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CLINICAL STUDY

Prognostic value of anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis

Omer Kuru[1], Ayhan Bilgici[1], Asuman Birinci[2], Hasan Ulusoy[3], Belma Durupinar[2]

Ondokuz Mayis University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Samsun, Turkey. **ulusoyh@mynet.com**

Abstract: *Objectives:* To determine the predictive value for radiological damage of anti-cyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) in patients with rheumatoid arthritis (RA).
Methods: Ninety patients with RA were enrolled in this study. All patients had symptom duration of at least one year. Anti-CCP and IgM-RF were evaluated with enzyme linked immunosorbent assay and nephelometry methods, respectively. Radiological damage was assessed by Larsen score.
Results: In forward stepwise logistic regression analysis, anti-CCP positivity and RF positivity were seen as significant independent predictors of the radiological outcomes ($p=0.01$, $p<0.05$, respectively). The combination of these antibodies had the highest risk for erosive joint damage (odds ratio=25.71; 95% confidence interval, 4.7 to 140.13; $p=0.001$).
Conclusion: Our results suggest that the combined use of RF and anti-CCP has greater predictive value for erosive RA than anti-CCP or RF alone, and may facilitate to make a decision about the individual treatment in RA *(Tab. 4, Ref. 37)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: rheumatoid arthritis, anti-CCP antibodies, rheumatoid factor, radiographic damage, Larsen score.

Rheumatoid arthritis (RA) is a chronic, inflammatory disease of unknown cause. It has the potential to cause severe physical disability and shortens the average life expectancy. Joint damage accounts for a considerable part of the disability caused by RA. The most effective way to manage RA patients is early diagnosis and timely treatment with disease modifying antirheumatic drugs (DMARDs), which prevent the exacerbation of disease, reduce the probability of joint destruction, and improve the outcome (1–4). However, the course of RA is varied, ranging from mild to aggressive forms. Availability of better prognostic markers would make it possible to select predictably severe cases for aggressive therapy at an early stage, while at the same time avoiding unnecessary exposure of patients with mild disease. To be able to identify ,the right patient for the right treatment, good predictors are needed (5–9).

Antibodies against cyclic citrullinated peptide (anti-CCP) are a new and highly specific marker for RA. Anti-CCP antibodies are now considered as an important serological marker for the diagnosis of RA and as a possible prognostic marker for the development of erosive disease (2, 5, 10–17).

We investigated the radiological and clinical value of the anti-CCP and RF antibodies in a cross sectional study.

[1]Ondokuz Mayis University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Samsun, [2]Ondokuz Mayis University, Faculty of Medicine, Department of Microbiology and Clinical Microbiology, Samsun, [3]Gaziosmanpasa University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Tokat, Turkey

Address for correspondence: Hasan Ulusoy, MD, Cay mahallesi, Karahafiz sokak, No:37, 55500, Carsamba, Samsun, Turkey.
Phone: +90.362.8342702

Methods

We included 90 patients with RA fulfilling the American College of Rheumatology criteria for diagnosis (18). All patients had symptom duration of at least one year. Before study entry all patients gave their written informed consent.

Clinical evaluation of disease was based on the number of swollen joints, number of tender joints, the patient's global assessment of disease severity, pain on a 100 mm visual analog scale (VAS) and morning stiffness duration. Disease activity was assessed by the 28 joint disease activity score (DAS28). Functional disability was assessed using the Health Assessment Questionnaire (HAQ).

All patients had venous blood taken for full blood counts, erythrocyte sedimentation rates (ESR), renal and liver function, C-reactive protein (CRP) and plasma proteins.

Radiographic measurement

Standardized radiographs of hands were performed to calculate the Larsen score (19). Radiographic damage was scored using the Larsen score by one observer (A.B.) who had no knowledge of the clinical and laboratory data for each patient. In each case, 22 joints were scored: all metacarpalphalangeal joints (=10), all proximal interphalangeal joints (=8), both first interphalangeal joints (=2), and wrists (n=2) in the hands. Each joint was scored from 0 to 5. The Larsen score is the total sum of the grading in all 22 joints, ranging from 0 to 110. Joint damage was defined as present if Larsen score was 10 or higher, otherwise it was not present (1).

Antibodies to cyclic citrullinated peptide and rheumatoid factor

Serum antibodies directed to cyclic citrullinated peptide were

Tab. 1. The comparison of characteristics of patients with RA according to anti-CCP or RF positivity.

	Anti-CCP (n=90)			RF (n=90)		
	Positive (n=36)	Negative (n=54)	P value	Positive (n=48)	Negative (n=42)	P value
Age (years)	48.72±14.4	48.43±14.6	NS	53.93±13.29	43.83±13.95	0.01
Disease duration (years)	10.90±11.6	7.64±6.5	NS	7.49±6.07	10.22±10.84	NS
Pain VAS (100mm)	42.8±25.9	42.8±24.5	NS	46.0±26.0	40.0±24.0	NS
Patient's global evaluation	3.89±1.94	4.02±2.13	NS	4.79±1.82	3.25±1.97	0.001
CRP (mg/l)	32.12±37.83	27.19±34.41	NS	40.03±42.87	21.50±27.20	<0.05
ESR (mm/l)	42.85±28.0	33.44±24.12	NS	48.31±29.28	31.02±21.63	0.01
DAS28	4.24±1.34	3.95±1.24	NS	4.68±1.23	3.63±1.16	0.001
RF level	199.0±234.7	69.04±125.49	<0.01	–	–	–
HAQ score(0-3)	0.96±0.94	1.63±5.9	NS	1.07±0.94	0.66±0.69	<0.05
Larsen score (0-110)	22.94±21.87	16.11±24.04	NS	26.45±26.75	14.75±17.37	<0.05

VAS – visual analogue score, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, RF – rheumatoid factor, HAQ – health assessment questionnaire, DAS – disease activity score. NS – not significant, A p<0.05 was accepted as statistically significant.

analysed using the enzyme linked immunosorbent assay (ELISA). Results were expressed in R units. The samples were considered positive if the antibody titre was greater than 5 RU/ml. IgM-RF was determined by standard Berling nephelometry method and the result of 20 IU/ml was regarded as RF positive.

Statistics

Comparisons between two groups were performed using t--tests. Proportions were compared using the chi-square test. Pearson correlation coefficients expressed the relations between the assessed variables. A forward stepwise logistic multivariate regression analyses were used to estimate the best model for predicting developed radiological erosion. Odds ratios with 95 % confidence intervals were calculated. A probable p value of <0.05 was considered statistically significant. To assess the utility of the anti-CCP and RF antibodies in detecting for developed erosive disease, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Results

The mean age of the patients was 47.83±12.36 years, and the mean disease duration was 8.9±8.2 months. Forty-eight (53.3 %) of the all 90 patients were RF positive and 42 (46.7 %) were negative. Fifty-four (60 %) of the all patients were positive for anti-CCP antibody and 36 (40 %) were negative. Thirty patients (33.3 %) were positive for both anti-CCP and RF whereas 18 (20 %) were negative for both. In addition, 24 (57.1 %) of the 42 RF negative patients were anti-CCP positive, whereas 30 (62.5 %) of the 48 RF positive patients were anti-CCP positive.

The comparison of characteristics of patients with RA according to anti-CCP or RF positivity are shown in Table 1. Only one significant difference between anti-CCP positive or negative patients was RF level. The level of RF was significantly higher in anti-CCP positive patients than in anti-CCP negative patients (p<0.01). No statistically significant difference was found for the other clinical or laboratory variables between patients with and without anti-CCP antibodies. Although the Larsen score and ESR in anti-CCP positive patients were higher than in anti-CCP negative patients, the difference was not statistically significant. Additionally, no significant difference was found in terms of DAS28 and HAQ score between the anti-CCP positive and negative groups.

Tab. 2. Pearson correlation coefficients for Larsen score versus other parameters.

Variables	Larsen score	
	r	p
Disease duration	r=0.39	p<0.001
Patient's global assesment	r=0.31	p<0.01
Morning stiffness duration	r=0.25	p<0.05
Number of tender joints	r=0.27	p<0.01
DAS 28	r=0.23	p<0.05
HAQ score	r=0.34	p>0.05
ESR	r=0.28	p>0.05
Anti-CCP level	r=0.32	p>0.05
RF level	r=0.34	p<0.01

DAS28 – disease activity score 28, HAQ – health assessment questionnaire, ESR – erythrocyte sedimentation rate, Anti-CCP – anti-cyclic citrullinated peptide antibodies, RF – rheumatoid factor. p<0.05 was accepted as statistically significant.

On the other hand, Larsen score and DAS28 were significantly higher in RF positive patients than in RF negative patients as well as HAQ score (p<0.05, p<0.001, p<0.05, respectively). Moreover, significantly higher ESR, CRP and the patient's global assessment of disease severity were found in RF positive patients than in RF negative patients (p<0.01, p<0.05, p<0.001, respectively).

The radiological damage (Larsen score) correlated significantly with disease duration (p<0.001, r=0.39), the patient's global assessment of disease severity (p<0.01, r=0.31), morning stiffness (p<0.05, r=0.25), number of tender joints (p<0.01, r=0.27), and DAS28 (p<0.05, r=0.23) (Tab. 2). Anti-CCP level was not significantly correlated with radiological damage, whereas there was a positive correlation between RF level and radiological damage (r=0.34, p<0.01).

Tab. 3. Results of logistic regression analysis of anti-CCP and RF to predict erosive disease.

	Coefficient SE		Wald	P value	Odds ratio	95% CI
Duration of disease	0.077	0.029	6.992	<0.01	1.080	1.020–1.143
Anti-CCP+	1.207	0.471	6.564	0.01	3.344	1.328–8.421
RF+	0.919	0.458	4.018	<0.05	2.506	1.021–6.155
Anti-CCP and RF+	3.147	0.865	14.088	0.001	25.714	4.718–140.13

SE – standard error, CI – confidence interval. $p<0.05$ was accepted as statistically significant.

Tab. 4. The sensitivity and specificity of anti-CCP and RF for presence of erosive damage in rheumatoid arthritis.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Anti-CCP+	76	56	63	69
RF+	59	68	64	63
Anti-CCP and RF+	51	84	77	63
Anti-CCP or RF+	33	46	38	41
Anti-CCP and RF+ (disease duration <2 years)	63	88	71	84

PPV – positive predictive value, NPV – negative predictive value.

In forward stepwise logistic regression analysis, anti-CCP positivity and RF positivity were seen as significant independent predictors of the radiological outcomes ($p=0.01$, $p<0.05$, respectively) (Tab. 3). The combination of these antibodies showed the highest risk for erosive joint damage (odds ratio=25.71; 95 % confidence interval, 4.7 to 140.13; $p=0.001$). Additionally, disease duration was also an independent predictor of the erosive joint damage ($p<0.01$).

The specificity of anti-CCP was 56 % with a sensitivity of 76 % for erosive damage (Tab. 4). The specificity and sensitivity for erosive disease were 68 % and 59 % for RF, respectively. The sensitivity of anti-CCP was higher than RF for erosive damage, while the specificity was lower than RF. The positive predictive value and negative predictive value of two tests were similar and around 60 %. A combination of the anti-CCP and the RF resulted in a higher specificity (84 %) and a higher PPV (77 %) as compared with the use of the anti-CCP or RF alone. Furthermore, in a subanalysis of the patients with early disease (less than two years duration), the sensitivity of this combination increased to 63 % without decreasing the specificity (88 %).

Discussion

The critical strategy to prevent joint damage in RA is to initiate DMARD therapy early in the disease course (3, 4, 20–22). However, disease severity varies widely, and it is difficult to predict the course for the individual patient. The disease may remain benign for prolonged time in many patients. The ability to predict a severe disease outcome is as important as a correct diagnosis. Therefore, specific and sensitive serological tests are needed to predict the development of erosive damage (1, 4, 22–25). Anti-CCP antibodies and RF are shown as an important serological marker for RA diagnosis and as a possible prognostic marker for the development of erosive disease (10–17). A recent study showed that in patients with synovitis of three months' duration, a combination of anti-CCP antibodies and RF has a high specificity (97 %) and PPV (83 %) for the development of persistent RA (2). Furthermore, anti-CCP have been incorporated into newly proposed diagnostic criteria for rheumatoid arthritis and proved to be strongly associated with erosive arthritis (7).

In this study, the results of the stepwise logistic regression showed that anti-CCP and RF positivities and the duration of disease were independent predictors of the erosion development, and the combination of these antibodies had the highest risk (OR=25.71; 95 % CI 4.7 to 140.13) for erosive damage. In our population, both anti-CCP and RF alone had a moderate specificity and moderate PPV for erosive damage. When combined the anti-CCP and RF, a higher specificity and PPV could be achieved. Moreover, the sensitivity and specificity of this combination increased when we focused on early RA (duration less than two years).

Most studies agree that a positive RF is an important predictor for joint damage over the years of disease. Also for the long term, RF positivity is associated with an unfavourable prognosis (3, 26–31). Jansen et al (5) concluded that radiographic progression at one year was predicted by a positive RF. Similar to previous studies, our results suggested the prognostic value of RF. We found significantly higher disease activity scores in RF positive patients than in RF negative patients for Larsen score, DAS28, HAQ score, patient's global evaluation, ESR and CRP. In forward stepwise logistic regression analysis, the presence of RF positivity was seen as an independent predictor for erosive damage. Moreover, there was a significant positive correlation between RF levels and erosive damage, in concordance with the literature (32–34).

It appears that anti-CCP antibodies have prognostic relevance similar to RF (1, 6, 8, 10, 25, 30, 35, 36). Vencovsky et al (16) found that anti-CCP positivity was better than RF at predicting progression of Larsen score over two years. Also, in a prospective cohort study of 242 patients with early RA followed up for three years, the anti-CCP antibody results correlated with RF, but were better than RF as predictor of a more aggressive disease course (13). Kroot et al (21), in a study of patients with early rheumatoid arthritis, found that anti-CCP positive patients at follow up had developed significantly more radiological dam-

age than patients without this antibody. However, the presence of RF was a better predictor of radiological change (modified Sharp score) after three years than the presence of anti-CCP. In the current study, Larsen score and ESR were higher in the anti-CCP positive patients than in the anti-CCP negative patients, but these differences did not reach statistical significance. Additionally, we did not found a significant correlation between anti-CCP concentration and radiological damage. These results can be explained by the use of a lower cut-off value in this study. A lower cut-off point would increase the number of "incorrect" positive ELISA results. Similar to our study, Meyer et al (23) reported that anti-CCP antibody concentration was not correlated with x-ray damage determined using Sharp's total score at five years. On the contrary, few studies of patients with RA showed that high titres of anti-CCP antibodies at baseline were related to greater radiological progression during the follow up (11, 37).

Earlier studies on the possible predictive value of anti-CCP antibodies for x-ray changes have reported various results. Meyer et al (23) reported that sensitivity of anti-CCP for predicting total Sharp score progression was 67 %, specificity was 56 %, PPV was 64 %, and NPV was 58 %. An other study showed that the sensitivity and specificity for radiological progression of the anti-CCP were 68 % and 58 %, respectively. Their results were very similar to the data reported here. Schellekens et al (10) found that anti-CCP had a PPV of 91 % for erosive disease at two years of follow up in patients with RA. In that study the predictive value for radiographically severe disease was higher than in our study.

In concordance with Meyer et al (23), we found higher predictive values for radiological damage in patients with positive tests for both anti-CCP and RF than those in patients who were positive for only one of the two tests. Anti-CCP combined with RF is highly specific (84 %) and has a reasonable sensitivity of 51 % in the prediction of erosive disease. Furthermore, we observed that the sensitivity of this combination, without loss of specificity (88 %), increased up to 63 % in early disease. But, in some studies, the presence of both anti-CCP and RF did not increase the predictive value for radiological damage as compared with patients who were positive for only one of the two tests (1, 16).

As mentioned above, there are important differences among results of previous studies. These differences might be explained by methodological differences in the assays used, or by different cut-off values chosen for anti-CCP and RF. The other explanation for this is probably differences in patient selection. These results emphasize the need for more rigorous standardization of laboratory tests and patients.

Finally, this study showed that the presence of anti-CCP and RF antibodies was associated with a higher probability of erosive disease. The combined use of RF and anti-CCP had greater specificity and PPV for erosive damage than anti-CCP or RF alone. Because the prediction of radiological outcome is still far from perfect, the combined use of these antibodies may facilitate to make a decision about the individual treatment in RA. Further studies of clinical, laboratory, and genetic parameters are needed to improve RA outcome prediction in clinical practice.

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