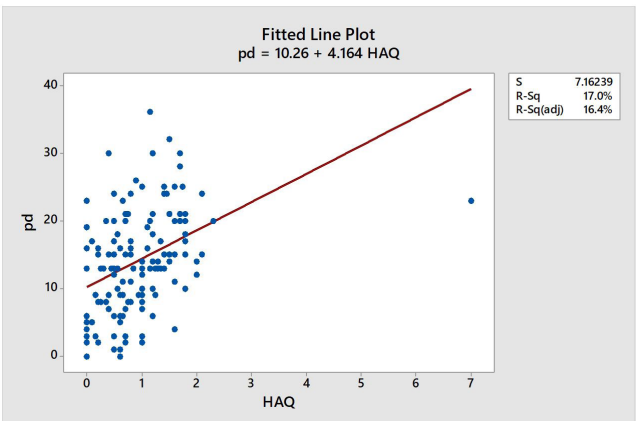


***Figure 3.*** *The relationship Between PDQ and HAQ.*

The factors associated with NP were BMI, pain severity and functionality. There was no relationship between NP and age, disease duration, disease activity, and inflammation.

Pain is one of the most common complaints in RA. 68% of RA patients identified a reduction in pain as their first priority (14). McWilliams et al. (15) evaluated patients with RA after one year of DMARD therapy and did not determine a significant difference in pain levels. Patients are asked to score their pain levels, but the pain character is not questioned in pain assessment with VAS. The pain score may be affected by NP.

Ahmed et al. (8) found a correlation between PDQ score and pain severity. This result supports the idea that pain character should be questioned before treatment. Only patient-reported poor health scores may lead to failure to achieve remission in some patients (16,17). It was reported that the patient's global assessment correlated with the patient's pain score (18). Health scores can be affected by pain. This may lead to a high account of disease activity. Although DAS28 is associated with inflammatory activity, it has been shown to be affected by factors such as chronic pain (19). In our study, there was a relationship between DAS28 and pain severity, but no relationship was found between DAS28 and disease duration. This result does not support that disease activity is associated with chronic pain.

Koop et al.(7) reported that although 75% of patients were in remission, 44% had significant pain. According to PDQ, they found likely NP in 17% of patients and possible NP in 21%. We detected a higher rate of NP in our patients compare with previous studies (7, 20, 21). We think that this result may be due to two reasons. First, there may be differences in the perception of pain between societies. Second, our study was conducted with only female patients.

Previously, obesity has been identified as a risk factor for chronic pain (22, 23, 24). Fantuzzi (25) reported that white adipose tissue plays an active role in the regulation of physiological and pathological processes, including immunity and inflammation. It was determined a significant difference between normal, overweight and obese patients in pain scores evaluated with the VAS in patients with RA in another study (8). In our study, there was no relationship between VAS and BMI, but there was a relationship between NP and BMI. The increase in BMI may increase NP not only by mechanical factors but also by different mechanisms.

Schaefer et al. (26) observed that high pain levels were associated with functionality in patients with NP. Doth et al. (27) stated that neuropathic pain negatively affects the quality of life, and this effect increases with the severity of the pain. Rocha et al. (20) reported an association between NP and functional score (HAQ).

Noda et al.(18) investigated the characteristics of pain and the impact of NP-like symptoms (with PDQ) on health-related quality of life (HRQoL) with RA. They detected how the HRQoL of RA patients was effected by NP-like symptoms. In patients with NP-like symptoms, they discoveredinconsistencies between the overall assessments provided by patients and raters. Consequently, they have suggested that more attention should be paid to NP-like symptoms when treating patients with RA. A measure called HRQoL is used to assess a patient's level of pain and physical and mental health. In our study, we did not assess mental health. We discovered a connection between NP and the functionality of the patients consistent with the literature. While no relationship was found between pain and functionality in our study, there was a relationship between NP and functionality. We care about this result for RA. Any condition that may contribute to increased functionality, especially in RA patients, should be evaluated for treatment.We have not found a relationship between NP and disease activity and ESR value. Previously, no relationship was found between NP and DAS28, CRP and ESR (7). This indicates that NP is not associated with inflammation. The mean disease activity levels of our patients were also higher than we expected. This may be related to the high NP scores of our patients. NP may have affected the general health score in the disease activity calculation. In our study, a relationship was also found between DAS28 and VAS. While there is a relationship between NP and VAS, it is contradictory that there is no relationship between DAS28. This situation can only be clarified by controlled studies in which patients are re-evaluated with DAS28 after NP treatment.

NP and disease duration had no correlation. This result was compatible with previous studies (7,20,21). It has been discussed that pain persists with central sensitization mechanisms in tissues without inflammation in patients with chronic pain (28). According to this hypothesis, chronic pain and NP are expected to be associated. However, the fact that disease duration is not associated with NP confirms the need for further investigation. The gold standard diagnostic method for central sensitization does not exist, but there are studies that found a relationship between an increase in the 'PainDetect' pain score and central sensitization (21,29,30).

We also recorded the drugs used by the patients in the study. Patients are not homogeneous in terms of the drug therapy they use for RA. We also included patients using glucocorticoids in our study. There was no relationship between drugs and NP. This result showed that NP could not be controlled with RA treatment.

This study has some strengths and limitations. The strength is that all evaluations were made by the same researcher. The first limitation is a single method was used for NP assessment. Secondly, a cause and effect relationship cannot be established because of the cross-sectional design.

As a result, pain should be questioned in detail when evaluating RA patients. The presence of a neuropathic component must be investigated. Thus, the treatment approach of patients may change. Weight control might also decrease NP. However, controlled studies are needed to prove this possibility. Weight control of all RA patients should be considered and followed. Besides its beneficial effects on the heart and joints, it may also be effective in reducing NP. This should be taken into account, especially in drug dosing and switching decisions i. NP affects daily life functions. Controlling pain and improving the patient's functionality increase the quality of life. More studies on this subject will be beneficial for patients and professionals.

## DECLARATIONS

### *Ethics Committee Approval*

The Istanbul Kanuni Sultan Suleyman Training and Research Hospital ethics committee (KAEK/2022.12.235) gave its approval to the study protocol. The Declaration of Helsinki's guiding principles were followed in conducting the study.

### *Patient Consent for Publication*

Each patient provided written, fully informed consent.

### *Data Disclosure Statement*

Upon a reasonable request, the corresponding author will provide the data that underpin the study's conclusions.

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*Conflict of Interest*

There were no declared conflicts of interest that would have affected this article.

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