



DIAGNOSTIC UTILITY OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES IN COMPARISON WITH RHEUMATOID FACTOR, C-REACTIVE PROTEIN AND ERYTHROCYTE SEDIMENTATION RATE IN RHEUMATOID ARTHRITIS PATIENTS

Pathology

Dr. Nidhi Saradava Senior Resident, Shri M.P.Shah Government Medical College, Jamnagar.

Dr. Dhara P. Trivedi Associate professor, Shri M.P.Shah Government Medical College, Jamnagar.

Dr. Kinjal Nirmal* Second year resident, Shri M.P.Shah Government Medical College, Jamnagar.
*Corresponding Author

Dr. Kruti Ladani Senior Resident, Shri M.P.Shah Government Medical College, Jamnagar.

ABSTRACT

Background: Rheumatoid arthritis (RA) is the most common inflammatory joint disorder in adults and is characterized by chronic synovitis, systemic inflammation and autoantibody production. Rheumatoid factor (RF) and Anti cyclic citrullinated peptide antibodies (ACPA) are commonly found in the serum of this patients and are therefore established diagnostic markers. **Objectives:** To compare diagnostic utility of ACPA in comparison with Rheumatoid factor, CRP and Erythrocyte sedimentation rate (ESR). **Methodology:** Retrospective and prospective case control study was conducted in 80 patients and 20 control group at tertiary care center. **Results:** Anti-CCP was 92.5% positive in case group and 100% negative in control group with p value<0.00001 which was statistically significant. Correlation between Anti-CCP and RF showed significant titers with p value <0.001. Results were variable with respect to CRP and ESR. **Conclusion:** Anti-CCP is more specific than the other parameters for the diagnosis of RA.

KEYWORDS

Anti cyclic citrullinated peptide antibodies, C-reactive protein, Erythrocyte sedimentation rate, Rheumatoid arthritis, Rheumatoid factor.

INTRODUCTION:

Rheumatoid arthritis (RA) is the most common inflammatory joint disorder in adults. These biological agents are targeted against single components of the immune system, which are involved in the Suppressing disease activity is the major goal in RA therapy as uncontrolled activity causes acute symptoms, but also seems to be the main reason for the adverse longterm effects¹. Interestingly, in RA the fall incidence seems to be independent from age as well as from disease duration². RF and ACPA are commonly found in the serum of RA patients and are therefore established diagnostic markers³. For this reason changes of RF and ACPA (Anti CP igg) levels can be highly relevant for the long-term outcome of RA. Both studies can be seen in the context of current efforts of treating RA patients to a treatment target³ and the intentions of personalized medicine considering individual risk factors⁴.

AIMS AND OBJECTIVES:

- 1)To observe diagnostic accuracy of Anti-CCP antibodies in comparison with Rheumatoid factor, c-reactive protein and ESR in rheumatoid arthritis patients.
- 2)To evaluate the significance of Anti-CCP (Anti CP IgG) antibody in seronegative for Rheumatoid factor in Rheumatoid Arthritis patients.
- 3)To assess the sensitivity and Specificity of the Anti-CCP (Anti CP IgG) Antibody test, RF test, CRP & ESR in Rheumatoid Arthritis patients.

MATERIALS AND METHODS:

Design Of Study: longitudinal study

Duration Of Study: 2 years study

Sample Size: Total 80 cases 20 control

Study Area: Department of pathology.

Current study was conducted after Submitting ethical approval to Ethical Approval committee.

Inclusion Criteria:

- All ages of Both sexes
- 1-10 large joints involvement
- 1-10 small joint
- >10 joints
- With the synovitis and rheumatoid nodules ,extra articular manifestation of RA and with Radiographic changes (erosion)

Exclusion Criteria:

- Patients with history of trauma, radiological findings suggestive of Osteoarthritis , with Hemarthrosis and with Distal interphalangeal joint involvement

Material And Equipment :

Plain vacuette, EDTA vacuette, Aliquot tube, Distilled or deionized Centrifuge machine , ELISA kit for serum anti-cyclic citrullinated peptide antibody, Precision pipettes and disposable pipette tip, ELISA reader capable of reading absorbance at 450nm, Absorbance paper or paper towel, Graph paper

Method: Anti-CPIgG level in serum is determined by using ELISA kit.

RESULTS:

Age Wise Distribution:

24 (30%) among cases and 8 (40%) among controls were in the age group of 41- 50 years followed by 16 (20%) among cases and 5 (25%) among controls were between 31 and 40 years. A small number constituted extremes of age in both groups.

Gender Wise Distribution:

P=0.04, Significant, Chi-square test , it was observed that there was female preponderance in both cases and control groups. Among cases 64 (80%) were females and 16(20%) were males with male to female ratio being 1:4. Among controls 12 (60%) were females and 8 (40%) were males.

P=0.005, Significant, Chi-square test , Multiple joint involvement is seen more frequently in both cases (90%) and control groups (65%) then the single joint involvement.

In present study, Among cases we observed mainly small joint involvement (55%) followed combine small and large joint involvement (31%) and large joint involvement (6.25%). Among control groups we observed equally small joint and combine small and large joint involvement (40%) followed by large joint involvement (20%).

we observed out of 80 patients 22 patients (27.5%) having extra articular manifestations. Most commonly lung (12.5%) involvement followed by heart (10%) and skin (5%). All of this patients showing very high titers of Anti-CCP and ESR than patient without extraarticular manifestations.

Joint pain was the most common chief complaints, occurring in 90% of the patient followed by fatigue which occurred in 87.5% followed by

fever (50%), Joint swelling (43.75%) and Joint stiffness in (35%).

Fever was the most common chief complaints, occurring in 85% of the control groups followed by fatigue occurred in 75%, followed by Joint pain which occurred in 70% and Joint swelling (40%).

we observed out of 80 patients 22 patients (27.5%) having extra articular manifestations. Most commonly lung (12.5%) involvement followed by heart (10%) and skin (5%). All of this patients showing very high titers of Anti-CCP and ESR than patient without extra articular manifestations.

Table I : (Statistical Analysis Of Anti CCP, RA Factor, CRP And ESR Values In Cases And Control)

	Cases	Controls	Total	p-value
Anti CCP				
<10 AU/ml	06	20	26	
>10 AU/ml	74	0	74	
RA factor				
<10 IU/ml	12	16	28	
>10 IU/ml	68	04	72	
CRP				
<0.6mg/dl	24	05	29	
>0.6mg/dl	56	15	71	
ESR				
<10 mm/1 st hr for male	16	04	20	
>10 mm/1 st hr for female	64	16	80	

Chi square test, Out of 80 patients who were clinically suspected cases of RA, 74 had positive Anti CCP while 68 had positive RF. None of the controls were positive for Anti CCP. Results were variable with respect to CRP and ESR. When a comparative evaluation of Anti-CCP, RA factor, CRP and ESR was made, a positive correlation was seen in Anti CCP and RA factor with P value < 0.00001 which was statistically significant.

Table II:

Sr. No.	Test	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
1.	Anti-CCP Antibody	92.50%	100%	100%	76.92%	94%
2.	RF test	85.0%	80%	94.44%	57.14%	84%
3.	CRP	70%	25%	78.87%	17.24%	61%
4.	ESR	80%	20%	80%	20%	68%

-In present study, we observed that sensitivity, specificity, PPV and diagnostic accuracy of Anti CCP is high being 92.50%, 100%, 100%, 94% respectively then other biomarkers.

Out of 80 patients who were clinically suspected cases of RA, 74 had positive Anti CCP while 68 had positive RF. Out of 12 RF negative patients 6 had positive Anti CCP.

Utility Of Anti CCP Test In Sero Negative RA Patients:

we observed that 50% of seronegative arthritis patients were positive for Anti CCP

DISCUSSION:

In the present study, clinically suspected RA patients belonged to age group of 11-80 years with maximum patients in the age group of 41-50 years and male to female ratio being 1:4.

In the present study, the mean age of presentation in both the groups was 44 years which was comparable to Shamanna P et al (107) with 45 years in cases and 44 years in controls as the mean age. All most all the studies showed that the age of presentation in case group was in the 4th and 5th decade.

All of the studies had predominant female patients with 80% in cases and 60% in controls group respectively in present study. Rongchun et al (105), Al-Shukaili et al (106) and Shamanna P et al (107) had 75.37%, 88.75% and 80% female in case group respectively and 58%, 52.63 and 66.25% female in control group respectively.

In present study, sensitivity, specificity, PPV and diagnostic accuracy of Anti-CCP were also high being 92.50%, 100%, 100%, 94% respectively. The results show that the diagnostic sensitivity of Anti-

CCP antibodies in patients with recent onset RA is greater than that of RF and specificity of RF was lower than that of anti CCP antibody and that seropositivity for the two tests correlate significantly.

In present study, we observed sensitivity and specificity of RF test 85% and 80% respectively which is comparable with Rongchun et al (105) which had sensitivity and specificity 87% and 74.4% respectively. Lin et al (108) in their study showed the sensitivity and specificity 80% and 62.7% respectively which was lower than present study.

Comparison Of Statistical Values Of Anti-CCP And RF With Other Study Results (All values in percentage)

Authors	Sensitivity	Specificity
Anti CCP:		
Rongchun et.al(105)	90.4	91
Shamanna Pet al (107)	100	80
Lin et al (108)	82.1	88
Garcia-Berrocal et al (109)	43	85
Van Schaaedenburg et al (110)	57.8	94.2
Current study	92.50	100
RF:		
Rongchun et.al (105)	87	74.4
Lin et al (108)	80	62.7
Current study	85	80

In present study, we observed sensitivity and specificity of AntiCCP test was 92.50% and 100% and RF factor 85% and 80% respectively, which was comparable with other studies which showed lower sensitivity and specificity than present study.

Diagnostic accuracy of Rongchun et al (105), Shamanna P et al(107) an present study was 88.1%, 87.2% and 94% respectively. Such differences can be explained by the use of various ELISA kits with different cut off values, sample selection, detailed history and thorough evaluation of patients.

There was no significant statistical correlation between anti -CCP and CRP with p value being 0.66. This shows that acute phase reactant protein like CRP was elevated in both RA patients and controls without any significant correlation with disease activity. Patients with RA show considerable variability in disease activity that can be difficult to predict at the onset of disease. The characterization of acute phase reactants responses in RA is essential to gain insight into the activity of this disease and to assess the degree of inflammation.

A significant statistical correlation of Anti CCP with another inflammatory marker (ESR) was not observed.

Though RA is a disease defined by well accepted criteria, the clinical presentation and pathogenesis of this disease are varied and complex due to which prioritizing diagnostic tests or predicting treatment responsiveness is not easy.

CONCLUSION:

The objective of the study was to observe sensitivity, specificity and diagnostic accuracy of Anti-CCP in comparison with RA factor, CRP and ESR in rheumatoid arthritis patient. It can be stated that RF and Anti CCP antibody both are sensitive marker but performing anti-CCP test in the diagnosis of RA could be beneficial since it has high specificity, PPV and diagnostic accuracy. Anti-CCP antibodies determination, proved to be a powerful diagnostic tool, especially in sero negative (RF negative) patients. Although CRP and ESR are nonspecific for the diagnosis of RA, they are important auxiliary markers for the diagnosis of RA. Simultaneous detection of all the four markers is helpful for the confirmed diagnosis of RA. Anti - CCP has already been induced in new ACR / European League Against Rheumatism (EULAR) classification criteria, as it provides additive sensitivity to rheumatoid factor for diagnosis of rheumatoid arthritis.

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