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Original article

Anti-CCP antibodies are not a marker of severity in established rheumatoid arthritis: a magnetic resonance imaging study☆

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ABSTRACT

Introduction: The presence of anti-CCP is an important prognostic tool of rheumatoid arthritis (RA). But research is still ongoing on its relationship with disease activity and functional capacity.
Objectives: To study the relationship between anti-CCP and disease activity, functional capacity and structural damage indexes, by means of conventional radiography (CR) and magnetic resonance imaging (MRI), in cases of established RA.
Methods: Cross-sectional study with RA patients with 1–10 disease duration. Participants underwent clinical evaluation with anti-CCP. Disease activity was assessed using the Clinical Disease Activity Index (CDAI), and functional capacity through the Health Assessment Questionnaire (HAQ). CR analysis was carried out by the Sharp van der Heijde index (SvdH), and MRI analysis by RAMRIS (Rheumatoid Arthritis Magnetic Resonance Image Scoring).
Results: We evaluated 56 patients, with a median (IqR) age of 55 (47.5–60) years; 50 (89.3%) participants were female and 37 (66.1%) were positive for anti-CCP. Medians (IqR) of CDAI, HAQ, SvdH 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 and SvdH and RAMRIS scores.
Conclusion: Our results have not established an association of anti-CCP with the severity of disease. To date, we cannot corroborate anti-CCP as a prognostic tool in patients with established RA.

☆ Study conducted at the Rheumatoid Arthritis Outpatient Clinic, Service of Rheumatology, Santa Casa de Belo Horizonte, and at the Post-Graduate Program in Adult Health, Medicine School, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.

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O anti-CCP não é um marcador de gravidade da artrite reumatoide estabelecida: um estudo de ressonância magnética

Palavras-chave:
Anti-CCP
Atividade de doença
Capacidade funcional
Dano estrutural

RESUMO

Introdução: A presença do anti-CCP constitui importante ferramenta prognóstica da artrite reumatoide (AR). Mas, ainda, investiga-se sua relação com a atividade de doença e a capacidade funcional.

Objetivos: Estudar a relação o anti-CCP e os índices de atividade da doença, de capacidade funcional e de dano estrutural, através de radiografia convencional (RC) e de ressonância magnética (RM), em AR estabelecida.

Métodos: Estudo transversal com pacientes com AR, com um a 10 anos de doença. Os participantes foram submetidos à avaliação clínica com pesquisa do Anti-CCP. A atividade de doença foi avaliada através Clinical Disease Activity Index (CDAI) e a capacidade funcional através do Health Assessment Questionnaire (HAQ). A análise da RC foi feita pelo índice de Sharp van der Heijde (SmvH) e da RM pelo Sistema de Pontuação de Imagem por Ressonância Magnética na Artrite Reumatoide (RAMRIS, Rheumatoid Arthritis Magnetic Resonance Image Scoring).

Resultados: Foram avaliados 56 pacientes, com mediana (IIq) de idade de 55 (47,5-60) anos, sendo 50 (89,3%) do sexo feminino e 37 (66,1%) anti-CCP positivos. As medianas (IIq) do CDAI, do HAQ, de SmvH e do RAMRIS foram de 14,75 (5,42-24,97), 1,06 (0,28-1,75), 2 (0-8) e 15 (7-35), respectivamente. Não houve associação do anti-CCP com o CDAI, com o HAQ e com os escores SmvH e RAMRIS.

Conclusão: Nossos resultados não estabeleceram a associação do anti-CCP com a gravidade da doença. Até o momento, não podemos corroborar o anti-CCP como uma ferramenta prognóstica em AR estabelecida.

Introduction

The progression of rheumatoid arthritis (RA) brings an evolutionary potential to varying degrees of joint damage and functional disability. Thus, special attention should be given to the identification of poor prognostic indicator parameters, because ideally the definition of therapeutic intensity level should be based on reliable predictors of severity. It is already known that some features, when present, are associated with a worse outcome of the disease, such as the presence of high-titer rheumatoid factor, smoking and HLA-DRB1.[1,2]

Regarding the prognostic role of anti-CCP, its association with disease activity and functional capacity has still not been clarified, although many studies suggest that these antibodies are associated with more severe and erosive disease,[3–22] especially in cases of initial RA.[9,19–21,23–30] It is worth noting the methodological heterogeneity of the studies that analyzed the association of anti-CCP with structural damage. Although most studies have made use of conventional radiography (CR) as an evaluation tool, different radiographic score systems were used. Additionally, only one study also made use of ultrasonography (US) in a small subgroup of patients.[6] There are no studies that have used magnetic resonance imaging (MRI) for this purpose.

This study aimed to investigate the association of anti-CCP positivity with disease severity as measured by disease activity, functional capacity and structural damage, measured using CR and MRI.

Patients and methods

This is a cross-sectional study, which involved patients seen in an outpatient clinic. All participants were diagnosed with established RA according to the American College of Rheumatology (ACR – 1987)[31] or the American College of Rheumatology/The European League Against Rheumatism (ACR/EULAR – 2010[32]) criteria, aged 18 or more years old and with 1–10 years of disease duration.

Because of the possibility of performing MRI, patients with creatinine clearance <60 ml/min/1.73 m^2, metal prosthesis users, patients with an inability to access the examination table, and pregnant women were excluded from the study. On the other hand, patients with previous surgery and/or fracture in the hand also were excluded.

The study was approved by the Research Ethics Committee and, after signing the consent form, patients who agreed to participate in the study underwent a clinical evaluation and completed a specific questionnaire containing demographic and clinical data (duration of disease, time elapsed between onset of symptoms and RA diagnosis, smoking history, rheumatoid factor status, presence of extra-articular manifestations, treatment, and CDAI[33] and HAQ validated for Portuguese idiom[34]). A sample of blood was collected for anti-CCP survey with the use of second-generation methods: EliA CCP™ fluorenzyme-immunoassay test (Pharmacia Diagnostics, Germany) and chemiluminescent microparticle assay ARCHITECT™ anti-CCP (Abbott Laboratories, USA).

Patients were divided into two groups, according to test positivity and to the reference value of the kit used (>10 U/ml for fluorenzyme-immunoassay and >5 U/ml for chemiluminescence).

Radiographic evaluation was performed by means of hand and wrist CRs in a posterior–anterior view. X-rays carried out in the period up to three months before or after the data collection were accepted. The SvdH method[35] was chosen for an analysis of hands and wrists.[21]

A subgroup of 35 patients was referred for MRI examination in up to four weeks after the interview; for this purpose, a GE Signa 1.5 T HDxT system (GE Healthcare, Milwaukee, WI, USA) was used. For resonance analysis, the RAMRIS[36] protocol of the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) for wrist and metacarpophalangeal analysis was used. The examinations were performed on the dominant hand, using coronal (T1- and T2-weighted imaging with fat suppression), axial (T1-weighted imaging before and after the use of intravenous gadolinium contrast) and axial and coronal (T1-weighted imaging with fat saturation) sequences.

The MRI and X-ray analyzes were performed by a single radiologist who was unaware of the clinical condition of the patient. The intraobserver agreement for SvdH score was calculated, and the intraclass correlation coefficient was 0.958. We were unable to calculate the intraclass coefficient for RAMRIS because, to obtain this data, it would be necessary to calculate the variation component, which resulted in a negative value. Thus, a decision was made in favor of calculating the Spearman coefficient, with a value of 0.96.

Storage of data and all statistical analyzes were performed with the IBM Statistical Package for Social Sciences software (SPSS version 19). For categorical variables, frequency distributions were presented; and for continuous variables, measures of numerical synthesis were employed. The association between categorical variables was analyzed using the chi-squared or Fisher's exact test. The normality of continuous variables was verified by the Shapiro–Wilk test. For variables without normal distribution, the analysis was performed using the nonparametric Mann–Whitney *U* test. To verify the association between two non-normal continuous variables, the nonparametric Spearman test was used. For this study, a 5% significance level was set.

Results

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

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 = 6.6; 95% CI, 1.9–22.9; $p < 0.01$) and smoking (OR = 7.8; 95% CI, 1.9–31.6; $p < 0.01$).

Univariate analysis of anti-CCP association with CDAI, HAQ, SvdH, and RAMRIS are presented in Table 2. As to disease activity, the CDAI median value was higher in the group of

Table 1 – Characteristics of the patients.

Variables	Measures
Age: Median (IqR)	55 (47.5–60.0)
Females: n (%)	50 (89.3)
Disease duration in years: Median (IqR)	6 (3–9)
Time elapsed between disease and diagnosis, in years: Median (IqR)	0 (0–1)
Positive rheumatoid factor: n (%)	31 (55.4)
Positive anti-CCP: n (%)	37 (66.1)
Smoker or former smoker, n (%)	25 (44.6)
Presence of rheumatoid nodules: n (%)	8 (14.3)
Pulmonary involvement: n (%)	6 (10.7)
Presence of Sjögren's syndrome: n (%)	2 (3.6)
Patients taking corticosteroids: n (%)	49 (87.5)
Patients taking synthetic DMARDs: 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/sulfasalazine: n (%)	1 (1.8)
Cyclosporin: n (%)	1 (1.8)
Patients on 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: (IqR)	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 (IqR)	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 (IqR)	2 (0–8)
Erosion: Median (IqR)	1 (0–6)
Joint Space Narrow: Median (IqR)	1 (0–5.5)
RAMRIS[b]	
Total: Median (IqR)	15 (7–35)
Erosion: Median (IqR)	8 (1–19)
Bone edema: Median (IqR)	6 (2–14)
Synovitis: Median (IqR)	4 (2–6)

n, number of patients with rheumatoid arthritis; IqR, interquartile range; anti-CCP, anti-cyclic citrullinated peptide antibody; CDAI, clinical index of disease activity; HAQ, Health Assessment Questionnaire; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Image Scoring; DMARDs Disease modifying antirheumatic drugs.

[a] 55 patients underwent CR.

[b] 35 patients underwent MRI.

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

Variables	Anti-CCP		*p*-Value OR (IC 95%)
	Negative	Positive	
CDAI, median (IqR)	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 (IqR)	1 (0.25–1.50)	1.13 (0.31–2.00)	$p = 0.49$[a]
Sharp van der Heijde			
Total: Median (IqR)	1 (0–7)	3.5 (0–8)	$p = 0.29$[a]
Erosion: Median (IqR)	1 (0–4)	2 (0–6.7)	$p = 0.31$[a]
Joint Space Narrow: Median (IqR)	1 (0–4)	1(0–2.7)	$p = 0.39$[a]
RAMRIS			
Total: Median (IqR)	14 (8.5–30.5)	23 (6.7–42.0)	$p = 0.55$[a]
Erosion: Median (IqR)	8 (2–15)	10 (1–22.2)	$p = 0.50$[a]
Bone edema: Median (IqR)	5 (2–12.5)	8 (2.7–16)	$p = 0.37$[a]
Synovitis: Median (IqR)	3 (1.5–5.5)	4 (3–7.2)	$p = 0.20$[a]

n, number of patients; anti-CCP, anti-cyclic citrullinated peptide antibody; CDAI, clinical index of disease activity; HAQ, Health Assessment Questionnaire; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Image Scoring.

[a] Mann–Whitney *U* test.

[b] Chi-squared test.

patients positive for anti-CCP, but this ratio was not significant ($p = 0.06$). Moreover, the presence of a negative anti-CCP was not associated with the occurrence of remission or a state of low disease activity (OR = 2.9; 95% CI, 0.9–9; $p = 0.09$). HAQ, SvdH (total, erosion, joint space narrowing) 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 anti-CCP variable, a logistic regression model was adjusted. All variables correlating with anti-CCP with $p < 0.20$ (gender, time of diagnosis, smoking, rheumatoid factor, extra-articular manifestations, rheumatoid nodules, pulmonary involvement, CDAI and HAQ) were used in the initial model adjustment. In the final model, anti-CCP was related only with smoking and rheumatoid factor ($p < 0.05$). The model indicated that smokers and former smokers are 5.3 times more likely to have a positive result for anti-CCP (95% CI, 1.2–22.9) and those with positive RF are 4.4 times more likely to have a positive result for anti-CCP (95% CI, 1.2–16.6). The logistic regression model is shown in Table 3.

The Spearman correlation coefficient between CDAI and image (SvdH and RAMRIS) indexes was calculated, and no association among these was found. Of the 35 patients who underwent MRI, 13 were in remission or in low-disease activity (CDAI $\leq$ 10). Of these, 12 (92.3%) patients had edema and 12 (92.3%) had synovitis, and in only two of them the synovitis was >5.0 mm (16.6%). Regarding RAMRIS, the following medians (IqR) were obtained: Total index, 21 (11.5–34), erosion score, 9 (3.5–15.1), edema score, 6 (3.5 –12.5) and synovitis score, 3 (2.1–5.7). Among the 22 (95.6%) patients showing moderate-to-high activity, 21 (95.6%) patients had edema and 21 patients had synovitis. Regarding RAMRIS, the following medians (IqR) were obtained: Total index, 13 (6–31), erosion score, 5 (1–17), edema score, 5 (2–14) and synovitis score, 3.5 (2–6). For all RAMRIS indexes, no statistically significant difference between patients in remission and with low disease activity *versus* those at moderate-to high disease activity was observed.

Discussion

The present study examined the demographic, clinical, functional, and image characteristics of Brazilian patients with established RA, in order to determine the relationship of anti-CCP with severity of disease.

In the study population, anti-CCP positivity reached 66.1%, a rate similar to that found by Silva et al.[18] for Brazilian patients with established RA. RF positivity was 55.4%. This low prevalence can be explained by the fluctuation of antibody

Table 3 – Multivariate logistic regression with respect to anti-CCP.

Variables	Beta	Standard error	OR	CI 95% 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

levels during the course of disease in response to treatment,[19] or due to the study design, in which the information on RF positivity was based on medical record data. It is known that anti-CCP and RF tests are related. Studies have shown that most patients with RA and with a positive result for RF are also positive for anti-CCP.[3,19] Thus, our study is consistent with the literature.

Smoking is the main environmental process related to RA, mainly in HLA-DRB1-positive patients, and the citrullination is induced by tobacco substances - the potential pathophysiological mechanism of this process.[37] This study showed a significant association between smoking and anti-CCP positivity. This result is in agreement with that found by Pedersen et al.,[38,39] whose study evaluated various environmental risks associated with anti-CCP and HLA-DRB1, and with the findings of Goeldner et al.,[40] who studied the association of smoking with anti-CCP in Brazilian patients with established RA.

The assessment of disease activity in our study was carried out by CDAI, which correlates well with the other assessment indexes.[29,33,41] Our results showed that anti-CCP-positive patients had a median value of CDAI greater than anti-CCP-negative patients, but with marginal statistical significance ($p = 0.06$). Our results are in agreement with those of Choe et al.,[29] who evaluated the association of anti-CCP levels with DAS28, SDAI and CDAI activity indexes in patients with established RA, with no significant association.

Since the remission or low disease activity state is the main therapeutic target,[42] we opted also by an analysis of anti-CCP association with the occurrence of remission and low disease activity. Our results showed that an anti-CCP negative result was not associated with the occurrence of remission and low disease activity ($p = 0.08$). Mota et al.,[30] who evaluated Brazilian patients with early RA, found no relationship between negative findings for anti-CCP and remission by DAS28.

In prospective studies on early RA, Kastbom et al.[24] and Rönnelid et al.[10] found an association of anti-CCP with ESR and CRP levels and with DAS28. On the other hand, Nell et al.[9] noticed a worse therapeutic response in DAS28 in seropositive patients after 5 and 10 years of follow-up; nevertheless, this result did not achieve statistical significance. In established RA, disease activity relates irregularly with anti-CCP positivity.[19,20,23]

Our study found no association between anti-CCP and HAQ. Functional disability in early RA, assessed by HAQ, seems not to be associated with the presence of anti-CCP.[24,26] The same result has been reported in established RA.[19,23] In their evaluation of the association of anti-CCP with a Japanese version of HAQ, Shidara et al.[28] found a significant association; but the higher degree of disability resulting from a 20-year mean duration of disease challenges an independent association between the antibody and functional outcomes of RA. In Brazil, Silva et al.[18] studied 100 patients with established RA, with a mean of eight years of disease. These authors found an association between anti-CCP and HAQ, while Mota et al.,[26] in their cross-sectional study evaluating 65 patients with early RA, found no such association.

Radiographic analysis is considered one of the more objective methods to assess severity of RA. The SvdH method, although the most detailed and difficult to implement, is considered the most sensitive and accurate tool in the detection of small changes over time.[43] Although the literature show an association between the presence of anti-CCP and structural damage measured by CR in early RA,[3–15] in the case of established RA the results were not as conclusive.[15–23] It is noteworthy that most of these studies used the Larsen or Sharp method in their radiographic evaluation. Håfström et al.,[44] in a prospective study examining the role of RF and anti-CCP based on the radiological progression with the use of the SvdH method in patients with early RA, according to prednisolone use, found that RF and anti-CCP were predictors of radiographic progression only in patients who did not use steroids. Our work also did not establish an association of anti-CCP with structural damage, as assessed by SvdH in established RA cases, which is in accordance with Håfström et al.'s study, since 87.5% of our patients were still being medicated with prednisone. On the other hand, Gandjbakhch et al.,[45] in a prospective study which analyzed the factors involved with radiographic progression (SvdH) in a group of patients in remission and showing low disease activity, also found no significant association between anti-CCP and structural damage. The mean structural damage index in our sample was much lower, when compared to other studies in patients with established RA with the use of SvdH method.[19,21] This suggests that our sample consisted of patients with less severe and erosive disease and/or with a good response to therapeutic intervention.

To the best of our knowledge, this study is the first to examine the association of anti-CCP with structural damage in RA as measured by MRI. Our results showed no statistically significant differences in the parameters evaluated by MRI among anti-CCP positive and negative patients. In comparison with other studies,[46,47] we found lower values for the RAMRIS score for synovitis, bone edema and erosion, indicating once again that our sample was composed of a majority of individuals with a milder and less erosive disease. It is noteworthy that the use of MRI for monitoring treatment with biological agents can select high disease activity patients.

Patients in remission and showing low disease activity can, in spite of clinical control, exhibit signs of activity on MRI,[48,49] and these changes may determine a future radiographic progression.[50] The results of this study indicated no association 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 a synovitis >5 mm. According to Gandjbakhch et al.,[45] in patients in remission or with low activity disease, only the synovitis index of RAMRIS is associated with radiographic progression, with a cutoff point of 5 mm. Thus, it is believed that 84% of our patients in remission and with low disease activity are protected. It is suggested that patients in remission or with low disease activity, but with a synovitis >5 mm on MRI, exhibit the same potential of radiographic evolution; thus, these patients must be monitored in the same way, regardless of anti-CCP presence.

In conclusion, in the sample investigated the results did not establish an association of anti-CCP with disease severity. The presence of confounding variables, such as an early diagnosis and an appropriate response to therapeutic intervention, contributed to setting up a group of patients with less severe and slightly erosive disease. It is believed that the way of selecting participants in our study (only individuals under 10 years of disease duration and without difficulty to meet the research protocol were accepted) may also have limited the exposure of the entire universe of RA. None the less, this result allows us to question if anti-CCP would have less influence on prognosis for patients with a more favorable disease profile. On the other hand, due to the small sample size, this study may have failed to detect the most significant differences. Therefore, it is believed that the evaluation of a larger number of individuals, possibly with a multicentric distribution in long-term prospective observational studies and, if possible, with greater control of confounding variables, could contribute to the ultimate resolution of this issue. To date, we cannot support the indication for anti-CCP determination as a prognostic tool in established RA.

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Conflicts of interest

The authors declare no conflicts of interest.

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