Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without manifestation of joint inflammation.

Concise report

Authors’ affiliations
Gerd Marie Alenius, Ewa Berglin, Solbritt Rantapaa Dahlqvist.
Department of Public Health and Clinical Medicine, Rheumatology, University Hospital, Umeå, Sweden

Corresponding author
Gerd Marie Alenius, Dept of Rheumatology, University Hospital, SE-901 85 Umeå, Sweden,
Phone: +46907851676
Fax: +4690131567
email: gerdmarie.alenius@vll.se

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in ARD editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://ard.bmjjournals.com/misc/ifora/licenceform.shtml).

Keywords; anti-CCP antibodies, psoriasis, psoriatic arthritis
Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without manifestation of joint inflammation.

ABSTRACT
Objective: To examine the presence of anti-CCP antibodies in psoriatic patients with and without manifestation of joint inflammation relative to patients with early rheumatoid arthritis (eRA) and controls.
Methods: Anti-CCP antibodies were measured in 160 patients with psoriatic arthritis (PsA), 146 patients with psoriasis of the skin but no arthritic disease, 101 patients with eRA and 102 healthy controls by ELISA. The cut-off level for the presence of anti-CCP antibodies was 5 U/mL.
Results: 11 patients with PsA (6.9%; median titre 67 U/mL), 75 patients with eRA (74.3%; median titre 85 U/mL), two healthy controls (2%) and one patient with psoriasis without arthritis (0.7%) had titres of anti-CCP antibodies above the cut-off level. The presence of anti-CCP antibodies was not related to radiological changes and/or deformity and functional impairment in PsA.
8/11 patients with PsA and anti-CCP antibodies had a polyarthritic disease, and all fulfilled the ACR criteria for RA at a 4-year follow-up examination. Five of these 8 patients also had manifestations such as dactylitis, DIP-involvement, radiological changes associated with PsA, and/or enthesitis. In multiple logistic regression analysis with polyarthritis as the dependent variable, anti-CCP antibodies and rheumatoid factor significantly distinguished RA from PsA.
Conclusions: Anti-CCP antibodies were more prevalent in patients with PsA than in patients with psoriasis without arthritis, but less so than in patients with eRA. Patients with PsA positive for anti-CCP antibodies more often had polyarthritic disease but the presence of anti-CCP antibodies did not relate to radiological changes and/or deformity and functional impairment.

Psoriatic arthritis (PsA) is a heterogeneous disease with disease patterns that vary between patients, as well as within an individual patient over time. The patients may have symptoms and signs, such as mild mono-oligoarthritis or very severe, erosive and destructive polyarthritis, that are possibly indistinguishable from those observed in patients with rheumatoid arthritis (RA) (1). Other common manifestations are spondyloarthropathy with axial involvement (1), dactylitis and/or enthesitis (2). Rheumatoid factor (RF) is usually absent, albeit there are reports of a slightly increased frequency of RF in patients with psoriasis and inflammatory joint manifestations (3). In the Moll and Wright (1) criteria for PsA, RF should be negative for diagnosis but in clinical practice there are patients diagnosed as having PsA if the disease pattern is more consistent with PsA (e.g., dactylitis, enthesitis, distal interphalangeal (DIP) joint involvement) rather than RA even with a positive RF result. Laboratory assessment of inflammatory activity, such as increased erythrocyte sedimentation rate (ESR), is often sparse, and to data a laboratory test with specificity for PsA is unavailable.

During the past decade new, aggressive treatments against arthritic diseases, such as RA, have become available and the possibility of treating the disease efficiently has changed the outcome for many patients.
A positive RF test is included in the diagnostic criteria for RA even though RF is detected in other rheumatic diseases as well (4). The development of the tests for antibodies against cyclic citrullinated peptide (anti-CCP) has increased the possibility to distinguish between RA and other rheumatic diseases (5-7). The specificity for RA has been shown to increase by combining the presence of anti-CCP antibody with that of RF (5, 8). Furthermore, the presence of anti-CCP antibodies and of RF’s of all isotypes predate the onset of RA by several years (8). Anti-CCP antibodies have the highest predictive values for the development of RA; however, the predictive value is increased by the concurrent presence of anti-CCP antibodies and IgA-RF (8). It is also evident that anti-CCP antibody positive patients with RA have a more erosive disease compared with RA patients negative for anti-CCP (5).

The specificity of anti-CCP antibodies for other arthritic diseases is low compared with RA (4-7). A recent report has shown that anti-CCP antibodies occurred in 7.8% of patients with PsA (9). In that report some of the patients had a disease pattern typical of PsA whilst others could be psoriatic patients with concurrent RA.

The objective of the present study was to examine the presence of anti-CCP antibodies in psoriatic patients with and without manifestation of joint inflammation in comparison with patients with early rheumatoid arthritis (eRA) and healthy controls.

METHODS AND MATERIAL
A total of 306 consecutively examined patients with psoriasis, of whom 160 (76 females, 84 males) were diagnosed as having joint inflammation, and 146 (81 female, 65 male) of the patients had psoriasis of the skin with no arthritic disease were recruited into this cross-sectional study. Additionally, 101 patients (74 females, 27 males) attending the eRA clinic were consecutively included, together with 102 randomly selected self-stated healthy controls from the same geographic area, and with the same ethnic background. Anti-CCP antibodies were measured in plasma from patients and controls using the Diastat kit from Axis-Shield Diagnostics Limited (The Technology Park, Dundee DD2 1XA, Scotland, UK). The cut-off level for a positive test for anti-CCP antibodies was 5 U/mL.

The mean age of all subject groups was between 50 and 53 years, and the mean disease duration for the PsA patients was 16 years and eRA patients <1 year. For the patient groups, ESR and RF were also analysed; the number of tender and swollen joints were counted according to the ACR 68 joint count for tender and 66 joint count for swollen joints (10) excluding the DIP-joints of the fingers and IP-, PIP- and DIP-joints of the toes which are rarely involved in RA.

Statistics
Differences between continuous data were tested using the Mann-Whitney test and between categorical data using the Chi-square test. Spearman rank-order correlation was used to test for correlations between variables in small samples. Multiple logistic regression analysis was used to test the predictive value of variables that were unevenly distributed between the groups.

The study was approved by the Regional Research Ethics Committee.

RESULTS
Eleven patients with PsA (6.9%; median titre 67.3 U/mL, IQR=19.6-122.5), 75 patients with eRA (74.3%; median titre 85.2 U/mL, IQR=50.2-118.2), two healthy controls (2%) and one patient with psoriasis without arthritis (0.7%) had titres of anti-CCP antibodies above the cut-off level. The difference between PsA patients and psoriatic patients without arthritis was significant (p=0.006), as was that between PsA patients and eRA patients (p<0.001) whereas the difference between PsA patients and controls was not significant (p=0.086). Eighteen patients with PsA (11.4%) and 84 of the patients with eRA (83.2%) were positive for RF (p<0.001); furthermore, 9 patients with PsA (5.6%) and 70 patients with eRA (69.3%) were positive for both anti-CCP and RF. The number of tender joints and the number of swollen joints were higher in patients with eRA than in patients with PsA (median 10.0 v 3.0, p<0.001 and 11.5 v 5.0, p<0.001, respectively). There were no correlations between the titres of anti-CCP antibodies and the number of swollen or tender joint count, either in the patients with PsA or with eRA. Nor was the presence of anti-CCP antibodies related to aggressive manifestations such as radiological changes and/or deformity and functional impairment in PsA.

At a 4-year follow-up examination, 8 of the 11 patients with PsA positive for anti-CCP had a polyarthritic disease and all fulfilled ≥4 of the ACR criteria for RA (11). Five of these 8 patients also had manifestations such as dactylitis, DIP-involvement, radiological changes associated with PsA, and/or enthesitis (Table 1). In multiple logistic regression analysis with polyarthritis (based on ACR joint count) as a dependent variable, anti-CCP antibodies (p<0.001, OR=6.530, CI 95%=2.322-18.365) and RF (p<0.001, OR=11.104, CI 95%=4.087-30.164) significantly distinguished RA from PsA (data not shown).

DISCUSSION
In this study the prevalence of anti-CCP antibodies was increased in patients with psoriasis with arthritis compared with patients with psoriasis without arthritis, however the frequency was significantly lower than in patients with eRA. Only 11 patients with PsA were positive for anti-CCP antibodies, most of whom fulfilled the ACR-criteria for RA at 4-year follow up. Most frequently they fulfilled the criteria of positive RF, polyarthritis, arthritis in hands, and morning stiffness. However, some of the patients fulfilling the criteria for RA had clinical signs associated with PsA indicating the complexity and difficulty in diagnosing the two diseases. The number of patients with PsA positive for anti-CCP antibodies was not sufficient to stratify for sub-group analysis. Although the presence of anti-CCP antibodies did not correlate with the number of swollen or tender joints it seemed, when evaluating each positive patient separately, that anti-CCP antibodies in PsA-patients were related to polyarthritis and the presence of RF rather than to RA as defined by the ACR criteria. On the other hand, there is a possibility that the patients have both PsA and RA since both diseases are quite common in the population. This explanation would further strengthen the association between anti-CCP antibodies and RA. However, in multiple logistic regression anti-CCP antibodies, and more stronger, RF distinguished RA from PsA.

Recent studies report an association between radiological progression and the presence of anti-CPP antibodies in patients with RA (4). In the present study, the patients with RA had short disease duration (< 1 year) and, consequently, radiological progression was not evaluated. In the PsA-patients there was no association between radiological changes and/or deformity/functional impairment with anti-CCP antibodies.

CONCLUSIONS
Anti-CCP antibodies were more common in patients with PsA than in patients with psoriasis without arthritis, but less common than in patients with eRA, which confirms findings of a recent report (9). Patients with PsA and positive for anti-CCP antibodies more often had polyarthritic disease but the presence of anti-CCP antibodies was not associated with radiological changes and/or deformity and functional impairment. Anti-CCP antibodies and RF predicted RA in patients with polyarthritic disease.

ACKNOWLEDGEMENT
We are grateful to Tord Johansson of the Department of Medical Biochemistry and Biophysics/Omnio, University Hospital Umea, for excellent technical assistance. The study was supported by grants from the Swedish psoriasis association.

Competing interests. None declared.

REFERENCES
<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Disease pattern</th>
<th>RF</th>
<th>anti-CCP antibody (titre)</th>
<th>≥4 of the ACR criteria for RA</th>
<th>Disease manifestations and actual treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>68/m</td>
<td>axial disease</td>
<td>0</td>
<td>60.0</td>
<td>0</td>
<td>No disease activity</td>
</tr>
<tr>
<td>48/f</td>
<td>mono-oligoarthritis</td>
<td>0</td>
<td>80.4</td>
<td>0</td>
<td>Medium disease activity. Methotrexate+Sulfasalazine</td>
</tr>
<tr>
<td>30/m</td>
<td>ologoarthritis</td>
<td>320</td>
<td>67.3</td>
<td>0</td>
<td>No disease activity, no radiological changes in the joints of the feet</td>
</tr>
<tr>
<td>67/f</td>
<td>polyarthritis + axial disease</td>
<td>80</td>
<td>35.6</td>
<td>1</td>
<td>Low disease activity. Sulfasalazine.</td>
</tr>
<tr>
<td>63/m</td>
<td>polyarthritis + axial disease</td>
<td>80</td>
<td>19.6</td>
<td>1</td>
<td>Low-medium disease activity, enthesitis, DIP- and MTP-joints, knees, back involvement. Sulfasalazine</td>
</tr>
<tr>
<td>65/m</td>
<td>polyarthritis</td>
<td>160</td>
<td>113.2</td>
<td>1</td>
<td>High disease activity, back involvement, enthesitis, no swollen joints, DIP-joint involvement</td>
</tr>
<tr>
<td>50/f</td>
<td>polyarthritis</td>
<td>80</td>
<td>13.1</td>
<td>1</td>
<td>Medium-high disease activity, radiological destruction hands, feet, destruction MCP II sin, joint/tuft osteolysis MTP I (pencil in cup). Remicade</td>
</tr>
<tr>
<td>33/f</td>
<td>polyarthritis</td>
<td>160</td>
<td>5.4</td>
<td>1</td>
<td>Medium disease activity, clinically PsA, joint function impairment, radiological destruction MCP I sin. Methotrexate + gold injections.</td>
</tr>
<tr>
<td>61/m</td>
<td>polyarthritis</td>
<td>320</td>
<td>122.5</td>
<td>1</td>
<td>Low disease activity. Predisolone</td>
</tr>
<tr>
<td>56/f</td>
<td>polyarthritis</td>
<td>320</td>
<td>123.3</td>
<td>1</td>
<td>Disease activity</td>
</tr>
<tr>
<td>75/m</td>
<td>polyarthritis</td>
<td>320</td>
<td>256.3</td>
<td>1</td>
<td>Low disease activity. Auranofin</td>
</tr>
</tbody>
</table>

**Table 1.** The eleven patients positive for anti-CCP diagnosed as PsA at inclusion in the study, and disease manifestations at four-year follow-up examination.