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SITE-SPECIFIC ASSOCIATIONS OF DISEASE ACTIVITY, PSYCHOLOGICAL DISTRESS, AND PRESSURE PAIN THRESHOLDS IN MALE PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract. Pain in rheumatoid arthritis (RA) is not always explained by synovitis alone. Patient-reported disease burden and psychological distress may also influence pain sensitivity. Pressure pain threshold (PPT) testing is a practical method for assessing pain sensitivity at articular and non-articular sites. Objective to examine the relationship between disease activity parameters, psychological distress, and PPTs in male patients with RA. This cross-sectional study included 50 consecutive male patients with RA who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria. Patients with fibromyalgia and other conditions known to affect pain thresholds were excluded. PPTs were measured bilaterally at the thumbnail, wrist, and trapezius muscle using a pressure algometer. Disease activity was assessed using DAS28-ESR, and the patient-reported component of DAS28 was calculated as DAS28-P. Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale. Correlation analyses and multivariable linear regression models adjusted for age and disease duration were performed. Lower PPTs were significantly associated with higher tender and swollen joint counts, patient global assessment, ESR, DAS28-ESR, DAS28-P, and anxiety and depression scores. In multivariable analysis, ESR was independently associated with lower wrist PPT (beta = -0.34, P = 0.014). At the trapezius muscle, lower PPT was independently associated with higher depression scores (beta = -0.36, P = 0.018) and DAS28-P (beta = -0.28, P = 0.044). In male patients with RA, pain sensitivity appears to reflect both inflammatory and non-inflammatory influences. ESR was mainly associated with pain sensitivity at the wrist, whereas depression and patient-reported disease impact were associated with pain sensitivity at a non-articular site. These findings support a broader approach to pain assessment in RA that includes inflammatory activity, patient-reported disease burden, and psychological distress.

Keywords: Rheumatoid arthritis, pressure pain threshold, pain sensitivity, DAS28, depression, psychological distress, algometry, male patients.

1. INTRODUCTION AND PROBLEM STATEMENT

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, joint damage, functional disability, and a substantial systemic burden [1]. Pain is one of the symptoms that matters most to patients. Although inflammation remains a central cause of pain in RA, pain may persist even when inflammatory activity is controlled [2]. This observation has shifted attention from a purely inflammatory explanation toward a broader model that includes peripheral and central pain-processing mechanisms.

Pressure pain threshold (PPT) assessment using algometry is a validated quantitative method for studying pain sensitivity in rheumatic diseases [3,4]. Lower PPT indicates greater sensitivity to pressure pain. Measuring PPTs at joint and non-joint sites can provide useful information because pain sensitivity at an inflamed joint may reflect peripheral sensitization, whereas reduced PPTs at sites away from inflamed joints may suggest more widespread pain amplification [5].

Psychological distress is another important factor in RA pain. Depression and anxiety are common in RA and may influence pain reporting, function, treatment response, and global disease assessment [6]. Patient-reported components of disease activity may therefore carry information that is not fully explained by synovitis or inflammatory markers. DAS28-P, the patient-reported component of the Disease Activity Score in 28 joints (DAS28), has been proposed as a useful way to explore the subjective contribution to disease activity assessment [7,8].

Sex differences are a major methodological issue in PPT research. Women generally have lower PPTs than men and often report higher pain burden in rheumatic diseases [5]. Mixed-sex cohorts may therefore make it difficult to interpret the relationship between inflammation, psychological distress, and pain sensitivity. For this reason, the present study focused only on male patients with RA. Patients with fibromyalgia and other conditions that could alter pain thresholds were also excluded. The aim was to examine the relationship between disease activity parameters, psychological distress, and PPTs at articular and non-articular sites in male patients with RA.

2. MATERIALS AND METHODS

Study Design and Participants

This was a cross-sectional observational study conducted at a rheumatology outpatient clinic in Baghdad, Iraq, from November 2018 to June 2019. Fifty consecutive male patients with RA were recruited. Eligible patients were adults older than 20 years who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA [9].

Patients were excluded if they fulfilled the 2016 revised fibromyalgia criteria [10]. Additional exclusion criteria were concomitant rheumatic disease other than RA, diabetes mellitus, known peripheral neuropathy, previous stroke, chronic opioid use, opioid use within 24 hours before PPT testing, and current use of medications known to affect pain thresholds, such as amitriptyline or gabapentinoids.

The study was approved by the Ethics Committee of the Department of Internal Medicine, College of Medicine, University of Baghdad. Written informed consent was obtained from all participants before enrolment. If an institutional approval number was assigned, it should be inserted in the final submission file.

Pressure Pain Threshold Assessment

PPTs were assessed using a digital pressure algometer (Orchid Scientific and Innovative, Nashik, India) by a single trained examiner. Measurements were obtained bilaterally at three predefined sites: the thumbnail, the dorsum of the wrist, and the trapezius muscle. The thumbnail was selected as a distal non-articular site, the wrist as an articular site commonly affected in RA, and the trapezius muscle as a proximal non-articular site.

Before testing, the examiner explained the procedure and performed a trial measurement on the right thumbnail. During testing, the algometer probe was placed perpendicular to the skin

surface, and pressure was increased at approximately 0.4 kg/s. Participants were instructed to report the moment when the sensation changed from pressure to pain. The pressure recorded at that point was considered the PPT. Two measurements were obtained at each site on each side, separated by a short rest period. The mean of repeated bilateral measurements was used for analysis. PPT values are reported as kg/cm2.

Clinical and Psychological Assessment

Demographic and clinical data were collected through interview, questionnaire, and review of available medical records. Height and weight were measured, and body mass index (BMI) was calculated. Rheumatoid factor and anti-citrullinated peptide antibody status were obtained from medical records when available. Tender joint count, swollen joint count, and patient global assessment were recorded for each participant. ESR was measured using the Westergren method.

Disease activity was assessed using DAS28-ESR. DAS28-P was calculated to represent the patient-reported component of the DAS28 [7]. Psychological distress was evaluated using the validated Arabic version of the Hospital Anxiety and Depression Scale (HADS), which includes separate anxiety and depression subscales [11,12].

Statistical Analysis

Continuous variables were summarized as means and standard deviations or medians and interquartile ranges according to distribution. Normality was assessed using the Shapiro-Wilk test and visual inspection of distributions. Categorical variables were summarized as frequencies and percentages.

Intra-rater reliability of PPT measurements was examined using intraclass correlation coefficients (ICCs) with 95% confidence intervals. Paired t-tests were used to compare right and left PPT measurements. Bivariate associations between PPTs and clinical or psychological variables were examined using Pearson or Spearman correlation coefficients as appropriate. Patients were also grouped according to disease activity, with DAS28 < 3.2 representing remission or low disease activity and DAS28 >= 3.2 representing moderate or high disease activity.

Multivariable linear regression models were constructed separately for thumbnail, wrist, and trapezius PPTs. Age and disease duration were included as adjustment variables. ESR was used as an inflammatory marker, DAS28-P as a patient-reported disease activity component, and HADS depression and anxiety scores as psychological variables. Standardized beta coefficients and P values were reported. Statistical significance was set at a two-sided $P < 0.05$. Analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS AND DISCUSSION

Table 8 shows the results with irrigation having the highest percentile weight of 73.33%, followed by pest management with a percentile weight of 68.50%, and varietal selection with a percentile weight of 67.00%, harvesting with a percentile weight of 65.67%, and fertilization the lowest at 61.00%. The findings are similar to the findings of this study which reported that irrigation was the highest ranked domain among the agricultural domains related to the servicing of the crops, whereas the lowest was fertilization.

Participant Characteristics

Fifty male patients with RA were included. The mean age was 51.2 +/- 13.5 years, and the median disease duration was 4 years (interquartile range, 0.5-7.5 years). The mean BMI was 26.8 +/- 2.8 kg/m2. Nineteen patients (38%) were current smokers. Thirty-three patients (73.3% of those with available serology) were positive for rheumatoid factor and/or anti-citrullinated peptide antibody. The mean DAS28 was 3.5 +/- 1.3, indicating that the cohort included patients across different levels of disease activity. Most patients were receiving conventional synthetic disease-modifying antirheumatic drugs, and two-thirds were receiving biologic therapy. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of the study participants

Characteristic	Value
Number of patients	50
Age, years, mean (SD)	51.2 (13.5)
BMI, kg/m2, mean (SD)	26.8 (2.8)
Disease duration, years, median (IQR)	4 (0.5-7.5)
Current smokers, n (%)	19 (38)
Rheumatoid factor positive, n (%)	31 (68.9)*
Anti-citrullinated peptide antibody positive, n (%)	18 (48.6)*
RF or ACPA positive, n (%)	33 (73.3)*
ESR, mm/hour, median (IQR)	17.5 (5-30)
Tender joint count, median (minimum-maximum)	4 (0-20)
Swollen joint count, median (minimum-maximum)	1 (0-11)
Patient global assessment, mean (SD)	4.4 (2.4)
DAS28-ESR, mean (SD)	3.5 (1.3)
DAS28-P, median (IQR)	0.34 (0.21-0.47)
HADS depression, mean (SD)	6.8 (4.0)
HADS anxiety, median (IQR)	5 (2-7)
HADS total, mean (SD)	12.8 (6.9)
Conventional synthetic DMARD use, n (%)	46 (92)
Biologic DMARD use, n (%)	33 (66)
Corticosteroid use, n (%)	20 (40)

**Percentages are based on available results: rheumatoid factor, n = 45; anti-citrullinated peptide antibody, n = 37. ACPA: anti-citrullinated peptide antibody; BMI: body mass index; DAS28: Disease Activity Score in 28 joints; DAS28-P: patient-reported component of DAS28; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; RF: rheumatoid factor; SD: standard deviation.*

Pressure Pain Thresholds and Reliability

The mean PPT was highest at the thumbnail and lowest at the trapezius muscle. The measurements showed good to excellent intra-rater reliability. ICC values ranged from 0.89 for the right trapezius to 0.97 for the left wrist. There were no statistically significant differences between right- and left-sided measurements at the thumbnail, wrist, or trapezius muscle. Therefore, averaged values from both sides were used in subsequent analyses.

Half of the patients scored at or above the usual HADS cut-off of 8 on either the depression or anxiety subscale. Eleven patients (22%) had scores of 11 or more on either subscale, consistent with marked psychological distress.

Bivariate Associations

Lower PPTs were consistently associated with higher disease activity and psychological distress. Tender joint count, swollen joint count, patient global assessment, ESR, DAS28-ESR, and DAS28-P were all inversely correlated with PPTs at the thumbnail, wrist, and trapezius muscle. HADS depression and anxiety scores were also inversely correlated with PPTs at all three sites. No clear associations were observed between PPTs and age, disease duration, or BMI (Table 2).

When patients were grouped according to disease activity, those with DAS28 >= 3.2 had significantly lower PPTs than those in remission or with low disease activity. This difference was seen at the thumbnail, wrist, and trapezius muscle.

Table 2. Unadjusted correlations between clinical variables and pressure pain thresholds

Variable	Thumbnail r (P value)	Wrist r (P value)	Trapezius r (P value)
Tender joint count	-0.50 (<0.001)	-0.50 (<0.001)	-0.50 (<0.001)
Swollen joint count	-0.50 (0.001)	-0.50 (<0.001)	-0.40 (0.001)
Patient global assessment	-0.40 (0.002)	-0.50 (<0.001)	-0.30 (<0.001)
ESR	-0.40 (0.005)	-0.40 (0.004)	-0.30 (0.028)
DAS28-ESR	-0.50 (<0.001)	-0.60 (<0.001)	-0.50 (0.001)
DAS28-P	-0.40 (0.011)	-0.30 (0.015)	-0.40 (0.006)
HADS depression	-0.39 (0.005)	-0.52 (<0.001)	-0.53 (<0.001)
HADS anxiety	-0.37 (0.008)	-0.41 (0.003)	-0.37 (0.008)
HADS total	-0.41 (0.002)	-0.52 (<0.001)	-0.52 (<0.001)
Age	0.02 (0.46)	0.07 (0.30)	-0.06 (0.30)
Disease duration	0.07 (0.30)	0.01 (0.47)	0.04 (0.39)
BMI	-0.02 (0.44)	-0.09 (0.26)	-0.12 (0.21)

BMI: body mass index; DAS28: Disease Activity Score in 28 joints; DAS28-P: patient-reported component of DAS28; ESR: erythrocyte sedimentation rate; HADS: Hospital Anxiety and Depression Scale; r: correlation coefficient. Lower PPT indicates higher pain sensitivity.

Multivariable Regression Analysis

In multivariable linear regression models adjusted for age and disease duration, the independent predictors differed according to anatomical site. At the wrist, ESR was independently associated with lower PPT (beta = -0.34, P = 0.014). At the trapezius muscle, HADS depression (beta = -0.36, P = 0.018) and DAS28-P (beta = -0.28, P = 0.044) were independently associated with lower PPT. Anxiety was not independently associated with PPT after adjustment and was removed from the final models. The final wrist model had an adjusted R2 of 0.34, and the final trapezius model had an adjusted R2 of 0.33 (Table 3).

Table 3. Multivariable associations of pressure pain thresholds with psychological distress and disease activity parameters

Model and predictor	Thumbnail beta (P value)	Wrist beta (P value)	Trapezius beta (P value)
Model 1: HADS depression	-0.32 (0.048)	-0.44 (0.005)	-0.49 (0.001)
Model 1: HADS anxiety	-0.26 (0.260)	-0.22 (0.290)	-0.20 (0.179)
Model 2: HADS depression	-0.34 (0.024)	-0.45 (0.002)	-0.45 (0.002)
Model 2: DAS28-P	-0.23 (0.112)	-0.16 (0.257)	-0.27 (0.045)
Model 3: HADS depression	-0.23 (0.155)	-0.29 (0.055)	-0.36 (0.018)
Model 3: DAS28-P	-0.25 (0.097)	-0.17 (0.202)	-0.28 (0.044)
Model 3: ESR	-0.23 (0.114)	-0.34 (0.014)	-0.17 (0.217)
Adjusted R2, final model	0.21	0.34	0.33

Each PPT site was entered as a separate dependent variable. Values are standardized beta coefficients. Models were adjusted for age and disease duration. DAS28-P: patient-reported component of Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HADS: Hospital Anxiety and Depression Scale.

4. DISCUSSION

This study examined pressure pain sensitivity in a carefully selected group of male patients with RA after excluding fibromyalgia and other major factors known to influence PPTs. The main finding was that the associations of PPTs differed by anatomical site. ESR was

independently related to lower PPT at the wrist, whereas depression and DAS28-P were independently related to lower PPT at the trapezius muscle. This pattern supports the idea that RA pain is not a single process and that inflammatory and non-inflammatory factors may contribute differently across articular and non-articular sites.

The wrist finding is clinically plausible. The wrist is commonly affected in RA, and inflammatory activity can increase local nociceptive input. Such input may lower the pain threshold at articular sites through peripheral sensitization and activation of nociceptive pathways around inflamed joints [13,14]. In the present study, ESR remained associated with wrist PPT after adjustment for age, disease duration, depression, and DAS28-P. This suggests that systemic inflammatory activity still has a measurable relationship with articular pain sensitivity in male RA patients.

The trapezius findings should be interpreted more cautiously. A lower PPT at a non-articular site does not by itself prove central sensitization. However, the independent associations with depression and DAS28-P rather than ESR suggest that non-inflammatory factors are important contributors to pain sensitivity outside the joints. This is consistent with previous work showing that pain in RA may involve altered central pain processing and patient-reported disease burden in addition to peripheral inflammation [2,15,16].

The association between DAS28-P and trapezius PPT is particularly relevant in clinical practice. DAS28 includes patient-reported elements, and these elements can be influenced by pain processing, mood, and global illness perception. A high DAS28 score does not always mean that inflammation is the only driver of symptoms. In patients with high patient-reported burden but limited objective inflammation, escalation of immunosuppressive therapy alone may not address the main pain mechanism. Careful interpretation of DAS28 components may therefore help clinicians identify patients who need broader pain assessment rather than only stronger anti-inflammatory treatment.

Depression was also independently associated with lower trapezius PPT. The direction of this relationship cannot be determined from a cross-sectional study. Depression may amplify pain sensitivity, persistent pain may worsen depressive symptoms, or both may interact over time. Nevertheless, the finding is clinically useful because it highlights psychological distress as part of pain assessment in RA. Screening for depression and anxiety may help identify patients whose pain burden is disproportionate to objective inflammatory findings.

The male-only design is a strength of the study. Sex differences in PPT are well recognized, and mixed-sex analyses may introduce heterogeneity that is difficult to control in small samples [5]. By focusing on men, the study reduced this source of variability. Excluding fibromyalgia, diabetes, neuropathy, stroke, opioid use, and medications affecting pain thresholds also improved internal validity. The good to excellent intra-rater reliability of the algometric measurements further supports the reliability of the PPT data.

The study also has limitations. The sample size was modest, and the study was conducted in a single clinical setting, which limits generalizability. The cross-sectional design prevents causal inference. A control group was not included, so the study cannot determine whether male patients with RA have lower PPTs than healthy men. Central sensitization was inferred indirectly from non-articular PPT findings and was not measured using a full quantitative sensory testing battery, conditioned pain modulation, or a central sensitization questionnaire. Sleep quality and pain catastrophizing were not assessed, although both may influence pain thresholds and psychological distress. Finally, the probe size and calibration details of the algometer should be reported if available in the original device documentation.

Despite these limitations, the findings support a multidimensional approach to RA pain. Pain sensitivity at a joint site appears more closely related to inflammatory activity, whereas pain sensitivity at a non-articular site appears more related to depression and patient-reported disease impact. This distinction may help clinicians avoid a narrow interpretation of pain as either purely inflammatory or purely psychological. In practice, both domains should be considered.

5. CONCLUSSION

In male patients with RA, PPTs were associated with both inflammatory and non-inflammatory clinical domains. ESR was independently associated with wrist PPT, whereas depression and DAS28-P were independently associated with trapezius PPT. These findings suggest that articular and non-articular pain sensitivity may reflect different influences in RA. Assessment of pain in RA should therefore include inflammatory activity, patient-reported disease burden, and psychological distress.

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