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Anticyclic citrullinated peptide antibody in rheumatoid arthritis: a cross-sectional study in Iran

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Background/aim: Studies have shown that anticyclic citrullinated peptide antibody (anti-CCP) titers can be useful in the diagnosis of rheumatoid arthritis (RA). We evaluate the association between anti-CCP antibody titers and the demographic, clinical, and laboratory characteristics of RA patients. Moreover, we explore whether there is any relation between joint destruction and demographic and clinical characteristics of RA patients.

Materials and methods: One hundred and four RA patients with positive anti-CCP titers were compared to 104 RA patients with negative anti-CCP titers. The activity of RA was evaluated using the Disease Activity Score 28 (DAS28). Joint destruction was assessed in the subjects by X-rays of the wrists. Blood samples were collected for assessment of anti-CCP, rheumatoid factor (RF), and erythrocyte sedimentation rate.

Results: Forty-eight (23.0%) males and 160 (76.9%) females were included in this study. RF, DAS28, and joint destruction were significantly different between patients with and without anti-CCP ($P < 0.0001$). DAS28, duration of disease, hospitalizations, and occupation differed significantly between patients with and without joint destruction ($P < 0.0001$).

Conclusion: This study indicates that anti-CCP is correlated with a high disease activity index and more joint destruction in RA patients and it may be used as a prognostic factor for RA.

Key words: Anti-CCP, disease activity, joints, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory multisystemic disease with a prevalence of about 1% in the general population (1). Although the etiology of RA is unknown, it seems that infectious, immunological, hormonal, environmental, and genetic factors have an effect on the development of the disease (2). Peripheral symmetric polyarthritis in RA can lead to joint deformity. In addition, other organs such as the lungs, heart, eyes, and nervous system can be affected by this disease (1).

Definitive diagnosis of RA is based mainly on articular manifestations of the disease, radiographic findings, serological markers, and the exclusion of other inflammatory processes (1,3). Recently, the American College of Rheumatology (ACR) classification criteria for RA has been used for clinical diagnosis, but it cannot be used in the first stages of the disease because of the absence of signs and symptoms of RA. On the other hand, rheumatoid factor (RF), as the only serologic marker in the ACR classification criteria, is not specific for RA because it can be positive in many other diseases such as systemic lupus erythematosus, leprosy, hepatitis B, tuberculosis, and Sjögren syndrome, and even 5% of healthy people have such a result (1).

Recent studies have shown that anticyclic citrullinated peptide antibody (anti-CCP) titers can be useful in diagnosing RA (with a sensitivity of 88% and a specificity of 98%) and have a prognostic value in destruction of the joints in this disease. Moreover, some other studies have shown that anti-CCP can be found in the serum of RA patients about 1.5 years prior to the onset of clinical symptoms (4–6). It is clear that detecting RA in its first stages is more effective for treatment and prevention of its later complications.

Therefore, we decided to evaluate the association between anti-CCP antibody titers and the demographic, clinical, and laboratory characteristics of RA patients. Moreover, we wanted to find out whether there is any relation between joint destruction and demographic and clinical characteristics of RA patients.

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2. Materials and methods

In this study, 104 patients with RA with positive anti-CCP titers were compared to 104 RA patients with negative anti-CCP titers. These two groups were matched in terms of age, sex, job, lodging, duration of the disease, hospitalizations, and family history of RA.

An expert rheumatologist confirmed RA in patients according to ACR-EULAR Classification Criteria for Rheumatoid Arthritis 2010 (7).

Patients with a history of systemic diseases with ability to cause clinical, paraclinical, and/or radiological involvement of the wrist and finger joints, including calcium pyrophosphate deposition disease, polyarticular gout, Sjögren syndrome, mixed connective tissue disease, scleroderma, and RA overlap with other connective tissue diseases, and patients with a history of wrist fractures were excluded.

Demographic and clinical data of patients including sex, age, job, duration of RA, and drug history were gathered.

The activity of RA was evaluated in all patients using the Disease Activity Score 28 (DAS28), which is based on the number of tender and swollen joints and the erythrocyte sedimentation rate (ESR) (8).

Joint destruction was assessed according to the erosive changes, decreased joint space, and articular cystic changes in the X-rays of the patients' wrists. One hundred and ninety-five patients were assessed by X-ray, while in 13 subjects joint destruction was not evaluated because of unwillingness of these patients.

Blood samples were collected to measure anti-CCP, RF, and ESR.

Anti-CCP reactivity was detected in all patients by ELISA method with a commercially available citrullinated protein antibody kit. Anti-CCP antibodies were measured in U/mL and were considered to be positive at a cut-off value of ≥6.25 U/mL.

RF was determined qualitatively (positive or negative) based on a nephelometric test (9) and ESR was measured in mm/h by the Westergren method (10) in all subjects.

This study was approved by the Ethics Committee of Guilan University of Medical Sciences and informed consent was obtained from all participating patients.

Statistical analysis was performed using the chi-square test. All statistical analyses were done by SPSS 17.0. $P < 0.05$ was considered significant.

3. Results

Forty-eight (23.0%) males and 160 (76.9%) females were included in this study.

Demographic, clinical, and laboratory characteristics of patients with and without anti-CCP are shown in Table 1.

According to these data, RF, DAS28, and joint destruction were significantly different between the two groups. Other parameters had no significant differences.

Table 2 shows demographic and clinical characteristics of patients with and without joint destruction. Based on this table, DAS28, the duration of the disease, patients' hospitalizations, and patients' occupations were significantly different between the two groups. There was no significant difference between other parameters.

4. Discussion

In the present study, the majority of RA patients with positive RF also had positive anti-CCP (56.7% of subjects). This is similar to the results of the study by Spadaro et al.; in that study, 64% of subjects were positive for both RF and anti-CCP (11). These results show that anti-CCP is efficient in identification of RA patients, which is similar to RF, and these two serological markers can be interchangeably used for the diagnosis of RA.

On the other hand, 43.3% of our subjects with negative RF had positive anti-CCP. Thus, it seems that in cases where the diagnosis of RA is suspected, anti-CCP may be useful for predicting RA due to the absence of clinical criteria and negative RF. Moreover, significant changes in the serum concentration of anti-CCP do not occur over time or with underlying treatments, while RF may return to a normal level over time (12).

In the present study we found that high activity of RA in patients with positive anti-CCP was significantly more common than in the control group (35.6% versus 7.7%). The study by Del vla del Amo et al. also showed that the mean RA activity in positive anti-CCP patients was higher than in patients with negative anti-CCP (13). Thus, we can conclude that RA patients with positive anti-CCP may be at risk for high disease activity.

The distribution of joint destruction in the two groups showed that out of 98 patients with positive anti-CCP that were assessed by X-ray, the majority had joint destruction (69.3%), while only 21.6% of negative anti-CCP patients who were assessed by X-ray had joint destruction. This is similar to the results of studies by Del vla del Amo et al. (13) and Mewar et al. (14). These findings indicate the capability of anti-CCP in prediction of joint destruction in RA patients.

In our study, 30.3% of patients with joint destruction according to X-ray findings had a high disease activity index versus 15.1% of patients without joint destruction. Obviously, higher disease activity of RA is associated with more complications and disabilities and these effects may confirm the need for a predictive marker for assessing the activity of RA.

Some previous studies showed that joint destruction and its severity are related to female sex (15), while in our

Table 1. Demographic, clinical, and laboratory characteristics of patients (based on anti-CCP).

		Anti-CCP, positive (n = 104)	Anti-CCP, negative (n = 104)	P-value
Male/female		29/75	19/85	NS
Age (years)				NS
	<50	63	61	
	50–65	29	30	
	>65	12	13	
Job				NS
	Self-employed	13	15	
	Housekeeper	48	52	
	Farmer	7	2	
	Student	8	9	
	Employee	16	20	
	Laborer	3	1	
	Unemployed	9	4	
Lodging				NS
	City	75	85	
	Village	29	19	
Duration of disease (months)				NS
	<12	17	8	
	12–36	25	33	
	>36	62	63	
Hospitalizations (count)				NS
	0	73	84	
	1	20	16	
	≥2	11	4	
Family history (positive/negative)		39/65	22/82	NS
RF (positive/negative)		59/45	26/78	<0.0001*
DAS28				<0.0001*
	Inactive phase (<3.2)	18	53	
	Half off phase (3.2–5.1)	49	43	
	Active phase (>5.1)	37	8	
Joint destruction (positive/negative)		68/30	21/76	<0.0001*

*P-values of less than 0.05 were considered significant; NS: not significant.

study there was no significant correlation between sex and joint destruction. This difference between our study and others, apart from genetic differences between races, may be due to some environmental factors such as smoking rates (which maybe higher in women of western countries than women in Iran), cultural issues, and the differences in body mass index, dietary habits, physical activity, and some other factors.

In the study by Guillemin et al., the duration of the disease was mentioned as an effective factor in the creation and progression of radiological damages in RA patients (16). Similarly, in our study, the majority of patients with joint destruction suffered from RA for more than 36 months (58.6%). Due to the chronic and inflammatory process of RA, which leads to deformation and destruction of the joints, sensitive markers for early diagnosis of the

Table 2. Demographic and clinical characteristics of patients based on joint destruction.

		With joint destruction (n = 89)	Without joint destruction (n = 106)	P-value
Male/female		22/67	23/83	NS
Age (years)				NS
	<50	46	72	
	50–65	30	25	
	>65	13	9	
Job				<0.002*
	Self-employed	10	18	
	Housekeeper	42	50	
	Farmer and worker	9	3	
	Student	1	15	
	Laborer	19	16	
	Unemployed	8	4	
Lodging				NS
	City	65	87	
	Village	24	19	
Duration of disease (months)				<0.0001*
	<12	9	15	
	12–36	12	43	
	>36	68	48	
Hospitalizations (count)				<0.01*
	0	56	88	
	1	22	14	
	≥ 2	11	4	
Family history (positive/negative)		62/27	73/33	NS
DAS28				<0.008*
	Inactive phase (<3.2)	19	44	
	Half off phase (3.2–5.1)	43	46	
	Active phase (>5.1)	27	16	

*P-values of less than 0.05 were considered significant; NS: not significant.

disease before the onset of joint destruction seem to be important.

In the recent literature, 73.3% of patients with two or more hospitalizations had joint destruction. It is obvious that patients with a high activity index of RA experience a higher number of hospitalizations, and accordingly the risk of joint damage increases in this group of patients.

Moreover, in our study, 75% of workers and farmers had joint destruction, while 93.7% of students had no joint destruction. This difference may be due to the higher amount of physical activity or hand microtrauma among workers and farmers. On the other hand, disease duration among students is probably shorter than in workers and farmers, and the sociocultural level of students is higher.

This study indicates that anti-CCP is correlated with a high disease activity index and more joint destruction in RA patients regardless of age, sex, job, lodging, or duration of disease, and it may be used as a prognostic factor for RA, particularly in the absence of complete clinical criteria, and in RF-negative patients.

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