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Research Article

ANTI CCP AND RHEUMATOID FACTOR IN RHEUMATOID ARTHRITIS – CLINICAL AND RADIOLOGICAL SIGNIFICANCE

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A B S T R A C T

Objective : To estimate anti CCP titres, rheumatoid factor, CRP in rheumatoid arthritis and correlate with disease activity and joint erosion. **Methods**: 100 patients with history of pain selected for study for a period of two years, 50 were of rheumatoid arthritis and the rest were of non-specific and inflammatory arthritis. Clinical assessment with radiology done coupled with serological estimations of CReactive Protein, Rheumatoid Factor and anti-CCP titres. **Results**: The sensitivity and specificity of anti-CCP reactivity for the diagnosis of rheumatoid arthritis were 70.3% and 92.4%, respectively whereas, the sensitivity and specificity of Rheumatoid Factor for RA were 68.6% and 80.2%. Furthermore, 4 seronegative patients with RA demonstrated reactivity to CCP. The presence of either anti-CCP or RF increased testing sensitivity for diagnosis of RA to 77.6%;the presence of both RF and anti-CCP demonstrated a testing specificity similar to that of anti-CCP reactivity alone for the diagnosis of RA (93.1%).**Conclusion**: The detection of anti-CCP is useful for the diagnosis of RA, even more than RF because of its higher specificity . Combination of anti CCP , RF and ultrasonography helps in diagnosis of RA , evaluating the severity of disease activity and joint affection .

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic joint inflammation that ultimately leads to joint destruction.RA affects approximately 1% of world's population.The morbidity and mortality it causes are a consequence of local and systemic inflammatory processes that damage cartilage, bone and soft tissue, as well as blood vessels and viscera. Until recently, treatment for RA was limited, and severe joint damage and overall debility were common.(Afzal N et.al 2011)

Early and aggressive intervention with new and effective biological treatments can alter the course of the disease, lengthen life, and improve function. The diagnosis of RA depends on clinical and serological findings. Although 50-90% of patients with rheumatoid arthritis are positive for rheumatoid factor (RF) ; specificity for RF tests are relatively poor. Serological studies form a cornerstone of laboratory based patient assessment in rheumatology. The presence of RF was identified in patients with RA over 50 years age; assays for RF remain one of the American College of Rheumatology (ACR) classification criteria for RA. (Niewold TB et.al 2007)

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The RFassay, in its current manifestation, remains suboptimal as a diagnostic test, as it lacks sensitivity (54–88%) and specificity (48–92%); it is present frequently in many other disease states (reviewed by Shmerling and Delbanco, Carson,and Bridges), and its incidence increases with age.Although RF significantly predicts worse outcome from both functional status and radiographic joint destruction standpoints, there is substantial room for improvement in predicting disease severity.RF is found in other autoimmune diseases , infectious diseases and some healthy individuals.(Shmerling RH, Delbanco TL 1991) (CarsonDA 1997) (Bridges SL 2001)

Consequently, search for better diagnostic markers with improved specificity ensued.Antiperinuclear factor and antikeratin antibodies identified by immunofluorescence found to have specificity close to 90% for RA but testing for these autoantibodies has never become popular. They react to citrullinated form of filaggrin. Synthetic cyclic citrullinated peptide (CCP) variants also react with anti-filaggrin autoantibodies and serve as substrate for detecting anti-CCP antibodies serologically; whose improved specificity is reflected in many studies. (Niewold TB et.al 2007) (Hamad MB et.al 2014) Anti-CCP antibodies hold promise for earlier and more accurate diagnosis of disease, improved prognostic information, and have been implicated in RA pathogenesis. A positive CCP antibody increases likelihood of more erosive disease in RA.Positive results for anti-CCP antibodies also

encountered in systemic lupus erythematosus and other connective tissue disorders. Anti- CCP scores over RF test for early and specific diagnosis of RA. Several studies have examined the performance characteristics of anti-CCP antibodies in RA, using both anti-CCP1 andanti-CCP2 assays. Sensitivity and specificity using the anti-CCP1 assay ranged from 44% to 56% and 90% to 97%, respectively. Detection of antibody with CCP2 assays resulted in improved sensitivity (64–89%), and specificity (88–99%). Rheumatoid factor sensitivity ranged from 59% to 79% and specificity from 80% to 84% in the same groups. Many patients in the study groups had both RF and anti-CCP antibodies, but a significant number had only one or the other. Some of the variability in the sensitivity and specificity between studies may relate to slightly different cut-off points for positivity, and differences in disease duration, severity and other clinical characteristics of the groups being tested. (Gao T et.al 2012) (Hamad MB et.al 2014) (Schellekens GA et.al 1998)

Anti CCP antibodies predate diagnosis of RA and can be found years before symptoms of RA develop. An early diagnosis would mean early administration of disease modifying anti rheumatoid drugs (DMARDs) with higher chances of remission. However, a negative CCP does not completely rule out RA. The key to therapeutic success lies in identifying subjects who will have severe destructive disease as early as possible to initiate therapy before any irreversible damage. (Schellekens GA et.al 2000)

METHODS

The hospital based prospective observational study included 100 patients suffering from pain; 50 were found suffering from rheumatoid arthritis and of the rest 50 ; 15 were of non-specific inflammatory arthritis, 5 of spondylitis, 20 of osteoarthritis, 5 of fibromyalgia and 5 of mechanical pain. The study period was two years and was conducted in a tertiary care hospital following approval from institutional ethical committee. The inclusion criteria being patients of middle aged people (30 – 55 yrs) suffering from joint pain and exclusion criteria being age below 30 yrs, suffering from chronic diseases. Clinical assessment made by questionarre and clinical examination done for assessing disease activity followed by radiological study (X-ray) and ultrasonography to look for status of joint involved. Serological estimations of C-Reactive protein (CRP), RF, anti CCP titres done .

CRP measured by immunoturbidimetry method and cut off value was 6mg/L. RF measured by immunoturbidimetry method and cut off value was 20 IU/ml. Anti CCP titres measured by enzyme linked immunosorbent assay method and the cut off value was 5 U/ml. Presence or absence of joint erosion seen from X-ray alongwith narrowing of joint space, if present.

Ultrasonography was done with Doppler study to look for presence of joint effusion and grading synovial proliferation. The sensitivity, specificity of RF and anti-CCP titres estimated enabling diagnosis of rheumatoid arthritis. The levels of CRP, RF and anti CCP titres correlated with joint damage evident from ultrasonography. Statistical calculations were performed with SPSS version 13.0 for Windows .

RESULTS

The mean age of patients suffering from rheumatoid arthritis was 43 years (lowest age being 30 years and highest age being 55 years) with mean duration of symptoms of six months and the female to male ratio was 4 : 1 (80 females and 20 males).

Among all patients; 40 patients showed CCP positivity and 34 showed only RF positivity. 58 patients showed high CRP levels . RF positivity found in 3/10 patients with negative anti CCP. RF negativity found in 4/15 patients with positive anti CCP. The lowest value for anti CCP antibody titre was 2.89 U/ml and highest 860.23 U/ml; cut off being 5 U/ml. The lowest value for RF was 6.89 IU/ml and highest value 987.65 IU/ml; cut off being 20 IU/ml. The lowest value for CRP was 4.73 mg/L and highest 83.47 mg/L; cut off being 6 mg/L.

Present study shows the sensitivity and specificity of anti CCP for diagnosing a case of RA as 70.3% and 92.4 % respectively with a positive predictive value (PPV) of 82.2 and negative predictive value (NPV) of 78.0.

The sensitivity and specificity of RF in diagnosing RA are 68.6 % and 80.2 % respectively with PPV of 75.4 and NPV of 72.6.

Table 1 Sensitivity and specificity of anti CCP , RF in RA.

	Sensitivity	Specificity	PPV	NPV
CCP	70.3 %	92.4%	82.2	78.0
RF	68.6%	80.2%	75.4	72.6
Either CCP/RF	77.6%	81.8%	79.2	71.4
Both CCP & RF	57.5%	93.1%	87.1	69.6

The presence of either RF or anti-CCP increased the sensitivity for detecting RA to 77.6 % with specificity for RA (81.8 %)when compared to that of RF (80.2%). But, on the contrary, presence of both RF and anti-CCP decreased sensitivity for diagnosis of RA to 57.5% and showing increase in specificity (93.1%) compared to anti CCP reactivity independently (92.4 %).

When the levels of reactivity of RF and CCP assays were compared ; however no substantial correlation found reflected by correlation coefficient being 0.36. There happens to be a direct correlation with the levels of CRP, RF and anti CCP titres with disease activity and status of joint. Active disease activity presented as red, swollen joint with restricted joint movement which is encountered with high positive CRP levels ($p<0.001$). High RF and high CCP levels of positivity show presence of synovial proliferation, joint effusion in ultrasonography.

High positive anti CCP titres with presence of synovitis while comparing those with absence of synovitis presents as 25.6% and 4.5%; with odd's ratio, 6.18; 95% confidence interval, 1.50-25.52; thus with $p<0.05$; statistically significant. Similarly, high positive RF values with presence or absence of synovitis presents 28.9% and 4.5%; with odd's ratio, 7.29; 95% confidence interval, 1.79 – 29.60; $p<0.01$; statistically significant. Higher the levels of serum RF and anti CCP ; more is the disease activity and more is the grade of synovial proliferation presented with high vascularity in power Doppler ultrasonography (PDUS).

DISCUSSION

Historically, the use of RF as a diagnostic tool for RA has been and remains problematic. Unfortunately, the latex fixation assay lacks specificity, being positive in many patients with various chronic disease states (reviewed by Shmerling and Delbanco, Carson, and Bridges). Although nephelometry, which also detected IgM anti-IgG RF, was technically more reproducible and easier to perform, it did not improve sensitivity (82%) or specificity (92%) for RA relative to latex agglutination. Subsequent characterisation demonstrated that much of the reactivity to these autoantigens was contained in citrulline containing regions of the antigens. Antibodies to citrullinated proteins can be detected by enzyme immunoassay, which is much more reproducible and easier to perform than the IF assays for perinuclear factor. (Shmerling RH, Delbanco TL 1991) (CarsonDA 1997) (Bridges SL 2001)

Initial studies using citrullinated peptide as substrate demonstrated a sensitivity of 76% and a specificity of 96% for RA. Subsequently, a modified assay was developed using CCP. This assay detected IgG antibodies to CCP in 68% of patients with RA. Although it had a somewhat lower sensitivity than the RF test, the specificity of anti-CCP for RA in that population was 96%—better than that previously reported in the RF test for RA –92%. This represented a great clinical diagnostic improvement.(Afzal N et.al 2011) (Bizzaro N et.al 2001)

Present study shows 80 % females compared to study by Lee D M *et al* who found 84% females. The mean age found in the present study is 43 yrs whereas in study by Lee *et al* found mean age of 57 yrs. Present study showed the highly specific nature of anti-CCP activity in patients with RA and correlated the presence of anti-CCP with erosive disease. High levels of anti CCP and RA are associated with severe disease activity and on ultrasonography, grade of synovial hyperplasia with vascularity and articular damage are directly proportional to increasing positivity of anti CCP , RF. (Chen HH et.al 2009)

The sensitivity and specificity of RF for RA in the present study is 68.6% and 80.2% respectively, compared to 71.6% and 80.3 % in study by Lee *et al*; 63% and 54% in study by Quinn *et al*; 67% and 79% in study by Chang P Y *et al*. The sensitivity and specificity of anti CCP for RA in the present study is 70.3% and 92.4 % respectively; compared to 66% and 90.4% in study by Lee *et al*; 84% and 93% in study by Quinn *et al* ; 79% and 98% in study by Chang P Y *et al*. Either RF/anti CCP shows a sensitivity of 77.6% in the present study comparable to 78% in study by Sun J *et al*; 85% in study by Chang P Y *et al*. Combination of RF and anti CCP for RA shows specificity of 93.1% in present study compared to 87.9% in study by Li H *et al*; 98% in study by Chang P Y *et al*; 96% in study by Sun J *et al*. (Lee DM et.al 2003) (Quinn MA et.al 2005) (Chang PY et.al 2016) (Sun J et.al 2014) (Li H et.al 2010)

Table 2 Comparative study of various authors

	RF		Anti CCP	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Lee *et al*	71.6%	80.3%	66%	90.4 %
Quinn *et al*	63%	54%	84%	93%
Chang P Y *et al*	67%	79%	79%	98%
Present study	68.6%	80.2%	70.3%	92.4%

Furthermore, both RF and anti-CCP are moderately strongly associated with articular erosions, suggesting that they reflect in some way the severity and progression of RA. Therefore we conclude that detection of anti-CCP is very useful for the diagnosis of RA, in fact even more so than RF, because of its higher specificity. Preliminary observations also suggest that the combination of testing for both RF and anti-CCP may be even more useful.

The results of this study demonstrate the anti-CCP antibody test to be both specific (92.4%) and sensitive (70.3%) for early RA patients when compared with non-specific arthritis controls. This is in agreement with previously published studies . An ideal control population would have been an age-matched normal control population. An alternative explanation may be the inclusion of patients with short disease duration; however, evidence suggests that anti-CCP antibodies precede RA by many years.

The high prevalence of anti-CCP positivity showed significant associations with both radiographic and functional outcome . Such findings are of practical importance for clinical decision-making in early disease. Prognostic assessment at the time of first presentation is crucial, particularly given the new early aggressive therapeutic approaches and the availability of expensive biological agents. Using anti-CCP antibodies would appear to select seronegative RA patients with poor prognosis and so may have important implications for patient management. In conjunction with the referenced studies, these findings may have a significant impact on the management of early arthritis patients.In this study, a low positive rate of anti-CCP antibodies was observed in the patients who had no ultrasonographic findings of synovitis. In contrast, a higher positive rate of anti-CCP antibodies was observed in the patients who had ultrasonographic features of synovitis. Accumulating evidence suggests that the immune response to citrullinated peptides could play an important role in the pathogenesis of synovitis in RA. The introduction of PDUS allows the detection of smaller degrees of synovitis with a reported accuracy equal to that of dynamic magnetic resonance imaging.(Chen HH et.al 2009)

Moreover, a significant correlation between the Doppler signal and the degree of vascularity of the synovial tissue has been reported. However, the absence of a Doppler signal does not exclude the possibility of synovitis, and the sensitivity for detecting Doppler signals has been shown to vary with different ultrasound devices. (Chen HH et. al2009)There is an association of ultrasonographic findings of synovitis with anti-CCP antibody and RF levels. Whether this association is consistent in each patient needs further longitudinal study.

CONCLUSION

Low sensitivity with high specificity of anti CCP antibodies indicate that positive result markedly increase the probability of patient having RA and high positive levels of anti CCP bears a direct relationship with severity in disease activity and synovial proliferation in involved joints. So, combination of anti CCP, RF and ultrasonography helps in diagnosis of RA , evaluating the severity of disease activity and joint affection .

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Nil.

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