Assessment of serum levels of anti-cyclic citrullinated peptide antibodies in patients with psoriatic arthritis: A cross-sectional study in a Brazilian cohort

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Received March 12, 2020; Accepted July 10, 2020

DOI: 10.3892/br.2020.1343

Abstract. Presence of the anti-cyclic citrullinated peptide (CCP) antibody is considered a hallmark of rheumatoid arthritis, and may be found in patients with other rheumatic diseases, including psoriatic arthritis (PsA). The aim of the present study was to determine whether the anti-CCP antibody was present in patients with psoriasis with and without arthritis. and to determine whether its presence was associated with clinical, serological and treatment data in patients with PsA. The present study was a cross-sectional study, which included 91 patients with psoriasis (41 with arthritis and 48 without arthritis) as well as an age and sex matched control group consisting of 100 healthy individuals. Presence of the anti-CCP antibody was determined using commercially available ELISA kits. Data on clinical, serological and treatment characteristics was obtained from reviewing each patient's medical history. The quality of life and articular inflammatory activity were assessed using the Short Form Health Survey-12 questionnaire. Skin disease was evaluated using the Psoriasis Area Severity Index and body surface area. In the control group, 1% of individuals were positive for the anti-CCP antibody, whereas 17.5% of the psoriasis patients were positive (P<0.001). In the patients with PsA, 20.9% were positive for the antibody, and in patients with psoriasis without joint disease, 14.5% were positive (P=0.58). Patients with polyarticular forms of PsA were more likely to be anti-CCP positive compared with patients with skin disease without arthritis (P=0.009). In the group of patients with PsA, those who were anti-CCP positive were more likely to suffer from polyarticular forms of arthritis, but no differences were found in the quality of life, joint disease activity, degree of skin involvement and treatment requirements (all P>0.05). In conclusion, 17.5% of patients with psoriasis and 20.9% of patients with PsA were positive for anti-CCP antibodies. Polyarticular arthritis was more common in the anti-CCP positive patients compared with the anti-CCP negative patients.

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Key words: psoriasis, anti-cyclic citrullinated peptides, autoantibodies

Introduction

Psoriasis is an autoimmune skin disease that affects 0.91% of the population in the USA and 8.5% in Norway (1). Certain patients with psoriasis will develop psoriatic arthritis (PsA) that causes pain and functional impairment, bringing additional burden to these individuals (2). It is commonly observed that individuals with a family history of PsA (3), psoriasis in the nail (4), scalp (5) or intergluteal region (5) are at an increased risk of developing arthritis; however there are no established serum markers to predict this risk.

PsA is one of the spondyloarthritides that are seronegative, as there are no autoantibodies which assist with diagnosis (6). However, despite the fact that the CASPAR classification criteria for diagnosis of PsA includes the presence of negative rheumatoid factor (RF) (6), certain patients do present positive for this autoantibody (7) and its significance is not completely understood.

Anti-cyclic citrullinated peptides (CCPs) are autoantibodies that recognize citrulline-containing peptides (8). Citrulline may be formed as the result of posttranslational modifications (citrullination/deamination) of arginine, which are catalyzed by intracellular enzymes, such as peptidylarginine deaminases (8). Anti-CCP antibodies are present in the sera of 60-80% of patients with rheumatoid arthritis (RA) with a specificity of 85-99% (8). In some patients with PsA, anti-CCP antibodies have also been detected (9). A study by Perez-Alamino *et al* (9) showed that 13.5% of their 81 patient cohort were positive for anti-CCP antibodies, and that the presence of these antibodies was more common in patients with erosive arthritis.

The aim of the present study was to evaluate the frequency of presence of anti-CCP antibodies in patients with psoriasis with and without arthritis in a cohort recruited from Southern

Brazil. Additionally, the clinical characteristics between patients with PsA with and without anti-CCPs antibodies were compared.

Materials and methods

Ethical approval. The present study was approved by the Local Committee of Ethics in Research of the Sociedade Evangélica Beneficente de Curitiba (approval no. CAAE 73205317.2.0000.0103) and all participants provided signed informed consent. All procedures involving participants were performed in accordance with the ethical standards of the institutional and national research committees, and the 1964 Helsinki declaration including its later amendments or comparable ethical standards (10).

Sample and data collection. Patients with psoriasis with and without arthritis were included in the present study. PsA patients were classified according to the CASPAR criteria (11). This was a convenience sample that included all patients that attended the hospital for a regular appointment during a period of 10 months (between September 2018 and July 2019) that agreed to participate in the present study. As controls, self-declared healthy individuals from the hospital staff, paired for sex and age were used. Epidemiological and clinical data, and data on the presence of RF and treatment information were obtained retrospectively through analysis of medical records. Serum sample and data collection were performed between September 2018 and July 2019. These patients attended the Rheumatology and Dermatology Clinics of the Mackenzie University Hospital in Curitiba, Brazil periodically to monitor the disease.

The inclusion criteria were: Patients who had a diagnosis of psoriasis confirmed by a dermatological clinician. Patients with arthritis had to fulfil the criteria outlined in the CASPAR Classification system (6). Pregnant patients, individuals <18 years of age and those diagnosed under the age of 16 years were excluded.

Simultaneously with blood collection, Psoriasis Area Severity Index (PASI) and body surface area (BSA) (12), nail involvement were determined in the patients with psoriasis, and they were asked to answer a quality of life questionnaire SF-12 (Short Form Health Survey-12) (13).

PASI is an index used to express the severity of psoriasis; it combines the severity (erythema, induration and desquamation) and percentage of affected skin. PASI score ranges from 0 (no disease) to 72 (maximal disease) (12). BSA classifies the severity of skin psoriasis according to the amount of affected surface area. Values <3% are considered as mild disease, between 3-10% is considered moderate and >10% is considered severe (12). SF-12 is a survey used to evaluate the quality of life, with 12 questions that are divided into physical and mental status; it ranges from 0 (worst case scenario) to 100 (best case scenario) (13).

Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Ankylosing Spondylitis Disease Activity Score (ASDAS)-ESR (14) and ASDAS-CRP (14) were measured to evaluate articular inflammatory activity. ASDAS is a composite instrument that takes into account duration of morning stiffness, degree of back and peripheral pain (or swelling), patient's global assessment and C reactive protein (for ASDAS-CRP) or ESR (for ASDAS ESR). ASDAS is scored as follows: <1.3, inactive disease; 1.3-<2.1, low disease activity; 2.1-<3.5, high disease activity; and >3.5, very high disease activity (15).

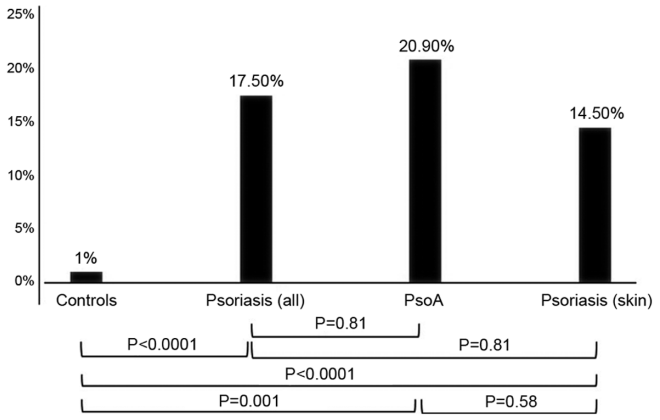

Figure 1. Comparison of the presence of anti-cyclic citrullinated peptide antibodies in the healthy sample and patients with psoriasis with and without arthritis.

A total of 91 patients with psoriasis (53.6% female; mean age 54.4±12.1 years; age range 21-76 years) and 100 healthy controls (51% female; mean age 52.8±10.8 years; age range 18-77 years) were recruited for the present study.

Determination of anti-CCP antibodies. A total of 5 ml venous blood from each patient and control was collected. Serum aliquots were stored at -80˚C until the assays were performed. Serum levels of anti-CCP were measured using a commercial ELISA kit (cat. no. ORG301 anti-CCP high sensitive; Orgentech Diagnostika) according to the manufacturer's protocol. The cut-off point was set as 20 units/ml.

Statistical analysis. Anti-CCP positivity between patients with psoriasis (with and without arthritis) and controls was compared. In addition, epidemiologic and clinical data of PsA patients positive or negative for anti-CCP antibodies was compared. For comparisons, the data was collected in a frequency and contingency table. To compare nominal data, a Fisher's exact test was used. To compare numerical data, an unpaired t-test or Mann-Whitney U test was used. Data distribution was evaluated using a Shapiro Wilk's test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 91 patients with psoriasis were included in the present study, of which 43 (47.2%) had arthritis and 48 (52.7%) did not. For the control group, 100 healthy controls were recruited matched for age and sex. In the PsA subgroup, 44.1% of the patients had axial involvement and 88.3% had peripheral involvement (41.8% had the polyarticular form; 46.5% had the oligoarticular form). Dactylitis was present in 37.1%, distal interphalangeal involvement in 6.9% and enthesitis in 69.7%, with several patients exhibiting more than one manifestation.

The presence of anti-CCP antibodies in the studied samples is shown in Fig. 1. Anti-CCP antibodies were found in 17.5% of the psoriasis group and in 1% of the control

Table I. Comparison of anti-CCP positive and negative psoriatic arthritis patients.

Characteristics	Anti-CCP positive, n=9	Anti-CCP negative, n=34	P-value
Sex, n			0.47[e]
Male	5	14	
Female	4	20	
Age, years[c]	54.2±12.4	54.4±11.2	0.95[g]
Ethnic background			
Caucasains	88.90%	80%	
African descendent	11.10%	20%	1.00[e]
Smoker	57.10%	48.10%	1.00[e]
Skin disease duration, months[d]	348 (78-448)	132.0 (80.0-240)	0.18[h]
Articular disease duration, months[d]	60 (36.0-132.0)	76.0 (36.0-108.0)	0.99[h]
Rheumatoid factor positive	11.10%	0	0.20[e]
Form of arthritis			
Axial + peripheral (oligo or polyarthritis)	66.60%	29.40%	0.15[e]
Only axial involvement	0	14.70%	0.56[e]
Only peripheral involvement	100%	85.20%	0.56[f]
Polyarthritis	88.80%	29.40%	0.002[b,e,i]
Oligoarthritis	11.10%	55.80%	0.02[a,e,j]
Distal interphalangeal joint involvement	11.10%	5.80%	0.51[e]
Dactylitis	28.50%	39.20%	0.68[e]
Entesitis	88.80%	64.70%	0.23[e]
Nail involvement	48.80%	58.30%	1.00[e]
CRP, mg/dl[d]	7.8 (2.0-22.1)	2.4 (1.1-5.5)	0.08[h]
ESR, mm/h[d]	27.6 (13.7-67.5)	30.0 (21.0-40.5)	0.94[h]
Conventional DMARD use	66.60%	63.30%	1.00[e]
Biological drugs use	44.40%	54.80%	0.71[e]
ASDAS ESR[d]	3.60 (1.37-14.9)	2.65 (1.34-3.30)	0.28[h]
ASDAS CRP[d]	2.13 (1.17-4.78)	1.69 (1.09-2.64)	0.52[h]
Quality of life			
SF12-physical domain[c]	31.7±11.6	36.5±8.8	0.25[g]
SF-12-mental domain[c]	47.7±14.1	41.1±11.05	0.21[g]
PASI[d]	0.80 (0-3.0)	1.20 (0-4.15)	0.92[h]
BSA[d]	1.0 (0-4.0)	2.0 (0-5.0)	0.97[h]

[a]P<0.05, [b]P<0.01. [c]Mean ± standard deviation; [d]Median (interquartile range). [e]Fisher' exact test; [f]χ^2-test; [g]unpaired t-test; [h]Mann Whitney test. [i]OR=19.20, 95% CI=2.1-174.4; [j]OR=0.09; 95% CI=0.01-0.87. CCP, cyclic citrullinated peptide; ASDAS, ankylosing spondylitis disease activity score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; SF, short form-12 quality of life questionnaire; PASI, Psoriasis Area Severity Index; BSA, body surface area; DMARD, disease modifying anti rheumatic drugs; OR, odds ratio; CI, confidence interval.

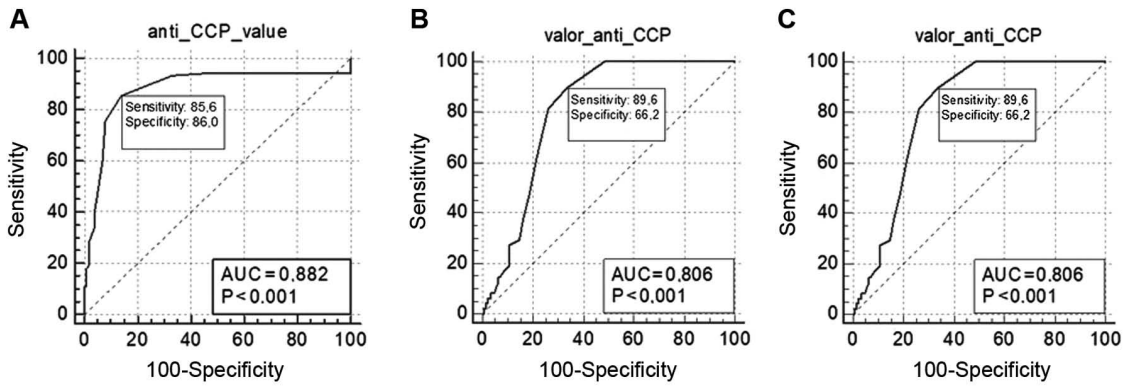

Figure 2. Sensitivity and specificity of the anti-CCP antibodies in the patients with psoriasis for patients (A) with psoriasis with and without arthritis; (B) with psoriatic arthritis; and (C) with psoriasis without arthritis. AUC, area under the curve; CCP, cyclic citrullinated peptide.

group (P<0.001). In patients with PsA, 20.9% were positive for anti-CCP antibodies and 14.5% of patients without joint disease were positive (P=0.58).

The sensitivity and specificity of anti-CCP antibodies in each studied group is shown in Fig. 2A for the entire psoriasis group (with and without arthritis), Fig. 2B for patients with PsA and Fig. 2C for patients with psoriasis without arthritis.

Anti-CCP antibodies were more commonly present in patients with a polyarticular form of PsA compared with those with skin disease only (44.4 vs. 14.5%, respectively; P=0.009), and there was a trend of increased frequency in patients with polyarticular arthritis compared with olygoarticular peripheral arthritis (5 vs. 33.3%; P=0.06).

The results of analysis of samples from patients with PsA with and without anti-CCP antibodies are shown in Table I. The presence of anti-CCP was significantly higher in patients with polyarthritis (P=0.002; OR=19.20, 95% CI=2.1-174.4). In addition, psoriatic patients with oligoarthritis showed lower positivity for anti-CCP (P=0.02; OR=0.09; 95% CI=0.01-0.87).

Discussion

The results of the present study show that the prevalence of anti-CCP antibodies in patients with psoriasis was significantly higher than patients without psoriasis, and this increase in prevalence was not altered by the complication of arthritis. However, patients who were anti-CCP positive and had arthritis exhibited a higher prevalence of polyarticular forms of arthritis.

Eker *et al* (16) studied patients with PsA and found that the prevalence of patients with anti-CCP antibodies was 20.6% in the 44 patient cohort recruited from Turkey. Inanc *et al* (17) studied patients with PsA, and found that the prevalence of patients with anti-CCP antibodies was 12.5%. Conversely, Korendowych *et al* (18) did not find any differences in anti-CCP antibody levels in patients with PsA compared with the control group. Differences in the results may be due to the influence of the genetic background of the studied populations, or due to the commercial kits used for anti-CCP antibody detection. In addition, it is necessary to take into account that PsA is a very polymorphic disease with several forms of clinical presentations (5). Different proportions of these various forms in the different samples may have influenced the results.

Very few studies have determined the presence of anti-CCP antibodies in patients with skin disease without joint involvement, as was performed in the present study. Of the previous studies where skin involvement without joint involvement was assessed, the prevalence of anti-CCPs antibodies in patients with PsA was higher in patients with arthritis compared with patients without arthritis (19,20). In the present study, the proportion of patients with anti-CCP antibodies was similar between patients with skin-only involvement when compared with patients with PsA. However, when considering only patients with the polyarticular form of PsA, the prevalence of anti-CCP antibodies was higher in patients with arthritis. Again, the different proportions of arthritis subtypes may have served a role in the observed results. The presence of anti-CCP antibodies in patients with RA is known to precede manifestation of clinical disease, occasionally by several years (8,21). The same phenomena may be observed in patients with PsA. Similarly, it is possible that some of the positive patients in the present study with just skin disease will develop arthritis in the future.

In patients with RA, anti-CCP positivity is implicated in the pathogenesis of the disease, and is associated with a worse disease prognosis (8). The presence of anti-CCP antibodies is associated with HLA-DRB1 alleles containing a shared epitope. In PsA, it is generally accepted that when this autoantibody is present, the disease is more aggressive (9). Associations between HLA DRB1 alleles (18,22) with the polyarticular forms (17,23-25) have also been found. However, the association between the presence of anti-CCP with higher degrees of erosion is contested (17,18,23-24), as is the necessity for initially treating patients with immunobiologics (18,23). Behrens *et al* (24) suggested that anti-CCP antibodies mediate bone destruction in PsA through an osteocatabolic effect. In the present study, a higher prevalence of the anti-CCP antibodies in polyarticular forms was observed, but there was no increased requirement for therapeutic intervention in the present study, and the quality of life was not altered, suggesting no effect on disease severity. However, a tendency towards higher levels of CRP was observed, showing that the presence of anti-CCP antibodies may be associated with increased inflammatory activity. The degree of bone erosion was not analyzed in the present study, making this a limitation. Other limitations were the cross-sectional design of the study, and the small sample size, which may have resulted in a statistical bias.

Studies have shown that patients with PsA who are positive for anti-CCP antibodies may indeed be patients with RA and psoriasis, as separate conditions, rather than RA being a complication of psoriasis (23,25). Differentiation between patients with PsA from patients with RA and psoriasis as separate conditions may be quite difficult, particularly in those without distal interphalangeal involvement with the presence of RF. In the present study, only one patient was positive for RF. This patient was male with association of a polyarticular form of arthritis and axial involvement-with severe bilateral sacroiliitis and extensive syndesmophytosis, making a RA diagnosis unlikely. However, in the other patients this possibility still remains, and was not addressed in the present study.

In conclusion, the prevalence of anti-CCP antibodies was more common in patients with psoriasis and with PsA compared with healthy controls. Additionally, these autoantibodies were more common in patients with the polyarticular form of arthritis. Additional studies are required, ideally prospectively designed with larger sample sizes, to determine the value of anti-CCP autoantibodies more accurately in the diagnosis and prognosis of patients with psoriasis and PsA.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CG, TS, APBC, JS, VM and RN conceived and designed the study, and acquired the data. CG, TS and RN analyzed and interpreted the data. CG, TS and RN drafted the manuscript and revised it critically for important intellectual content. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Local Committee of Ethics in Research of the Sociedade Evangélica Beneficente de Curitiba (approval no. CAAE 73205317.2.0000.0103) and all participants provided signed informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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