

# Diagnostic Value and Clinical Significance of Anti-CCP in Patients with Advanced Rheumatoid Arthritis

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**Financial support:** This study was supported by Akdeniz University Research Project Unit.

**Objectives:** To investigate the prevalence of anticyclic citrullinated peptide (anti-CCP) in patients with advanced rheumatoid arthritis (RA) and to compare it with those in control subjects. Further, to study the relation between the anti-CCP and the disease activity parameters in these patients.

**Patients and Methods:** Seventy-six RA patients who had a mean disease duration of 9.8 years were included. Eighty-three age-matched non-RA volunteers were enrolled as the control group. Disease duration, duration of morning stiffness, swollen and tender joint counts, hand deformity, patient's assessment of pain, anti-CCP, rheumatoid factor (RF) and acute phase proteins were evaluated. The functional disability was also assessed with the Modified Health Assessment Questionnaire (HAQ).

**Results:** Thirty-seven sera (48.7%) in the patient group and one serum (1.2%) in the control group were positive for anti-CCP. RF was positive in 45% of the RA cases and in 5% of controls. Sensitivity and specificity of anti-CCP reactivity for RA were 49.0% and 99.0%, respectively. HAQ score and duration of morning stiffness were found to be significantly associated with anti-CCP positivity. Disease duration, swollen joint count and anti-CCP positivity were the most important variables predicting hand deformity.

**Conclusion:** The prevalence, sensitivity and specificity of anti-CCP in patients with advanced RA were found to be similar to those reported in patients with early disease. Anti-CCP was significantly associated with some parameters of both disease activity and severity. Anti-CCP might be a useful parameter in clinical evaluation of patients with advanced RA.

**Key words:** rheumatoid arthritis ■ anticyclic citrullinated peptide ■ rheumatoid factor ■ disease activity parameters

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## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease of unknown etiology, characterized by chronic polyarthritis. RA is diagnosed primarily according to clinical manifestations, and serologic support is restricted to the determination of rheumatoid factor (RF). However, its diagnostic specificity for RA is poor since RF is also found in many other rheumatic and nonrheumatic diseases and even in a noticeable proportion of normal healthy subjects, particularly in ageing individuals.<sup>1-3</sup>

The other most specific autoantibody system for RA is the family of autoantibodies directed to citrulline-containing proteins, including antiperinuclear factor (APF), antikeratin antibodies (AKA), antifilaggrin antibodies (AFA) and anti-Sa.<sup>4-7</sup> Recently, a new serological test, the anticyclic citrullinated peptide (anti-CCP) was developed. Anti-CCP was reported to have a high specificity for the diagnosis of RA, especially in patients with early disease.<sup>8-14</sup> It was also found that there is an association between anti-CCP and the disease severity in early RA.<sup>15-21</sup>

At all stages of RA, disease activity has a crucial role in disability.<sup>22</sup> Both cross sectional and prospective studies showed strong correlations between RF and disease activity parameters.<sup>23-26</sup> However, there is little information about the prevalence and the association of anti-CCP with the disease activity parameters in patients with advanced RA.<sup>27-28</sup> The present investigation was undertaken to determine the prevalence of anti-CCP in patients with advanced RA and to compare it with those in age-matched control subjects. We also investigated the relation

between anti-CCP and some clinical and laboratory variables of the disease.

## MATERIAL AND METHODS

### Patients

In this cross-sectional study, two groups were compared: 76 RA patients, according to the RA criteria revised by the ACR in 1987,<sup>29</sup> with disease duration of more than two years, admitted to our outpatient rheumatology clinics consequently were included in the patient group. All patients underwent complete clinical evaluation by the same physician (NS) and the following data were recorded; age, gender, disease duration, duration of morning stiffness, swollen and tender joint count (both by 28 joint), presence of hand deformity, patient's assessment of pain [visual analog scale (VAS)], disease-modifying antirheumatic drug (DMARD) intake as well as anti-CCP, RF, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC), platelet (PLT), and hemoglobin values (Hb). Daily life function was assessed with the Modified Health Assessment Questionnaire (HAQ).<sup>30</sup>

Eighty-three age-matched non-RA volunteers, recruited over the same period as the RA patients in the outpatient clinic were enrolled in the study as the control group. The control group included both healthy volunteers (n=32) and non-RA patients (n=51), which included those with osteoarthritis, fibromyalgia, myofascial pain, acute lumbar and cervical strain. Additionally, patients with granulomatous, lymphoproliferative, neoplastic and chronic viral diseases, such as hepatitis C, were excluded from the study because of the possibility of positive RF in these diseases. Informed consent was obtained in all study subjects.

### Laboratory Analysis

Serum RF and CRP concentrations determined by immunonephelometry method on BNII nephelometer (Dade Behring, Marburg, Germany). The concentrations were expressed as IU/ml for RF and mg/dl for CRP. RF concentrations higher than 15 IU/ml were considered positive. Our upper limit for CRP was 0.5 mg/dl.

Anti-CCP antibodies were tested using commercially available ELISA kit (Euroimmun, Germany). Briefly, 100 µl anti-CCP standards (0, 2, 8, 30 and 100 RU/ml), controls and patient samples (1:100 in sample buffer) were distributed into the appropriate wells. The microtiter plates were coated with highly purified synthetic cyclic peptides. After incubation for 60 minutes at room temperature, the wells were washed three times with 300 µl wash buffer. The microplates were then incubated for 30 minutes at room temperature with alkaline phosphate-labeled antibody to human IgG and washed again three times. A chromogenic substrate solution (p-nitrophenylphosphate solution) was added to each well. After 30 minutes, the reaction was stopped using sodium hydroxide stop solution. The absorbance was read at 405 nm on a microplate reader (Sirios, Seac Radim Group, Italy). Serum anti-CCP concentrations were calculated according to standard curve. Results were expressed as RU/ml. Serum samples were evaluated in duplicate, and the upper normal limit (5 RU/ml) was assumed according to the manufacturer's recommendations. The anti-CCP and RF measurements were also dichotomized as present or

**Table 1. Characteristics and the clinical and laboratory variables in patients with advanced rheumatoid arthritis (n=76). Continuous variables are expressed as means ± SD. Numbers in parenthesis represent the percentages of total number of patients**

Age (years)	53.07 ± 10.83
Number of male/female patients	9/67
Duration of disease (years)	9.82 ± 6.76
Morning stiffness (minutes)	36.51 ± 52.13
Patient's assessment of pain (100 mm VAS)	20.55 ± 20.35
Tender joint count (0-28)	4.42 ± 5.63
Swollen joint count (0-28)	0.92 ± 1.35
Presence of rheumatoid hand deformity	37 (48.7%)
HAQ score	0.25 ± 0.34
C-reactive protein (mg/dl)	2.14 ± 2.85
RF (IU/ml)	120.98 ± 217.01
Anti-CCP (RU/ml)	33.85 ± 50.55
ESR (mm/1st h)	41.65 ± 30.04
WBC (1000/mm <sup>3</sup> )	7.54 ± 2.23
PLT (1000/mm <sup>3</sup> )	280.73 ± 92.89
Hb (g/l)	12.23 ± 1.36

#### Number of Patients Taking One or More DMARD

Methotrexate	5 (6.6%)
Chloroquine	11 (14.5%)
Sulfasalazine	1 (1.3%)
Leflunamid	3 (3.9%)
Remicade/methotrexate	3 (3.9%)
Chloroquine/sulfasalazine	3 (3.9%)
Chloroquine/methotrexate	7 (9.2%)
Sulfasalazine/methotrexate	5 (6.6%)
Methotrexate/leflunamid	7 (9.2%)
Chloroquine/methotrexate/sulfasalazine	4 (5.3%)

DMARD: disease-modifying antirheumatic drug

not for statistical analysis.

ESR was measured with a fully automated system working on the basis of Westergren method controlled by a microprocessor (SRS 100, Greiner Bio-one, FL). The complete blood count (WBC, PLT, and Hb) was determined on a GEN-S automated hematology analyzer (Beckman Coulter Inc., Miami, FL).

### Statistical Analysis

Statistical analysis was performed using the SPSS 11.0 for Windows® statistical package. Means, standard deviations (SD) and confidence intervals (CI) were used where appropriate. The significances of the differences between the means were tested using the Student's t test (two-tailed). Comparison of proportions was performed using  $\chi^2$  analyses. The relationship between the anti-CCP and RF was assessed by Pearson correlation. The distribution of anti-CCP and RF levels was also converted to a four-cell (2x2) table using the cut-points 350 IU/ml for RF and 30 RU/ml for anti-CCP and analyzed by McNemar test. Receiv-

er operating characteristic (ROC) curve was used to calculate cut-off values for sensitivity and specificity. In the logistic regression analysis (forward conditional) for anti-CCP or RF positivity, the independent variables were selected according to the univariate analysis ( $p < 0.05$ ). Presence of hand deformity was taken as the primary outcome measure and dichotomized as present or not. Age, duration of disease, HAQ, swollen joint count, CRP, ESR, RF and anti-CCP were entered as continuous independent variables in the logistic regression analysis for the presence of hand deformity. In all instances, p values of  $< 0.05$  were considered significant.

### RESULTS

We analyzed data from 76 RA patients and 83 controls. The two groups were similar with respect to percentages of female gender (88% and 90% for patient and control groups, respectively) and mean ages ( $53.0 \pm 10.8$  and  $54.1 \pm 11.3$  years, respectively). The most common treatments received by RA patients were chloroquine, methotrexate and their combinations with other DMARD. The clinical and laboratory variables and the detailed characteristics of the RA patients were shown in Table 1.

Thirty-seven RA patients (48.7%) were found to be positive for anti-CCP, whereas only one (1.2%) had an anti-CCP-positive serum in the control group. RF was positive in 34 (44.8%) of the RA cases and in four (4.8%) of controls. The proportions of serum samples positive for anti-CCP and RF were significantly ( $p < 0.001$  for both) higher in patients with RA as compared with control subjects (Table 2).

At selected cut-off levels, sensitivity (49.0%) and specificity (99.0%) of anti-CCP reactivity for the diagnosis of RA were slightly higher than those of RF (46.0% and 95.0%, respectively). The area under the ROC curve was 0.73 (95% CI: 0.65–0.81) for anti-CCP and 0.68 (95% CI: 0.59–0.77) for RF.

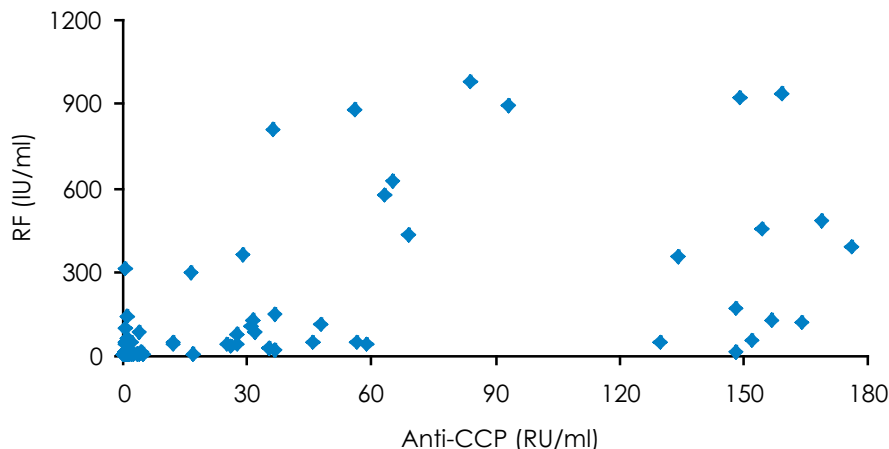
We found a moderate correlation between the levels of anti-CCP and RF ( $r = 0.57$ ,  $p < 0.001$ ) (Figure 1). A detailed inspection of the distribution of anti-CCP and RF levels suggested that RA patients with anti-CCP levels  $> 120$  RU/ml constituted a distinct subgroup, with equally represented low and high RF values. How-

**Table 2. The comparison of anti-CCP and RF reactivities in the study groups**

	RA Patients (n=76)	Controls (n=83)	P Value
<i>Anti-CCP</i>			
Positive	37 (48.7%)	1 (1.2%)	<0.001
Negative	39 (51.3%)	82 (98.8%)	
<i>RF</i>			
Positive	34 (44.8%)	4 (4.8%)	<0.001
Negative	42 (55.2%)	78 (95.2%)	

Numbers in parenthesis represent the percentages of total numbers in corresponding patient and control groups.

**Figure 1. Scatter plot of RF and anti-CCP values in patients with advanced rheumatoid arthritis (n=76,  $r = 0.57$ ,  $p < 0.001$ )**



ever, there were no statistically significant differences in terms of age, gender, disease duration and DMARD intake between this subgroup and the RA patients with anti-CCP levels <120 RU/ml. There were no patients with anti-CCP and RF levels <30 RU/ml and >350 IU/ml, respectively, and the distribution was skewed towards higher (>30 RU/ml) anti-CCP values ( $P < 0.05$ , McNemar test).

The relations of anti-CCP and RF positivities with clinical and laboratory variables of the disease in univariate analysis are presented in Table 3. There were no significant differences in anti-CCP and RF positivities with respect to gender, VAS, CRP, WBC and Hb values. On the other hand, anti-CCP and RF positivities were found to be significantly associated with duration of morning stiffness, swollen joint counts and ESR values in patients with RA. Although there was no relation between anti-CCP and age, the patients who were positive for RF were older than those who were negative. The tender joint counts were significantly higher in anti-CCP positive than anti-CCP negative patients ( $6.0 \pm 6.4$  and  $2.8 \pm 4.3$ , respectively). In addition, anti-CCP positive RA patients had more functional disability than anti-CCP negative ones according to HAQ (Table 3).

The forward conditional logistic regression analysis with the variables significantly associated with anti-CCP and RF positivities in univariate analysis (i.e., duration of morning stiffness, swollen joint counts and ESR values) showed that HAQ score and the duration of morning stiffness were the independent predictors of anti-CCP positivity in patients with advanced RA (Table 4).

The rheumatoid hand deformity was present in 37 (48.7%) RA patients (Table 1). The presence of

hand deformity was taken as the primary outcome measure related to the severity of the disease. In logistic regression analysis where the presence of hand deformity was the dependent variable, duration of disease, swollen joint count and anti-CCP positivity were found to be the independent predictors (Table 5).

## DISCUSSION

The clinical course of RA is variable and its prognosis difficult to predict. In many patients, the disease process is severe and results in progressive joint destruction and serious disabilities. At all stages of RA, disease activity has a crucial role in disability.<sup>22</sup> The importance of anti-CCP in both the diagnosis and the prognosis of RA has been the subject of several studies. However, there is very little information about the prevalence and the association of anti-CCP with the disease activity parameters in patients with advanced RA.<sup>27-28</sup> Therefore, we investigated the specificity and the clinical importance of anti-CCP in advanced RA patients with a mean disease duration of 9.8 years.

It has been reported that the sensitivity of RF for RA is around 50–85%.<sup>2</sup> In the present study, we found that RF was positive in 45% of the advanced RA cases. A possible explanation for the finding of a low prevalence of RF positivity in our advanced RA patients might be the intake of DMARD: most of our patients with advanced RA received DMARD during the course of their disease (Table 1). Several studies documented the level of the RF decrease with the administration of effective disease-modifying therapies.<sup>31-33</sup> Besides that, the sensitivity of RF for RA varies, depending on the patient population.<sup>2,3</sup>

**Table 3. The relations of anti-CCP and RF positivities with clinical and laboratory variables in patients with advanced rheumatoid arthritis. Continuous variables are expressed as means  $\pm$  SD**

	Anti-CCP Positive (n=37)	Anti-CCP Negative (n=39)	P Value	RF Positive (n=34)	RF Negative (n=32)	P Value
Age (years)	55 $\pm$ 8.9	52 $\pm$ 12.3	NS	55.6 $\pm$ 9.1	50.3 $\pm$ 12.0	0.018
Male/female (n)	31/6	36/3	NS	28/6	39/3	NS
Duration of disease (years)	10.2 $\pm$ 7.6	9.9 $\pm$ 6.5	NS	10.6 $\pm$ 7.9	9.4 $\pm$ 5.2	NS
Morning stiffness (minutes)	54.3 $\pm$ 63.2	19.6 $\pm$ 31.3	0.003	54.9 $\pm$ 63.9	21.7 $\pm$ 34.4	0.005
VAS pain (mm)	30.1 $\pm$ 29.4	19.7 $\pm$ 20.6	NS	25.1 $\pm$ 24.4	18.2 $\pm$ 21.5	NS
Swollen joint count	1.35 $\pm$ 1.5	0.5 $\pm$ 1.0	0.006	1.2 $\pm$ 1.4	0.6 $\pm$ 1.2	0.038
Tender joint count	6.0 $\pm$ 6.4	2.8 $\pm$ 4.3	0.013	5.6 $\pm$ 6.0	3.2 $\pm$ 4.9	NS
HAQ	0.39 $\pm$ 0.32	0.18 $\pm$ 0.20	0.001	0.31 $\pm$ 0.29	0.27 $\pm$ 0.25	NS
CRP (mg/dl)	2.8 $\pm$ 3.6	1.6 $\pm$ 1.9	NS	2.8 $\pm$ 3.5	1.6 $\pm$ 1.8	NS
ESR (mm/first hour)	51 $\pm$ 31.9	33 $\pm$ 25.5	0.009	53 $\pm$ 32.4	31.9 $\pm$ 23.8	0.01
WBC (1,000/mm <sup>3</sup> )	7.7 $\pm$ 2.2	7.4 $\pm$ 2.3	NS	7.7 $\pm$ 2.0	7.4 $\pm$ 2.4	NS
PLT (1,000/mm <sup>3</sup> )	301 $\pm$ 119.9	261 $\pm$ 51.8	NS	303 $\pm$ 113.6	258 $\pm$ 59.8	0.049
Hb (g/l)	12.0 $\pm$ 1.5	12.4 $\pm$ 1.2	NS	12.0 $\pm$ 1.5	12.5 $\pm$ 1.2	NS

NS: not significant

and factors, such as the geographical and racial differences, may have an impact on RF positivity.<sup>34-37</sup> It is also known that the specificity of RF is limited since RF is also found in patients with malignancy, other autoimmune and infectious diseases and to a certain extent in the healthy population.<sup>2,3</sup>

We found that 37 out of 76 advanced RA patients (49%) were positive for anti-CCP, whereas only one (1%) of the control subjects had a positive serum for anti-CCP. Diagnostic sensitivity and specificity of anti-CCP reactivity were 49.0% and 99.0%, respectively, which were similar to values reported in patients with early RA.<sup>8-14</sup> These findings about the diagnostic value of anti-CCP in RA suggest that anti-CCP can be found in both the early and chronic RA cases with the same specificity. Furthermore, the findings of the present study confirmed that the anti-CCP is independent of the age, but RF is found more frequently in older RA patients.<sup>1,38</sup>

Bizzaro et al. reported that anti-CCP level in RA patients was related with the duration of disease.<sup>39</sup> Furthermore, Mikuls et al. noted that the reduction in anti-CCP level after a one-year RA treatment was related with both the duration of the disease and the initial anti-CCP levels.<sup>40</sup> On the other hand, in this present cross-sectional study, although we could not measure the temporal changes in the levels of anti-CCP in our RA patients, we found no relation between the anti-CCP level and duration of disease. The reasons for these discrepancies are not clear and need further research. It should also be noted that these authors, in contrast to us, studied early RA in patients.

The relations between the disease activity parameters and autoantibodies directed to various citrulline-containing proteins in RA patients have been investigated in several studies. Vasiliauskiene et al. investigated the relations of disease activity parameters with RF, AKA, ANCA and ANA autoantibodies in RA patients with a disease duration of approximately eight years and found a significant relation

between AKA and functional disability.<sup>41</sup> Similarly, Mallya et al. reported that AKA had significant relations with articular index, grip strength, ESR, CRP and RF in follow-up RA patients.<sup>42</sup> On the other hand, Goldbach-Mansky et al. noted that anti-Sa positivity was significantly associated with swollen joint counts and CRP levels in patients with early RA.<sup>5</sup> In the present study, we investigated the relation between anti-CCP and clinical and laboratory variables in patients with advanced RA. Although both RF and anti-CCP positivities were significantly associated with duration of morning stiffness, swollen joint counts and ESR values in univariate analysis (Table 3), logistic regression has shown that only the HAQ score (functional disability) and the duration of morning stiffness were the variables significantly associated with anti-CCP positivity in patients with advanced RA (Table 4).

The value of anti-CCP in predicting the outcome of RA has been investigated recently.<sup>15-21</sup> Forslind et al. assessed anti-CCP in early RA patients and measured radiological joint damage and disease progression after two years of follow-up. They reported that the presence of anti-CCP at baseline was associated with significantly higher Larsen scores both at baseline and at endpoint compared to RF and other disease parameters.<sup>18</sup> Kastbom et al. followed 242 patients with recent-onset RA for three years and noted that anti-CCP2 was better than RF as a predictor of the disease course.<sup>19</sup> Similarly, Lindquist et al. reported anti-CCP and CRP were the only significant predictors of joint damage in RA.<sup>20</sup> It was also noted that anti-CCP positivity was significantly higher in RA patients with severe than those with minimal joint destruction.<sup>28</sup> In the present study, in advanced RA patients, we used the presence of rheumatoid hand deformity as an endpoint measure of the course and severity of the disease. We found that anti-CCP together with duration of disease and swollen joint count to be an important predictor of hand deformity.

**Table 4. Independent predictors of anti-CCP positivity in patients with advanced rheumatoid arthritis (logistic regression, dependent variable: anti-CCP positivity)**

	<b>B</b>	<b>SE</b>	<b>OR (95% CI)</b>	<b>P Value</b>
HAQ	3.04	1.15	20.99 (2.21-109.14)	0.008
Duration of morning stiffness	1.66	0.52	5.25 (1.68-16.35)	0.004

B: logistic regression coefficient, SE: standard error, OR: odds ratio, CI: confidence interval

**Table 5. Independent predictors of the presence of rheumatoid hand deformity in patients with advanced rheumatoid arthritis (logistic regression, dependent variable: presence of rheumatoid hand deformity)**

	<b>B</b>	<b>SE</b>	<b>OR (95% CI)</b>	<b>P Value</b>
Duration of disease	0.64	0.22	1.89 (1.22-2.94)	0.004
Swollen joint count	1.97	0.68	7.21 (1.90-27.42)	0.004
Anti-CCP	0.32	0.01	1.03 (1.00-1.06)	0.023

The relationship among anti-CCP, joint swelling and hand deformity suggested that they might reflect a single underlying pathological process, though further work is needed to define why anti-CCP is associated with joint deformity and disease activity.

The present study had some limitations: although it was controlled, it had a relatively small number of advanced RA patients and was not a prospective one. Another limitation of the present study was that the clinical evaluation of the severity of RA-specific joint destruction was based on the joint deformity instead of radiography. However, it is also known that radiological joint damage is closely related with the clinical findings of the disease as a cumulative and irreversible indicator of structural joint destruction.

## CONCLUSION

The findings of the present study showed that anti-CCP was a specific marker in advanced RA, the prevalence, sensitivity and specificity being similar to those reported in patients with newly diagnosed RA. Additionally, anti-CCP was found to be significantly associated with some parameters of both disease activity and severity. Therefore, it might be suggested that anti-CCP might be useful in clinical practice in evaluation of both disease activity and therapeutic response in patients with advanced RA. However, further prospective studies with larger numbers of RA patients are needed to confirm the findings of the present cross sectional, case-controlled study.

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