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Association between Anti-Citrullinated Peptide Antibodies (ACPA) Levels and Disease Severity in Patients with Rheumatoid Arthritis

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Abstract

Background & Objectives: This case–control study was conducted to assess the diagnostic accuracy of serum anti-cyclic citrullinated peptide (anti-CCP) antibodies in rheumatoid arthritis (RA) and to determine their correlation with disease activity, as measured by the Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP).

Materials & Methods: A total of 70 patients with RA (85.7% female; mean age = 55.7 ± 11.73 years) and 70 age- and sex-matched healthy controls were included. Serum anti-CCP levels were measured using an enzyme-linked immunosorbent assay (ELISA), and disease activity was evaluated based on DAS28-CRP scores. Pearson's correlation coefficient was applied to assess the relationship between anti-CCP levels and RA disease activity.

Results: Anti-CCP exhibited a sensitivity of 61.4% and a specificity of 98.6% for the diagnosis of RA. The mean serum anti-CCP concentration was significantly elevated in RA patients (220.2 ± 27.5 IU/mL) compared with controls (1.57 ± 0.52 IU/mL; $p < 0.001$). However, no statistically significant correlation was observed between anti-CCP levels and disease activity as determined by DAS28-CRP ($p = 0.4$).

Conclusion: Anti-CCP is a highly specific serological biomarker for the diagnosis of RA but does not demonstrate a significant association with disease activity as measured by DAS28-CRP. Further large-scale, longitudinal investigations are warranted to elucidate its potential role in predicting long-term joint destruction and disease progression.

Keywords: Anti-CCP, Rheumatoid Arthritis, DAS28-CRP, Disease Activity, Case-Control Study

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Introduction

Rheumatoid arthritis (RA) is a prevalent systemic autoimmune disease, affecting approximately 1% of the global population. It is approximately three times more common in women than in men and typically manifests between 20 and 60 years of age, with peak incidence reported in the 35–50-year age group (1). RA is characterized by symmetric inflammation of the synovial membrane, involving both small and large joints. Early diagnosis and prompt initiation of treatment are essential to limit disease progression and prevent irreversible joint damage (2).

Historically, clinical diagnosis of RA dates to the 1987 criteria established by the American College of Rheumatology (ACR). However, these criteria have limited sensitivity for early disease diagnosis (1). Consequently, paraclinical diagnostic tests have assumed

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increasing importance. Among these, the rheumatoid factor (RF) test is commonly used. RF is positive in approximately 60% of RA patients but can also be detected in a subset of healthy individuals. In particular, IgM-class RF demonstrates insufficient sensitivity and specificity for definitive diagnosis of RA (3). Given the critical importance of early diagnosis to optimize management and prevent irreversible joint damage, more accurate biomarkers are required to facilitate RA early diagnosis (4).

Anti-cyclic citrullinated peptide (anti-CCP) antibodies are highly specific serological markers for RA. As such, the 2010 ACR/EULAR classification criteria for RA included anti-CCP as a diagnostic component (5). Anti-CCP antibodies recognize citrullinated proteins, namely arginine-containing proteins that have undergone post-translational deimination to citrulline. These autoantibodies include the antiperinuclear factor, antikeratin, anti-filaggrin, and IgG-class anti-CCP specificities (6–9). Notably, anti-CCP antibodies can be detected in serum years before clinical onset, with anti-citrullinated protein antibodies (ACPAs) appearing as early as 18 years prior to diagnosis (10). Their titers are strongly associated with joint destruction, and they are approximately 97% specific for RA, mostly presenting early disease with high predictive value (7). Patients who are anti-CCP positive typically exhibit greater radiographic progression and joint damage than those anti-CCP negative cases (11).

Multiple studies substantiate the prognostic significance of anti-CCP. For example, Jafarzadeh et al. (2015) found that more than half of RA patients exhibited high anti-CCP titers, although decreases in clinical disease activity among patients with high titers did not reach statistical significance (8). In contrast, Sulaiman et al. (2019) reported a significant association between anti-CCP positivity and radiological joint damage (12). Similarly, Rydel et al. (2021) reported that anti-CCP antibodies predict radiographic progression in early RA (13). Most recently, Smolen et al. (2023) identified the presence of autoantibodies, high disease activity, and early erosions as principal poor prognostic indicators in RA management (14).

Despite its diagnostic utility, the role of anti-CCP in monitoring RA disease activity remains controversial, particularly in understudied regions such as southwest Iran. In light of conflicting evidence and the imperative for early, precise therapeutic strategies, the present study aimed to evaluate the association between anti-CCP levels and disease severity in RA patients. To our knowledge, this is the first case-control study conducted in southwest Iran to examine the relationship between anti-CCP status and disease activity, as measured by DAS28-CRP, while adjusting for age, sex, and body mass index (BMI).

Materials and Methods

This case–control study enrolled 70 patients with RA and 70 healthy controls matched for age, sex, and BMI. RA patients were identified from individuals registered in the first phase of the Fasa Adult Cohort Study and from attendees of Fasa Health Centers. Eligible participants were ascertained on the basis of documented rheumatic disease or current use of anti-rheumatic medications. Disease duration was not used as an inclusion or exclusion criterion. The control group was drawn from the same cohort database and matched accordingly.

Sample size estimation was performed with Stata 11 software and was based on a comparison of two means. In the formula, X_1 and X_2 denote the mean DAS28 scores for the remission and low-disease-activity groups (20.5 and 32.3, respectively), and S_1 and S_2 represent their corresponding standard deviations (7.16 and 18.2). The type I error (α) was set at 0.05 and the type II error (β) at 0.1, yielding 90% power. Under these assumptions, a minimum of 47 participants per group was required. To

increase statistical power and to accommodate potential data loss, we ultimately included 70 individuals in each group.

RA diagnosis was confirmed according to the ACR clinical criteria. Exclusion criteria comprised the presence of other autoimmune or systemic conditions—such as type 1 diabetes, thyroid disease, other inflammatory conditions, or malignancy—or the use of biologic disease-modifying antirheumatic drugs (bDMARDs), including therapeutic monoclonal antibodies (for example, anti-TNF and anti-CD20 agents).

According to ACR diagnostic criteria relevant to the clinical approach to RA, patients were selected from the population by available (convenience) sampling. Because an adequate number of RA cases (70 individuals) could not be identified solely from the Fasa cohort, we supplemented cohort recruitment by contacting health centers and health houses in the region to achieve the required sample size. For this purpose, patients were contacted prior to definitive diagnosis or at the time of clinical suspicion. After scheduling and during scheduled visits to the health centers and health houses where patients resided, we collected clinical history, performed physical examinations, recorded follow-up and medication data, and extracted relevant medical records, all of which were documented on a predesigned case-report form. Patient recruitment and information collection spanned six months. During this interval, seventy healthy individuals matched on age, sex, and BMI were selected from the cohort dataset to serve as the control group. Healthy controls underwent screening by medical history and physical examination and demonstrated no evidence of autoimmune or inflammatory disease. Prior to participation, all individuals in both groups provided written informed consent.

Laboratory personnel were blinded to participant group (patient versus control) during sample testing. ACPA/ anti-CCP assays were performed for both groups, whereas C-reactive protein (CRP) was measured only in patients. Serum ACPA concentrations were determined automatically by ELISA using the LDN kit and an ELISA reader. Values below 12 IU/mL were considered negative, and values above 12 IU/mL were considered positive. Serum CRP concentrations were quantified by a CRP-latex immunoturbidimetric assay on an automated clinical chemistry analyzer (Hitachi 902) with the BIONIC kit and reported on an mg/L scale. The mean ± SD CRP level in patients was 2.6 ± 1.12 mg/L.

DAS28-CRP is a clinically valid instrument for assessing RA disease activity. The assessment employed the clinical examination of the 28 joints commonly involved in RA (15, 16). For the purposes of the DAS28, any joint demonstrating tenderness or swelling on clinical examination was considered active. In addition to the joint count, the DAS28-CRP incorporates the patient's global assessment (PGA) of disease activity, which is reported on an 11-point numeric scale from 0 to 10; a score of 0 indicates optimal health and 10 indicates maximal disease activity from the patient's perspective (15, 16). Joint examinations were performed by a single rheumatologist with eight years of clinical experience. The quantitative serum CRP served as the laboratory component of the DAS28-CRP index. After data collection, we used the online *Calculator - CRP DAS28* application to compute DAS28-CRP scores. Based on these values, patients were stratified into four categories: remission, low activity, moderate activity, and high activity, using the EULAR thresholds: remission < 2.6, low activity 2.6–3.2, moderate activity 3.2–5.1, and high activity > 5.1 (15, 16).

Given the volume of information captured on the case-report forms, data were codified into 188 variables and entered into SPSS software for analysis. The relationships among these variables, RA disease activity, and serum ACPA levels were examined under the supervision of a statistician.

This study received ethical approval from the Ethics Committee of Fasa University of Medical Sciences (ethics code: IR.FUMS.REC.1397.158).

Statistical Analysis

SPSS software (version 24) was used for data analysis**.** Student's *t*-test and the Chi-square test were applied to evaluate differences between groups, depending on the type of outcome variable. In this study, serum ACPA levels were analyzed both as continuous and categorical variables. The level of statistical significance was set at 0.05.

Results

The mean age of participants in the control group was 53.3 ± 11.12 years, whereas in the patient group it was 55.7 ± 11.73 years. Of the 70 individuals in the control group, 56 (80%) were female and 14 (20%) were male; in the patient group, 60 (85.7%) were female and 10 (14.3%) were male. The most frequent occupation in both groups was homemaking (64.3% in the control group and 77% in the patient group). Approximately 67.1% of the control participants had primary-level education, while in the patient group, 47.1% were illiterate. Among the patients, the largest proportion fell within the moderate disease activity category (Table 1).

The highest frequencies of movement limitation were observed in the knee (5.7%), shoulder (5.7%), and elbow joints (5.7%), respectively. In total, 20% of patients (n = 14) exhibited restricted mobility in at least one joint. The most common joint deformities were ulnar deviation (17.1%), hallux valgus (12.9%), and boutonnière deformity (8.6%), respectively. Overall, 25.7% of patients (n = 18) presented with at least one joint deformity. The presence of joint deformity, as determined by clinical examination, was not significantly associated with RA disease activity. Figure 1 illustrates the distribution of primary joint involvement among patients based on medical history (Figure 1).

Table 1. Frequency distribution of patients by disease activity based on DAS 28-CRP.

Rheumatoid arthritis disease activity based on DAS.28	Statistical results
Remission activity	22 (31.4 %)
Low activity	10 (14.3 %)
Moderate activity	29 (41.4%)
High activity	9 (12.9%)

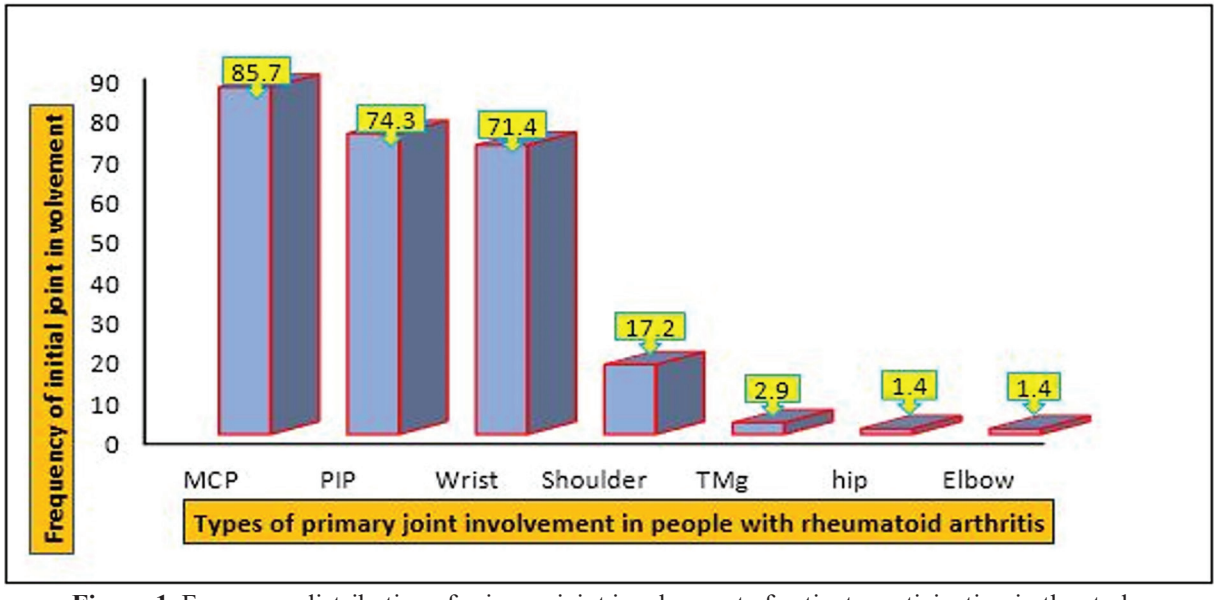


Figure 1. Frequency distribution of primary joint involvement of patients participating in the study.

Table 2. Mean serum ACPA levels in both study groups. (µg/L).

	Disease group	Control group	P-value
Mean ± SD	220.2±27.5	1.57±0.52	<0.001

Table 3. *Relationship* between ACPA levels and disease activity based on DAS 28-CRP with the chi-square test.

	ACPA Level Range	Remission Activity	Low Activity	Moderate Activity	High Activity	P-value
Relationship between ACPA and disease activity based on DAS.28	Negative ACPA	11 (50%)	3 (30%)	11 (31.9%)	2 (22.2 %)	0.4
	Positive ACPA	11 (50 %)	7 (70%)	18 (62.1 %)	7 (77.8%)	

The metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist joints demonstrated the highest frequencies of involvement, whereas the shoulder and hip joints exhibited the lowest. The frequency distribution of dry eye symptoms, as reported in participant histories, showed that 12.9% of the control group and 57.1% of the patient group had a history of dry eye. This difference was statistically significant ($P < 0.05$).

The sensitivity of the ACPA test was 61.4% (95% CI: 49.1–72.5%), and its specificity was 98.6% (95% CI: 92.7–99.8%). The positive predictive value was 97.7%, and the negative predictive value was 71.8%. The prevalence of a positive ACPA test was 61% among patients and 1.4% among controls. Table 2 presents the mean serum ACPA levels in both groups. The mean serum ACPA concentration was significantly higher in the patient group than in the control group ($P < 0.001$).

The results showed that the mean serum level of ACPA in the patient group was higher than in the control group ($P < 0.001$). Table 3 shows the relationship between ACPA levels and DAS28-CRP disease activity.

The analysis revealed no significant association between mean serum ACPA levels and disease activity as determined by DAS28-CRP ($P = 0.4$). To control for potential confounding, multivariate linear regression was conducted, adjusting for age and sex, which also demonstrated no significant relationship between these variables and disease activity.

In further statistical analyses, neither occupational status nor educational level in the patient group showed a significant association with disease activity ($P > 0.05$). Mean serum ACPA levels increased between the ages of 20 and 60 years and declined thereafter. Mean ACPA concentrations did not differ significantly between sexes. Similarly, serum ACPA levels were not significantly correlated with the number or location of involved joints, the presence of extra-articular manifestations, or the type of organ involvement ($P > 0.05$).

Furthermore, the mean serum ACPA level did not differ significantly between patients with inactive disease and those with high disease activity ($P > 0.05$). Among patients with RA, no significant difference was observed in mean serum ACPA levels between those receiving pharmacological treatment (excluding anti-TNF and anti-CD20 therapies) and those not taking RA medications ($P > 0.05$).

Discussion

This study aimed to examine the association between serum ACPA levels and disease severity among patients with RA at Fasa University of Medical Sciences. The mean serum ACPA levels differed significantly between the control and patient groups, as anticipated. In this regard, Poormoghim et al. reported mean serum ACPA concentrations of 36.5 IU/mL in patients and 7.35 IU/mL in controls, findings that are consistent

with those of the present study (17). In contrast, Bizzaro et al. observed markedly higher antibody titers, with mean levels of approximately 1,100 IU/mL in anti-citrullinated antibody–positive RA patients and 6.8 IU/mL in controls, exceeding the values observed here. This discrepancy in antibody concentrations between studies is likely attributable to methodological and technical variations in assay sensitivity, calibration, or sample handling.

It remains a matter of debate whether serum ACPA levels have prognostic or monitoring value in RA. Esalatmanesh et al. reported that the disease activity index was higher among patients with positive anti-CCP levels than among those who were anti-CCP negative; moreover, the number of painful joints was greater in the anti-CCP–positive group (18). Similarly, Papadopoulos et al. found a significant association between anti-CCP positivity and both the number of painful and swollen joints in RA patients, indicating a link between clinical manifestations and seropositivity (6). Shakiba et al, in a study of 418 RA patients, suggested that both anti-CCP and RF titers may be valuable indicators for estimating disease activity (19). Conversely, Ziegelasch et al. (2020) reported that baseline anti-CCP positivity was not associated with changes in disease activity over time, although it correlated with increased radiographic damage during follow-up (20). Likewise, Jafarzadeh et al. found no association between ACPA levels and disease activity in 64 RA patients (8), and Münevver Serdaroğlu et al, in a study of 40 patients, also failed to demonstrate such a relationship (21).

Consistent with these findings, the present study did not identify a significant association between anti-CCP titers and disease activity. This lack of correlation may be explained by the fact that disease activity is influenced by clinical and inflammatory parameters—including swollen and tender joint counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and patient-reported outcomes such as pain and fatigue—whereas ACPA levels tend to remain relatively stable and are not directly modulated by these factors. Patients may therefore exhibit persistent ACPA positivity despite low clinical activity, particularly under effective therapeutic control. Although ACPA contributes to osteoclastogenesis and the release of pro-inflammatory cytokines, promoting structural joint damage (22), such damage is more accurately assessed through imaging modalities rather than serological quantification alone.

While anti-CCP antibodies are widely recognized for their diagnostic and prognostic significance in RA, their utility for monitoring disease activity remains contentious. Several investigations have demonstrated that anti-CCP titers remain relatively constant over time and exhibit poor correlation with temporal changes in disease activity, thereby limiting their value in routine follow-up assessments (23). Nonetheless, emerging evidence indicates that in specific patient subgroups—such as those with early RA or individuals receiving targeted immunomodulatory therapy—longitudinal variations in anti-CCP titers may hold prognostic relevance. Repeated serological testing may therefore be justified in certain clinical contexts, for example, in patients who are initially seronegative for both RF and anti-CCP but present with severe disease, where evolving autoantibody status may guide therapeutic choices, including the consideration of agents such as rituximab, which demonstrate reduced efficacy in seronegative patients (23). These observations suggest that although anti-CCP measurement is not a dependable marker for monitoring short-term disease activity, it retains prognostic value in anticipating long-term outcomes and therapeutic responsiveness in selected clinical scenarios (24).

In this study, mean serum ACPA levels exhibited an age-dependent pattern, increasing from early adulthood to midlife and declining thereafter. The lowest mean ACPA levels were observed in participants aged 20–30 years,

whereas the highest occurred between 51 and 60 years. This age-related variation is most likely attributable to immunosenescence—progressive alterations in immune function that accompany aging (25).

The study by Vos et al. (2017) reported that both the sensitivity and specificity of anti-CCP assays exceed those of the rheumatoid factor (RF) test. Consequently, anti-CCP serves as a valuable and robust diagnostic tool for RA, a finding that aligns with the results of the present study (26). Serological assays facilitate prompt diagnosis across many clinical contexts. During inflammatory processes, arginine residues within proteins are enzymatically converted to citrulline, generating neoantigens recognized by the immune system (27). Peptidylarginine deiminases (PADs) catalyze the conversion of arginine to citrulline, a modification that can precipitate the generation of anti-CCP antibodies. Accordingly, anti-CCP is detectable in various conditions but is particularly prevalent in early RA, where it constitutes one of the most important and predictive diagnostic markers (28).

The present study demonstrated that histories of dry eye and dry mouth were more frequent among patients than among controls, an observation that may reflect the association between RA and Sjögren's syndrome. Despite the higher prevalence of sicca symptoms in the patient group, neither dry eye nor dry mouth was significantly associated with RA disease activity. Moreover, these sicca manifestations were not correlated with mean serum ACPA concentrations. Other extra-articular manifestations of RA similarly showed no significant association with mean serum ACPA levels.

Several limitations warrant consideration. First, the absence of radiographic and imaging data constrains the ability to evaluate the relationship between anti-CCP status and structural joint damage progression, an important outcome given anti-CCP's established predictive role for radiographic progression. Second, we did not perform subgroup analyses stratified by anti-CCP titer (for example, low-positive versus high-positive), which could have detected clinically meaningful differences. Third, disease duration was not accounted for in participant selection or analysis, a factor that may influence antibody titers and clinical associations.

Finally, both environmental exposures and host genetics substantially affect the presence and magnitude of anti-CCP antibodies. Specific genetic variants, particularly within the HLA region, interact with environmental factors—such as cigarette smoking, hormonal contraceptive use, and infectious exposures—to modulate the risk of developing anti-CCP–positive RA. These interactions must be considered when interpreting inter-study differences and when generalizing the present findings to other populations.

Mean serum ACPA concentrations differed significantly between patient and control groups. However, serum ACPA levels were not associated with disease severity, the number of involved joints, the anatomical distribution of joint involvement, the presence of extra-articular manifestations, or the type of organ involvement. Accordingly, ACPA measurement is not recommended as a routine tool for assessing current disease activity. Nevertheless, the anti-CCP assay remains a powerful and reliable diagnostic marker for RA.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Consideration

This study received ethical approval from the Ethics Committee of Fasa University of Medical Sciences (ethics code: IR.FUMS.REC.1397.158).

Code of Ethics

IR.FUMS.REC.1397.158.

Author Contributions

Poopak Mohaghegh: corresponding author and principal investigator. Mohammad Sadegh Ghasempuor: data collection. Azizallah Dehghan: data analysis.

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