

# Anti-CCP antibody in rheumatoid arthritis patients and its relation with severity of the disease

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic and erosive polyarthritis causing irreversible joint disability. It is the most common persistent inflammatory arthritis, affecting from 0.5 to 1% of the general population worldwide. Antibodies to citrullinated proteins (anti-CCP antibody) have been described in patients with RA and these appear to be the most specific marker of the disease.

**Methods:** This cross-sectional study was carried out at department of medicine, Sher-E-Bangla Medical College Hospital, Barisal from July' 2016 to December' 2016. All rheumatoid arthritis patients attending at OPD and those got admitted under Medicine Dept, who was satisfying the inclusion and exclusion criteria were included consecutively and purposively in this study.

**Results:** Total 70 cases were included; the mean age was found 46.57±13.10 years in anti-CCP antibody positive group and 44.19±11.21 years in anti-CCP antibody negative group. Female were predominant in both groups. Duration of disease was around 8 years in both groups. Mean ESR was 29.0±22.0 mm in anti-CCP antibody positive group and 12.25±10.6 mm in anti-CCP antibody negative group. Mean rheumatoid factor was 189.4±102.1 U/L in anti-CCP antibody positive group and 66.5±36.0 U/L in anti-CCP antibody negative group. Mean DAS 28 score was 4.6±1.4 and 3.6±1.3 in anti-CCP antibody positive and negative group respectively. The mean difference was statistically significant ( $p<0.05$ ) between the groups. Patients in disease remission had lower anti-CCP antibody titer than those with low, moderate or high disease activity. Significantly positive correlation ( $r=0.596$ ;  $p=0.001$ ) between severity of rheumatoid arthritis and anti CCP antibody level was observed.

**Conclusion:** In RA patients' disease was more severe in anti-CCP antibody positive group and significantly positive correlation between anti-CCP antibody level with disease severity of RA was observed.

**Key words:** Rheumatoid arthritis, anti-CCP antibody, disease severity.

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## INTRODUCTION

Rheumatoid arthritis (RA) is the most common persistent inflammatory arthritis, occurring throughout the world.<sup>1</sup> It is the commonest joint disease with considerable morbidity and mortality.<sup>2</sup> The prevalence of rheumatoid arthritis is 1.6% of the respondents having disability from rheumatic problems in Bangladesh.<sup>3</sup> Diagnosis depends on 1987 classification criteria of ARA.<sup>4</sup> The functional status of patients within their first year of RA is often predictive of long-term outcome.<sup>5</sup> The modern

treatment strategy is to institute early aggressive treatment with disease modifying anti-rheumatic drugs (DMARDs), which has improved disease outcome compared with the old "pyramid approach".<sup>6-9</sup> There is a window of opportunity early in the disease course during which DMARDs have the greatest effect in altering disease progression, as measured by the development of radiologic erosions.<sup>10-11</sup> Therefore early diagnosis and treatment is the cornerstone for preventing joint damage and severe morbidity from RA.

For the last few decades laboratory diagnosis of RA has relied on detection of rheumatoid factor (RF). Another new assay technique that detects antibodies to citrullinated peptides, named anti-CCP antibody, has demonstrated a comparable sensitivity but a much higher specificity than the RF test. Anti-CCP antibodies recognize peptides in which the amino acid arginine has been converted to citrulline by peptidyl arginine deaminase, an enzyme abundant in inflamed synovium

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and in a variety of mucosal structures. Anti-CCP antibody is associated with more severe disease progression, and can be detected in asymptomatic patients several years before development of RA.

Around 85% of patients with RA become positive for RF over the first 2 years of disease onset.<sup>12</sup> On the other hand anti-CCP antibody appears about 2 years earlier than clinical onset of disease.<sup>13</sup> Anti-CCP antibodies are a stronger predictor of the severity of RA than RF.<sup>14-15</sup> The aims of this study are to examine frequency of anti-CCP antibody in RA patients and its relation with the severity of the disease.

## METHODS

This cross-sectional study was done from July 2016 to December 2016 at the department of Medicine, Sher-E-Bangla medical college Hospital, Barisal to evaluate the frequency of anti-CCP antibody in RA patients and its relation with the severity of the disease. All rheumatoid arthritis patients fulfilling the criteria of 1987 ARA classification criteria and who were tested positive for RF attending at OPD and those got admitted under Medicine Dept, were included consecutively and purposively in this study as per inclusion and exclusion criteria. All patients were interviewed directly, detailed informations regarding history and physical examinations were recorded. Disease activities were assessed by DAS 28 score, so informations regarding DAS 28 score were recorded. Relevant investigations like ESR, CRP, RF and anti-CCP antibody were done in the laboratory of department of Pathology of the same institute. The synthesized cyclic citrullinated peptide was used as substrate for ELISA. Anti-CCP antibody was detected by ELISA technique and RF was done by latex agglutination method. All the informations were recorded in the fixed protocol. Collected data was classified, edited, coded and entered into the computer

for statistical analysis by using statistical package for social science (SPSS) version-22.0 for Windows and result presented in figures and tables. This study protocol was reviewed by BIRDEM ethical committee, Sher-E-Bangla medical college hospital, Barisal ethical committee and RTMD, BCPS.

## RESULTS

Total 268 suspected patients were evaluated; among them 85 patients were eligible according to 1987 ARA classification criteria and RA positivity. However, 15 patients did not give consent. Therefore, total study subjects were 70, among them 45 patients were anti-CCP antibody positive and 25 patients were negative. Majority patients were belonged to age >50 years, female was predominant and majority of them were housewife in both groups. Mean duration of disease in both groups was (mean±SD) 7.8±6.7 years and 7.9±9.5 years respectively (Table I). There was no statistically significant difference regarding disease duration among two groups. Regarding laboratory profile of study population ESR and CRP both was high in anti-CCP positive group but there was no statistically significant difference in between groups. Mean titer of RF in anti-CCP positive group (189.4) was higher than anti-CCP negative group (66.5), which was statistically significant (P-value=0.001). Similarly, disease activity in anti-CCP positive group was significantly higher than negative group (P value=0.005) (Table II). Figure 1 showed that the titer of anti-CCP antibody is lowest in patients in disease remission, it increases with the increase of disease activity, and highest in patients with maximum disease activity. There is positive significant correlation ( $r=0.596$ ;  $p=0.001$ ) between disease severity of rheumatoid arthritis and anti-CCP antibody level (Figure 2). Total 25 patients had negative anti-CCP antibody among them 5 were in remission, 10 were mild, 8 were moderate and 2 were severe evaluated by DAS-28 score (Table III).

**Table I** Distribution of the study patients by socio-demographic data and clinical profile (n=70)

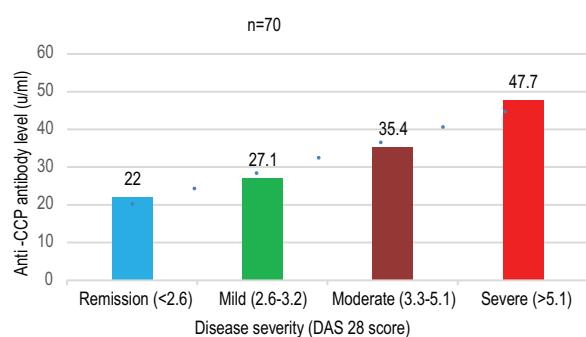
Profile	Anti-CCP antibody positive n, (%)	Anti-CCP antibody negative n, (%)	P value
Age (median±SD)	46.57±13.10	44.19±11.21	0.447*
Gender			
Male	12(26.7)	09(36.0)	0.414**
Female	33(73.3)	16(64.0)	
Occupational status			
Housewife	30(66.7)	14(56.0)	0.843*
Service	05(11.1)	04(16.0)	
Businessman	06(13.3)	04(16.0)	
Others	04(8.9)	03(12.0)	
Duration of disease(median±SD)	7.8±6.7	7.9±9.5	0.959*

\*Unpaired t test, \*\*Chi square test, P value significant if  $p<0.05$

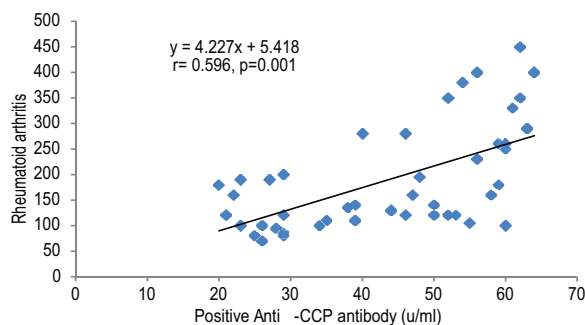
**Table II** Distribution of the study patients by laboratory parameters and DAS 28 score (n=70)

Laboratory parameter	Anti-CCP antibody positive (n=45) Mean±SD	Anti-CCP antibody negative (n=25) Mean±SD	P value
ESR (mm/hr)	29.0±22.0	25.0±23.0	0.476
CRP (mg/L)	18.7±12.3	12.25±10.6	0.031
Rheumatoid factor (U/L)	189.4±102.1	66.5±36.0	0.001
DAS 28 score	4.6±1.4	3.6±1.3	0.005

P value significant if p<0.05, p value obtained by Mann–Whitney U test



**Figure 1** Anti-CCP antibody titer in relation to disease severity



**Figure 2** Scatter diagram showing positive significant correlation (r=0.596; p=0.001) between rheumatoid arthritis and positive anti CCP antibody. (Pearson correlation graph)

**Table III** DAS-28scoreinrelation to anti-CCP antibody level (n=70)

Anti-CCP antibody (u/ml)	Disease severity (DAS 28 score)			
	Remission(<2.6)	Mild(2.6-3.2)	Moderate(3.3-5.1)	Very severe(>5.1)
<20 (Negative)	5	10	8	2
20-39 (Weakly positive)	2	3	10	4
40-59 (Moderately positive)	1	3	10	4
>60 (Strongly positive)	0	1	2	5

**DISCUSSION**

Rheumatic disorders are common causes of morbidity, disability, and work loss in rural and urban communities of Bangladesh. Rheumatoid arthritis is the most common form. Anti-CCP antibody have similar sensitivity to RF for RA (70%) but much higher specificity (>95%), and are increasingly being used in preference to RF in the diagnosis of RA. Anti-CCP antibody is associated with more severe disease progression. In our study, we found that females are more affected than males in RA, which are similar with the findings of different studies from different countries.<sup>16-18</sup>There was no statistically

significant difference of mean duration between the groups in our studies which is also similar with other studies done earlier in different countries.<sup>16-18</sup>In this present study, it was observed that the difference of mean ESR and CRP in two groups were not statistically significant, which doesn't support the findings of other studies<sup>16-17</sup>, it may be due to the small study population. In this study, we found that mean value of titer of RF is higher in anti-CCP antibody positive patients and which is also statistically significant. The difference of DAS 28 score was also statistically significant between the groups. There are substantial data that RF are high in

patients with high disease activity. In our study we also observed the similar type of association.<sup>17-18</sup>

Another important finding in this study is patients with disease remission had lower anti-CCP antibody titer than those with low, moderate or high disease activity. Del Amo et al.<sup>18</sup> study was found a significant association between the presence and the level of anti-CCP antibody and greater RA activity, with higher values of DAS 28 and ESR. This study showed that among anti-CCP antibody positive patients the disease was severe in those who were in high titer of anti-CCP level evaluated by DAS-28 score. The difference was statistically significant when compared anti-CCP antibody and DAS-28 score. Serdaroflu et al. showed the high prevalence of anti-CCP in RA patients with extensive disease activity.<sup>17</sup> Bas et al. showed an association of RF and anti-CCP with clinical signs of disease activity. Present study also showed positive significant correlation between rheumatoid arthritis and positive anti CCP antibody.<sup>19-20</sup> Del Amo et al.<sup>18</sup> study showed there was a significant correlation between the presence of RF and positive anti-CCP antibody. Serdaroflu et al.<sup>17</sup> observed that a small but significant correlation was found between RF and anti-CCP antibody.

### Conclusion

In conclusion, it can be said that, this study has shown anti-CCP antibody was positive in majority of patients and significantly positive correlation between disease severity of rheumatoid arthritis and anti-CCP antibody level was observed.

### Limitations of the study

The study population was selected from one selected hospital in Barisal city, so that the results of the study may not be reflect the exact picture of the country. The present study was conducted at a very short period of time. Small sample size was also a limitation of the present study. Therefore, in future further study may be under taken with large sample size.

### Recommendations

So anti-CCP antibody could be used for early diagnosis of RA and level of it could be used for prediction of disease severity of RA. Further studies can be undertaken by including large number of patients.

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**Authors' contribution:** RY planned the research, searched literature, collected analyzed data and drafted the manuscript, HNS revised the manuscript. Both authors read and approved the final version of the manuscript for submission.

**Conflict of interest:** Nothing to declare.

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