EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheumatol.2014.022

Original Investigation

The Frequency of anti-CCP antibodies in patients with rheumatoid arthritis and psoriatic arthritis and their relationship with clinical features and parameters of angiogenesis: A comparative study

Yeliz Özkaya Eker[1], Ömer Nuri Pamuk[2], Gülsüm Emel Pamuk[3], Salim Dönmez[2], Necati Çakır[4]

Abstract

Objective: Macrophage migration inhibitory factor (MIF) and vascular endothelial growth factor (VEGF), as crucial parameters of angiogenesis and inflammation, were evaluated to identify the role of cyclic citrullinated peptide antibodies (anti-CCP) during angiogenesis in rheumatoid arthritis (RA) and psoriatic arthritis (PsA).

Material and Methods: A total of 145 patients with RA, 44 patients with PsA, and 73 healthy subjects were included in this study. The clinical features, total blood counts, and acute phase parameters of RA and PsA patients were recorded. Anti-CCP antibody, VEGF, and MIF levels were determined with enzyme-linked immunosorbent assay (ELISA).

Results: Anti-CCP positivity was significantly higher in the RA group (69%) than in both PsA (20.6%) and controls (8.2%) (p values<0.001). There was no difference between anti-CCP-positive and -negative RA patients regarding the extra-articular manifestations (p>0.05). VEGF and MIF levels were similar in anti-CCP-positive and -negative RA patients (all p values>0.05). The specificity of anti-CCP antibodies for RA was found to be 87.2%. No relationship was found between anti-CCP antibody positivity and clinical features, disease activity, functional disability as assessed by health assessment questionnaire scores, and extra-articular manifestations. There was no relationship between parameters of angiogenesis and anti-CCP antibody positivity. Both RF and anti-CCP antibodies were observed to be positive in most patients with RA.

Conclusion: Either RF or anti-CCP antibody was positive in a considerable proportion of our RA patients. Therefore, anti-CCP antibodies are important in the diagnosis of RF-negative patients who present with clinical findings of RA.

Key words: Rheumatoid arthritis, anti-cyclic citrullinated peptide antibodies, angiogenesis.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects many organs and systems and has a frequency of 0.5%-1% in the population. The disease is characterized by chronic inflammation of the synovial joints, and the chronic inflammation in RA causes erosions and deformities of the articular cartilage and bones (1). Recently, cyclic citrullinated peptide antibodies (anti-CCP) have come into use for the diagnosis of RA. It has been reported that anti-CCP has quite a high specificity for RA (98%), together with a sensitivity similar to that for rheumatoid factor (RF) (2, 3). Although different studies reported variable results, it is known that anti-CCP antibodies are associated with active and erosive disease, like high RF titers (4-6).

The primary mechanism causing joint destruction in RA is the chronic inflammation of the synovium. Angiogenesis contributes to the development of chronic inflammation and plays an important role in the pathogenesis of RA (7). Another disease in which angiogenesis is important is psoriatic arthritis (PsA). Psoriasis is quite common in the population, and about 10% of these patients have different types of joint involvement (8).

Vascular endothelial growth factor (VEGF) has been detected to be present in very large amounts in the inflammatory synovium in both RA and PsA (9). Various studies showed that both VEGF and macrophage migration inhibitory factor (MIF) are associated with disease activity parameters and with each other in RA (10, 11).

There is no study in literature evaluating the relationships between anti-CCP in RA and PsA and angiogenesis. In this study, we determined the prevalence of anti-CCP in RA and PsA. In addition, we evaluated the association of anti-CCP antibodies with clinical features of RA and PsA. In order to understand the link

1 Department of Internal Medicine, Edirne State Hospital, Edirne, Turkey
2 Department of Rheumatology, Trakya University Faculty of Medicine, Edirne, Turkey
3 Department of Hematology, Trakya University Medical Faculty, Edirne, Turkey
4 Department of Rheumatology, Fatih Sultan Mehmet Education and Research Hospital, İstanbul, Turkey

Address for Correspondence: Ömer Nuri Pamuk, Department of Rheumatology, Trakya University Faculty of Medicine, Edirne, Turkey

E-mail: onpamuk@gmail.com

Submitted: 07.04.2014
Accepted: 08.05.2014

between anti-CCP antibodies and angiogenesis in RA and PsA, we determined levels of MIF and VEGF, which are useful parameters of inflammation and angiogenesis.

Material and Methods

We included 145 RA patients diagnosed according to American College of Rheumatology (ACR) criteria (12) and 44 PsA patients diagnosed according to the ClASsification criteria for Psoriatic ARthritis (CASPAR) study group criteria (13). All patients were being followed up at the rheumatology division of our university. In addition, 73 apparently healthy individuals were included. The study protocol was approved by the local ethical committee. All RA and PsA patients and controls were told the aim of the study, and written informed consent was obtained from all participants.

Rheumatoid arthritis and PsA patients underwent a physical examination, and the numbers of tender and swollen joints were determined. Disease Activity Score (DAS28) was calculated for all RA patients. One dermatologist evaluated Psoriasis Area and Severity Index (PASI) scores in PsA patients. In order to determine functional capacity in RA and PsA patients, the Health Assessment Questionnaire (HAQ) was utilized. Other clinical features of the patients were recorded from the medical charts. Age, sex, and health history of the control group were questioned at the time of withdrawal of blood. Erosive disease was defined when an erosion (as a cortical break) was seen in at least 3 separate joints at any of the following sites: the proximal interphalangeal joints, the metacarpophalangeal joints, the wrist, and the metatarsophalangeal joints on radiographs of both hands and feet (14).

Ten milliliters of peripheral blood was obtained from all participants of the study. Blood samples were centrifuged at 3000 g for 10 minutes, and plasma samples were kept at -80°C until analysis. On the same day, whole blood count, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and antinuclear antibody (ANA) were determined in RA and PsA patients. At the end of the study period, plasma samples were thawed, and anti-CCP (ImmuLisa CCP, IMMCO Diagnostics Inc., Buffalo, NY, USA), MIF (Human MIF Quantikine ELISA kit, R&D Systems Inc., Minneapolis, MN, USA), and VEGF-A (VEGFA ELISA kit, Bender MedSystems GmbH, Vienna, Austria) levels were determined with ELISA. The minimum detectable levels of VEGF and MIF were 5.0 pg/mL and 14.6 pg/mL, respectively. Anti-CCP testing was performed according to the manufacturer's instructions by using the recommended cut-off of >5 U/mL as positive.

Table 1. The clinical features and treatment of patients with RA and PsA

	Rheumatoid arthritis	Psoriatic arthritis	p
n (Female/Male)	145 (108/37)	44 (29/15)	NS
Age (years)	53.8±13.1	50.1±12	NS
Disease duration (years)	10.1±8.5	7.7±7.9	NS
Methotrexate usage, n (%)	103 (71.5)	32 (72.7)	NS
Steroid usage, n (%)	137 (95.1)	14 (31.8)	<0.001
Anti-TNF-α usage, n (%)	18 (12.5)	8 (18.2)	NS
Leflunomide usage, n (%)	16 (11.1)	2 (4.5)	NS
Antimalarial usage, n (%)	57 (39.6)	0	NS
Sulfasalazine usage, n (%)	70 (48.6)	5 (11.4)	<0.001
Azathiopurine usage, n (%)	6 (4.2)	0	NS
DMARD usage, n (%)	139 (95.9)	39 (88.6)	NS
DAS28 score	3.45±1.32	-	-
HAQ score	0.91±0.76	-	-
Sedimentation (mm/hour)	54.1±34.5	-	-
CRP (mg/dL)	4.86±8.7	-	-

NS: not significant, Anti-TNF-α: anti-tumor necrosis factor-α, DAS: disease activity score, DMARD: disease-modifying anti-malarial drags, HAQ: health assessment questionnaire

Table 2. Anti-CCP and RF frequencies in the RA, PsA, and control groups

	Rheumatoid arthritis	Psoriatic arthritis	Controls
N	145	44	73
Anti-CCP positivity, n (%)	100 (69)*	9 (20.6)	6 (8.2)
Anti-CCP titer (U/mL)	8.6±7.1*	5±4.4	3.5±0.4
RF positivity, n (%)	96 (66.2)*	4 (9.1)	3 (4.1)

(*): p<0.001, RA group is different from PsA and controls
Anti-CCP: anti-cyclic citrullinated peptide; RF: rheumatoid factor

When comparing categorical variables related to groups, chi-square test was used; when needed, Fisher's exact test was used. In order to compare data of the groups, one-way analysis of variance and post hoc Tukey tests were used. Unpaired t-test was used to compare continuous variables of the two groups. To determine the relationships among the groups, Pearson correlation test was used.

Results

The age and sex distribution of RA patients (108 females, 37 males, mean age: 53.8±13.1), PsA patients (29 females, 15 males, mean age: 50.1±12), and the control group (43 females, 30 males, mean age: 52.6±12.1) was similar. Most of the PsA patients (71.1%) had polyarticular involvement. The general clinical features and therapies of RA and PsA patients are seen in Table 1.

Anti-CCP was significantly higher in RA patients than in PsA and control groups (p values <0.001). Although anti-CCP positivity in the PsA group tended to be higher than in the control group, the difference was not significant (p=0.055). Anti-CCP titers in the RA group were significantly higher than in the PsA and control groups (p values <0.001). Anti-CCP titers in the PsA group were higher than in the control group; but, the difference did not reach statistical significance (p=0.057). The specificity of anti-CCP for RA was found to be 87.2%. RF was positive in 96 (66.2%) RA patients. RF positivity was similar in the PsA and control groups (9.1% vs. 4.1%, p>0.05). The frequencies of anti-CCP positivity and RF positivity and median anti-CCP titers of the RA, PsA, and control groups are seen in Table 2.

When anti-CCP-positive patients were compared with anti-CCP negative patients, their age; sex; disease duration; extraarticular involvement; erosive disease; smoking; frequency of hepatitis B and C; frequency of drug usage, including TNF-blockers; and mean ESR, CRP, HAQ, and DAS28 scores were similar (p values >0.05). ANA positivity was significantly higher in the anti-CCP positive RA group when compared to the negative group (9% vs. 0%, p=0.04), and the frequency of diabetes was significantly lower (6% vs. 17.8%, p=0.035). Anti-CCP-positive RA patients had similar mean VEGF levels (533.9±385.7 vs. 442.1±177.4) and mean MIF levels (4.6±2.7 vs. 4.3±2.9) when compared to anti-CCP-negative RA patients (p values>0.05). We did not detect any correlation between anti-CCP titers and VEGF, MIF, RF, and

Table 3. The mean MIF and VEGF levels in RA, PsA, and control groups.

	Rheumatoid arthritis	Psoriatic arthritis	Controls
MIF (ng/mL)	4.53±2.7*	2.85±2.6**	1.2±2.3
VEGF (pg/mL)	512.8±350.3***	417.1±284.8	381.3±208.4

MIF: macrophage migration inhibitory factor, VEGF: vascular endothelial growth factor
*RA group is different from PsA and controls (p values, respectively, 0.002 and <0.001)
**PsA group is different from controls (p=0.013)
***RA group is different from controls (p=0.05)

CRP levels and DAS28 and HAQ scores in RA patients.

In 68 (46.9%) of our RA patients, both antibodies were positive, and in 17 (11.7%), both antibodies were negative. Only RF was positive in 28 (19.3%) cases, and only anti-CCP was positive in 32 (22.1%) cases. When RA patients with double positivity for RF and anti-CCP were compared with others, it was seen that patients with double positivity had significantly higher ANA positivity (12.9% vs. 0.0%, p=0.002) and HBsAg positivity (7.4% vs. 1.3%, p=0.07) and that serum VEGF levels (570.6±440.9 vs. 447.6±190.3, p=0.06) tended to be higher.

RF-positive RA patients were older than RF-negative RA patients (55.32±12.5 vs. 50.8±14.0, p=0.048), and they had more extraarticular involvement (21.9% vs. 4.1%, p=0.006). Although not statistically significant, VEGF levels were higher in RF-positive patients (553.76±403.78 vs. 433.29±192.73, p=0.09).

When the features of 9 PsA patients with anti-CCP positivity were compared to PsA patients with negative anti-CCP, it was observed that VEGF levels were significantly higher in the former (860.4±426.4 vs. 320.1±100.7, p=0.015), and MIF levels tended to be higher (4.4±3.4 vs. 2.5±2.4, p=0.085). Anti-CCP titer in the PsA group correlated significantly with age (r=0.31, p=0.04), MIF (r=0.33, p=0.037), and VEGF (r=0.89, p=0.001).

The mean MIF level in RA patients was significantly higher than in patients with PsA and healthy controls (p values, respectively, 0.002 and <0.001). Patients with PsA had higher MIF levels than controls (p=0.013). The mean VEGF level in RA patients was borderline significantly higher than in controls (p=0.05). The mean serum MIF and VEGF levels of the groups are seen in Table 3.

Discussion

In our study, the frequency of anti-CCP positivity in our RA patients was 69%. The specificity of anti-CCP for RA was 87.2%. In the literature, the sensitivity of second-generation anti-CCP was reported to be 64%-89%, and the specificity was between 88%-99% (5, 15-21). The sensitivity of RF in the same groups was 59%-79%, and the specificity was between 80%-84% (15-17, 20, 22).

One study from Turkey reported that anti-CCP positivity in RF-positive RA was 81% and that it was only 20% in RF-negative RA (23). Korkmaz et al. (23) found that anti-CCP positivity in early RA was 75%, and in longstanding RA, it was 64%. When these frequencies are considered altogether, they are somewhere at the lower limits when compared to western publications. In this study, we did not detect any significant difference in the frequencies of anti-CCP positivity in early- and late-stage RA patients.

Many of our patients had double positivity for RF and anti-CCP. Inanc et al. (24) stated that anti-CCP and RF were positive in 50% of the cases, and both antibodies were negative in 30% of the patients. In this study, the percentage of patients with double positivity (46.9%) was similar to the frequency in the study by Inanc et al. (24); however, the percentage with double negativity was lower (11.7%).

In this study, we found no association between anti-CCP positivity and clinical features, like extraarticular involvement, disease activity, and HAQ questionnaire. Nevertheless, we detected that RF-positive RA patients had more extraarticular involvement. Inanc et al. (24) reported that anti-CCP-positive cases had more severe disease and serious functional impairment. There was no association between anti-CCP titer and extraarticular manifestations in the study of Korkmaz et al. (23). Similarly, De Rycke et al. (20) observed that anti-CCP antibody was not associated with extraarticular involvement but with RF positivity. As a result, we might conclude that RF is a more important predictor of extraarticular involvement. Also, genetic and environmental factors may affect disease manifestations.

It has been suggested that anti-CCP has an important role in grading clinical activity (15, 25). It was proved that anti-CCP titer correlated with disease activity in RA (26, 27). In this study, we did not find any associations between anti-CCP positivity or titer and any of the activity parameters, like ESR, CRP, and DAS28. Our study included patients with relatively long follow-ups, and it might be argued that this might have resulted in a lower association with disease activity. When we took early patients as a different group, we could not demonstrate any association between anti-CCP and activity. It was stated that radiologic damage in RA patients correlates with anti-CCP, similar to RA (4, 15). However, we did not analyze radiological data.

Although not significant, one noteworthy finding in the RF-positive RA group was the tendency of higher VEGF levels. There are no data in the literature about any relationship between RF and VEGF. MIF levels did not differ among the groups.

Macrophage migration inhibitory factor induces angiogenesis and stimulates the formation of the endothelial tube by increasing the production of VEGF and IL-8 (28). It was shown that MIF levels in synovial fluid in RA correlate with disease activity (11). Recent studies have claimed a role for MIF in the tendency toward atherosclerosis in RA, which is an important player in the angiogenesis and inflammation relationship (10). In this study, serum MIF levels in RA were significantly higher than in PsA and in the control group. In contrast, different from other studies, we did not find any relation between MIF levels and disease activity and functional impairment. Neither anti-CCP nor RF was associated with MIF levels. We might say that MIF levels in RA probably increase independently of disease activity. Different from results of previous studies, we did not demonstrate any relationship between MIF and VEGF levels in RA.

Vascular endothelial growth factor which is an angiogenic parameter, was relatively higher in RA patients than in controls. However, VEGF was not associated with MIF, anti-CCP, or RF. Previous studies found correlations between VEGF and MIF (29). Nevertheless, there was no significant association between anti-CCP positivity in RA and the inflammatory cytokine subgroup in the study of Correa et al. (30). In contrast, Hueber et al. (31) observed that anti-CCP was more frequently positive in the RA subgroup with high levels of cytokines, like TNF-alpha, IL-1, IL-6, IL-13, and IL-15.

Psoriatic arthritis patients had a frequency of 20.5% anti-CCP positivity, which tended to be higher than in controls. One study from Turkey reported that anti-CCP was positive in 12.5% of its PsA patients. In that study, all of the anti-CCP PsA patients were in the symmetrical polyarthritis group (24). In our study, most of the PsA patients had polyarticular joint involvement. Another study reported 5.6% anti-CCP positivity in PsA (32). The frequency of anti-CCP

positivity in one study from Italy was 15.7%, which was similar to our study (33). In the aforementioned study, anti-CCP was especially positive in the symmetrical polyarthritis group. One study from Belgium (34) detected that anti-CCP was positive in 7.8% of their patients. As a result, anti-CCP positivity in our series seems to be more frequent than in western series. We need more data about these results.

Angiogenesis plays an important role in the pathogenesis of PsA, and the most important difference from RA is the histopathologically proven increased angiogenesis of the joints. It has been reported that VEGF levels are increased in psoriasis and PsA patients (8, 35, 36). However, there is no study evaluating MIF levels in PsA. In our study, MIF levels in PsA were significantly lower than in the RA group, but they were higher than in controls. We might think that MIF has a role in the increased angiogenesis of PsA. One interesting finding was the similar levels of VEGF in PsA and in the control group. Fink et al. (9) reported that VEGF levels were higher in active PsA. Different from our RA patients, anti-CCP titers in our PsA patients had a weak correlation with MIF but quite a good correlation with VEGF. Our small group of anti-CCP-positive PsA patients had quite a high mean VEGF level when compared to mean VEGF levels in the RA group. This suggests a pathogenic role for VEGF in the anti-CCP-positive PsA group. Further studies should be conducted in this PsA subgroup to investigate the association between VEGF and histologically increased angiogenesis.

As a conclusion, we found that anti-CCP had similar sensitivity to RF in our RA group; some patients (22.2%) had positive anti-CCP while having a negative RF. In RA patients, there seemed to be an association between extraarticular involvement and RF positivity but not with anti-CCP positivity. Although VEGF and MIF levels were increased in RA, they did not seem to be associated with disease activation and anti-CCP. In addition, a considerable percentage of PsA patients (22.2%) had anti-CCP positivity. MIF levels in PsA were similar to controls; however, VEGF levels were similar. One important point was that VEGF was prominently elevated in the anti-CCP-positive PsA group. The association of increased angiogenesis with higher levels of VEGF in this subgroup and the increase in MIF in PsA patients in general merit further research.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University Medical Faculty.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Ö.N.P., G.E.P., N.Ç.; Design - Ö.N.P., G.E.P., N.Ç.; Supervision - Ö.N.P., N.Ç.; Resource - Y.Ö.E, S.D.; Materials - Ö.N.P., Y.Ö.E,; Data Collection&/or Processing - Y.Ö.E., S.D.; Analysis&/or Interpretation - Ö.N.P., G.E.P.; Literature Search - Y.Ö.E., S.D.; Writing - Ö.N.P., G.E.P.; Critical Reviews - Ö.N.P.

Acknowledgements: This Project was supported by our university's Scientific Research Foundation. We thank our university's Microbiology Department for laboratory support.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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