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The Relationship Between Serum Levels of Anti-Cyclic Citrullinated Peptide Antibodies and Disease Activity in Patients With Rheumatoid Arthritis

Romatoid Artritli Hastalarda Serum Anti-Cyclic Citrullinated Peptid Antikor Düzeyleri ve Hastalık Aktivitesi Arasındaki İlişki

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Summary

Objective: Although there is an opinion that anti-cyclic citrullinated peptide antibody (anti-CCP) is a reliable diagnostic and prognostic indicator in rheumatoid arthritis (RA), its association with disease activity and severity is uncertain. This study has been planned to determine the relationship between anti-CCP antibody levels and the disease activity in patients with RA.
Materials and Methods: A total of 48 patients, who have been diagnosed with RA, were included in the study. After physical examination, all patients were evaluated with clinical and laboratory parameters. The clinical symptoms were assessed using visual analog scale (VAS), disease activity score (DAS-28) and Health Assessment Questionnaire (HAQ). Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thrombocyte, leukocyte, hemoglobin and anti-CCP levels were investigated.
Results: The anti-CCP results were positive in 33 patients (68.7%) and negative in 15 patients (31.3%). Anti-CCP was positive in 30.4% of RF-negative patients. A significant difference was observed in average RF levels when the anti-CCP positive and negative patients were compared, however, there was no significance between other parameters. In logistic regression analysis of multiple parameters, higher DAS-28 scores and RF positivity were associated with 5.95 and 5.4 times greater risk of being anti-CCP positive, respectively.
Conclusion: Anti-CCP can be used in the diagnosis of patients with seronegative RA and also may be useful for reflecting disease activity. *Turk J Phys Med Rehab 2012;58:267-71.*
Key Words: Rheumatoid arthritis; anti-CCP antibodies; disease activity; rheumatoid factor

Özet

Amaç: Anti-cyclic citrullinated peptide (anti-CCP) antikorunun romatoid artritde güvenilir tanısal ve prognostik bir gösterge olduğu düşüncesine rağmen hastalık aktivitesi ve şiddeti ile ilişkisi belirsizdir. Bu çalışma, romatoid artrit hastalarındaki anti-CCP antikor düzeylerinin hastalık aktivitesi ile olan ilişkisini saptamak amacı ile planlandı.
Gereç ve Yöntem: Çalışmaya RA tanısı almış olan toplam 48 hasta alındı. Hastalar fizik muayene sonrasında klinik ve laboratuvar parametreleri açısından değerlendirildiler. Klinik bulgular görsel analog skala (GAS), hastalık aktivite skoru (DAS 28) ve Health Assessment Questionnaire (HAQ) ile değerlendirildi. Laboratuvar incelemesinde romatoid faktör (RF), eritrosit sedimentasyon hızı (ESH), C-reaktif protein (CRP), trombosit, lökosit, hemoglobin ve anti-CCP düzeylerine bakıldı.
Bulgular: Anti-CCP sonuçları 33 hastada (%68,7) pozitif, 15 hastada (%31,3) negatif bulundu. RF negatif hastaların %30,4' de anti-CCP pozitif bulundu. Anti-CCP pozitif ve negatif hastalar karşılaştırıldığında; ortalama RF düzeyleri arasında anlamlı fark saptanırken, diğer parametreler arasında anlamlı bir fark saptanmadı. Parametrelerin çoklu logistik regresyon analizinde, yüksek DAS-28 skoru ve RF pozitifliği, anti-CCP pozitifliği ile sırasıyla 5,95 ve 5,4 kat yüksek risk ile ilişkiliydi.
Sonuç: Anti-CCP seronegatif RA'lı hastalarda RA teşhisini koymada kullanılabilir. Ayrıca, anti-CCP antikorları hastalık aktivitesini yansıtmada faydalı olabilir. *Türk Fiz Tıp Rehab Derg 2012;58:267-71.*
Anahtar Kelimeler: Romatid artrit; anti-CCP antikor; hastalık aktivitesi; romatoid faktör

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the presence of autoantibodies such as rheumatoid factor (RF) (1). Various criteria are used to determine the disease activity of RA. There are laboratory findings such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); clinical findings including swollen joints, number of tender joints, morning stiffness, pain, functional condition, disease duration, life quality and fatigue; and complex criterion methods such as disease activity score (DAS 28) to evaluate the disease activity (2,3).

In the last few years, several other autoantibodies have been described of which anti-cyclic citrullinated peptide (CCP) antibody is the most specific. Anti-CCP antibodies can be defined in quite early period of the disease despite the lower sensitivity. Anti-CCP is a good prognostic indicator for RA, and it has a discriminating power between erosive and non-erosive RA. Radiological damages develop in patients with anti-CCP positive RA, more than in patients with anti-CCP negative RA (4,5).

Although the presence of anti-CCP is accepted to be reliable diagnostic and prognostic tool in RA (6,7), its association with disease activity and severity remains unclear. Data on the role of anti-CCP in established RA is limited. In the present study, we have investigated the relationship of the presence of anti-CCP with clinical manifestations and disease activity in a cohort of patients with established diagnosis of RA.

Materials and Methods

A total of 48 patients (41 females and 7 males), who attended Izmir Ataturk Training and Research Hospital, 2nd Physical Medicine and Rehabilitation Clinic between January 2008 and July 2008 with RA diagnosis established according to the 1987 American College of Rheumatology (ACR) Criteria were randomly included in the study. The study was approved by the local ethics committee of Izmir Ataturk Training and Research Hospital. The patients who met four or more ACR 1987 criteria were considered as having RA. All patients were questioned in terms of age, body mass index (BMI), gender, smoking history, diagnosis time, used drugs and treatment durations, morning stiffness and duration, and the presence of any other systemic disease.

In this cross-sectional study, the patients were assessed by the same researcher. Demographic, clinical and laboratory data were recorded after a detailed physical examination of the patients. All patients were followed-up for at least nine months with the diagnosis of RA. The patients with a history of malignant disease, any collagen tissue disease out of RA and those who had an active infection and could not cooperate were excluded from the study. RA patients were assigned into two groups (anti-CCP positive group and anti-CCP negative group) according to their levels of anti-CCP. Clinical data of each group were comparatively evaluated.

In addition to physical examination, data of disease-related parameters such as duration of disease, medications, degree of pain (visual analog scale - VAS), disease activity score 28 (DAS-28), and health assessment questionnaire (HAQ) were recorded. The patients were requested to assess the pain severity and disease activity (PGA-VAS) on a 100-mm VAS. In addition, global assessment of the physician for the disease activity (PSGA-VAS) was recorded on a 100mm-VAS. The Stanford Health Assessment Questionnaire (HAQ) was used to assess physical disability. When HAQ was calculated, 8 activities were evaluated and 2-3 items for each subscale, totally 20 questions were asked.

Venous blood samples were drawn in a sitting position following an 8-12-hour fasting. The blood samples were divided into to 5 ml citrated tubes for ESR and separately to 10 ml jelly-coated flat tubes for anti-CCP, RF and CRP measurements. Serum samples for anti-CCP measurement were studied using microparticle enzyme immunoassay (MEIA) method in Axsym Plus immunodetection analyzer using anti-CCP kit of the Abbott Company. The patients with anti-CCP outcomes ≥5 U/mL were included in anti-CCP positive group and <5 U/mL in anti-CCP negative group. Levels of CRP and RF were measured by immunoturbidimetric method on an Olympus AU 2700 autoanalyzer, while the levels of hemoglobin, leukocyte and platelet were measured using Abbott Cell-DYN 3700 with blood count automated Western Green method.

SPSS (Statistical Package for Social Sciences) version 14.0 for Windows was used for statistical evaluation of the obtained results. The quantitative variables were expressed as average SD (standard deviation). Statistical significance between the two groups in terms of calculated difference variable was carried out using the Mann-Whitney U test. The Chi-square test was used for the comparison of the qualitative data. Logistic regression was used to detect factors associated with anti-CCP positivity. The results were considered in the confidence interval of 95% and a p value less than 0.05 was considered statistically significant.

Results

The socio-demographic and disease-associated characteristics of patients with RA are summarized in Table 1. 48 patients that included to the study, 41 (85.4%) were female and 7 (14.6%) were male. The mean age of the patients was 54.42±11.9 years (26-78). RF was found to be positive in 27 patients (56.2%) and negative in 21 patients (43.8%) (Table 1). In RF-positive patients, anti-CCP autoantibody was positive at 23 (85.2%), while it was negative in 4 patients (14.8%). Anti-CCP outcomes were found to be positive in 33 patients (68.7%) and negative in 15 patients (31.3%) (Table 2). Forty-one patients (86.42%) were using the disease-modifying anti-rheumatic drugs (DMARD). Two patients (4.16%) had not received any treatment, while 5 patients had received only corticosteroid therapy. The average daily dose of the corticosteroids was 4 to 16 mg.

Twenty-five patients (52.1%) had morning stiffness. Morning stiffness was found in 15 (45.4%) of anti-CCP-positive patients, while 10 (66.6%) anti-CCP-negative patients had morning stiffness. The patients were examined for the presence of joint deformities. Although the joint erosions and deformities were seen in anti-CCP-positive patients more than in anti-CCP-negative patients, there was no significant difference between these two groups in the incidence of deformities. Extraarticular

Table 1. Age, sex and disease-associated characteristics of RA patients (n=48).

Age, mean ± SD	54.42±11.90
Female	41 (85.4%)
Disease duration (month), mean ± SD	107.85±106.7
PGA (VAS-cm), mean±SD	3.93±2.04
PGHA (VAS-cm), mean±SD	4.45±2.34
DAS-28 score	
İnactive	11 (22.9 %)
Moderate	24 (50.0%)
Very active	13 (27.1%)
Stanfort HAQ score <0,3	10 (20.8%)
Morning stiffness >60 min	25 (52.1%)
Joint erosions and deformities	21 (43.8%)
Treatment	
Steroid	25 (52.1%)
DMARD	41 (86.42%)
ESR (mm/h), mean±SD	40.20±22.86
CRP (mg/dl), mean±SD	6.16±9.32
RF positive	27 (56.2%)
Anti-CCP positive	33 (68.7%)

Anti-CCP, Anti-Cyclic Citrullinated Peptide; CRP, C-reactive protein; DAS, Disease Activity Score; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; PGHA, physician global assessment; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue scale.

findings were eye involvement in 3 patients (9.1%), kidney involvement in 1 patient (3%) and Sjogren's syndrome in 2 anti-CCP-positive patients (6.1%), while only 1 anti-CCP-negative patient had eye involvement.

Table 2. The rates of anti-CCP in RF positive and RF negative patients with RA.

N=48	Anti-CCP positive		Anti-CCP negative		Total	
	n	%	n	%	n	%
RF positive	23	69.6	4	26.6	27	56.2
RF negative	10	30.4	11	73.4	21	43.8
Total	33	68.7	15	31.3	48	100.0

Anti-CCP, Anti-Cyclic Citrullinated Peptide; RF, rheumatoid factor.

Table 4. Logistic regression analysis with anti-CCP positivity as the dependent variable.

	OR	95 % CI	P
Joint erosions and deformities	1.911	0.408-8.947	0.411
Morning stiffness	0.388	0.068-2.216	0.287
VAS	0.668	0.405-1.101	0.668
DAS-28	5.956	1.211-29.305	0.028
ESR (+)	0.763	0.088-6.648	0.763
RF (+)	5.407	1.177-24.836	0.030

Anti-CCP, Anti-Cyclic Citrullinated Peptide; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; VAS, visual analogue scale.

Table 3. Comparison of parameters in Anti-CCP positive and negative patients with RA.

	Anti-CCP positive group n=33	Anti-CCP negative group n=15	Z value	P* value
Male/female	5/ 28 (%17.5)	2/ 13 (%15.3)	-0.37	>0.05
Age (year)	57.06±10.7	48.60±12.7	-2.05	0.039
BMI	28.16±4.4	29.66±7.1	-0.44	>0.05
Disease duration (month)	122.63±105.2	104.13±148.5	-1.35	>0.05
Disease beginning age (year)	48.06±13.0	39.93±13.6	-1.90	>0.05
PGA (VAS-cm)	4.42±2.2	4.53±2.5	-0.07	>0.05
PGHA (VAS-cm)	3.87±2.0	4.06±2.1	-0.29	>0.05
ESR (mm/s)	41.03±23.0	38.40±23.0	-1.18	>0.05
RF	85.84±77.1	15.12±20.1	-3.98	<0.001
CRP (mg/dl)	5.91±8.9	6.70±10.3	-0.05	>0.05
Leukocyte	7714.68±2351.2	6947.9±2328.0	-0.70	>0.05
Platelet (10^3/mm^3)	339.06±113.5	291.53±55.4	-1.18	>0.05
Hemoglobin (g/dL)	12.16±1.5	12.50±1.0	-0.33	>0.05
DAS28 (0.49-9.07)	4.37±1.2	4.09±1.7	-0.85	>0.05
HAQ (0 -3)	1.13±0.7	1.22±0.9	-0.14	>0.05

*Mann-Whitney U Test
Anti-CCP, Anti-Cyclic Citrullinated Peptide; BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; PGHA, physician global assessment; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue scale.

When anti-CCP-positive and negative patients were compared (Table 2); the mean age in the anti-CCP-positive group (57.06±10.7) was found to be significantly higher than in anti-CCP-negative group (48.6±12.7) (p=0.039). The mean RF value in anti-CCP-positive group (85.84±77.1) was also found significantly higher than in anti-CCP-negative group (15.12±20.1) (p<0.001). There was no significant difference in mean ESR and CRP values and DAS 28, PDA-VAS, PHDA-VAS and HAQ scores between the groups (p>0.05). Furthermore, there was no statistically significant difference in BMI, disease duration, hemoglobin values and platelet count between anti-CCP-positive and negative groups (p> 0.05).

In multivariate logistic regression analysis, DAS-28 (OR: 5,956 % CI: 1,211-29,305, p=0,028) and RF positivity (OR: 5,407, 95% CI: 1,177-24,836, p=0.030) were associated with anti-CCP positivity (Table 3).

Discussion

RA is an autoimmune disease characterized by the production of specific antibodies such as RF and anti-CCP, and non-specific antibodies like ANA. RF is the first identified biological marker for RA and approved by ACR, as a criterion for RA classification in 1987 (8). RF is a parameter to be considered in the definition of severity and activity of RA disease. Anti-CCP antibodies have been demonstrated to have the highest specificity and sensitivity for RA. Hence, some authors suggested including anti-CCP antibodies to the diagnostic criteria for RA (9). However, despite the high specificity of anti-CCP for RA, several recent studies had reported, increased levels of anti-CCP in some diseases, such as psoriatic arthritis and pulmonary tuberculosis (10,11). Predeteanu et al. (12) stated that anti-CCP antibodies are highly specific but moderately sensitive for RA. In this study, only 30.4% of RF-negative RA patients were anti-CCP-positive. This result is similar with the results of studies where anti-CCP positivity in RF-negative patients was found to be between 20 and 43% (13,14).

Several studies demonstrate the association of anti-CCP positivity with joint destruction in patients with established RA (15, 16,17). In our study, joint erosions and deformities were not associated with anti-CCP positivity.

Despite the view of anti-CCP is a reliable diagnostic and prognostic indicator, its relationship with the activity and severity of the disease is unclear (18). Anti-CCP has been reported to be better than RF, to predict the disease activity over 3 years. In addition, percentages of the anti-CCP-positive patients were reported to be higher among patients with severe disease activity than in those with mild disease activity (19,20). Although Kastbom et al. (21) did not observe a significant difference between anti-CCP-positive and anti-CCP-negative patients in number of the total swollen joints, CRP level and DAS-28; they defined a positive correlation between the incidence of anti-CCP positive and the number of met ACR criteria. Landmann et al. (22) found that the individual follow-up of the levels of anti-CCP was not useful for monitoring the disease activity. In their study on 37 patients diagnosed with RA, Dundar et al. (23) could not find a significant difference between anti-CCP positive and negative patients in mean ESR and CRP values, DAS 28 and VAS scores. In their study investigating anti-CCP and RF isotypes in patients with RA and the controls, Vallbracht et al. (24) assessed the clinical findings such as disease duration, joint destruction and disease activity and other laboratory tests. They found that anti-CCP was more commonly positive than all the RF isotypes in patients with RA having a severe disease activity and joint damage (81.4% and 83.6%). Sockalingam et al. (25) found that anti-CCP levels correlated with RF but not with DAS. In this study, HAQ, VAS, morning stiffness, CRP, ESR, hemoglobin and platelet levels were not associated with anti-CCP positivity.

There is considerable disagreement about the relationship between anti-CCP positivity and DAS-28 scores in RA patients (26-29). In this study, DAS-28 scores and serum RF positivity were found to be associated with anti-CCP positivity. In logistic regression analysis of multiple parameters, higher DAS-28 scores and RF positivity were associated with 5.95 and 5.4 times greater risk of being anti-CCP positive, respectively.

Conclusion

Since anti-CCP was found highly positive in RF-negative RA patient, anti-CCP is helpful to establish RA diagnosis in seronegative RA patients. Our study demonstrates an association between clinical activity of the disease and anti-CCP positivity. Anti-CCP antibody may be useful in identifying RA patients as it had an association with activity of the disease. Further studies are needed to incorporate anti-CCP tests into the routine management of RA patients.

Conflict of Interest:

Authors reported no conflicts of interest.

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