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RESEARCH ARTICLE

Association of Elevated Anti-Cyclic Citrullinated Peptide Antibody Titer with Increased Cardiovascular Risk

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Abstract

Objective: To determine if anti-cyclic citrullinated peptide antibody (anti-CCP) positivity is associated with elevated cardiovascular risk in patients with rheumatoid arthritis (RA) and in patients without any autoimmune disease.

Method: This is a retrospective chart review of 2,030 records at a tertiary care center. Patients with known non-RA rheumatologic autoimmune disease were excluded. Primary outcomes included coronary artery disease (CAD), stroke (CVA), and the combined outcome of CAD or CVA. Outcomes were compared by anti-CCP titer group (defined as <6, 6-150, 151-300, and >300 U/mL) using Fisher's exact tests. Binary logistic regression models were then used to estimate the odds of experiencing CAD and/or CVA as a function of univariable and multivariable demographics and comorbidities.

Result: A total of 1,721 records were included, with 399 in the RA group and 1,322 in the non-RA group. There was a significant association between the increase in anti-CCP levels (delineated in four groups) and higher prevalence of the combined outcome in all patients (p = .002) and in RA patients (p = .05) with trend preservation in non-RA patients. On univariable logistic regression analysis, there was an increased risk of the combined outcome associated with increasing anti-CCP titer in all patients (p = .002); subgroup analysis of RA and non-RA patients did not reach statistical significance

Conclusion: This study demonstrates progressively increased risk of cardiovascular disease with extent of anti-CCP elevation in a population of all patients who received the test (excluding those with non-RA autoimmune disease).

Keywords: Rheumatoid Arthritis; Cardiovascular Risk; Myocardial Infarction; Stroke; Anti-CPP; Anti-Cyclic Citrullinated Peptide

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that carries substantial morbidity and reduced life expectancy. RA patients have a 50-60% increase in cardiovascular mortality compared to the general population [1,2]. Risk factors for development of CVD in RA patients include: advanced age, male gender, smoking, disease activity/severity, autoantibody positivity such as rheumatoid factor or anti-cyclic citrullinated peptide antibodies (anti-CCP), disease duration, and extra-articular manifestations [3]. The 2010 European League Against Rheumatism (EULAR) guidelines recommend adapting risk score models for CVD with a 1.5 multiplication factor when patients with RA meet two of the following criteria: disease duration for greater than 10 years, rheumatoid factor or anti-CCP positivity, the presence of specific extra-articular manifestations [4]. Cardioprotective treatments, such as statins, are initiated when the 10-year CVD risk reaches a threshold; the recommended multiplication factor would result in earlier cardioprotective treatment for many RA patients.

Anti-CCP antibodies are highly specific for RA and are directed against citrullinated proteins. Citrullination is a post-translational modification of proteins that occurs in the context of inflammation. Because inflammation has been identified as a key component in the pathophysiology of atherosclerosis, anti-CCP seropositivity may help identify those patients with RA who carry a particularly high risk of CVD. It has been shown that there are citrullinated epitopes within atherosclerotic plaques that are targeted by

anti-CCP antibodies and that these immune complexes may promote plaque inflammation and progression [5].

The existing literature on the association between anti-CCP positivity and cardiovascular risk is mixed. Anti-CCP positivity has been associated with subclinical CVD in the form of intimal medial thickness [6]. Studies have shown a positive association between clinical CVD and anti-CCP antibodies in African American women with and without RA, RA patients, and healthy men; others have shown no association in female RA patients, RA patients, a general population of patients who had anti-CCP tested, and early RA patients [7-13]. Of note, there are no published studies demonstrating that increasing anti-CCP titer is associated with progressively increased cardiovascular risk. Additionally, there is currently no data that compares the association of anti-CCP positivity with CVD in RA patients to patients without autoimmune disease.

In this study, we investigated whether the presence of anti-CCP positivity is associated with CVD in both RA and non-RA patients, and whether higher levels of the anti-CCP antibody are associated with a higher risk of CVD.

Patients and Methods

This is a retrospective chart review of all patients over 18 years of age with anti-CCP testing performed between January 1, 2007 and December 31, 2012 at Loyola University Medical Center. Chart review was performed by two physicians. Study data was collected and managed using REDCap (Research Electronic Data Capture), which is a secure web-based application [14].

A total of 2,030 records for patients who received testing for anti-CCP antibodies were reviewed. Patients diagnosed with the following non-RA autoimmune diseases (n = 309) were excluded: systemic lupus erythematosis, Sjogren's, mixed connective tissue disease, scleroderma, Raynaud's, celiac disease, vasculitis, undifferentiated connective tissue disease, inflammatory bowel disease, non-RA inflammatory arthritis, polymyositis/dermatomyositis, anti-synthetase syndrome, anti-phospholipid antibody syndrome, IgG4-related disease, and polymyalgia rheumatica. Unclear cases of unclassified inflammatory conditions were reviewed by a rheumatologist for exclusion or inclusion. `

The remaining 1,721 patients were separated into an RA group and a non-RA group. RA diagnosis was defined as either meeting 2010 American College of Rheumatology (ACR) criteria or diagnosis by a practicing rheumatologist [15]. Chart information was collected and recorded as of the date the anti-CCP lab was drawn. The electronic medical record was reviewed (including demographics, physician notes, billing codes, lab results, imaging studies, medications, and vital signs) for clinical information pertaining to cardiovascular risk factors and RA diagnosis and disease course.

Patient demographics collected included date of birth, gender, race, and ethnicity. Information pertaining to cardiovascular risk factors included tobacco use, body mass index, hypertension (defined as a listed diagnosis physician notes or billing codes, blood pressure greater than 140/90 on two occasions, or the use of an anti-hypertensive medication), hyperlipidemia (defined as a listed diagnosis, low-density lipoprotein greater than 130, or the use of cholesterol lowering medication), use of aspirin and statin medications, and the listed diagnoses of diabetes mellitus, chronic kidney disease, peripheral arterial disease and congestive heart failure.

Information collected pertinent to RA diagnosis and course included: rheumatoid factor, anti-CCP, erythrocyte sedimentation rate (ESR), date of diagnosis, and treatments for RA (corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs)). If multiple anti-CCP measurements were obtained, the first result was analyzed. The method of estimating anti-CCP level was an automated semi-quantitative ELISA platform. Among RA patients, these anti-CCP measurements were taken at any point from diagnosis to well-established disease undergoing therapy. Patients were separated into four groups based on titer: <6 U/mL (negative titer), 6-150 U/mL (low titer), 151-299 U/mL (moderate titer), and >300 U/mL (high titer). The groups were arbitrarily selected prior to data collection.

Data pertaining to endpoints were collected as of the date that chart review started (November 15, 2015). Primary endpoints included coronary artery disease (CAD, defined as acute coronary syndrome or intervention), stroke (CVA, defined as clinical or radiographic stroke or transient ischemic attack), and the combined outcome of CAD or CVA. Events at any time before data review started were analyzed. Mortality was a secondary outcome. Deaths between the date of anti-CCP lab collection and date data review started were included.

Statistical Analysis

Pearson chi-square and Fisher's exact tests were used to assess differences on all categorical variables by RA diagnosis. Results included the number and percentage of patients within each level. Independent samples t-tests and Wilcoxon Rank Sum tests were employed for continuous variables with results expressed as means and standard deviations or medians and interquartile ranges.

Binary logistic regression models were then used to estimate the odds of experiencing CAD, CVA, and CAD *or* CVA as a function of univariable and multivariable demographics and comorbidities. In these models, a binomial distribution was specified for each response variable, while logit links were used to estimate the odds ratio for each explanatory variable. A Cox proportional hazards model was also employed to estimate the hazard of inpatient mortality at any given time. The proportional hazards assumption for each predictor was assessed using Martingale residuals. Only those clinically relevant explanatory variables that best minimized

Akaike's information criterion (AIC) were retained in multivariable analysis. A *p*-value <.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Of the 1,721 patients included, 399 carried a diagnosis of RA (RA group), and 1,322 did not (non-RA group). The mean disease duration was 12.1 years in the RA group. The RA and non-RA groups were similar in gender distribution, ethnicity, tobacco status, statin usage, prevalence of chronic kidney disease and diabetes, as well as non-steroidal anti-inflammatory drug (NSAID) and aspirin usage (Table 1). Patients in the RA group had a higher median age and higher blood pressure compared to the non-RA group. In addition, patients in the non-RA group had a higher body mass index and a higher prevalence of hyperlipidemia. As expected, the RA group had substantially higher prevalence of DMARD and prednisone usage and higher average rheumatoid factor and ESR levels. A positive anti-CCP antibody (defined as ≥ 6 U/mL) was present in 72.5% of RA patients compared to 3.2% of non-RA patients.

	Non-RA (N=1322)	RA (N=399)	*P-value*
Age (years, median, IQR)	51 (40-61)	57 (46-65)	<.001
Male (N, %)	264 (20)	80 (20)	.99
Race (N, %)			.01
White	926 (70)	251 (63)	
Black	182 (14)	82 (21)	
Asian	33 (2.6)	10 (2.5)	
Hispanic (N, %)	160 (12)	41 (10)	.44
Tobacco use (N, %)	172 (14)	48 (15)	.48
BMI (kg/m^2, mean, StDev)	30 (7.3)	29 (6.5)	.01
SBP (mmHg, mean, StDev)	126 (19)	132 (22)	<.001
Hyperlipidemia (N, %)	565 (43)	146 (37)	.03
Statin (N, %)	346 (26)	106 (27)	.88
Aspirin (N, %)	252 (19)	84 (21)	.38
CKD (N, %)	53 (4)	16 (4)	.99
Diabetes (N, %)	173 (13)	51 (13)	.87
RF≥20 (N, %)	202 (19)	248 (72)	<.001
ESR (median mm/hr, IQR)	14 (8-24)	25 (15-47)	<.001
NSAID (N, %)	1037 (78)	324 (81)	.23
Prednisone (N, %)	498 (38)	287 (72)	<.001
DMARD (N, %)	178 (13)	369 (92)	<.001

*ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor; CKD: Chronic Kidney Disease; SBP: Systolic Blood Pressure; IQR: Interquartile Range; NSAID: Non-Steroidal Anti-Inflammatory Drug; DMARD: Disease-Modifying Antirheumatic Drug; StDev: Standard Deviation

Table 1: Patient Characteristics

For the entire cohort, the combined outcome (CAD or CVA) occurred in 173 patients (10.1%), CAD in 126 patients (7.3%), and CVA in 68 patients (4.0%). The proportion of patients with the combined outcome and CVA alone was higher in RA patients compared to non-RA patients (13% versus 9%, $p = .02$ for the combined outcome; 6.3% versus 3.3%, $p = .01$ for CVA). However, the difference in the proportion of CAD diagnoses between RA and non-RA patients did not reach statistical significance (7.8% versus 7.2%, $p = .70$).

There was a significant association between the increasing anti-CCP levels (delineated in four groups) and a higher proportion of the combined outcome in all patients ($p = .002$) and in RA patients ($p = .05$). A similar trend was seen in non-RA patients, but did not reach statistical significance (Figure 1). With the exception of the low-positive anti-CCP titer group (6-150 U/mL), the prevalence of the combined outcome in all patients increased with higher anti-CCP titers.

The association between anti-CCP group and the proportion of patients with only CAD or only CVA was also statistically significant in all patients (by increasing group, CAD: 6.9%, 5.4%, 14.0%, 12.0%, $p = .04$; CVA: 3.5%, 3.6%, 2.8%, 9.2%, $p = .02$). Similar trends were observed in the isolated RA and non-RA groups, but did not reach significance.

On univariable logistic regression analysis, there was a progressively increased risk of the combined outcome with each increasing anti-CCP group in all patients (Figure 2). Patients with an anti-CCP value >300 were 2.32 (95 CI: 1.45-3.72) times more likely to

experience the combined outcome (CAD or CVA) compared to those with <6 U/mL (p = .001). Subgroup analyses of the RA and non-RA groups did not reach statistical significance, though the trend was preserved. Similarly, there was a progressively increased risk of the combined outcome with each increasing anti-CCP group for CAD alone and CVA alone. Patients with an anti-CCP value >300 were 1.87 (95 CI: 1.45-3.72) times more likely to have CAD compared to those with <6 U/mL (p = .03) and 2.75 (95 CI: 1.43-5.32) times more likely to have CVA compared to those with <6 U/mL (p = .003). The trend was preserved in RA and non-RA groups, but was not statistically significant.

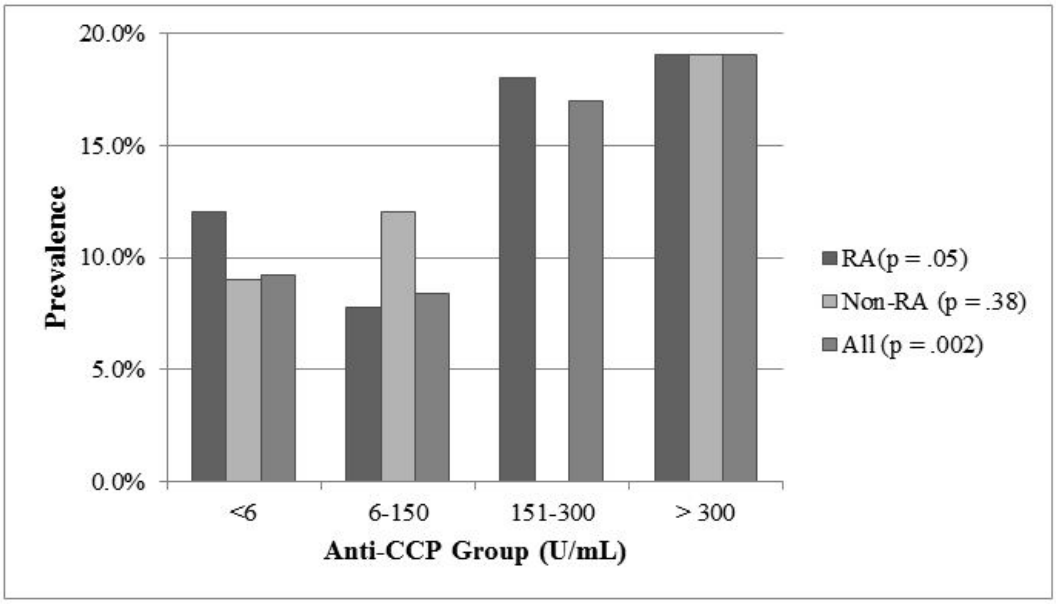

Figure 1: Prevalence of combined outcome (CAD or CVA) by anti-CCP group. The prevalence of the combined outcome in RA patients with increasing anti-CCP groups was 12.0%, 7.8%, 18.0%, and 19.0%, respectively. For all patients, the prevalence was 9.2%, 8.4%, 17.0%, 19.0%, respectively. There were no patients in the non-RA third group

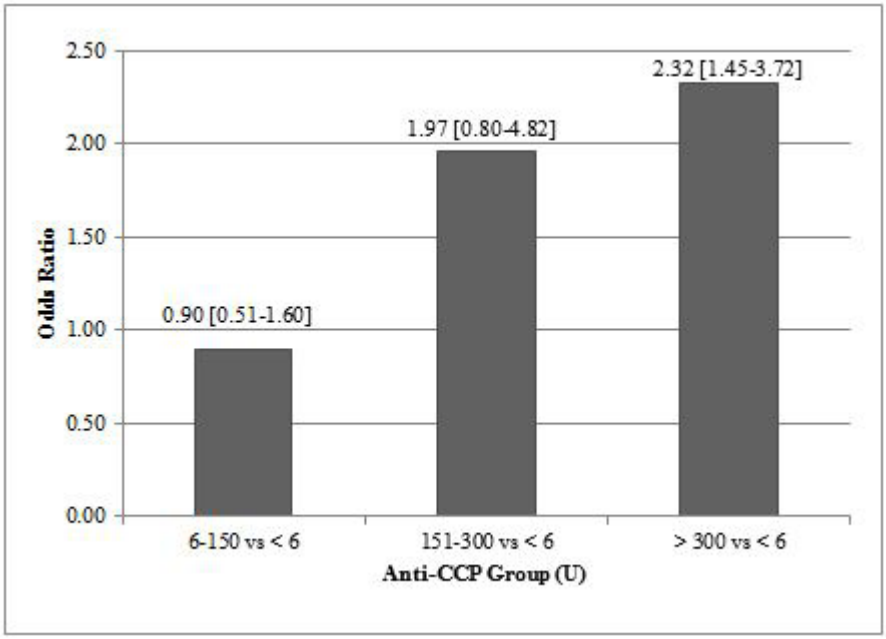

Figure 2: Risk of combined outcome (CAD or CVA) by anti-CCP group in all patients (p = .002). Odds ratios with associated 95% confidence interval are listed above each bar

The risk of the combined outcome increased with RA diagnosis (*OR* = 1.49, 95 CI: 1.05-2.10, p = .02), hyperlipidemia (*OR* = 4.87, 95 CI: 3.40-6.96, p < .0001), gender (Males vs. Females, *OR* = 2.63, 95 CI: 1.89-3.70, p < .0001), age (*OR* = 1.09, 95 CI: 1.07-1.11, p < .0001), systolic blood pressure (*OR* = 1.01, 95 CI: 1.00-1.02, p = .04), chronic kidney disease (*OR* = 8.12, 95 CI: 4.89-13.46, p < .0001), diabetes (*OR* = 3.93, 95 CI: 2.75-5.62, p < .0001), and NSAID usage (*OR* = 2.15, 95 CI: 1.31-3.48, p < .0001). By contrast, race, ethnicity, body mass index, and tobacco status were not found to independently increase patients' risk of either CAD or CVA. In the RA group alone, risk of the combined outcome was increased with elevated ESR (*OR* = 1.02, 95 CI: 1.00-1.03, p = .01); notably, though, there was no change in risk with DMARD use, prednisone use, NSAID use, elevated rheumatoid factor, or RA duration.

Analysis of the 55 deaths revealed a trend toward increased risk associated with elevated anti-CCP. Nonetheless, elevated anti-CCP group was not meaningfully associated with the instantaneous hazard of death (>300 versus <6 group, Hazard ratio [*HR*] = 1.08, 95 CI: 0.81-4.06, $p = .15$).

After adjusting for select confounders, including age, gender, statin use, NSAID/prednisone use, and ESR, in the logistic regression model, the increased risk of the combined outcome by anti-CCP group did not reach statistical significance (all patients, by group, compared to <6: *OR* = 0.75, 95 CI 0.33-1.67; *OR* = 1.81, 95 CI: 0.58-5.61; *OR* = 1.91, 95 CI: 0.91-4.01, $p = .20$).

Discussion

Cardiovascular disease is an important cause of morbidity and mortality in patients with rheumatoid arthritis. Anti-CCP positivity is a characteristic commonly used in the diagnosis of rheumatoid arthritis and may also be a key player in the pathogenesis of atherosclerosis. Anti-CCP antibodies have been shown to directly induce inflammatory and atherosclerosis-inducing activity in immune cells, including lymphocytes, monocytes, and neutrophils [16]. They have also been shown to activate platelets, which may also contribute to atherosclerosis via recruitment of mediators that promote inflammation, endothelial injury, and vascular permeability [17].

The objective of this study was to determine if anti-CCP positivity is associated with elevated cardiovascular risk in patients with RA and in patients without any known rheumatologic autoimmune disease. While there was not an increased risk in each of these groups in isolation, the authors believe that the elevated risk in the entire group warrants reporting so that further investigation can be pursued. This study adds to the existing body of literature that demonstrates anti-CCP positivity is a risk factor for CVD. Further, it suggests that the extent of anti-CCP elevation is correlated with progressively increased cardiovascular risk, which is a finding that has not been demonstrated before to the authors' knowledge.

Subgroup analysis of the non-RA population did not reveal statistically significant results. This may have been due to low numbers of positive anti-CCP results in this population (44 out of 1322 patients). Anti-CCP is expected to be positive in a very small proportion of non-RA patients because of its high specificity and low false positive rate. Because of this test characteristic, it would likely not be a clinically useful test to identify those at high cardiovascular risk in the general population. However, this study suggests that if a positive result is obtained, that patient may be at higher cardiovascular risk regardless of whether or not they have a diagnosis of RA. One explanation for this observation may be the association of elevated anti-CCP titers with smoking and COPD, both known risk factors for cardiovascular disease [18-20].

Several known cardiovascular risk factors were not associated with increased cardiovascular risk in our study: non-white race, body mass index, and tobacco status. While these results may be an artifact of study limitations described below, it is also possible that traditional cardiovascular risk factors do not contribute the same risk in RA patient as they do in non-RA patients, as has been suggested in other studies [21].

This study also attempted to identify risk factors outside of anti-CCP positivity to help identify RA patients at particularly high risk of CVD. Interestingly, the only RA-specific clinical variable associated with increased risk was ESR. This is consistent with the known association between active systemic inflammation and a higher risk of cardiovascular disease. Other proposed risk factors such as disease duration and rheumatoid factor positivity were not associated with an elevation in risk. In addition, this study suggests that DMARD use and prednisone use do not modify RA patients' cardiovascular risk.

Several limitations of this study deserve mention. The study population consisted of all patients who had the anti-CCP study drawn in a tertiary care center. The non-RA population in this study likely had more comorbidities than the average non-RA patient. Comparison of cardiovascular risk in non-RA and RA populations was limited by the inability to control for confounding factors due to retrospective nature of study. The higher median age, higher non-white population, and higher systolic blood pressure all may have contributed to the increased CVD in the RA group. The non-RA population had higher body mass index and higher prevalence of hyperlipidemia, which may have increased the event rate in that group. Variables such as disease activity, extra-articular manifestations, newer therapies for RA, and C-reactive protein were not included due to limitations of the data set. In addition, CVA/CAD events at any time point were considered, including those that occurred before the date of the anti-CCP test. This study was also limited by short and variable follow-up (3-9 years) depending on when the anti-CCP test was drawn.

To the authors' knowledge, this is the first study to demonstrate progressively increased risk of CVD with extent of anti-CCP elevation. Although statistical significance was not reached in non-RA patients, the observed trends warrant larger studies to evaluate this population. In a patient that is not identified as high risk for CVD based on standard cardiovascular risk models, a high-titer anti-CCP may warrant earlier cardioprotective treatment.

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