Electronic Journal of Medical Research
https://ejmr.respublishers.com
ISSN: 3106-1362/3106-1370

Review article

Correlation of C-reactive protein, antinuclear antibodies and anti-cyclic citrullinated peptide with rheumatoid arthritis: A mini review

Rimsha Irshad [1], Hira Yaseen [1], Tasra Bibi [1], Talha Saleem [1] and Zubair Sharif [1,*]

[1] Department of Medical Laboratory Technology, Faculty of Allied Health Sciences, Superior University, Lahore, Pakistan

*Correspondence: zubair.sharif@superior.edu.pk

Article information:
Received: 03-12-2025
Revised: 05-01-2026
Accepted: 16-01-2026
Published: 19-01-2026

Academic Editor:
Dr. Naveed Ahmed

Keywords:
Rheumatoid arthritis
C-reactive protein
Anti-CCP antibodies
Antinuclear antibodies
Autoimmune

Abstract: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder affecting approximately 0.5-1% of the global population and is characterized by persistent inflammation and progressive joint damage. This review aims to examine the association between RA and key inflammatory and autoimmune biomarkers, including C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and antinuclear antibodies (ANAs), and to evaluate their clinical relevance in RA patients. Relevant peer-reviewed literature was analyzed to assess the role of these biomarkers in disease activity, diagnosis, and systemic involvement in RA. CRP, a highly conserved acute-phase protein synthesized by the liver, increases in response to pro-inflammatory cytokines and correlates with disease activity; serum CRP levels typically decline with effective treatment and rise during clinical deterioration. Anti-CCP antibodies, directed against citrullinated proteins, are highly specific for RA and are valuable for early diagnosis and prognostic assessment, while ANAs are present in a subset of patients, reflecting overlapping autoimmune features. Although RA primarily affects synovial joints, extra-articular manifestations occur in approximately 40% of patients and may involve multiple organ systems. Biomarkers such as CRP, anti-CCP antibodies, and ANAs play a critical role in the diagnosis, monitoring, and prognostication of rheumatoid arthritis, particularly given the challenges associated with early disease detection.

Article citation: Irshad, R., Yaseen, H., Bibi, T. et al. Correlation of C-reactive protein, antinuclear antibodies and anti-cyclic citrullinated peptide with rheumatoid arthritis: A mini review. Electron J Med Res. 2026. 2(1): 1-5. https://doi.org/10.64813/ejmr.2026.066.

Introduction

Rheumatoid arthritis (RA) is a persistent, immune system infection. The pathogenesis of rheumatoid arthritis isn't surely known. It could be as a result of a complex interaction of genetics and environment, as a result of which immunological system response stimulation and synovial inflammatory processes arranged in a symmetrical pattern. Despite the fact that RA primarily affects joints, extra-articular involvement also can rise in patients. As an autoimmune disease, RA is distinguished by the manufacturing of autoantibodies specific to the disease, inclusive of the rheumatoid factor, autoantibodies in opposition to cyclic citrullinated peptides and nonspecific autoantibodies, such as antinuclear autoantibodies [1].

C-reactive protein (CRP) levels may be used to differentiate between rheumatoid arthritis and osteoarthritis. CRP levels might indeed rise in certain types of rheumatoid arthritis. CRP is more responsive than Erythrocyte sedimentation rate (ESR) in detecting variations in disease activity because of the previously mentioned properties. Immunoglobulin antibodies formed against citrulline peptides are found in a large quantity of RA sufferers. For sufferers who are clinically suspected of having Anti-Cyclic citrullinated peptide (Anti-CCP), and RA test should be desired. There is no need to repeat if it is positive the first time because titrations of Anti-CCP antibody are completely unconnected to infection activity. As an outcome, it is unable to track the infections progression [2].

Anti-CCP antibodies have excessive predictive specificity for RA sufferers from the United States and Europe according to research. RA is characterized by Anti-CCP sufferers from Beijing and the southern China area. Antibodies have a predictive specificity of 90% and also can be used to assess infection activity. According to the findings, the reactivity and specificity of Anti-CCP antibodies for RA diagnosis may differ depending on the patient's race. Anti-CCP antibodies have been linked to disease activity and joint damage, according to research. Anti-CCP antibody-positive sufferers have more severe joint damage and morning stiffness than antibody-negative sufferers. A higher Anti-CCP antibody titer indicates a more severe ailment and a worse medical prognosis. This remark is compatible with the findings of Anti-CCP antibodies in foreign RA patients [3].

Rheumatoid arthritis is a heterogeneous disorder that can be subdivided into positive and negative RA based on data combining autoantibodies and genetic risk factors. Previous research supports the theory that there is a link for both thyroid dysfunction and RA, most likely because of autoimmunity; moreover, the results of these studies were conflicting. Rheumatoid factor is vigorously caused by chronic ExRA indications in RA patients, and Anti-CCP have a comparable but poor correlation [4]. An increase in autoantibodies to CENP-F could be thought to be due to an acute inflammatory response to RA. As a result, periodic antinuclear antibodies (ANAs) tests to detect a CENP-F-like pattern are required [5].

Rheumatoid arthritis and systemic lupus erythematosus are common examples systemic autoimmune disorders, with early arthritis being the most common clinical manifestation. CRP levels were useful in differentiating two subsets of patients. In one, patients have erosive arthritis with a congruent CRP response; within side the other, the arthritis is non-erosive and the CRP reaction is inhibited. CRP is a highly conserved protein that is a homopentameric intense inflammatory protein.

Rheumatoid arthritis is a commonly diagnosed incendiary autoimmune disorder that mainly affects small joints and causes pain, bloating, disfigurement, and functional limitations. Anti-CCP antibodies have a high specificity and sensitivity in the treatment of RA, and therefore a correlation with disease activity and ligament injuries [6].

The liver produces CRP. When there is inflammatory condition all across the body, the level of CRP begins to rise. It is one of a group of proteins known as acute phase reagents, which boost in inflammatory process. The levels of acute phase reactants rise in response to cytokines.

During inflammatory process, white blood cells generate these proteins. Because of the correlation between matrix metalloproteinase-3 and serum CRP, serum can be used to analyze rheumatoid arthritis activity and predict joint destruction. As a necessary consequence, many research suggests that habitually elevated serum CRP levels in patients with RA would be an obvious sign for immunotherapy.

Rheumatoid arthritis and systemic lupus erythematosus are two of the most common systemic autoimmune disorders, with early arthritis being the most common clinical manifestation. Anti-CCP antibodies have recently been described as being gift with comparable frequency in SLE sufferers with erosive arthritis as in RA sufferers, being considerably better than in people with non-erosive arthritis. Although anti-CCP antibodies are linked to disease severity and erosion, they do not appear to be linked to extra-articular manifestations of RA [7].

Disease duration, Age, HAQ-DI score and DAS-28 score were all associated with extra. This study found no link between ExRA as a whole and the titer of or presence of Anti-Cyclic Citrullinated Peptide or anti-mean cell volume antibodies. Although there was a weak association between positivity for these rheumatoid and autoantibodies. More research with more severe ExRA should be done to see whether these autoantibodies are linked to these specific expression [8].

This review article would help to understand the Correlation of CRP, Anti-CCP, and antinuclear antibodies with RA. It would contribute in the specific literature and highlight the association between variables being discussed under the light of literature.

Literature review

The influence of rheumatoid arthritis treatment on thyroid autoimmune disorders is incompletely understood. Moreover, the benefits of biological treatment, specifically tumors necrosis factor inhibitors to regulate and even suppress thyroid autoimmunity, have recently been discussed, indicating a possible role for TNF- in a shared disease between rheumatoid arthritis and thyroid autoimmune disorders. Thyroid disorders associated with poor initial treatment response measured by infection activity score in 28 joints in patient with newly diagnosed rheumatoid arthritis. C-reactive protein thyroid disorders in RA sufferers are associated with a more serious infections and a poor outcome, with either a direct impact on

initial treatment response. Commonly performed evaluation of serum thyroid-stimulating hormone is strongly advised in all rheumatoid arthritis patient at the time of diagnosis and at yearly intervals thereafter to diagnose multiple simultaneous thyroid disorders at an earlier stage [9].

In RA patients, CAR concentration was increased. while AFR concentration was diminished. In rheumatoid arthritis patients, CAR and AFR and are associated with Th17 cell ratios , ESR, RF and CRP could be used as possible determinants of RA(rheumatoid arthritis) inflammatory processes [10]. Apoptosis in RA patients may be suppressed due to IL17 expression. Th1 and Th17 functions, on the other hand, may be enforced by P53 in those patients. Earlier research had discovered a P53 genetic change in rheumatoid arthritis synovium. The minimal expression of p53 has just been linked to the initiation and progression. However, the role of PERP, as a gene transcription target of p53, in the pathophysiology of RA and in regulating IL17 remained unclear. IL17 and PERP can be used as markers for high disease activity and, potentially, as a treatment option for patient with aggressive disease and/or a poor prognosis, and they can play a role in the pathophysiology and disease activity of RA. RA is an autoimmune sickness that reason continual inflammation. Lower apoptosis is expected to be a significant root of autoimmune diseases [11]. In RA the presence of ANA has been related with large amount of C-reactive protein or psoriatic arthritis. As per the evidence, ANA positivity at the outset may predict poor response to both traditional disease-modifying agents and genetic medication. ANA may also be linked to an increased risk of eye disease [12].

Anti-CCP-positive RA patients had a significantly lower RHI (RHI = 1.78, SD = 0.30 n = 33) than anti-CCP-negative rheumatoid arthritis (RHI=2.19, SD=0.59, p=0.008, n = 20). RF IgM-positive patients (RHI = 1.77, SD = 0.30) n = 34) had a similar result to RF IgM-negative patients (n = 19, SD = 0.58; p = 0.003 RHI = 2.23). There were no important differences between groups in terms of, ESR, extra-articular manifestations (EAMs), and use of glucocorticosteroids, statins, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) age, gender, traditional cardiovascular risk markers, Disease Activity Score using 28 joint counts (DAS28), CRP. In RA patients, the presence of rheumatoid factor and anti-CCP antibodies was associated with poorer endothelial function impartial of other cardiovascular risk factors. As a direct consequence, these autoimmune reactions may represent an early transient stage of the atherosclerotic process and may suggest a higher risk of heart disorder [13].

Serological markers for RA include antibodies to IgM rheumatoid factor (IgM-RF) and anti-CCP, RA. Lupus-like disease with ANA has been reported during TNF antagonist therapy. IgM-RF titres dropped significantly more than anti-Cyclic citrullinated peptide titers during infliximab therapy used to treat existing RA. Variations in IgM-RF and Anti-CCP) did not correlate with treatment reaction at 48 weeks [14]. In Systemic lupus erythematosus, an "unreliable intense reaction" has been explained, and it seems to be more than an emergent phenomenon. Patients with active SLE have elevated serum IL-6 and TNF levels; however, CRP levels are regular only if patients have synovitis, serositis, or a concurrent infection [15].

It has been proposed that anti-CCP plays an essential part in development division classification. It was identified that anti-CCP titer was related to disease activity in rheumatoid arthritis. Rheumatoid arthritis group, anti-CCP had similar sensitivity to RF; some patients had positive anti-CCP while having negative RF. Extraarticular involvement and RF positivity appeared to be associated in RA patients, but not with Anti-CCP positivity [16]. It has been well acknowledged that autoimmune disorders play a role in the pathophysiology of RA. Different types of autoantibodies, including anti-citrullinated protein antibodies and immunoglobulin rheumatoid factor can be detected in the serum of RA patients. These are antibody indicators of RA that play an chief role not only in the treatment but also in the analysis of disease activity [16].

So many studies on the occurrence of a PL in RA sufferers have been published in the literature. The prevalence is estimated to be between 4% and 49%. In RA patients, the prevalence of APL is considerably large. There is a direct connection between APL and an anti-CCP-serological RA indicator; moreover, no link between APL and disease activity is found [17]. Anti-CCP prevalence, sensitivity and precision were found to be close in sufferer with advanced RA to those observed in patients with early disease. Anti-CCP was found to be positively related to some specifications of infection activity and consequences. Anti-CCP may be a useful clinical parameter in the evaluation of sufferers with advanced RA [18].

In RA patients, a decrease in Treg cells and an increase in inflammatory mediators Th17 cells were accompanied with RA clinical symptoms [19]. ACPAs are autoantibodies directed against citrullinated peptide and proteins. They are identified in the overwhelming

majority of RA patients. CCP are frequently used in clinical settings to detect these antibodies in patient plasma or serum [20].

Rheumatoid arthritis can be difficult to diagnose, especially in the early years. The American College of Rheumatology established seven criteria for rheumatoid arthritis diagnosis in 1987, four of which must be met for diagnosis. The creation of the (Anti-CCP) anti-cyclic citrullinated peptide assay, which enables the detection of Anti-CP autoantibodies in the serum many rheumatoid arthritis patients. The Anti-CCP assay has been shown to be just as delicate as the RF test, but with much higher specificity [21].

Discussion

The study of literature review suggested that it needs more practical observations to completely understand the phenomenon. The correlation of CRP, ANAs and Anti-CCP with RA is discussed under the light of previous research works. Because of the connection between matrix metalloproteinase-3 and serum CRP can then be used to analyze rheumatoid arthritis operation and foresee joint damage. As argued previous study, RA patients face an increase in inflammatory mediators and a decrease in Treg cells were accompanied with RA clinical symptoms. It is observed from the review that the higher the Anti-Cyclic Citrullinated Peptide infection rates, the more likely it is that RA is existent. When a sufferer develops positive Anti-Cyclic Citrullinated Peptide, it usually remains positive even when the patient is in recovery phase. A decrease in Treg cells and an increase in inflammatory mediators Th17 cells were associated with RA clinical manifestations in RA patients. Rheumatoid arthritis is incredibly difficult to detect, especially in the initial stages.

As an outcome of analysis, it is also revealed that another marker of clinical inflammation is CRP. In many labs, the ordinary size is much less than 1.0. This test, however, is not specific to RA and may be inspired through elements together with weight problems and infection. ESR and C-reactive protein are both non-RA-specific inflammatory markers. Both tests are used to assess disease activity; when they are elevated, it indicates that the disease is highly active (assuming no different reasons for excessive results, which include infection, are present). These labs are ordered on a regular basis by the healthcare team to monitor the patient's disease and how well his or her medications are working.

In the early stages of rheumatoid arthritis, it can be difficult to diagnose. Anti CCP with RA give positive association in sufferers with some specifications. CRP, ANAs and Anti-CCP with RA has a correlation among them in a larger percentage of patients. According to [17], 4 % to 49% patients have the prevalence of anti-CCP. According to a previous study, the existence of ANA has a correlation with CRP [18] Another study, also supported the proof of correlation between CRP, ANAs and anti-CCP with RA by concluding that Anti-CCP has positive relationship to some provisions of disease. CCP is also useful in clinical parameters.

A previous study [8] discussed how anti-CCP plays a chief role in RA growth division classification. CCP may be a useful clinical parameter in the evaluation of sufferers with advanced RA. There is a direct link between APL and an Anti-CCP-serological RA indicator; furthermore, there is no link between APL and disease activity as per the study conducted by [17]. To diagnose multiple concurrent thyroid problems at an in advance stage, a commonly performed evaluation of serum thyroid-stimulating hormone is strongly advised in all rheumatoid arthritis sufferers at the time of diagnosis and at yearly intervals thereafter.

The study of [14] argues and concluded that Antibodies to a IgM rheumatoid factor (IgM-RF) and cyclic citrullinated peptide are two serological markers for RA. During TNF antagonist therapy, a lupus-like infection with ANA has been reported. During infliximab therapy to treat pre-existing RA, IgM-RF titers dropped significantly more than Anti-CCP titers. At 48 weeks, differences in Anti-CCP and IgM-RF did not correlate with treatment reaction.

Conclusion

The review concludes that the correlation of CRP, ANAs and Anti-CCP with RA has a positive association. the review suggests that patients are observed with the symptoms of CRP, ANAs with rheumatoid arthritis. The study has attempted to understand the role played by the variables and their association in different patients. Previous studies have attempted to explore the phenomena through various aspects. However, the role of CRP, ANAs and anti CCP with RA has more scope to be explored further in other dimensions. The review suggested that CRP, ANAs have a strong correlation with the rheumatoid arthritis and the practitioners need to consider this correlation to form practical solutions to cure the disease and reduce its occurrence in public.

Author Contributions: Conceptualization, R.I. and Z.S.; methodology, R.I.; validation, H.Y., T.B. and T.S.; resources, Z.S.; writing—original draft preparation, R.I. and Z.S.; writing—review and editing, H.Y., T.B. and T.S.; supervision,

Z.S.; project administration, Z.S. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding.

Acknowledgments: Authors would like to thank Superior University for providing facilities to conduct this literature review.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Papadopoulos, N.G., Tsiaousis, G.Z., et al. Does the presence of anti-CCP autoantibodies and their serum levels influence the severity and activity in rheumatoid arthritis patients? Clinical reviews in allergy & immunology. **2008**. 34(1): 11-15.
2. Birtane, M., Yavuz, S., and Taştekin, N. Laboratory evaluation in rheumatic diseases. World journal of methodology. **2017**. 7(1): 1.
3. Hui, L., Wuqi, S., et al. Diagnostic value of anti-cyclic citrullinated peptide antibodies in northern Chinese Han patients with rheumatoid arthritis and its correlation with disease activity. Clinical rheumatology. **2010**. 29(4): 413-417.
4. Turesson, C., Jacobsson, L., et al. Rheumatoid factor and antibodies to cyclic citrullinated peptides are associated with severe extra-articular manifestations in rheumatoid arthritis. Annals of the rheumatic diseases. **2007**. 66(1): 59-64.
5. Hur, K., Jearn, L.-H., and Kim, T.-Y. Centromere protein-F-like pattern in a patient with rheumatoid arthritis. Annals of Laboratory Medicine. **2019**. 39(2): 227-228.
6. Ahmed, S.A., Darwish, E.M., et al. Anti-carbamylated Protein Antibodies and Serum Level of 14-3-3 Protein for Early Detection of Rheumatoid Arthritis Patient in Correlation with Rheumatoid Factor, Anti-CCP Antibodies, Disease Activity and Joint Damage using High Frequency Musculoskeletal Ultrasound. Applied Clinical Research, Clinical Trials and Regulatory Affairs. **2020**. 7(2): 141-153.
7. Korkmaz, C., Us, T., et al. Anti-cyclic citrullinated peptide (CCP) antibodies in patients with long-standing rheumatoid arthritis and their relationship with extra-articular manifestations. Clinical biochemistry. **2006**. 39(10): 961-965.
8. Gonzalez-Lopez, L., Rocha-Muñoz, A.D., et al. Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) relation with extra-articular manifestations in rheumatoid arthritis. Journal of Immunology Research. **2014**. 2014(1): 536050.
9. Emamifar, A., Hangaard, J., and Hansen, I.M.J. Thyroid disorders in patients with newly diagnosed rheumatoid arthritis is associated with poor initial treatment response evaluated by disease activity score in 28 joints-C-reactive protein (DAS28-CRP): An observational cohort study. Medicine. **2017**. 96(43): e8357.
10. He, Y., Tang, J., et al. Correlation between albumin to fibrinogen ratio, C-reactive protein to albumin ratio and Th17 cells in patients with rheumatoid arthritis. Clinica chimica acta. **2020**. 500: 149-154.
11. El-Maghraby, H.M., Rabie, R.A., and Makram, W.K. Correlation between relative expression of IL 17 and PERP in rheumatoid arthritis patients and disease activity. Egypt J Immunol. **2019**. 26(2): 9-29.
12. Guruparan, T., Hutchinson, M., et al. P130 The relationship between antinuclear antibodies and erosive disease in patients with rheumatoid arthritis. Rheumatology. **2021**. 60(Supplement_1): keab247. 125.
13. Hjeltnes, G., Hollan, I., et al. Anti-CCP and RF IgM: predictors of impaired endothelial function in rheumatoid arthritis patients. Scandinavian journal of rheumatology. **2011**. 40(6): 422-427.
14. Bruns, A., Nicaise-Roland, P., et al. Prospective cohort study of effects of infliximab on rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies in patients with long-standing rheumatoid arthritis. Joint Bone Spine. **2009**. 76(3): 248-253.
15. Amezcua-Guerra, L., Márquez-Velasco, R., and Bojalil, R. Erosive arthritis in systemic lupus erythematosus is associated with high serum C-reactive protein and anti-cyclic citrullinated peptide antibodies. Inflammation Research. **2008**. 57(12): 555-557.
16. Eker, Y.Ö., Pamuk, Ö.N., et al. The Frequency of anti-CCP antibodies in patients with rheumatoid arthritis and psoriatic arthritis and their relationship with clinical features and parameters of angiogenesis: A comparative study. European journal of rheumatology. **2014**. 1(2): 67.
17. Jeleniewicz, R., Majdan, M., et al. Prevalence of antiphospholipid antibodies in rheumatoid arthritis patients and relationship with disease activity. Pol Arch Med Wewn. **2012**. 122(10): 480-486.
18. Samanci, N., Ozdem, S., et al. Diagnostic value and clinical significance of anti-CCP in patients with advanced rheumatoid arthritis. Journal of the National Medical Association. **2005**. 97(8): 1120.
19. Taha, H.A., Hozayen, W.G., et al. Investigating the balance between Th17/Treg cells in rheumatoid arthritis and its association with disease activity. Journal of Child Science. **2019**. 9(01): e75-e83.
20. Rahali, F.Z., Tarmidi, M., et al. Clinical significance of anti-cyclic citrullinated peptide (anti-CCP) antibodies in rheumatoid arthritis: Literature review. SN Comprehensive Clinical Medicine. **2023**. 5(1): 272.
21. Shen, L. and Suresh, L. Autoantibodies, detection methods and panels for diagnosis of Sjögren's syndrome. Clinical Immunology. **2017**. 182: 24-29.