

# Evaluation of clinical and laboratory findings of 147 patients with systemic lupus erythematosus: The relationship between anti-CCP and arthritis

## Sistemik lupus eritematozuslu 147 hastanın klinik ve laboratuvar bulgularının değerlendirilmesi: Anti CCP ile artrit arasındaki ilişkinin incelenmesi

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Ethics Committee Approval: Kocaeli University, Clinical Research Ethics Committee, Project code no: 2015/184 Decision No: 1/11.

Etik Kurul Onayı: Kocaeli Üniversitesi, Klinik Araştırmalar Etik Kurulu, Proje kod no: 2015/184 Karar No:1/11.

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

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.  
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 27.12.2018

Accepted / Kabul Tarihi: 19.02.2019

Published / Yayın Tarihi: 25.02.2019

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Published by JOSAM

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### Abstract

**Aim:** Anti-cyclic citrullinated peptide antibodies (Anti-CCP) is considered as a novel marker in the assessment of rheumatoid disorders. Some studies have emphasized the importance of anti-CCP in indicating erosive arthropathy in Systemic Lupus Erythematosus (SLE), like Rheumatoid Arthritis (RA). These studies have reported that the chance of erosive arthritis development is significantly increased in anti-CCP-positive patients. This study aimed to investigate the relationship between anti-CCP and arthritis along with other clinical and laboratory parameters in patients with SLE.

**Methods:** A total of 147 SLE patients who had been admitted to Kocaeli University Medical Faculty, Department of Internal Medicine, Division of Rheumatology between January 2001 and October 2015 were included in this retrospective study. SLE diagnosis was verified according to American College of Rheumatology (ACR) and/or The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria. Patients whose diagnosis was not definite and not having anti-CCP were excluded.

**Results:** Female/male ratio was found as 5.6, and the mean age was calculated as 43.9±11.85 years. The mean follow-up period was 73.3±44.97 months. Anti-CCP was found to be positive in ten patients whereas arthritis was found to be present in 100 patients. Anti-CCP was positive in seven patients with arthritis. RF (Rheumatoid Factor) was found as positive in 50 patients of whom 40 had arthritis. A relationship was found between Anti-CCP and RF. There was no relationship between anti-CCP and arthritis.

**Conclusions:** Anti-CCP has been reported to be significantly related to arthritis and other characteristics of rheumatoid disorders, particularly RA in several studies. There are conflicting results about the relationship between anti-CCP and arthritis in patients with SLE. These conflicting results may be derived from different subtypes of anti-CCP (citrulline-dependent), different cut-off values, and characteristics of the patient population. We did not observe any relationship between the Anti-CCP and arthritis.

**Keywords:** Systemic lupus erythematosus, Anti-cyclic citrullinated peptide antibodies, Arthritis

### Öz

**Giriş:** Anti-siklik sitrülline peptid antikorları (Anti-CCP), romatoid hastalıkların değerlendirilmesinde yeni bir belirteç olarak kabul edilir. Bazı çalışmalar Romatoid Artrit (RA) gibi sistemik lupus eritematozus'da (SLE) eroziv artropatinin gösterilmesinde Anti-CCP'nin önemini vurgulamıştır. Bu çalışmalar, Anti-CCP pozitif hastalarda eroziv artrit gelişme ihtimalinin anlamlı şekilde arttığını bildirmiştir. Bu çalışmanın amacı, SLE'li hastalarda Anti-CCP ve artrit ile diğer klinik ve laboratuvar parametreleri arasındaki ilişkiyi araştırmaktır.

**Yöntemler:** Ocak 2001 - Ekim 2015 tarihleri arasında Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı'na başvuran SLE'li toplam 147 hasta çalışmaya dahil edildi. SLE tanısı Amerikan Romatoloji Birliği (ACR) ve / veya Sistemik Lupus Eritematozus Uluslararası İşbirliği Klinikleri (SLICC) kriterleri ile doğrulandı. Kesin olmayan ve Anti-CCP si olmayan hastalar çalışma dışı bırakıldı.

**Bulgular:** Kadın / erkek oranı 5,6, yaş ortalaması 43,9±11,85 idi. Ortalama takip süresi 73,3±44,97 aydı. 10 hastada anti-CCP pozitif, 100 hastada ise artrit vardı. Artritli hastaların yedisinde Anti-CCP pozitif. RF (Romatoid Faktör), 40'ı artritli olan 50 hastada pozitif bulundu. Anti-CCP ile RF arasında bir ilişki olduğu tespit edildi. Anti-CCP ile artrit arasında ise ilişki yoktu.

**Sonuçlar:** Bazı çalışmalarda, özellikle RA gibi romatolojik hastalıkların artrit ve diğer özelliklerinin Anti-CCP ile bağlantısı olduğu rapor edilmiştir. SLE'li hastalarda anti-CCP ile artrit arasındaki ilişkiyle ilgili çelişkili sonuçlar vardır. Bu çelişkili sonuçlar farklı Anti-CCP alt tiplerden (sitrülin bağımlı), farklı cut-off değerlerinden ve hasta popülasyonunun özelliklerinden kaynaklanabilir. Anti-CCP ile artrit arasında herhangi bir ilişki gözlemlenmedi.

**Anahtar kelimeler:** Sistemik lupus eritematozus, Anti-siklik sitrülline peptid antikorları, Artrit

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disorder with an unknown etiology, which can lead to involvements of various tissues and organs. Autoantibodies and immune complexes play a role in the pathophysiology of SLE[1,2].The female/male ratio is 9/1 in general population, and it is most commonly seen in the 3<sup>rd</sup> and 4<sup>th</sup> decades[3].

Immune complexes and autoantibodies, which have developed against components of the nucleus, are responsible for tissue damage, causing various symptoms. Genetic factors, immune response disorders, defective immunological regulation, apoptosis, cytokine pathway disorders and hormonal and environmental factors play important roles in the etiology and pathophysiology of the disease. The primary pathological findings can be listed as inflammation, vasculitis, immune complex deposition, and vasculopathy [4].

Citrulline is an amino acid which is formed by the post-translational enzymatic alterations of arginine residues. It is located in filaggrin molecule. Citrulline autoantibodies are very specific to rheumatoid arthritis (RA), and they can be used in the differentiation of RA from other rheumatoid disorders [5]. Cyclic citrullinated peptide (CCP) antibodies have great importance in the early diagnosis of RA, with serum levels found to be increased in 79% of RA patients during the early stages of the disease. They can be found as positive in 40% of rheumatoid factor(RF)-negative patients[6]. Several studies have reported that the development of radiologically positive arthritis is more common in anti-CCP-positive patients when compared to the negative ones [5, 7]. Although there is a correlation between RF and anti-CCP in RA patients and it has been used mostly in the diagnosis of RA, anti-CCP can be helpful in the diagnosis of other rheumatological disorders such as SLE [8]. It was reported that anti-CCP test might result in positive up to 8% in Behcet's disease, fibromyalgia, gout, juvenile rheumatoid arthritis, reactive arthritis, and SLE [9,10].

RF is found as positive in 20-60% of SLE patients which makes it difficult to use RF in discriminating the RA and SLE patients, whereas anti-CCP is found less frequent in SLE compared to RF [11]. However, the rate of anti-CCP in SLE patients has been reported to be between 10-15% in some studies [12-15].

Anti-CCP was found to be higher in RA patients with erosive arthropathy. Some studies have emphasized the importance of anti-CCP in indicating erosive arthropathy in SLE like RA. These studies have reported that the chance of erosive arthritis development is significantly increased in anti-CCP-positive patients [16-23]. This study aimed to investigate the relationship between anti-CCP and arthritis, as well as other clinical manifestations and laboratory parameters in patients with SLE.

## Materials and methods

AA total of 147 SLE patients who had been admitted to Kocaeli University Medical Faculty, Department of Internal Medicine, Division of Rheumatology between January 2001 and October 2015 were included in this retrospective study. The

diagnosis was confirmed according to the diagnostic criteria of American College of Rheumatology (ACR) (1997 revised criteria) and/or 2012 SLICC criteria. Patients with indefinite diagnosis and those without anti-CCP result were excluded from the study.

Age, anti-CCP, the dates of disease onset, diagnosis, and hospital admission, the duration between the onset of symptoms and the diagnosis, total period of the disease, duration of the follow-up, presence of malar rash, discoid rash, photosensitivity, oral ulcer, presence and type of arthritis(mono, oligo, polyarthritis), proteinuria (>500 mg/day), renal, pulmonary, cardiac, neurological, and hematological involvements, the C3 (Complement 3) and C4 (Complement 4) levels, the cardiolipin antibody result, the lupus anticoagulant and/or Venereal Disease Research Laboratory (VDRL) result, direct coombs test result, RF result, and Extractable Nuclear Antigen (ENA) profile were recorded.

### Statistical analysis

IBM SPSS 20.0 0 (SPSS Inc. Chicago, IL, USA) was used for the statistical analysis. Normal distribution was evaluated by Kolmogorov-Smirnov test. Numerical variables with normal distribution were given as mean  $\pm$  standard deviation (minimum-maximum value, median) and numerical variables which did not show normal distribution were given as median (25<sup>th</sup> percentile - 75<sup>th</sup> percentile). Categorical variables were expressed as frequencies (percentages). The differences between the groups were analyzed by Mann-Whitney U test. The correlation between categorical variables was evaluated by Chi-square analysis.  $p < 0.05$  was considered as statistically significant.

## Results

The mean age was calculated as 43.9 $\pm$ 11.85 (min-max: 19-74, median: 42) years. 22 out of 147 patients were male, whereas remaining 125 patients were female. F/M (Female/Male) ratio was found as 5.6. Presence of malar rash, discoid rash, photosensitivity, oral ulcer, alopecia, arthritis, kidney involvement, serositis, neurological involvement, hematological involvement, and Raynaud's phenomenon were observed in 72 (49%), 23 (15.6%), 86 (58.5%), 43 (29%), 17 (11.5%), 100 (68%), 73 (49.6%), 43 (29%) 14 (9.5%), 131 (89.1%) and 14 (9.5%) patients, respectively (Table 1).

A total of 100 patients were found to have arthritis with none of them being erosive arthritis. Anti-CCP was found as positive in 10 (6.8%) patients, whereas the remaining 137 patients resulted as negative. The mean of anti-CCP measurement was found as 77.56 $\pm$ 74.62 (min-max: 5-200, median: 74.18). RF was found as positive in 50 (34%) patients, with 40 of these patients having arthritis. The mean RF measurement was found as 86.12 $\pm$ 93.35 IU/ml. There was no relationship between anti-CCP and arthritis ( $p=1.000$ ).

All clinical and laboratory parameters were included in the analysis. The p values of the tests were summarized in Table 2. Anti-CCP was found to be significantly correlated with RF only ( $p=0.032$ ). No other significant result was determined. Out of ten anti-CCP positive patients, seven had arthritis with all involvements having the polyarthritis form. RF was found to be

positive in five of seven anti-CCP-positive patients with arthritis. Both RF and anti-CCP were found to be positive in five patients.

Table 1: Clinical findings of the SLE patients

Clinical Findings	n	%
Malar rash	72	49.0
Discoid rash	23	15.6
Photosensitivity	86	58.5
Oral ulcer	43	29.0
Alopecia	17b	11.5
Arthritis	100	68.0
Kidney involvement	73	49.6
Serositis	43	29.0
Neurological involvement	14	9.5
Hematological involvement	131	89.1
Raynaud Phenomenon	14	9.5

Table 2: The relationship between the anti-CCP result, laboratory results, and clinical findings

	Anti-CCP (+) n:10	Anti-CCP (-) n:137	p
Gender (Female)	7	118	0.173
Malar rash (+)	4	68	0.746
Discoid rash (+)	2	21	0.656
Photosensitivity (+)	6	80	1.000
Oral ulcers (+)	2	41	0.724
Alopecia (+)	0	17	0.606
Arthritis (+)	7	93	1.000
Renal involvement (+)	5	68	1.000
Serositis(+)	5	38	0.157
Pleural involvement (+)	3	26	0.414
Pericardial involvement (+)	3	27	0.427
Neurological involvement (+)	0	14	0.599
Hematological involvement (+)	8	123	0.298
Hemolytic anemia (+)	0	14	0.599
Lymphopenia (<1500/mL) (+)	8	122	0.325
Leucopenia (<4000/ mL) (+)	2	61	0.189
Thrombocytopenia(<100.000/mL) (+)	2	24	0.691
Anti-dsDNA (+)	6	85	1.000
Anti-Sm(Smith) (+)	2	15	0.325
C3 (low)	6	80	1.000
C3 (normal)	4	56	
C4 (low)	6	65	0.561
C4 (normal)	4	71	
ACA (Anticardiolipin Antibodies) (+)	0	25	0.228
ACA (Anticardiolipin Antibodies) (-)	9	87	
LAK (Lupus Anticoagulant) (+)	2	23	0.832
LAK (Lupus Anticoagulant) (-)	5	58	
Direct Coombs (+)	2	39	0.768
Direct Coombs (-)	2	32	
ENA profile (+)	6	101	0.461
Ro-52 (+)	0	39	0.063
Ss-A(+)	0	41	0.062
Ss-B (+)	0	19	0.361
Nucleosomes (+)	3	51	0.746
dsDNA (+)	4	40	0.487
Sm-RNP (+)	2	28	1.000
Sm (+)	2	12	0.243
Histones (+)	4	32	0.260
Ribosomal Protein (+)	0	10	1.000
Rheumatoid Factor (RF) (+)	7	43	0.032*
Age of Diagnosis (y)	47.5 (30.50-59.25)	42.00 (34.00-52.00)	0.672
Time between symptoms and diagnosis(m)	7.00 (0.75-47.25)	5.00 (1.00-24.00)	0.856
Follow-up period (m)	54.00 (12.75-121.50)	73.72 (37.00-0.00)	0.595
Duration of the disease (m)	79.00 (13.50-121.75)	86.00 (48.00-145.00)	0.250

Ss-A: Sjögren's Syndrome related antigen A, Ss-B: Sjögren's Syndrome related antigen B, m: month, y: years

## Discussion

SLE is an inflammatory rheumatic disorder, characterized by autoantibody and immune complex production, heterogeneous clinical and laboratory findings as well as the involvements of the skin, serous membranes, joints, and the kidney [1, 2]. The prevalence of arthritis in SLE was reported to be 48-90%, and it is one of the most common symptoms of SLE [23-26].

Several studies have been recently conducted for investigation of the roles of various novel autoantibodies in SLE, including anti-CCP. Arthritis has non-erosive and non-deforming characteristics in most cases, not leading to direct irreversible

function loss. In our study, all arthritis cases had non-erosive and non-deforming characteristics.

It has been indicated that the risk of erosive arthritis development is increased in anti-CCP-positive patients [16-23]. However, there are also other studies indicating that there is no significant relationship between anti-CCP and arthritis [23,27]. None of the patients included in this study had erosive arthritis, and seven out of 10 anti-CCP-positive patients had arthritis in the type of polyarthritis. In another study, anti-CCP was found as positive in only one patient out of eight SLE patients with erosive arthropathy [23].

Citrulline-dependent anti-CCP reacts with citrullinated peptide, whereas it does not react with unmodified arginine-containing peptide. In most of the studies investigating the relationship between anti-CCP and SLE, commercial anti-CCP ELISA kit was used, and it was not investigated whether it was citrulline-dependent or not. In the study of Kakamanu et al. [17], including 329 SLE patients, and which indicated a relationship between citrulline-dependent anti-CCP and arthritis, anti-CCP was found as positive in 56(17%) patients. In the same study, citrulline-dependent anti-CCP was found as positive in 26 patients. Since most of the studies indicating the relationship between SLE and anti-CCP did not mention whether it was citrulline-dependent or not, it is likely that the relationship between anti-CCP and SLE might be associated with the citrulline-dependent portion of anti-CCP. This difference may be the reason of difference amongst studies conducted on this topic. It was also indicated that arthritis seen in SLE might also be related with citrulline-dependent anti-CCP, like RA [14,17-19,21-23].

A recent study has reported that the majority of anti-CCP-positive cases were citrulline-dependent in non-RA rheumatological disorders including six of nine SLE patients [28]. There are conflicting results about the relationship between anti-CCP and erosive arthritis. The rate of erosive or deforming arthritis with positive anti-CCP was reported to be 13% and 7% in studies of Mediwake et al. and Damian et al., whereas it was reported to be 80% and 50% in the studies of Martinez et al. and Chan et al. [18,21-23]. Furthermore, it was reported that the level of anti-CCP had not significantly increased in SLE patients, even with erosive arthropathy. It was asserted that anti-CCP could be used in the differential diagnosis of RA and SLE [18,23]. Although anti-CCP is not a definitive tool for distinguishing RA and SLE patients with erosive arthropathy, it can be used as a supportive parameter. It was asserted that conflicting results might be derived from different cut-off values, which leads to the miscalculation of positive and negative anti-CCP results [28]. There is another type of arthritis called Jaccoud's arthritis, which is a non-erosive type of deforming arthritis, developing in 4-13% of SLE patients [24,29-31]. The characteristic deformity in Jaccoud's arthritis is the reversible ulnar deviation in most cases, and the severity of lesions is much less when compared to the severity of the deformity. It was indicated that anti-CCP level was not significantly increased in SLE patients with erosive arthropathy, and the patients with significantly increased anti-CCP levels had Jaccoud's arthropathy which likely has different pathogenesis [17]. Although it is known that the deformity in Jaccoud's type arthropathy in SLE patients is different from the

deformity in RA, it may be possible that these two deformities can be somehow related with each other since the citrulline-dependent anti-CCP levels are significantly increased in these patients.

In a recent study of Ball et al., it has been reported that MRI was highly sensitive in identifying synovitis, bone edema, and erosive deformities, independent from anti-CCP and RF in SLE patients [32]. This finding indicates that arthritis can be present even when anti-CCP and RF levels are not elevated. This finding supports the studies that were unable to show the relationship between anti-CCP and arthritis in patients with SLE. It was also reported that several factors such as smoking could affect the result of the anti-CCP test. We did not record the smoking status; therefore, we cannot make any assumption about smoking. However, the different demographic and clinical features of the patients might have been associated with the conflicting results.

#### Limitations

Our study was conducted in a single hospital, and the design of the study was retrospective. Citrulline dependency of the anti-CCP test also was not evaluated, which could have provided a valuable data for the analysis. These factors can be listed as the limitations of the study.

#### Conclusion

This study aimed to investigate the relationship between anti-CCP and arthritis along with all other clinical and laboratory parameters in SLE patients. It is the study that includes all clinical and laboratory parameters in a large patient population in Turkey. Since the characteristics of SLE vary in different regions, we can assert that this study provides an important source of information about the diagnostic value of anti-CCP in SLE patients.

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