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ORIGINAL RESEARCH ARTICLE

Anti-CCP is not a marker of severity in established rheumatoid arthritis: An MRI study

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ABSTRACT

Introduction: the presence of anti-CCP is an important prognostic tool for rheumatoid arthritis (RA), but its relationship with the activity of the disease and functional capacity is still being investigated. **Objectives:** to study the relationship between anti-CCP and the indices of disease activity, functional capacity and structural damage, by means of conventional radiography (CR) and magnetic resonance imaging (MRI), in stabilized RA. **Methods:** cross-sectional study of RA patients with one to 10 years of disease. The participants were subjected to clinical evaluation with anti-CCP screening. Disease activity was assessed by means of the Clinical Disease Activity Index (CDAI) and functional capacity by means of the Health Assessment Questionnaire (HAQ). CR was analyzed by the Sharp van der Heijde index (SmvH) and MRI by the Rheumatoid Arthritis Magnetic Resonance Image Scoring System (RAMRIS). **Results:** 56 patients were evaluated, with median (IIq) of 55 (47.5–60.0) years, 50 (89.3%) were female among whom 37 (66.1%) were positive for anti-CCP. The median (IIq) of CDAI, HAQ, SmvH and RAMRIS were 14.75 (5.42–24.97), 1.06 (0.28–1.75), 2 (0–8) and 15 (7–35), respectively. There was no association between anti-CCP and CDAI, HAQ, SmvH and RAMRIS. **Conclusion:** our results did not establish the association of anti-CCP with the severity of the disease. So far, we cannot corroborate the anti-CCP as a prognostic tool in RA established.

Keywords: Anti-CCP Disease Activity; Functional Capacity; Structural Damag

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1. Introduction

The progression of rheumatoid arthritis (RA) brings with it an evolutionary potential for different degrees of joint damage and functional disability. Thus, special attention should be directed to the identification of parameters indicative of poor prognosis, since the definition of the level of the therapeutic intensity, ideally, should be based on reliable predictive factors of severity. It is already known that some characteristics, when present, are associated with a worse evolution of the disease, such as the presence of the rheumatoid factor in high titers, smoking and HLA-DRB1[1,2].

Regarding the prognostic role of anti-CCP, although many studies have suggested that these antibodies are associated with more severe and erosive disease[3-22] mainly in early RA, their association with disease severity and functional capacity is still unclear[9,19-21,23-30]. The methodological heterogeneity of the works that have analyzed the association of anti-CCP with structural damage is also highlighted. Although most of them made use of conventional radiography (CR) as a means of evaluation, different radiographic scanning systems were used. Additionally, only one study also made use of ultrasonography (US), in a small subgroup of patients[6]. There is still a lack of studies that have used magnetic resonance imaging (MRI) for this purpose.

The aim of this study was to investigate the association of the presence of anti-CCP with the severity of the disease, assessed by means of disease activity, functional capacity and structural damage measured by CR and MRI.

2. Patients and methods

This was a cross-sectional study involving outpatients. All participants had a diagnosis of RA established according to the criteria of ACR1987 (American College of Rheumatology)[31] or ACR/Eular 2010 (American College of Rheumatology/The European League Against Rheumatism)[32] with 18 or more years of age and with disease duration between one and 10 years.

Due to the possibility of performing MRI, patients with creatinine clearance less than 60 ml/min/1.73 m^2, metal prosthesis carriers, those unable to access the examination table and pregnant women were excluded from the study. Patients with a history of surgical procedures and/or hand fractures were also excluded from the study.

The study was approved by the Research Ethics Committee and, after the science, clarification and signing of the term of free and clear consent, patients who agreed to participate in the study were subjected to clinical evaluation, with the completion of a specific questionnaire in which demographic and clinical data (time of disease, time between the onset of symptoms and diagnosis, history of smoking, rheumatoid factor positivity, presence of extra-articular manifestations, treatment, CDAI[33] and HAQ, validated for Portuguese[34]) were involved. A blood sample was collected for anti-CCP screening with second generation methods: fluorenzyme immunoassay EliA CCP® (Pharmacia Diagnostics, Germany) and Architect anti-CCP microparticle chemiluminescent assay (Abbott Laboratories, USA). The patients were then divided into two groups, according to the positivity of the test, and the reference value of the kit used (greater than 10 U/ml for fluorenzyme immunoassay and greater than 5 U/ml for chemiluminescence).

The radiographic evaluation was carried out by means of CR of the hands and fingers, in postero-anterior incidence. Radiographs taken with a time difference of up to three months, before or after data collection, were accepted. For the analysis, the SmvH method was used[35], only of hands and fingers[21].

A subgroup of 35 patients was sent for MRI, up to four weeks after the interview, in the GE 1.5 tesla Signa HDxT device (GE Healthcare, Milwaukee, WI, USA). For the analysis of the scans, the RAMRIS protocol was followed[36], for the toe and metacarpophalangeal scans, from the Outcome Measures in Rheumatoid Arthritis Clinical Trials (Omeract) group. The examinations were performed on the dominant hand, in coronal (T1 and T2 with fat suppression), axial (T1 before and after the use of endovenous gadolinium contrast) and axial and coronal (T1 with fat saturation) sequences.

The analysis of the resonance and radiographs was performed by a single radiologist, who was unaware of the patient's clinical condition. Intraobserver agreement was calculated for the SmvH score and the intraclass correlation coefficient calculated was 0.958. It was not possible to calculate the RAMRIS intraclass coefficient, since this requires the calculation of the variance component, which resulted in a negative value. Thus, the Spearmam coefficient calculation was chosen and a value of 0.96 was found.

Data storage and all statistical analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS, version 19). Frequency distributions were presented for categorical variables and numerical synthesis measures for continuous

variables. The association between the categorical variables was analyzed using the chi-square test or Fisher's exact test. The normality of continuous variables was verified with the Shapiro-Wilk test. For non-normally distributed variables, the analysis was performed with the nonparametric Mann-Whitney U test. To verify the association between two non-normal continuous variables, Spearman's non-parametric test was used. A significance level of 5% was considered.

3. Results

From August 2011 to August 2013, 56 patients with a diagnosis of established RA were evaluated. **Table 1** summarizes the demographic, clinical, functional and imaging profile of the patients studied.

The univariate analysis of the association of demographic and clinical characteristics with the presence of anti-CCP showed that this antibody was significantly associated with RF (OR of 6.6 with 95% CI of 1.9–22.9 and $p < 0.01$) and with smoking (OR of 7.8 with 95% CI of 1.9–31.6 and $p < 0.01$).

The univariate analysis of the association of anti-CCP with CDAI, HAQ, SmvH and RAMRIS is presented in **Table 2**. In relation to disease activity, the median value of CDAI was higher in the group of patients with positive anti-CCP, but the relationship was not significant ($p = 0.06$). On the other hand, having negative anti-CCP was not associated with the occurrence of remission or low disease activity status (OR of 2.9 with 95% CI of 0.9–9 and $p = 0.09$). The HAQ, SmvH (total, erosion and space-reduction) and RAMRIS (total, erosion, bone edema and synovitis) scores were not associated with the presence of anti-CCP.

In search of a multivariate model to explain the anti-CCR variable, a logistic regression model was fitted. All the variables that correlated with anti-CCP with a $p < 0.20$ (sex, time of diagnosis, smoking, rheumatoid factor, extra-articular manifestations, rheumatoid nodules, pulmonary involvement, CDAI and HAQ) were used in the adjustment of the initial model. In the final model, anti-CCP was only related to smoking and rheumatoid factor ($p < 0.05$). The model indicated that those who smoke or have already smoked are 5.3 times more likely to have positive anti-CCP (95% CI of 1.2–22.9) and those who have positive RF are 4.4 times more likely to have positive anti-CCP (95% CI of 1.2–16.6). The logistic regression model is presented in **Table 3**.

Table 1. Characteristics of the patients studied

Variables	Measures
Age: Medium (IIq)	55 (47.5–60.0)
Female sex: n (%)	50 (89.3)
Time of disease in years: Median (IIq)	6 (3–9)
Time between disease and diagnosis in years: Median (IIq)	0 (0–1)
Positive rheumatoid factor: n (%)	31 (55.4)
Anti-CCP positive: n (%)	37 (66.1)
Smoke or have smoked: n (%)	25 (44.6)
Presence of rheumatoid nodules: n (%)	8 (14.3)
Presence of pulmonary involvement: n (%)	6 (10.7)
Presence of Sjogren's syndrome: n (%)	2 (3.6)
Patients using corticosteroids: n (%)	49 (87.5)
Synthetic DMARDs in use: n (%)	43 (76.8)
Methotrexate: n (%)	15 (26.8)
Leflunomide: n (%)	5 (8.9)
Hydroxychloroquine: n (%)	3 (5.4)
Methotrexate/leflunomide: n (%)	9 (16.1)
Methotrexate/hydroxychloroquine: n (%)	9 (16.1)
Methotrexate/hydroxychloroquine/sulfassalazina: n (%)	1 (1.8)
Cyclosporine: n (%)	1 (1.8)
Patients in the use of biological DMARDs: n (%)	11 (19.6)
Adalimumab: n (%)	4 (7.1)
Etanercept: n (%)	2 (3.6)
Infliximab: n (%)	3 (5.4)
Tocilizumab: n (%)	2 (3.6)
Patients without DMARDs: n (%)	2 (3.6)
CDAI: Median (IIq)	14.7 (5.4–25.0)
Remission (≤2, 8): n (%)	8 (14.3)
Remission and low activity (≤10): n (%)	23 (41)
Moderate activity (>10, ≤22): n (%)	17 (30.4)
High activity (>22): n (%)	16 (28.6)
HAQ: Median (IIq)	1.06 (0.28–1.75)
Normal (= 0): n (%)	9 (16.1)
Mild to moderate difficulty (>0 and ≤1): n (%)	19 (33.9)
Moderate to severe difficulty (>1 and ⩽2): n (%)	18 (32.1)
Severe to very severe difficulty (>2 and ⩽3): n (%)	10 (17.9)
Sharp van der Heijde[a]	
Total: Median (IIq)	2 (0–8)
Erosion: Medium (IIq)	1 (0–6)
Space reduction: Medium (IIq)	1 (0–5.5)
RAMRIS[b]	
Total: Median (IIq)	15 (7–35)
Erosion: Medium (IIq)	8 (1–19)
Bone edema: Medium (IIq)	6 (2–14)
Synovitis: Medium (IIq)	4 (2–6)

Note: n: number of patients with rheumatoid arthritis; Iiq: interquartile range; anti-CCP: anti-cyclic citrullinated peptide antibody; CDAI: clinical disease activity index; HAQ: health assessment questionnaire; RAMRIS: rheumatoid arthritis magnetic resonance imaging system; DMARDs: disease modifying antirheumatic drugs; DMARDs: disease modifying antirheumatic drugs. [a]:55 patients underwent CR. [b]: 35 patients underwent MRI.

Spearman's correlation coefficient between CDAI and imaging indices (SmvH and RAMRIS) was calculated and no association between them was found. Of the 35 patients who underwent MRI, 13 patients were in remission or low disease activity (CDAI ≤10). Of these, 12 (92.3%) had edema and 12 (92.3%) had synovitis and only two had synovitis greater than 5 mm (16.6%). The median (IIq) of the total RAMRIS index was 21 (1.5–34.0), the erosion index was 9 (3.5–15.1), the edema index was 6 (3.5–12.5) and the synovitis index was 3 (2.1–5.7). Of the 22 (95.6%) patients with moderate to high activity, 21 (95.6%) had edema and 21 had synovitis. The median (IIq) of the total RAMRIS index was 13 (6–31), the erosion index was 5 (1–17), the edema index was 5 (2–14) and the synovitis index was 3.5 (2–6). There was no statistically significant difference between patients in remission and low disease activity and those in moderate and high disease activity, in relation to all RAMRIS indices.

4. Discussion

This study analyzed characteristics of the demographic, clinical, functional and imaging profile of Brazilians with established RA, in order to know the relationship between anti-CCP and the severity of the disease.

In the study population, the frequency of positivity for anti-CCP was 66.1%, similar to that found by Silva *et al.*[18] in Brazilian patients with stable RA. Positivity for RF was 55.4%. This low prevalence can be explained by the fluctuation of antibody levels during the course of the disease in response to treatment[19] or by the design of the study, in which the information on RF positivity was based on medical record data. It is known that anti-CCP and RF tests are correlated. Studies have already shown that most RA patients with positive RF are also anti-CCP positive[3,19]. Thus, our study is in agreement with the literature.

Tobacco smoking is the main environmental process related to RA, mainly in HLA-DRB1-positive patients. Citrullination is induced by tobacco substances, which is the potential pathophysiological mechanism of this process[37]. The present study showed a significant association of smoking with anti-CCP positivity. This result is consistent with that found by Pedersen *et al.*[38,39] who evaluated several environmental risks related to anti-CCP and HLA-DRB1, and by Goeldner *et al.*[40] who studied the association of smoking with anti-CCP in Brazilian patients with stable RA.

The assessment of disease activity in our work was done by CDAI, which shows a good correlation with the other assessment indexes[29,33,41]. Our results show that anti-CCP-positive patients had a higher median CDAI value than anti-CCP-negative patients, but with limited statistical significance ($p = 0.06$). Our results are in agreement with Choe *et al.*[29] who evaluated the association of anti-CCP levels with DAS28, SDAI and CDAI activity indices in patients with stable RA and found no significant association.

Since remission status or low disease activity is the main therapeutic target[42], we also chose to analyze the association of anti-CCP with the occurrence of remission and low disease activity. Our results showed that having negative anti-CCP was not associated with the occurrence of remission and low disease activity ($p = 0.08$). Mota *et al.*[30] who evaluated Brazilian patients with initial RA, did not find a relationship between negativity for anti-CCP and remission by DAS28.

In prospective studies in initial RA, Kastbom *et al.*[24] and Ronnelid *et al.*[10] found an association between anti-CCP and HSV levels, CRP and DAS28. On the other hand, Nell *et al.*[9] despite having found a worse response to treatment in DAS28 in seropositive patients after five and 10 years of follow-up, showed that this result does not maintain statistical significance. In stabilized RA, disease activity is irregularly related to anti-CCP positivity[19,20,23].

Our study found no association between anti-CCP and HAQ. Functional disability in early RA, as assessed by HAQ, does not seem to be associated with the presence of anti-CCP[24,26]. The same result has already been reported in stable RA[19,23]. Shidara *et al.*[28] found a significant association when evaluating the association of anti-CCP with a Japanese version of HAQ, but the higher degree of functional disability due to the average disease duration of 20 years raises the question about the independent as-

Table 2. Association of anti-CCP with indexes of disease activity, functional capacity and structural damage

Variables	Anti-CCP		*p*-value OR (95% CI)
	Negative	Positive	
CDAI, median (IIq)	7.5 (4.2–21.4)	16.2 (5.7–31.4)	$p = 0.06^a$
CDAI			
Remission and low disease activity, n (%)	11 (47.8)	12 (52.2)	$p = 0.09^b$
Moderate and high disease activity, n (%)	8 (24.2)	25 (75.8)	OR = 2.7 (0.9–9.0)
HAQ, median (IIq)	1 (0.25–1.50)	1.13 (0.31–2.00)	$p = 0.49^a$
Sharp van der Heijde			
Total, median (IIq)	1 (0–7)	3.5 (0–8)	$p = 0.29^a$
Erosion, median (IIq)	1 (0–4)	2 (0–6.7)	$p = 0.31^a$
Space reduction, median (IIq)	1 (0–4)	1 (0–2.7)	$p = 0.39^a$
RAMRIS			
Total, median (IIq)	14 (8.5–30.5)	23 (6.7–42.0)	$p = 0.55^a$
Erosion, medium (IIq)	8 (2–15)	10 (1.0–22.2)	$p = 0.50^a$
Bone edema, median (IIq)	5 (2.0–12.5)	8 (2.7–16.0)	$p = 0.37^a$
Synovitis, medium (IIq)	3 (1.5–5.5)	4 (3.0–7.2)	$p = 0.20^a$

Note: n: number of patients; Anti-CCP: anti-cyclic citrullinated peptide antibody; CDAI: clinical disease activity index; HAQ: health assessment questionnaire; RAMRIS: magnetic resonance imaging scoring system in rheumatoid arthritis. [a]: Mann-Witney U-Test. [b]: Chi-square test

Table 3. Multivariate logistic regression in relation to anti-CCP

Variables	Beta	Standard error	OR	95% CI OR	*p*-value
Smoking	1.7	0.7	5.3	(1.2–22.9)	0.027
Rheumatoid factor	1.5	0.7	4.4	(1.2–16.6)	0.027

sociation between the antibody and the functional impairment of RA. In Brazil, Silva *et al.*[18] who studied 100 patients with established RA, with an average of eight years of disease, found an association between anti-CCP and HAQ, while Mota *et a.*[26] who evaluated 65 patients with initial RA in a cross-sectional study, did not find such an association.

Radiographic analysis is considered one of the most objective methods for assessing the severity of RA. The SmvH method, although the most detailed and the most difficult to perform, is considered the most sensitive and accurate in detecting small changes over time[43]. Although the literature shows an association between the presence of anti-CCP and the structural damage measured by CR in initial RA[3-15], when it comes to established RA the results were not so conclusive[15-23]. It should be noted that most of these studies used Larsen or Sharp as a radiographic evaluation method. Hafström *et al.*[44] analyzed the role of RF and anti-CCP in radiological progression in a prospective study, using the SmvH approach, in patients with early RA, based on prednisolone use, found that RF anti-CCP only predicted those radiographic progression in patients not using corticosteroids. Our study also did not establish an association between anti-CCP and structural damage assessed by SmvH in established RA and is consistent with the study by Hafström *et al.*, as 87.5% of our patients were still on prednisone. On the other hand, Gandjbakhch *et al.*[45] in a retrospective study, when analyzing factors involved with radiographic progression (SmvH) in a group of patients in remission and with low disease activity, also found no significant association between anti-CCP and structural damage. The mean rate of structural damage in our sample, when compared to other studies in established RA that used the SmvH method[19,21] was much lower. This suggests that our sample consisted of patients with less severe and erosive disease and/or with a good response to therapeutic intervention.

To our knowledge, this study was the first to analyze the association of anti-CCP with structural damage in RA, measured by MRI. Our results showed that there was no statistically significant difference in the parameters assessed by MRI between anti-CCP positive and negative patients. The RAMRIS score values for synovitis, bone edema and erosion, when compared with those of other studies[46,47] were lower and showed, once again, that our sample was formed by a majority of patients with milder and less erosive disease. It is emphasized that the use of MRI for monitoring treatment with biologic agents can select patients with high disease activity.

Patients in remission and low disease activity may, apart from clinical control, show signs of MRI activity[48,49] and these alterations may determine future radiographic progression[50]. The results of the present study did not indicate any associa-

tion between disease activity and RAMRIS scores. On the other hand, 92.1% of our patients who were in remission or in low disease activity showed signs of inflammation (edema and synovitis) on MRI, although only two of them (16.6%) had synovitis larger than 5 mm. According to Gandjbakhch *et al.*[45] in patients in remission or low activity, only the RAMRIS synovitis index is associated with radiographic progression, with a cut-off point of 5 mm. Thus, 83.4% of our patients in remission and in low disease activity were found to be protected. It is suggested that patients in remission or in low disease activity, but with presence of synovium larger than 5 mm at MRI, have the same potential for radiographic evolution. It is necessary that these patients are accompanied in the same way, independently of the presence of anti-CCP.

In conclusion, in the evaluated sample, the results did not establish the association of anti-CCP with the severity of the disease. The presence of confounding variables, such as early diagnosis and adequate response to therapeutic intervention, contributed to the constitution of a group of less severe and less erosive disease carriers. It is believed that the way of selecting the participants of our study, in which only individuals with less than 10 years of disease and without difficulties to comply with the research protocol were accepted, may also have limited the exposure of the entire RA universe. Even so, this result allows us to question whether anti-CCP would have less influence on prognosis in patients with a more favorable disease profile. On the other hand, due to the small sample size, the present study may have failed to detect the most significant differences. Thus, it is believed that the evaluation of a larger number of individuals, possibly with multicenter distribution, in studies with prospective design of long observation period and, if possible, with greater control of confounding variables, could contribute to the definitive resolution of this issue. So far, we cannot corroborate the indication for anti-CCP screening as an established prognostic tool in RA.

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Conflict of interest

The authors declare that they have no conflict of interest.

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