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Prevalence and clinical significance of serum anti-cyclic citrullinated peptide antibodies in primary Sjögren's syndrome

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ABSTRACT

Objectives: Although anti-cyclic citrullinated peptide (anti-CCP) antibody is a specific marker for rheumatoid arthritis (RA), it is also detected positively in some other rheumatological diseases including Sjögren's syndrome (SS) and even in healthy people. Studies have shown that anti-CCP guides the early diagnosis, prognosis and treatment of RA patients. SS and RA overlap syndrome are common. This study was conducted to determine the prevalence and clinical significance of serum anti-CCP in primary SS patients followed in our outpatient clinic.

Methods: Eighty-two primary SS, 100 RA patients and 100 healthy controls applied to rheumatology outpatient clinic were examined. Patients and control groups were compared in terms of demographic characteristics, laboratory results and anti-CCP.

Results: In the present study, anti-CCP was positive in 4 (4.9%) of 82 primary SS patients. In the SS group, among other autoantibodies, ANA was found to be positive at 88.8%, RF 45%, SS-A 64.6%, and SS-B 36.7%. There was no relationship between anti-CCP and joint involvement in patients with SS.

Conclusions: Anti-CCP antibody positivity can be found in SS patients. Acute phase proteins may be higher in primary SS patients with positive anti-CCP antibody. However, studies have found conflicting findings about the prevalence of erosive arthritis and the future development of RA in these patient groups.

Keywords: Primary Sjögren's syndrome, rheumatoid arthritis, anti-cyclic citrullinated peptide

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by mononuclear cell infiltration in organs, involving all exocrine glands, primarily the salivary and lacrimal glands. The spectrum of the disease ranges from autoimmune exocrinopathy to a systemic process with extraglandular manifestations. Dry mouth and eyes due to glandular involvement are among the most common symptoms of the disease. The disease is generally seen in women between the ages of 40-50. Although the cause of the disease is not known exactly, it can be seen together with other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis and polymyositis (secondary SS) or it can occur alone (primary SS) [1]. RA is the most common rheumatic disease associated with SS [2].

Anti-CCP antibodies are IgG-type antibodies that develop against citrullinated peptides and are called anti-citrullinated peptide antibodies (ACPA). The most commonly used ACPA tests are anti-cyclic citrulli-

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nated peptide (Anti-CCP) antibodies. Anti-CCP is 97-98% specific and 40-60% sensitive for RA [3]. In addition, they can be detected in a very early period (79%) in RA [4]. It has been reported that patients with positive anti-CCP antibodies develop more joint deformity and radiological damage [5]. Anti-CCP is reported as a much more specific parameter for RA than rheumatoid factor (RF) [6]. Anti-CCP may be also positive in some rheumatologic diseases, including SS, and even in healthy people, except for RA. The most common causes of anti-CCP positivity other than RA, in order of frequency, are psoriatic arthritis (9%), systemic lupus erythematosus (8%), juvenile idiopathic arthritis (8%), scleroderma and CREST syndrome (7%), Sjogren's syndrome (6%), vasculitis (5%); in addition, 3% positive in ankylosing spondylitis, 1% positive in chronic hepatitis C and Wegener granulomatosis [7]. It has been reported that ACPA is detected at a high prevalence in active tuberculosis, except autoimmune diseases [8]. These antibodies are found to be less than 1% positive in the normal population [3].

The aim of this study is to determine the prevalence of anti-CCP in primary SS patients and its relationship with joint and extra-articular involvement associated with the disease.

METHODS

Eighty-two patients with primary SS diagnosis, 100 patients with RA diagnosis and 100 healthy individuals as control group were included. Patients who met the AECG 2002 (American-European Consensus Group) criteria for the diagnosis of primary SS and the ACR/EULAR 2010 (American College of Rheumatology/European League Against Rheumatism) criteria for the diagnosis of RA were included in the study [9, 10].

Patients with secondary SS, patients with autoimmune diseases other than SS, and pregnant women were excluded from the study. Age, gender, symptoms at presentation, joint and extra-articular involvement, onset time of symptoms, time to diagnosis and given treatments were recorded. For each patient diagnosed with primary SS and RA, complete blood count, biochemical parameters, autoimmune markers and serum anti-CCP values available at the time of admission were recorded. Patients and control groups were compared in terms of demographic characteristics, laboratory findings and anti-CCP.

Ethics committee approval was obtained for the study. Anti-CCP serum levels were measured on the Roche cobas-e 601 immunoassay analyzer, a dual modular device, using the Elecsys® Anti-CCP kit from Roche Diagnostics. The measurement was made using the electrochemiluminescence method. The reference range was taken as 0-20 IU/mL.

Statistical Analysis

The compliance of the variables in the study to normal distribution was evaluated using the Shapiro-Wilks test. The median (Interquartile Range-IQR) was used to display descriptive statistics of discrete and non-normally distributed variables. In comparisons of parameters that do not show normal distribution between groups, Kruskall-Vallis H test was used for multiple groups and Mann-Whitney U Test was used for paired groups. Bonferroni-corrected paired comparisons were made for variables with significant differences as a result of the Kruskal-Wallis test. Whether the distribution of categorical variables differed by groups was evaluated using the Chi-square test. In case the number of subjects in the cells is insufficient; differences between groups were analyzed using Fisher's Exact test result. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used for statistical analysis and ± calculations. Statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 282 individuals were included in the study. Of these, 82 were primary SS (96.3% female [79/82] and median age 49.0 (IQR = 11.0) years), 100 patients with RA (69% female [69/100] and median age 50.0 (IQR = 21.0) years) and 100 healthy controls (78% female [78/100] and median age 41.5 (IQR = 14.0) years). The mean time elapsed since the onset of symptoms in SS patients was 39.17 ± 28.8 months, and the mean time after diagnosis was 27.04 ± 17.4) months. The average time between the onset of symptoms and diagnosis is 12.12 ± 23.6) months.

Table 1. Clinical features of the SS group

	SS n (%)		SS n (%)
First application complaints		**Joint involvement**	**66 (80.5)**
Dry mouth	24 (29.3)	Large joint (LJ) arthralgia	24
Dry eyes	12 (14.6)	LJ arthritis	4
Dry mouth + eyes	46 (56.1)	Small joint (SJ) arthralgia	5
Minor salivary gland biopsy	**41 (50)**	SJ arthritis	0
none	6	Arthralgia (LJ + SJ)	19
present	35	Arthritis (LJ + SJ)	1
Drugs		Arthritis and arthralgia	13
Methotrexate (Mtx)	9 (11.0)	**Extraarticular involvement**	**26 (31.7)**
Hydroxychloroquine (Hcq)	62 (75.6)	Raynaud syndrome	6
Sulphasalazine (Slz)+Hcq	3 (3.7)	Pulmonary involvement	1
Mtx + Hcq	5 (6.1)	Renal involvement*	14
Mtx + Hcq + Slz	1 (1.2)	Neurological involvement	3
Leflunomide	1 (1.2)	Dermatological + renal involvement	1
Azathioprine	1 (1.2)	Lymphoma	1

SS = Sjögren's syndrome

*According to the 24-hour urine results of SS patients, proteinuria > 150 mg/day was defined as proteinuria, and > 30 mg/day microalbumin detection was defined as microalbuminuria. Renal involvement was accepted in patients with microalbuminuria and proteinuria. 33 patients have 24-hour urine results. Proteinuria was found in 13 patients and microalbuminuria was found in 2 of them.

Extra-articular involvement was present in 26 (31.7%) patients with SS. Among the extra-articular involvement, renal involvement in 14 patients, Raynaud phenomenon in 6, neurological involvement in 3 , lung involvement in 1 and renal and skin involvement were found together in 1 patient. Non-Hodgin Lymphoma (NHL) was observed in only 1 of our patients.

The clinical characteristics of SS patients are shown in Table 1 and the frequency of autoantibodies in Table 2. Anti-CCP value > 20 IU/mL was considered positive. The frequency of anti-CCP positivity shows a significant difference between the SS, RA and control groups ($\chi^2 = 112.176$, $p < 0.001$). In the SS group, 4.9% (n = 4) , in the RA group, 56% (n = 56) were anti-CCP positive. Anti-CCP positivity (n = 0) was not detected in the control group. As a result of binary comparison; Anti-CCP distribution in SS and RA groups ($\chi^2 = 53.283$; $p < 0.001$), SS and control groups ($\chi^2 = 6.488$; $p = 0.011$), RA and control groups ($\chi^2 = 77.778$; $p < 0.001$) was significantly different (Table 2).

Anti-CCP values also differ significantly in the groups ($p < 0.001$). Anti-CCP values are similar in SS and control groups ($p = 0.143$). The median of anti-CCP in the RA group was 68.3 (IQR = 387.4), the median of anti-CCP in the SS and control group was 7.0 (IQR = 0.0), and the median values obtained for RA were significantly different from the other groups ($p < 0.001$) (Tables 3 and 4).

The median value of the erythrocyte sedimentation rate (ESR) variable of the SS group patients is 24.0 (IQR = 26.0), 36.0 (IQR = 36.0) for RA and 14.0 (IQR = 17.0) for the control group. A significant difference was found in terms of ESR variable in SS, RA and control group patients ($p < 0.001$). All pairwise comparison results were significant ($p < 0.05$) (Tables 3 and 4).

C-reactive protein (CRP), rheumatoid factor (RF) variable values differ in the groups. The median of CRP in the RA group was higher than the SS and control group, and the median of CRP in the SS group was higher than the control group ($p < 0.001$). In the RA group, the median of RF was found to be significantly higher than the median obtained for SS and the control

Table 2. The frequency of anti-CCP and other autoantibodies in patients with SS and RA

	SS n (%)	RA n (%)	χ^2	*p* value
Anti-CCP (+)	**4 (4.9)**	**56 (56.0)**	**112.176**	**< 0.001**
ANA (+)	**71 (88.8)**	**30 (33.7)**	**53.080**	**< 0.001**
"anti-dsDNA (+)	**6 (8.1)**	**3 (5.5)**		**0.732***
"Jo1 (+)	**1 (1.4)**	**0 (0.0)**		**1.000***
"Scl70 (+)	**-**	**-**		****
"Sm (+)	**5 (7.1)**	**0 (0.0)**		**1.170***
"SmRnp (+)	**1 (1.4)**	**0 (0.0)**		**1.000***
SS-A (+)	**50 (64.6)**	**2 (5.4)**	**35.531**	**< 0.001**
SS-B (+)	**29 (36.7)**	**1 (2.7)**	**15.198**	**< 0.001**
Anticardiolipin antibody (+)	**1 (3.6)**	**0 (0.0)**		**1.000***
Lupus anticoagulant (+)	**0 (0.0)**	**1 (50.0)**		**1.182***

CCP = cyclic citrullinated peptide, RA = rheumatoid arthritis, SS = Sjögren's syndrome

*Fisher Exact test result. / ** Since the number of subjects is insufficient, the test result cannot be given.

"These values were borderline positive and were not considered significant when evaluated together with the clinic. In the subsequent visits of the patients, especially the anti ds DNA values were found to be negative and no other collagen tissue disease clinic was detected in the patients. The B2 glycoprotein test was not performed at our center at the time of the study.

group ($p < 0.001$ and $p = 0.044$ respectively). RF medians were similar in SS and control groups ($p = 0.142$) (Tables 3 and 4).

No significant relationship between the anti-CCP and the number of joint involvement was detected in patients with SS ($p > 0.05$).

DISCUSSION

Primary SS is associated with many autoantibodies, mainly antinuclear antibody (ANA), anti-SSA, anti-SSB and RF. The frequent association of SS with RA (19.5%) [11] and the high prevalence of RF in SS make it difficult to differentiate RA from SS, especially in patients with arthritis. Anti-CCP is critical in detecting early stage RA patients. Therefore, anti-CCP positive SS patients should be closely monitored for the future development of RA and other overlap syndromes [12, 13]. In our study, the frequency of anti-CCP in primary SS was found to be 4.9%. There are few studies conducted on anti-CCP positivity in primary SS patients.

So far there was only one study in Turkey and it was conducted on a small number of patients [14]. In this study conducted in Istanbul in 2005, the frequency of anti-CCP was examined in 46 RA patients, 32 primary SS and 22 Wegener granulomatosis patient

Table 3. Comparison of ESR, CRP, RF and anti-CCP variables by groups

	Groups				
Variables	**SS Median (IQR)**	**RA Median (IQR)**	**Control Median (IQR)**	χ^2	***p* value**
ESR (mm)	24.0 (26.0)	36.0 (36.0)	14.0 (17.0)	37.475	**< 0.001**
CRP (mg/dL)	0.5 (1.8)	1.6 (3.6)	0.3 (0.5)	67.397	**< 0.001**
RF (IU/mL)	18.1 (25.0)	24.1 (91.8)	20.0 (0.0)	18.559	**< 0.001**
anti-CCP (IU/mL)	7.0 (0.0)	68.3 (387.4)	7.0 (0.0)	113.909	**< 0.001**

CCP = cyclic citrullinated peptide, RA = rheumatoid arthritis, SS = Sjögren's syndrome, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = rheumatoid factor

Table 4. Pairwise comparison results of ESR, CRP, RF and anti-CCP variables

		RA	Control
		p value	*p* value
ESR	SS	**0.008**	**0.014**
	RA		**< 0.001**
CRP	SS	**< 0.001**	**< 0.001**
	RA		**< 0.001**
RF	SS	**< 0.001**	0.142
	RA		**0.044**
Anti-CCP	SS	**< 0.001**	0.143
	RA		**< 0.001**

CCP = cyclic citrullinated peptide, RA = rheumatoid arthritis, SS = Sjögren's syndrome, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = rheumatoid factor

groups. Anti-CCP was positive in only 1 patient (3%) of primary SS patients. Our study is the second study conducted in the Turkish population and may reflect the prevalence of anti-CCP in primary SS patients more accurately in terms of the large number of patients. In our study, 4 (4.9%) of 82 primary SS patients were anti-CCP positive and the anti-CCP median was 7.0 (IQR = 0.0).

In the largest of the studies, Ryu *et al*. [15] followed 405 primary SS patients for an average of 60 months. RA developed in 23 (5.6%) patients after follow-up. Similar to our study, the frequency of women was 95.3% and the average age was 52.7 (range: 17-87) years. During the follow-up, 171 (42.2%) patients complained of arthralgia. A total of 73 (18%) patients have arthritis. Anti-CCP was positive in 38 (9.4%) patients. In the follow-up, 42 (10.3%) patients progressed to secondary SS. RA was developed in 23 (5.6%) of secondary SS, SLE in 13 (3.2%), systemic sclerosis in 4 (0.9%) and Behçet's disease in 22 (0.2%). Anti-CCP was positive in all patients who developed RA. Average RA development time was 60 months (7-98 months).

Goeb *et al*. [16] found positive anti-CCP autoantibodies in only 4% of 137 women and 16% of 11 male patients with primary SS. In a study conducted by Gottenberg *et al*. [17] in 134 patients with primary SS, anti-CCP antibodies were found positive with a rate of 7.5% and anti-keratin antibodies with a rate of 5.2%. Other studies have shown that anti-CCP antibodies were detected positively in a minority of primary SS patients, with or without erosive arthritis [14, 18-20].

Thirty-eight percent of primary SS cases have arthralgia and arthritis [21]. Chronic symmetrical arthritis rate in the small joints of the hand and wrist are 16%, and erosion is present on direct radiography in 1.5% of those with chronic arthritis [22]. In clinical practice, in the patient who applied with arthritis; anti-CCP positivity and presence of erosion on plain X-ray are interpreted in favor of RA in the differentiation of primary SS and RA. However, anti CCP can be detected positively in 3-22.1% of primary SS patients. Conflicting results have been found in studies on the clinical importance of anti-CCP positivity in primary SS. While some of them found that the incidence of arthritis increased in those who were anti CCP positive, other studies do not support this [12, 13, 23-25]. In two studies, one with joint ultrasonography in adults and the other in children, a correlation was found between anti-CCP positivity and arthritis frequency in primary SS [23, 24]. A systematic review and meta-analysis showed that anti-CCP positivity is associated with the development of arthritis and further progression to RA [12]. In a prospective study by Haga *et al*. [25], no correlation was found between anti-CCP and arthritis. In this study, only 5 of 62 primary SS cases were found to be anti-CCP positive. In our study, anti-CCP was found only in four of 82 cases, and similarly, no significant relationship was found with anti-CCP in terms of arthritis development.

Anti-CCP positive SS patients should be closely monitored for future risk of development of RA or any other rheumatic disease. In addition, the value of ACPA tests other than anti-CCP (such as anti-citrulline a-enolase antibody and anti-Ro) is gradually increasing [26]. Especially in the treatment of ACPA positive diseases; the blockade of the Peptidyl Arginine Deiminase (PAD) enzyme involved in the citrullination process may affect the course of the disease and prevent joint involvement.

Limitations

Limitation of our study was mean disease duration of sjogren syndrome patients were short (27-28 months). Anti-CCP antibody positivity can be found in SS patients. Acute phase proteins may be higher in

primary SS patients with positive anti-CCP antibody. However, studies have found conflicting findings about the prevalence of erosive arthritis and the future development of RA in these patient groups.

CONCLUSION

Anti-CCP antibody positivity can be found in SS patients. Acute phase proteins may be higher in primary SS patients with positive anti-CCP antibody. However, studies have found conflicting findings about the prevalence of erosive arthritis and the future development of RA in these patient groups.This study is the largest study in determining the prevalence of anti-CCP in primary SS in terms of the number of individuals conducted in the Turkish population. There was no significant relationship between anti-CCP and joint findings. It is necessary to study more patients to determine whether there is a significant relationship between anti-CCP and other clinical findings.

Authors' Contribution

Study Conception: TAK, ŞE; Study Design: İD, OK; Supervision: OK, ŞE; Funding: N/A; Materials: N/A; Data Collection and/or Processing: TAK, İD; Statistical Analysis and/or Data Interpretation: TAK, İD; Literature Review: TAK, İD; Manuscript Preparation: TAK, OK and Critical Review: OK, ŞE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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