Performance of Anticyclic Citrullinated Peptide Antibodies versus Rheumatoid Factor in diagnosis of Rheumatoid Arthritis

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Abstract

The aim of this study was to evaluate the performance of anti-cyclic citrullinated peptide antibodies (anti-ccp) versus Rheumatoid Factor (RF) in the diagnosis of rheumatoid arthritis in serum sample of patients with clinical manifestation of arthritis using ELISA technique.

One hundred and twenty patients with clinical presentation of rheumatoid arthritis and fifty apparently healthy individuals (25 males and 25 females) were enrolled in this study. The mean age of patients group and control was 36.45years versus 34.72 years .Among patients, males represented (8.3%) compared with (91.7%) of females. In control group males represented (52%) versus (48%) females.

There was a statistical significant difference ($p>0.05$) between patients and control group in RF and anti-ccp values. Eighty five percent of patients gave positive results for anti-ccp compared with (100%) negative results in control group. RF was detected in (41.66 %) of patients sera compared with (58.33 %) which gave negative results. RF ELISA gave negative results in (100%) of control group .

Only 10(8, 33%) out of 120 patients gave negative results in RF and anti-ccp ELISA, compared with 42(35%) out of 120 gave positive results in both tests. In 60(50%) out of 120 RA patients RF gave negative results and at the same time gave positive results when retested using anti-ccp ELISA .Only 8(6.66%) out of 120 RA patients gave negative result in anti-ccp ELISA technique and RF was detected in positive value.

The sensitivity of anti-ccp ELISA was (85%) versus (41.66%) for RF. The Specificity of anti-ccp ELISA was (55.55%) versus (14.28%) for RF. Positive predictive value for anti-ccp ELISA was 41.17% versus (84%) for RF. Negative predictive value for anti-ccp ELISA was 55.55% versus 14.28 for RF ELISA .False positive value in anti-ccp ELISA was 58.82% versus 16%for RF ELISA. False negative value in anti-ccp ELISA was 44.44% versus 85.71%for RF .

This study concludes that anti-ccp ELISA was more sensitive and specific in diagnosis of RA than RF ELISA technique.

Key words: RA, RF, Anti-ccp, ELISA, sensitivity, Specificity

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Introduction

Rheumatoid Arthritis (RA) is one of the most common systemic autoimmune diseases, affecting approximately 0.5–1.0% of the world population [1]. Historically the only serological test routinely performed for the detection of RA was for the presence of IgM RF. Rheumatoid factor (RF) is found in approximately 50%–90% of these patients, but it is also found in patients with infections, other autoimmune diseases, and some healthy individuals with increasing frequency in older age groups, thus limiting its specificity for RA.[1, 2]

Several studies have shown that anti-perinuclear autoantibodies, otherwise known as anti-keratin autoantibodies, are found in patients with RA[3].

It has been discovered that these antibodies recognize an epitope that contains the deamidated form of arginine called citrulline and such autoantibodies called anti-cyclic Citrullinated peptide (anti-CCP) antibodies.

The pathogenesis of anti-ccp antibodies in rheumatoid arthritis has been shown to be attributable to the body humeral response to citrulline. Citrullination is the post-translational conversion of arginine to citrulline by an enzyme called peptidylarginine deiminase (PAD). PAD activation is assisted by calcium ions. PAD is normally present as inactive intracellular enzymes. During apoptosis in the synovial joint of patients with rheumatoid arthritis, PAD may leak out of the dying cells. Once activated, PAD will cause citrullination of extracellular arginine. In the synovium, the citrulline acts as an antigenic stimulant to induce anti-Citrullinated protein antibodies (ACPA) locally produced by plasma cells [4] .The ELISA that detects these autoantibodies uses synthetic cyclical citrulline peptides[5].

Aim of the study:

To evaluate the performance of anti-ccp versus RF in the diagnosis of rheumatoid aarthritis in serum samples of patients with clinical manifestation of arthritis.

Patients And Methods

Patients selection

One hundred and twenty patients with clinical presentation of rheumatoid arthritis attended to outpatient clinic of Baghdad teaching hospital-rheumatology unit from September 2010 to January 2011 were chosen. All Patients were examined by rheumatologist and selection was according to criteria of the American Rheumatism association for the classification of RA which includes:

1) Morning stiffness 2) arthritis of 3 or more joint areas 3) arthritis of hand joints 4) symmetric arthritis 5) rheumatoid nodules 6) serum rheumatoid factor (RF) and 7) radiographic changes. A patient should have four of the seven criteria to be diagnosed with RA and the first four criteria should be present for at least six weeks [6].

The mean age of selected patients was 36.45 years with range (19-57) years .males represent (8.3%) and (91, 7%) were females. Fifty apparently healthy individuals (25 males and 25 females) with mean age 45years with range (16-61) years were enrolled in this study.

Methods:

Whole blood specimens were collected using acceptable medical techniques to avoid hemolysis. Blood clotting was allowed and the serum was separated by centrifugation. Test serum should be clear and non-hemolyzed. Specimens refrigerated at 2-8 °c for up to five days or stored at -20 °c up to six months[7].

Serum samples then used for determination of RF [8] and anti-ccp [9] using ELISA

technique according to manufacturer instructions.

The normal range of RF screening was 25U/ml. Elevated level of more than 25 U/ml usually associated with typical clinical presentation criteria of American Rheumatism association. For anti-ccp normal range was <12U/ml, equivocal range was 12-18U/ml and positive range was >18U/ml.

Statistical analysis:

Data were analyzed by SPSS for window TM version 17 and Microsoft Excel for windows 2007.

The level of significant was 0.05(two tails).

Results

This study includes (120) patients suffering from clinical manifestations of arthritis and (50) apparently healthy subjects. The mean age of patients group was 36.45years compared with 34.72 years in control group as shown in table(1)

Table 1: Patients versus control group demography.

Age (Year)	Patients (n=120)	Control (n=50)
Mean	36.45	34.72
Std. Error of Mean	0.95376	1.75547
Minimum	19	16
Maximum	57	61

Regarding gender of patients group, males represent only (8.3%) compared with (91.7%) which represent females. Among control group males represent (52%) versus (48%) females as shown in table (2).

The results of the present study found that the mean value of RF among control group was 12.04 U/ml with range 21 U/ml (2 U/ml -23 U/ml) compared with 61.18 U/ml with range 72 U/ml (26 U/ml -98 U/ml) among patients group. Regarding anti-ccp among control group the mean value was 8.44 U/ml with range 14 U/ml (0 U/ml -14 U/ml) compared with 27.8750 U/ml with range 58 U/ml (17 U/ml -75 U/ml) among patients group. There is a statistical significant difference p>0.05 between patients and control group in RF and anti-ccp values as shown in table (3).

As shown in table (4) 102 patients (85 %) gave positive results for anti-ccp compared with (100%) negative results for control group. RF was detected in (41.66 %) of patients sera compared with (58.33 %) gave negative results. control group gave negative results in 100% for RF.

Table (5) shown that among patients group only 10(8, 33%) out of 120 gave negative results for RF and anti-ccp, compared with 42(35%) out of 120 gave positive results for both tests. In 60(50%) out of 120 RA patients, RF was negative and anti-ccp was positive. Only 8(6.66%) out of120 RA patients gave negative result for anti-ccp ELISA and positive for RF.

Table (6) elucidates that in 120 RA patients the sensitivity of anti-ccp ELISA was (85%) v (41.66%) for RF ELISA. The specificity of anti-ccp ELISA was (55.55%) versus (14.28%) for RF ELIS .Positive predictive value for anti-ccp was 41.17% versus (84%) for RF. Negative predictive value for anti-ccp was 55.55% versus 14.28 for RF. False positive value in anti-ccp ELISA was 58.82% versus 16% for RF ELISA. False negative value in anti-ccp ELISA was 44.44% versus 85.71%for RF.

Table 2: Gender of patients and control group

Gender	Patients	Control
	No. (%)	No.(%)
Male	10 (8.3%)	26(52%)
Female	110 (91.7%)	24(48%)
Total	120 (100%)	50(100%)

Table 3: Descriptive statistics for RF and anti-ccp among patients and control group**.**

Parameters	RF		Anti-ccp	
	Control group	Patients group	Control group	Patients group
No.	50	120	50	120
Mean(IU/ml)	12.04	61.18	8.44	27.8750
Std. Error of Mean	0.75914	3.15267	0.50561	1.24918
Range(IU/ml)	21	72	14	58
Minimum(IU/ml)	2	26	0	17
Maximum(IU/ml)	23	98	14	75
P value	P<0.05		P<0.05	

Table 4: Results of anti-ccp and RF using ELISA in RA patients and control group.

Parameter	Patients (no=120)		Total No.(%)	Control (no=50)		Total No.(%)
	No.(%) of Positive Cases	No.(%) of Negative cases		No.(%) of Positive cases	No.(%) of Negative cases	
Anti-ccp	102(85 %)	18(15 %)	120(100%)	0(0%)	50 (100%)	50 (100%)
RF	50(41.66 %)	70(58.33 %)	120(100%)	0(0%)	50 (100%)	50 (100%)

Table 5: Results of Anti-ccp and RF using ELISA in RA patients

Anti-ccp	RF		Total
	negative	positive	
Negative	10(8, 33%)	8(6.66%)	18(15 %)
Positive	60(50%)	42(35%)	102(85 %)
Total	70(58.33%)	50(41.66%)	120(100%)

Table 6: Parameter of Anti-ccp and RF using ELISA in RA patients

Parameter	anti-ccp	RF
Sensitivity	85%	41.66%
Specificity	55.55%	14.28%
PPV*	41.17%	84%
PNV**	55.55%	14.28
False positive	58.82%	16%
False negative	44.44%	85.71%

*Predictive positive value
** Predictive negative value

Discussion

There is evidence that early intensive therapeutic intervention ("hit hard and early") in patients with RA may stop disease progression and joint damage, resulting in a better prognosis. It therefore is important to differentiate between RA and other forms of arthritis early after the onset of symptoms.(10)

In the present study the mean age of patients group was 36.45years compared with 34.72 years in control group .The result comes in agreement with that recorded by Huizinga and Pincus (2010)(11) they mentioned that the peaks of incidence of RA in 30s-40s of old . The present study recorded that the incidence of RA was higher in females (91.7%) compared with (8.3%) in males. this comes in agreement with that recorded by Huizinga and Pincus (2010)(12) ; Scott et al (2010) (13)they mentioned that the incidence of RA was 54/100000 among females compared with 25/100000 among males . Bridget et al (2010) (13) recorded that the majority of patients (83%) with RA under investigation were female, and the rest (17%) were males.

This study recorded negative detection (100%) of antibodies for RF and CCP in control group. a statistical significant difference ($p>0.05$) among patients and control group in RF and anti-ccp values .This result discordant to that reported by Swedler et al 1997(14) they mentioned that IgM RF, the isotype most typically detected, is seen not only in RA but also in up to 5-10% of healthy individuals. this may attributed to sample size that used in Swedler,s study .

Eighty five percent of patients with clinical manifestations of RA give positive results for anti-ccp compared with (41.66 %) for RF. anti-ccp was not detected in patients with clinical manifestations of RA in (15%) compared with (58.33 %) give negative results for RF. These results disagree with that recorded by Bridget et al (2010) (12), anti-ccp was detected in (82.5%), RF in (81.7%) while among control group anti-ccp was detected in (15.05%) and RF in (9.3%).

The results of the present study comes on agreement with several studies such that recorded by Schellekens et al in 1998(15), reported that antibodies reactive with synthetic peptides containing the unusual amino acid citrulline were present in 76% of RA sera. Furthermore, these antibodies displayed a specificity of 96% for RA. The antibodies in patients with RA that recognized the citrulline containing epitopes were predominantly of the IgG class and of relatively high affinity. Visser et al. (2002)(16) reported that In a sample group of 1020 sera with clinically confirmed RA (including 182 baseline sera), the sensitivity of the anti-ccp test was 78%. The RF IgM assay had a sensitivity of 74%. Not surprisingly, the specificity of the anti-ccp test was far superior to that of the RF test.

Visser et al. (2002) (16) reported that the strongest association with persistent arthritis was found for the criteria of symptom

duration and Anti-ccp positivity. Visser et al. (2005) (17) observed that anti-ccp antibodies can be detected very early in RA and as a marker appears to have a high prognostic value with good discriminating power between erosive and non-erosive RA.

The results recorded in the present study agree with that recorded by Griener et al (2005) (18) , they found that sensitivity (80%) and specificity (97%) while IgA RF sensitivity (63%) and specificity (94%) and IgM RF sensitivity (86%) and specificity (82%). It could be clearly shown that CCP ELISA provided the best combination of sensitivity and specificity for detecting RA with significant difference between the anti-ccp and RF. Griener et al (2005) (18) found that in 56.3% of the definite RA patients ,anti- ccp and RF were positive and in (11.5%) patients with clinically diagnosed RA, IgM-RF was negative. Griener et al (2005) (18) reported that in (40%) of IgM-RF–negative patients, anti-ccp tests were positive. Griener et al (2005) (18) reported that (10.3%) of patients with definite RA, anti-ccp was negative and in(11.11%) of these patients anti-citrulline was positive, in two patients IgA-RF was positive(22.22%) , and in (44.44%) patients IgM-RF was positive.

A very important finding from the data of patients was that anti-ccp is a highly specific marker in the diagnosis of RA. Comparable with the results of some other studies using the CCP assay, we found that sensitivity of anti-ccp ELISA was (85%) versus (41.66%) for RF ELISA. The Specificity of anti-ccp ELISA was (55.55%) versus (14.28%) for RF ELISA .positive predictive value for anti-ccp ELISA was 41.17% versus (84%) for RF ELISA.

The result of the present study discordant with that recorded by Bizaro et al(2001)(19) they found that the sensitivity of anti-ccp was (41%) and specificity was (98%), van Gallen et al (2005) (20) they reported that anti-ccp assays have high specificity(93%) and sensitivity (53.6%) this may reflect the difference in cutoff levels depends on assays and different patient populations. Suzuki et al (2003) (21) agree with results of our study, they reported that the sensitivity of anti ccp was (87%).lin et al(2008) (22) reported that Among patients with RA, (82.1%)of patients tested were positive for anti-ccp antibodies and , (80%) were positive for RF. The specificity was 88% and sensitivity (82%).

To explain the low sensitivity, it must be considered that anti-ccp antibodies are a heterogeneous group of antibodies directed against different epitopes on the citrulline molecule, that each patient's serum contains different subsets of antibodies, and that the synthetic peptide used in this assay represents a relatively small set of antigenic determinants that do not entirely encompasses the antigenic determinants present on the as yet unknown antigenic molecule in the joint (23).

The specificity is instead the most valuable aspect of this assay, and it may be proposed as the most important examination in the diagnosis of RA. The net and surprising difference in antibody concentration between anti-ccp positive and negative samples is noteworthy. Indeed, positive samples showed high antibody concentrations, with a mean value of 27.8750IU /ml (range=58 IU/ml), whereas negative samples were never higher than 8.44 IU/ml (range=14 IU/ml). This is the first study to report quantitative data on anti-ccp concentrations. Although our results require confirmation in larger studies, they show that a high antibody concentration is almost exclusively associated with RA.

It was interesting to evaluate anti-ccp and RF behavior in RA patients in relation to the

duration of disease. In patients with early arthritis (diagnosis made, 1 year before this study), the correlation with anti-ccp was highly significant, thus indicating that this assay may be used even in the early phases of disease. This aspect is important because an early diagnosis of RA may modify the therapeutic strategy substantially, suggesting the use of more aggressive pharmacological treatments that can delay the progression of joint damage and thus substantially change the natural history of the disease (24).Preliminary studies have demonstrated that the presence of anti-ccp antibodies also has a prognostic significance because it was shown that anti-CCP-positive patients develop significantly more severe radiologic damage than anti-CCP-negative patients (25). Therefore, serial assay of these antibodies could be useful in monitoring the clinical course.

We found low sensitivity (41.66%) of RF that disagree with Suzuki et al(2003)(21); Vallbracht et al (2004)(26) they recorded that sensitivity of RF-IgM isotype up to (65%). The lower sensitivity in those study cohorts may reflect the presence of a relatively high percentage of early rheumatoid patients and higher cutoff levels. The results of this study concordance with that recorded by schellekens et al (1998)(15) ;Lin et al (2008)(22) and kastbom et al(2004) (24);Vallbracht et al (2004)(26);Nielen et al (2005) (27) they reported that the frequency of anti-ccp antibodies in RF-negative RA patients near to 38%-40%. We could also find an additional diagnostic value of anti-ccp compared with RF; as in 60% of the seronegative (RF–negative) RA patients, anti-ccp antibodies were detected.

One of interesting points was the observation that all anti-CCP– positive patients had an articular disease manifestation. As it was shown that the anti-ccp antibody may precede the clinical manifestation of RA by many years, these patients may not have received false-positive results but may develop RA or have a clinically undiagnosed RA.

Lin et al (2008)(22) reported that positive predictive value, and negative predictive value of anti-ccp antibodies for diagnosing RA were 93.0%, and 71.7% respectively. Those for RF were 81.1%, and 61.0% respectively.

Lin et al(2008)(22) reported that the PPV of RF for RA (81.1%) was higher than that reported by Silveira et al (2007) (28) (56%); whereas the NPV (61%) was lower .The reason is that with RF, as with any diagnostic test, the predictive value is affected by the estimated likelihood of disease prior to conducting the test(29) . It has a lower PPV if the test is conducted among patients with non-RA rheumatic diseases (SLE, primary SS, and cryoglobulinemia) or few clinical features of systemic rheumatic disease.

In this study according to clinical presentation of patients under investigation agree with Rantapaa-Dahlqvist et al (2003) (30) ,they showed that anti-ccp and IgA-RF predict the development of RA, with anti-ccp having the highest predictive value of all tested antibodies (IgG-RF, IgA-RF, and IgM-RF and CCP). The value of anti-ccp and RF predicting the outcome of RA, clinical signs of disease activity, and the severity of radiographic joint damage.

As (60%) of patients under investigation was negative for RF and positive in anti CCP ELISA ,this result give great deal with that reported by Bas et al(31) and Vencovsky et al (2003) (32) ;chan et al (2008) (33) . showed an association of IgARF and anti-ccp with clinical signs of disease activity. The high prevalence of anti-ccp in RA patients with extensive disease activity and severe

radiological changes, and even more impressively in RA patients who are IgM-RF–negative, suggests that anti-ccp is more useful than the RF alone in the early prediction of disease outcome and disease activity.

In conclusion, anti-ccp antibodies have better diagnostic value than RF in diagnosing RA patients. This study recommended that anticcp must be used as a confirmatory diagnostic test in suspected cases of RA.

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