Comparison of Anti CCP Positivity in RA and Other Arthritic Patients Including Connective Tissue Disorders

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Abstract

Rheumatoid Arthritis (RA) is the most common systemic inflammatory, Auto immune Rheumatic disease of unknown etiology. Although the precise aetiology of RA remains unknown, there is strong evidence for autoimmunity, The present study is to evaluate the significance of AntiCCP antibodies in Rheumatoid Arthritis and to compare it with other Connective Tissue Disorders (CTD including SLE, and Osteo Arthritis (OA) and in Healthy Blood Donors as Control. From January 2016 to December 2016 a total number of 200 (each group50) subjects including both males and females were studied. Anti-CCP was positive in 39 of 50 RA patients (78%), 2 of 50 (4%) CTD (SLE) cases and none were positive among(50) OA and (50) HBD, Sensitivity and Specificity of AntiCCP test was 78% & 98.6% respectively and RF test results were positive in 38 of 50 RA patients (76%) 11 of 50 (22%) - CTD including SLE patients , 6 of 50 (12%) - OA patients and 4 of 50 (8%) - of HBD. Sensitivity and Specificity of RF test in RA was 76% and 86% respectively. In conclusion, based upon the higher sensitivity and specificity of the Anti CCP test in RA than other Connective Tissue Disorders including SLE, shows its significant association with RA. Thus it helps in distinguishing RA from other erosive disorders and excluding them from RA.

Keywords

Anti CCP positivity, Arthritic patients, Tissue disorder.

Introduction

Rheumatoid Arthritis (RA) is the most common systemic inflammatory, auto immune Rheumatic disease of unknown etiology, affecting nearly 1% of the adult population worldwide. Although the precise aetiology of RA remains unknown, there is strong evidence for autoimmunity, since several auto antibodies are associated with the disease.

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. The disease occurs 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. Genetic studies have demonstrated that a genetic predisposition resides in the HLA-DR locus. For decades, RA is diagnosed primarily according to clinical manifestations based upon ACR criteria, in which the only serological marker is RF test. Rheumatoid factor (RF) is an antibody directed against the Fc region of IgG that has been used as a diagnostic marker for Rheumatoid Arthritis, and is recommended as a screening test and can be
detected in up to 80% of RA patients\textsuperscript{6,17}. However it is nonspecific\textsuperscript{16} and may be present in 5-10 % of healthy elderly persons or in patients with other autoimmune and infectious diseases\textsuperscript{2,6,11}.

So it is therefore crucial to have a reliable and specific test to identify the RA\textsuperscript{17}. The other most specific auto antibody system for RA is the family of auto antibodies directed to Citrulline–containing proteins, including antiperinuclear factor (APF) in\textsuperscript{1964}\textsuperscript{7}, antikeratin antibodies (AKA) in\textsuperscript{1979},\textsuperscript{7} antifilaggrin antibodies (AFA) and anti-Sa\textsuperscript{3,7,11}. Because of rigorous technical requirements for their detection, they have never been widely used as markers despite their high specificity\textsuperscript{3,6}.

Recently, a new serological test (biological marker)\textsuperscript{20} the anti-Cyclic Citrullinated Peptide (anti-CCP)\textsuperscript{2,20} was developed\textsuperscript{6}.

Citrulline is formed by deamination of arginine residues in several proteins by the action of enzyme peptidyl arginine deiminase (PAD)\textsuperscript{6,7,16,21,20} which is present abundantly in inflammatory synovium & proteins such as fibrin\textsuperscript{6,7}. Citrullinated extracellular fibrin in the RA synovium may be one of the major autoantigens driving local immune response suggested by the discovery of local production anti – CCP antibodies in the joint.

The high specificity of anti-CCP in patients with RA can exclude other rheumatic or immune diseases,\textsuperscript{6,7,9} (like SLE & OA). So it is useful in diagnosis as well as exclusion of RA.\textsuperscript{24}. Hence the study.

**Materials and Methods**

**Study design**

This is a combined Cross Sectional & Case Control study

**Study subjects**

The total numbers of subjects in this study for evaluation were 200, which included both male and female patients who attended the Out Patient Clinics at the Rheumatology and Orthopaedics Department and Healthy Blood Donors who attended the Blood bank, Thanjavur Medical College Hospital, Thanjavur. This study period extended from January 2016 to December 2016.

The study subjects, in both genders were divided into four groups. Each group include 50 patients.

Three groups (Rheumatoid Arthritis (RA), Connective Tissue Disorders including Systemic Lupus Erythematosus (SLE), Osteo Arthritis (OA) are based upon the clinical and fourth group is healthy individuals (blood donors) as control conditions (inclusion and exclusion criteria’s in annexure).

**Sample**

3-5ml of Venous Blood was collected aseptically, Serum was separated and stored at 2-8\textdegree C, if delay at – 20\textdegree C.

**RF Test -Rheumatoid Factor**\textsuperscript{14}

Method of Detection: Serological test by the latex agglutination\textsuperscript{15} slide test.

**Principle**

Human globulin IgG is coated with latex particles. Serum was mixed with latex reagent. Agglutination appears if the sample is positive for Rheumatoid factor. Negative if no agglutination appears and remains as smooth suspension. (Latex coated with IgG + serum = IgG antibody binds with IgG & cause latex particles to flocculate.) It is a rapid qualitative slide test.
Also tested both Positive control & Negative control

**Interpretation of results**

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

**Anti CCP test**

Anti-CCP antibody was detected by ELISA technique 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°C / -20°C

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

**Results**

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

Samples with OD ≤ OD (optical density) of 6.25U/ml Standard are Negative. The results obtained were tabulated and analyzed.

**Results and Discussion**

In the present study carried out on patients having various arthritic diseases,

**Age wise distribution**

In RA was more in the age group of 50-60yrs, in SLE in 30-50yrs in OA in 40-50yrs.

**Sex wise distribution**

M/F ratio – RA -1:2.33, CTD– 1:2.12, OA – 1:2.84.

Age/sex distribution of various arthritic diseases male were affected < than female

**Anti-CCP**

It was positive in 39 of 50 (78%) RA patients, 2 of 50 (4%) CTD (SLE) cases, and none were positive among (50) OA and (50) HBD.

**RF test**

Positive in 38 of 50(76%) RA patients, 11 of 50 (22%) - CTD including SLE patients, 6 of 50(12%) - OA patients and 4 of 50 (8%) - of HBD (Table 3).

**Sensitivity and specificity of RF test**

For R A (RF Positive in RA -38, NON RA 17) was 76% and 86% respectively (Table 2).

**Sensitivity and specificity for Anti CCP test**

For RA was 78% and 98.6 % respectively (Table 2)

**Sensitivity, specificity, PPV and NPV of Anti CCP and RF tests in RA**

Sensitivity, Specificity, PPV & NPV of Anti CCP - 78%, 98.6%, 95.1% & 93%

RF - 76%, 86%, 64.4% & 91.4%.

Anti CCP & RF - 66%, 98.6%, 94.2 % & 89.7%.

ANTI CCP / RF - 88%, 86%, 67.7% & 95.5%.

RA is associated with only a few specific auto antibodies, including APF, AKA and anti-CCP and several less specific auto antibodies including RF. Despite a well-documented lack of specificity, RF continues to be a serological test for RA because of its...
inclusion in ACR criteria. However to date no single autoantibody has demonstrated adequate positive diagnostic value to form the basis of clinical decisions. So auto antibodies present in RA, connective tissue disorders including SLE and OA have been evaluated in the present study, mainly for their diagnostic value, and to differentiate various arthritic diseases.

In recent research by Schellekens GA,\textsuperscript{17} 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 and differentiating RA from other arthritis. To minimize the errors patients were selected according to the inclusion criteria’s. Of all the above different Rheumatological diseases (SLE and OA), Anti CCP was more sensitive and more specific for RA, whereas RF was almost equally sensitive but less specific than Anti CCP for RA, because it is positive in other arthritic diseases and healthy persons also (Table 4 and 5).

**Age/Sex distribution of various Arthritic diseases**

**Age**

The incidence of all types of arthritis is very low in age group of 20-30 years.

**Sex**

M/F ratio - Males are less affected than the females in all arthritic diseases.

**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 \textit{et al.},\textsuperscript{24} who found a sensitivity of 71.6% for RF.

But in the studies by Munever Serdaroflu \textit{et al.},\textsuperscript{25} 65% sensitivity, Sibel Altun \textit{et al.},\textsuperscript{5} 60% sensitivity, Machold \textit{et al.},\textsuperscript{19} 55% sensitivity, Nehir Samanci \textit{et al.},\textsuperscript{11} 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 \textit{et al.},\textsuperscript{24} 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 86%, which is in consistent with the study by Sibel Altun \textit{et al.},\textsuperscript{5} which showed the specificity of RF as 86.4%. But a study by Lee and Schur\textsuperscript{24} observed specificity of 80.3% which is lower than the present study. But in Dubucquoi \textit{et al.},\textsuperscript{24} study the specificity of RF was 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 98.6%, which is similar to the study by Sibel Altun \textit{et al.},\textsuperscript{5} with 98.6%. The present study goes in parallel with the previous studies by Bizzaro \textit{et al.},\textsuperscript{5} & Gerard A. Schellekens \textit{et al.},\textsuperscript{8} both showing 98, and Dmitry Karayev \textit{et al.},\textsuperscript{39} 97%. Lee and Schur\textsuperscript{24} observed 90%. But the studies by Nehir Samanci \textit{et al.},\textsuperscript{11} 99%, and Munever Serdaroflu \textit{et al.},\textsuperscript{25} 100%
which was higher than the present study. This discrepancy may be due to sample selection criteria’s and type of kits used for testing.

**Sensitivity of both RF and 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.*, 5 - 59.3% positivity. This value is higher than the study by Schellekens *et al.*, 5 (39%) In contrast a study by Dmitry Karayev *et al.*, 39 showed 99.6% sensitivity.

This may be due to prompt selection of cases in the present study and using advanced type of kit.

| CATEGORY | Anti CCP Positivity | RF Positivity |
|----------|---------------------|--------------|
| RA (50)  | 39 (78%)            | 38 (76%)     |
| CTD (50) | 2 (4%)              | 11 (22%)     |
| OA (50)  | 0                   | 6 (12%)      |
| HBD (50) | 0                   | 4 (8%)       |

| TEST | Anti CCP Positive | Anti CCP Negative | Total |
|------|-------------------|-------------------|-------|
| RA(50) | 39               | 11                | 50    |
| Non RA (150) SLE+ OA + HBD | 2               | 148               | 150   |
| Total | 41               | 159               | 200   |

Sensitivity: 78%, Specificity: 98.6 %

| Anti CCP positive | In RA patients n = (50) | SLE n = 50 | OA n = 50 | Control groups (HBD) n = 50 |
|-------------------|-------------------------|------------|-----------|-----------------------------|
| RF positive       | 33 (66%)                | 2 (4%)     | 0         | 0                           |
| RF negative       | 6 (12%)                 | 0          | 0         | 0                           |

| Anti CCP negative | In RA patients n = (50) | SLE n = 50 | OA n = 50 | Control groups (HBD) n = 50 |
|-------------------|-------------------------|------------|-----------|-----------------------------|
| RF positive       | 5 (10%)                 | 9 (18%)    | 6 (12%)   | 4 (8%)                      |
| RF negative       | 6 (12%)                 | 39(78%)    | 44(88%)   | 46 (92%)                    |
Table 5  Sensitivity, specificity, PPV and NPV of anti CCP and RF tests

| Tests             | Sensitivity % | Specificity % | PPV Test % | NPV Test % |
|-------------------|---------------|---------------|------------|------------|
| Anti CCP          | 78            | 98.6          | 95.1       | 93         |
| RF                | 76            | 86            | 64.4       | 91.4       |
| ANTI CCP & RF     | 66            | 98.6          | 94.2       | 89.7       |
| ANTI CCP / RF     | 88            | 86            | 67.7       | 95.5       |

Chart 1  Anti-CCP & RF test results in all arthritic groups and HBD

Chart 2  Sensitivity and specificity of RF Test in RA

Chart 3  Sensitivity and specificity of anti CCP Test in RA
**Chart.4** Distribution of positivities of Anti CCP and/or RF on the groups

**Chart.5** Sensitivity, specificity, PPV and NPV of Anti CCP and RF tests
Colour Plate.1 RA test kit with reagents

Colour Plate.2 RA test result

Colour Plate.3 Anti CCP Test Kit  Colour Plate.4 Anti CCP Test Reagents
**Colour Plate.5** Anti CCP Test Procedure

5a. Diluted Samples

5b. Test Procedure

5c. Results

### Inclusion Criteria

| 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, metacarpo phalangeal, 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. |
Interpretation of results

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

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

In the present study (88%) which is higher than the study by Bizzaro et al.,\(^5\) who reported 31.6% positivity in RA patients (Table 1).

Specificity of both Anti CCP & RF

The present study results were similar with the study by Sibel Altun et al.,\(^5\) who showed 98.6% for both tests positive in combination.

Anti CCP in CTD (SLE)

In CTD including SLE only (4%) which is similar to the study by Sibel Altun et al.,\(^5\) (4%). In another study by Medivake et al.,\(^5\) (1.2%). Ulrich sauer land \(^24\) and a recent article by Gottenberg et al.,\(^24\) also confirmed the lesser prevalence of anti CCP in SLE.

In a study by RDL \(^10\) 9.7%, In contrast O Kasapcopur et al.,\(^28\) study showed absence of anti-CCP antibody which is also not in agreement with the present study.

The indifference might have overcome if the study was carried with large sample size, and for a period of long duration.

RF in SLE

Likewise in the present study with SLE- RF was positive in (22%) which goes in parallel with the study by Sibel Altun et al.,\(^5\) -20% positivity. This indicates that anti-CCP antibody assay can be a useful indicator in differentiating SLE from RA than RF test.

Other Arthritis (OA) and HBD

The present study results showed none of the OA and Healthy Blood Donors had positive Anti-CCP values which is in positive correlation with the study by Sibel Altun et al.,\(^5\).

Another study by Nehir Samanci et al.,\(^11\) showed (1.2%) which is not in consistent with the present study. Absence of anti CCP antibodies in OA and HBD signifies its specificity in RA and will help in excluding them from RA.

In the present study RF was positive in (12%) OA patients and in (8%) HBD (all were anti CCP –ve), which goes in agreement with the study by Sibel Altun et al.,\(^5\) (10%) in OA patients and 10% in HBD. The result denotes the non-specificity of RF.

Another study by Nehir Samanci et al.,\(^11\) shows 44.8% RF positivity in OA cases and 4.8% in controls which is higher than the present study. This disparity of the results could be due to age mis- matched controls and small sample size (due to categorization of subjects into many groups). An ideal control population would have been an age-matched normal control population. In the present study, Anti CCP anti bodies in Rheumatoid Arthritis and other arthritis (SLE patients &OA) patients were assessed along with healthy blood donors as control.

The anti CCP test shows high positive rate in RA patients than other arthritic disease...
patients, and negative in OA and Healthy Blood Donors. This reconfirmed the better specificity of anti CCP test in RA and thus it can be used as a diagnostic tool.

Since Anti CCP positivity is very low in SLE it helps in differentiating RA from other connective tissue disorders including SLE patients.

Anti CCP was negative in OA and HBD. So it will be useful in excluding these cases from RA.

Even though RF is equally sensitive as Anti CCP in RA, it is less specific when compared with Anti CCP.

**Limitation**

A large sample size, and a longitudinal study with periodical follow up will definitely be of greater value in prediction of anti CCP positivity.

**Future scope of the present study**

The study can be further extended to involve different types of kits to test their sensitivity and specificity, for better prediction. Hope further research will reveal the significance of protein citrullination in the immunopathology of RA.

The ACPA era has just begun, and is creating a revolution in Rheumatology. As per the findings of the present study AntiCCP test is more sensitive and highly specific. AntiCCP antibody is a very valuable serological indicator in diagnosis of RA.

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.

**Inclusion criteria**

RA: According to the ACR (American College of Rheumatology) criteria\(^ {14}\). Criteria a–d must be present for at least 6 weeks. To diagnose as RA any 4 should present.

**CTD (SLE)**

Arthritis along with vasculitis, Photosensitivity & Malar rash

OA: Joint pain with no h/o injury or sepsis. Brief morning stiffness (< 30 mts)

Localised pain aggravated by use & relieved by rest. No symmetrical involvement of joints.

**Healthy blood donors**

Healthy persons without any infection, or any communicable diseases.

**Exclusion criteria**

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

CTD: Bony deformity without vasculitis.

OA: Joint pain with h/o injury or sepsis & Joint pain at rest.

HBD: Persons with any infection, or communicable diseases.

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