



## Use & Significance of Anti CCP in RA & Seronegative RF Patients

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### Abstract

*Rheumatoid Arthritis (RA) is the most common systemic inflammatory, auto immune Rheumatic disease. Although the precise aetiology of RA remains unknown<sup>1</sup>, there is strong evidence for autoimmunity,<sup>6</sup> The aim of the present study is to evaluate the use and significance of Anti CCP antibodies in Rheumatoid Arthritis with RF positive & in RF Sero Negative Rheumatoid Arthritis(early synovitis) and the Healthy Blood Donors as control. In this study a total number of 150 patients (each group50) including both males and females were studied. Anti-CCP was positive in 39 of 50 RA patients (78%), 14 of 50 (28%) Early Synovitis cases & no HBD were positive for Anti CCP. RF was positive in38 of 50 RA patients, 21 of 50 ES patients & 4 of 50 healthy blood donors. Sensitivity of RF Test in RA is 76% & Specificity is 92%. Sensitivity of Anti CCP test in RA is 78% & Specificity is 100%. Anti CCP Test in Sero Negative RA patients (6 out of 12) is 50%. Being a specific marker in advanced RA, the Anti CCP antibody in ES is a very important predictor. So Anti CCP has the hallmark of establishing as a diagnostic tool, early predictor and provides additive sensitivity to RF. The presence of both in serum is a strong indicator of RA. So it should also be included among the diagnostic criteria of RA along with RF. and as a prognostic indicator in RA patients on treatment.*

**Key Words:** Anti CCP, RA, Early Synovitis.

### INTRODUCTION

Rheumatoid Arthritis (RA) is the most common systemic inflammatory, auto immune Rheumatic disease of unknown etiology<sup>1,2,3,4</sup> affecting nearly 1%<sup>1,3,5,6,7,8,9,10</sup> of the adult population worldwide. It is characterized by chronic and erosive polyarthritis,<sup>10,11</sup> (usually involving small, peripheral joints in a symmetric distribution) caused by abnormal growth of synovial tissue or pannus, and causes irreversible joint deformity<sup>9</sup> that can lead to severe disability<sup>1,3,8,12,13</sup> with considerable morbidity<sup>6</sup>. Although the precise aetiology of RA remains unknown<sup>1</sup>, there is strong evidence for autoimmunity, since several auto antibodies are associated with the disease<sup>6</sup>.

The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, but most will have a relentless progressive polyarthritis with marked functional impairment.

The disease occurs more frequently in women than in men (2.5 – 3:1). The disease can begin at any age, peak onset typically occurs in the fourth and fifth decades of life.<sup>7</sup>

Genetic studies have demonstrated that a genetic

predisposition resides in the HLA-DR locus<sup>7,12</sup>. For decades, RA is diagnosed primarily according to clinical manifestations based upon ACR Criteria<sup>3,5,7,14,15</sup>, in which the only serological marker is RF test. Rheumatoid factor (RF) is an antibody directed against the Fc region of IgG<sup>2,3,6,7,16</sup> and is recommended as a screening test<sup>3</sup> and can be detected in up to 80% of RA patients<sup>6,17</sup>. However it is non specific<sup>16</sup> and may be present in 5-10 % of healthy elderly persons or in patients with other autoimmune and infectious diseases<sup>2,6,11</sup>. So it is therefore crucial to have a reliable and specific test to identify the RA patients prior to the occurrence of joint damage.<sup>17</sup> The other most specific auto antibody system for RA is the family of auto antibodies directed to Citrulline – containing proteins, including anti perinuclear factor (APF) in 1964<sup>7</sup>, antikeratin antibodies (AKA) in 1979,<sup>7</sup> antifilaggrin antibodies (AFA) and anti-Sa<sup>3,7,11</sup>. Because of rigorous technical requirements for their detection, have never been widely used as markers for Rheumatoid Arthritis, despite their high specificity<sup>3,6</sup>. Recently, a new serological test (biological marker)<sup>20</sup> the Anti Cyclic Citrullinated Peptide (anti-CCP)<sup>2,20</sup> was developed<sup>6</sup>. Citrulline is formed by deamination of arginine residues in several proteins by the action of enzyme peptidyl arginine deaminase (PAD)<sup>6,7,16,21,20</sup> which is present abundantly in inflammatory synovium & cause local citrullination of proteins such as fibrin<sup>6,7</sup>. Citrullinated extracellular fibrin in the RA synovium may be one of the major auto antigens driving local immune response suggested by the discovery of local production of anti – CCP antibodies in the joint. It was also found that there is an association between anti - CCP and the disease severity in early RA<sup>6,11,23</sup>. A-CCP is the predictor of bone damage.<sup>3,7,23</sup> . 20% of new patients with RA are RF seronegative in the first year, when early diagnosis is essential to prevent erosive joint disease<sup>7,18,24</sup>. It has been helpful to see the anti-CCP data during the first, vitally important year of

disease.

Around 40% of RF seronegative patient appear to be anti-CCP positive, which substantiates additional diagnostic potential of anti-CCP. It has been recognised in the last decade, RA needs to be diagnosed early & treated promptly with Disease Modifying Anti Rheumatic Drugs (DMARD) in order to successfully interfere with disease process<sup>18,19</sup>. The ultimate challenge for future is to initiate therapy in early phase for which early diagnosis is more important to limit the radiological progression of the disease (bony deformity) for best outcome and quality of life<sup>16</sup>. Hence the study.

## MATERIALS & METHODS

**Study Design:** This is a Cross Sectional study.

The present study was conducted at the Microbiology Diagnostic Laboratory, Thanjavur Medical College Hospital, Thanjavur. This study period extended from October 2016 to December 2016.

**Study Subjects:** The total number of subjects in this study for evaluation was 150, which included both males and females. The study subjects were from the patients who attended the Out Patient Clinics at the Rheumatology and Orthopaedics Department and Healthy Blood Donors who attended the Blood bank.

**Sample:** 3-5ml of Venous Blood was collected aseptically, Serum was separated and stored at 2-8<sup>0</sup>c, if delay at – 20<sup>0</sup> C .

**RF:** RF is an autoantibody directed to the Fc part of IgG molecules.<sup>6,3,7,16</sup> RF is detected by the method of latex agglutination slide test.

### Interpretation of Results:

Distinct agglutination indicates RF content > than 20 IU RF/ml -undiluted serum.

Interpretation	Observation
Distinct coarse agglutination	Within 0.5 mts - strong positive
Fine agglutination	After full 2 mts - weak positive
Smooth suspension	Negative

### Anti CCP Test

Anti-CCP antibody was detected by ELISA technique<sup>11</sup> by using GENESIS CPA (citrullinated protein antibodies) ELISA kit for detection of

Rheumatoid arthritis specific IgG antibodies to citrullinated protein.

**Sample:** serum. Storage-2-8<sup>0</sup>c / - 20<sup>0</sup>c

Test done as per kit instruction as a multistep procedure and took readings of the optical density of each well by using Micro plate Reader within 10 minutes. (620nm reference filter is used.)

**Results:** Samples with OD ≥ OD(optical density)of 6.25 U/ml Standard are positive.

**RESULTS**

In the present study Age wise distribution in RA 50-60yrs, in ES 30-50 yrs, Sex wise distribution of - M/F ratio – in RA was 1:2.33 & in ES(early synovitis) 1:2.57.

Anti-CCP was positive in 39 of 50 RA patients (78%), 14 of 50 (28%) ES cases & no HBD were positive for Anti CCP.

RF was positive in38 RA, in 21 ES patients & 4 healthy blood donors. Sensitivity of RF Test in RA is76% & Specificity is 92% .Sensitivity of Anti ccp test in RA is 78% & Specificity is 100%. Anti CCP Test in Sero Negative RA patients 6 out of 12(50%).

**TABLE – 1 Anti-CCP & RF Results**

CATEGORY	Anti CCP Positivity	RF Positivity
RA (50)	39 (78%)	38 (76%)
ES (50)	14 (28%)	21 (42%)
HBD (50)	0	4 (8%)

**TABLE – 2 Sensitivity & Specificity of RF Test in RA**

RF	Positive	Negative	Total
RA(50)	38	12	50
HBD	4	46	50
Total	42	58	100

Sensitivity 76%      Specificity 92 %

**TABLE- 3 Sensitivity & Specificity of Anti CCP Test in RA**

TEST	Anti CCP Positive	Anti CCP Negative	Total
RA(50)	39	11	50
HBD	0	50	50
Total	39	61	100

Sensitivity: 78%      Specificity: 100%

**TABLE-4 Distribution of Positivity of Anti CCP and /or RF**

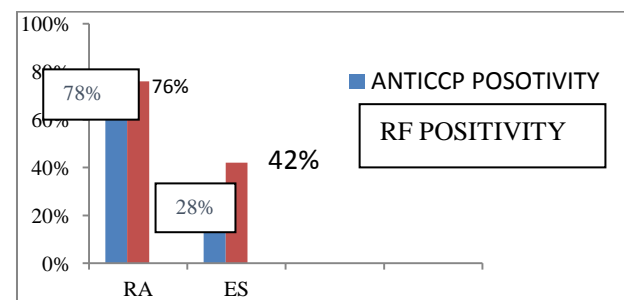
	In RA patients n = (50)	Control groups (HBD) n = 50
Anti CCP positive	39	0
RF positive	33 (66%)	0
RF negative	6 (12%)	0
Anti CCP negative	11	50
RF positive	5 (10%)	4 (8%)
RF negative	6 (12%)	46 (92%)

**TABLE 5 Use of Anti CCP Test in Sero Negative RA patients**

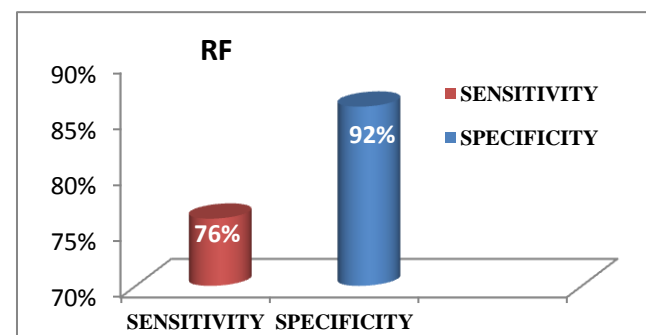
Anti CCP	Sero Negative (RF-ve) RA(12)
Positive	6
Negative	6

50 % of seronegative arthritis cases are positive for anti CCP.

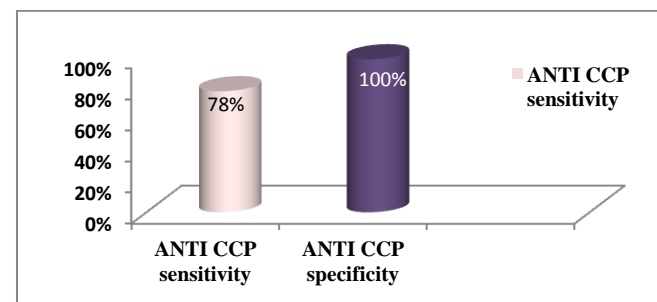
**Chart – I Anti-CCP& RF Test Results**



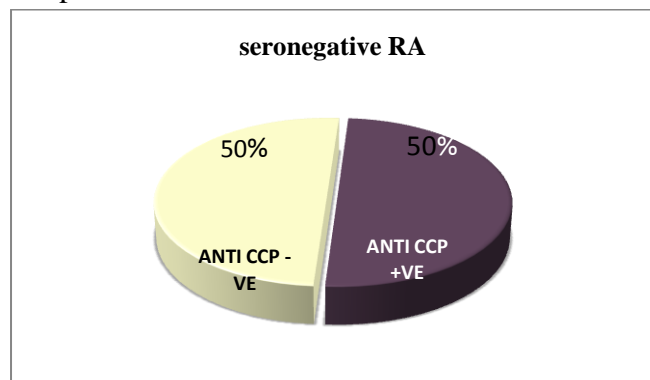
**Chart 2 Sensitivity & Specificity of RF Test in RA**



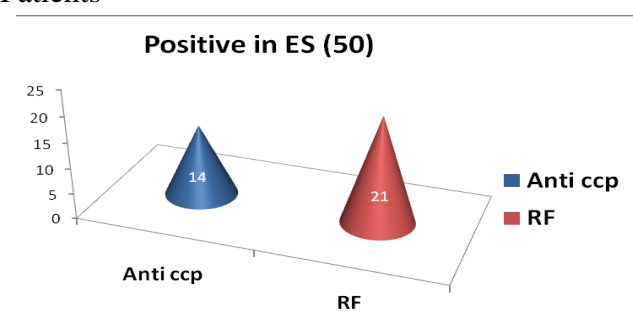
**Chart 3 Sensitivity & Specificity of Anti CCP Test in RA**



**Chart – 4** Use of Anti CCP Test in Sero Negative RA patients



**Chart-5** Anti CCP & RF Test Results in ES Patients



## DISCUSSION

The modern trend in management of RA is to start the treatment as early as possible, based on the concept that early control of inflammation results in reduced joint damage.

In recent research by Schellekens GA,<sup>17</sup> he has observed the diagnostic significance of a novel RA specific autoantibody, determined by ELISA using synthetic peptides containing citrulline. In this present study Anti CCP test results suggest the significance of anti CCP positivity in diagnosis of RA & early prediction of the disease. To minimize the errors patients were selected according to the inclusion criteria's.

### Age/Sex distribution

**Age:** In RA age group 51-60 years were more affected. In ES 31-40yrs & 41-50yrs. The incidence in both is very low in age group of 20-30 years.

**Sex:** M/F ratio - in RA - 1: 2.33, in ES1: 2.57. Males are less affected than the females in both.

### Sensitivity of RF in RA

On analyzing the sensitivity of RF, the present study shows 76% sensitivity in RA patients. This goes in parallel with the study by Lee and Schur et al<sup>24</sup> who found a sensitivity of 71.6% for RF.

The findings of the present study is comparable with the findings of the previous studies by Ulrich Sauerland et al<sup>24</sup> with 69.7%.

But in the studies by, Sibel Altun et al<sup>5</sup> 60%, K.P. Machold et al<sup>19</sup> 55% sensitivity, Nehir Samanci et al<sup>11</sup> 44.8%. Sensitivity for RF was higher in the present study than the previous studies. This discrepancy may be due to method of selection of cases, and type of kits used for testing.

In contrast a study by Dubucquoi *et al.*<sup>24</sup> showed 94% sensitivity for RF which is higher than the present study. The controversy may be due to low sample size, and short period of study.

### Specificity of RF

In the present study specificity of RF was 92%, which is in consistent with the study by Sibel Altun et al<sup>5</sup> 86.4%. But a study by Lee and Schur<sup>24</sup> 80.3% which is lower than the present study. But in Dubucquoi *et al*<sup>24</sup> study 53% only. The indifference may be due to small sample size because the study was carried out as a cross sectional study which included different groups, and also may be due to short duration of study.

### Specificity for Anti-CCP

In the present study specificity for anti-CCP is 100%, which is similar to the study by Münevver Serdaroflu et al<sup>25</sup> 100%. By Sibel Altun et al<sup>5</sup> with 98.6%. Gerard A. Schellekens et al<sup>8</sup> showing 98%, and Dmitry Karayev et al<sup>39</sup> 97%. Lee and Schur<sup>24</sup> observed 90%.

This discrepancy may be due to sample selection criteria's and type of kits used for testing.

### Sensitivity of both RF & Anti CCP antibody

In the present study both RF and Anti-CCP are positive in (66%) RA patients. The results are comparable with the study by Sibel Altun et al<sup>5</sup> - 59.3% positivity. This value is higher than the study by Schellekens et al<sup>5</sup> (39%) This may be due to prompt selection of cases in the present study and using advanced type of kit.

**Anti-CCP or RF Positive (any one +ve)**

In the present study (88%) which is higher than the study by Bizzaro et al<sup>5</sup> who reported 31.6% positivity in RA patients.

**Specificity of both Anti CCP & RF**

The present study results were higher than the study by Sibel Altun et al<sup>5</sup> who showed 98.6% for both tests positive in combination.

**RF –ve (sero negative)**

In the present study 6 of 12 (50%) sero negative patients were positive for anti CCP, this goes in parallel with Eric-Jan J. A. et al<sup>14</sup> study which showed 43% anti CCP positivity., Kroot EJ, and a Vallbracht et al,<sup>16</sup> 40% of which substantiates the additional diagnostic potential of Anti CCP in seronegative patients also. In another study by Quinn et al<sup>18</sup> 60%, which is higher rate than the present study.

Gerard A. Schellekens et al<sup>8</sup> study shows 35%. Even though the % is less, it also showed the anti CCP positivity in seronegative patients signifies the diagnostic potential of anti CCP which will help in treating the undiagnosed or missed diagnosis (seronegative) cases of RA and can prevent the post sequelae.

If positive, the anti-CCP test is an important surrogate marker especially for RF-negative RA.

**ES**

In present study 14 of the 50 ES patients were positive for Anti CCP and 21 of 50 were +ve for RF. A study by Sibel Altun et al<sup>5</sup> Bizzaro et al. and Visser et al.<sup>5</sup> also showed that a strong correlation was observed between Anti-CCP and RA and in ES patients. Jansen et al<sup>5</sup> study revealed a sensitivity of 55.4% and a specificity of 96.7%. In dubucquoi and colleagues<sup>24</sup> study the sensitivity was 65% (at 96% specificity).

In a study by Vangalen<sup>17</sup> 83% of anti CCP positive patients, and study by viteuco et al 90%, at base line fulfilled the ACR criteria after 1 year follow up. In Vangalen study 93% fulfilled the ACR criteria after 3 years follow up.

The above studies signifies that the Anti CCP is of more value in early diagnosis of Rheumatoid arthritis especially in ES patients even before the

symptoms appear. So anti CCP positivity (biomarker) in ES helps as an early predictor in diagnosing (future) RA.

**SUMMARY**

In the present study, Anti CCP anti bodies in Rheumatoid Arthritis and early synovitis (in sero negative for RF) were assessed and also in healthy blood donors as control.

Anti-CCP antibodies determination, proved to be a powerful diagnostic tool, especially in sero negative (RF negative) in Early Synovitis patients also. This confirms its importance in the discrimination of early diagnosis of RA in undifferentiated arthritis.

Even though RF is equally sensitive as Anti CCP in RA, it is less specific when compared with Anti CCP. Anti-CCP testing combined with RF testing has additional value over RF testing alone in patients with early undifferentiated arthritis.

**CONCLUSION**

Anti CCP antibody is a very valuable serological indicator in diagnosis of RA. Besides being a specific marker in advanced RA, the anti CCP antibody in ES & sero negative RF is a very important predictor (diagnostic marker) of RA. And helps in detection (not missing the diagnosis) of RA, very early in course.

Anti CCP has the hallmark of establishing as a diagnostic tool and provides additive sensitivity to RF. The presence of both RF and Anti CCP in serum is a strong indicator of RA.

In conclusion, based upon the higher sensitivity and specificity of the Anti CCP test in RA, the current study is of diagnostic, and public importance, because it suggests that Anti CCP test should be included in the investigation of undifferentiated arthritis, since a considerable amount of Rheumatic disease associated work, disability starts in the first few years of the disease.

Anti-CCP antibodies have all the hallmarks of establishing themselves firmly in the diagnostic algorithm of Rheumatoid Arthritis providing



additive sensitivity to Rheumatoid Factor. So it should also be included among the diagnostic criteria of RA along with RF.

It can also be used as a prognostic indicator in RA patients on treatment.

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## ANNEXURE INCLUSION CRITERIA

### Early Synovitis

- Patients with complaints of joint pain. (Synovitis - joint pain, blotted feeling, redness, fever for > 6wks & < 12 months duration.)<sup>5,18,19</sup>
- Joint pain with no h/o injury or sepsis<sup>1</sup>
- Without any bony deformity.
- Not already on treatment for RA.

(Inclusion<sup>19</sup> of patients fulfilling  $\geq 2$  clinical and  $\geq 1$  laboratory criterion and duration of symptoms  $\leq 12$  weeks.

### Clinical

Absence of trauma, Joint swelling in at least 1 joint, Joint pain in at least 1 joint, Morning stiffness > 60 minutes.

### Laboratory:

Positive Rheumatoid Factor, ESR > 20 mm/h & CRP > 5 mg/L

### Healthy Blood Donors:

Healthy persons without any infection, or any communicable diseases.

### RA:

RA patients were selected according to the ACR (American College of Rheumatology) criteria<sup>14</sup>. Criteria a–d must be present for at least 6 weeks. To diagnose as RA any 4 of the below should be present.

a. Morning stiffness	Stiffness in and around the joints lasting 1 hr before maximal improvement
b. Arthritis of three or > joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarso phalangeal joints)
c. Arthritis of hand joints	Arthritis of wrist, metacarpo phalangeal joint, or proximal interphalangeal joint.
d. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body.
e. Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician
f. Serum RF	Positive serum Rheumatoid Factor
g. Radiographic changes	Typical changes of RA on postero anterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

## EXCLUSION CRITERIA

**RA:** If does not fit in to the ACR criteria.

### Early Synovitis

- Complaints of joint pain (synovitis < 6wks & > 12months)
- Joint pain with h/o injury or sepsis.<sup>5</sup>
- With bone and joint deformity.
- Already on treatment for RA.

**HBD:** Persons with any infection, or communicable diseases.