Arthritis Care & Research
Vol. 69, No. 8, August 2017, pp 1276–1281
DOI 10.1002/acr.23106

BRIEF REPORT

Association of Anti–Citrullinated Peptide Antibodies With Coronary Artery Calcification in Rheumatoid Arthritis

LAURA GERALDINO-PARDILLA,[1] JON T. GILES,[1] JEREMY SOKOLOVE,[2] AFSHIN ZARTOSHTI,[1] WILLIAM H. ROBINSON,[2] MATTHEW BUDOFF,[3] ROBERT DETRANO,[4] SABAHAT BOKHARI,[1] AND JOAN M. BATHON[1]

Objective. **Citrullinated proteins have been found within atherosclerotic plaque. However, studies evaluating the association between anti–citrullinated protein antibodies (ACPAs) and imaging measures of atherosclerosis in patients with rheumatoid arthritis (RA) have been limited to seroreactive citrullinated fibrinogen or citrullinated vimentin and have rendered contradictory results. Therefore, our objective was to evaluate this association using an extended panel of ACPAs in a larger sample of RA patients without clinical cardiovascular disease (CVD).**

Methods. **ACPAs were identified using a custom Bio-Plex bead assay in 270 patients from 2 independent RA cohorts without clinical CVD, with the first one consisting of 195 patients and the other of 75 patients. Coronary artery calcium (CAC) was assessed by computed tomography as a measure of coronary artery disease.**

Results. **High levels of anti–citrullinated histone H2B antibodies were strongly associated with higher CAC scores, compared with lower antibody levels ($P = 0.001$); this remained significant after adjustment for traditional CV and RA-specific risk factors ($P = 0.03$). No association between levels of ACPAs and CAC progression at 3 years was seen ($P = 0.09$); however, the number of progressors was small (n = 92).**

Conclusion. **Higher levels of ACPAs targeting Cit-histone H2B were associated with higher CAC scores when compared to lower antibody levels, suggesting a potential role for histone citrullination seroreactivity in atherosclerosis.**

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD), is the leading cause of death in rheumatoid arthritis (RA) (1). RA poses an increased risk for accelerated atherosclerosis that is only partially explained by traditional CV risk factors (2). Inflammatory and immune-mediated pathway interactions play an essential role in atherosclerotic plaque development and rupture (3). The recent demonstration of citrullinated proteins within atherosclerotic plaque (4) and the relative specificity of anti–citrullinated protein antibodies (ACPAs) for RA suggest that ACPAs play a role in the acceleration of atherosclerosis in RA. However, investigations to date in this regard have been limited to anti–citrullinated fibrinogen and anti–citrullinated vimentin antibodies and have yielded contradictory results (4–6). We investigated the association of seroreactivities with a broader panel of autoantigens with coronary artery calcium (CAC), as a surrogate measure of atherosclerosis, in a larger sample consisting of 2 independent RA cohorts without clinical CVD.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant AR-050026) and by the Clinical and Translational Science Award (grant UL1-TR000040) of the NIH. Dr. Bathon's work was supported by the NIH (grant AR-050026-08S1).

[1]Laura Geraldino-Pardilla, MD, MSc, Jon T. Giles, MD, MPH, Afshin Zartoshti, MSc, Sabahat Bokhari, MD, Joan M. Bathon, MD: Columbia University College of Physicians & Surgeons, New York, New York; [2]Jeremy Sokolove, MD, William H. Robinson, MD, PhD: Stanford University School of Medicine and VA Palo Alto Health Care System, Palo Alto, California; [3]Matthew Budoff, MD: Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance; [4]Robert Detrano, MD: University of California, Irvine.

Address correspondence to Laura Geraldino-Pardilla, MD, MSc, Division of Rheumatology, Columbia University, College of Physicians & Surgeons, 630 West 168th Street, P&S 10-445, New York, NY 10032. E-mail: lbg2124@columbia.edu.

Submitted for publication April 13, 2016; accepted in revised form September 27, 2016.

Significance & Innovations

- This study is the first to test the association between anti–citrullinated peptide antibodies (ACPAs) and coronary artery calcium (CAC) using a broad panel of ACPAs in a large sample of rheumatoid arthritis (RA) patients without clinical cardiovascular disease (CVD) and comprehensively phenotyped for CV risk factors.
- High levels of anti-Cit-H2B antibodies were found to be associated with a higher burden of atherosclerosis, measured by CAC, in RA patients without CVD. This adds to the mechanistic understanding of the increased prevalence of atherosclerosis and CVD in RA by suggesting a potential role for anti-Cit-H2B histones in this process.

Materials and methods

Patients. The study included 195 patients from the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE RA) study who underwent cardiac computed tomography (CT) for CAC score measurement and concurrent serum testing for ACPAs. In brief, ESCAPE RA participants were 45–84 years old, met 1987 American College of Rheumatology RA criteria (7), and had RA for ≥6 months and had no clinical CVD (defined as coronary artery disease, myocardial infarction, heart failure, or stroke) (8). A second independent cohort consisted of the first 75 participants in the Rheumatoid Arthritis Study of the Myocardium (RHYTHM), an ongoing study to identify factors associated with myocardial phenotypes in RA patients without CVD. Participants had similar inclusion criteria as those in ESCAPE RA (except for an age requirement of ≥18 years) and underwent similar CAC score measurement and concurrent testing for an expanded ACPA panel. The studies were approved by the Johns Hopkins Medical Institutional Review Board and the Columbia University Institutional Review Board, respectively. Enrollment for ESCAPE RA took place from 2004–2006. Enrollment for RHYTHM started in 2011 and is ongoing.

Outcome assessment: CAC. All participants underwent cardiac CT scanning as previously described (8,9). CAC, quantified by the Agatston method (10), was used as the primary outcome, given its noninvasiveness, high reproducibility, high sensitivity and specificity in measuring atherosclerosis, and its ability to predict CV events (11).

Measurement of ACPAs. Serum samples were obtained on the same day as the cardiac CT scanning for both cohorts. Reactivity to citrullinated and noncitrullinated/control (native) proteins/peptides were quantified using a custom Bio-Plex bead assay, as previously described (12,13). A high autoreactivity level was defined as greater than or equal to the 75th percentile. The ESCAPE RA patients underwent ACPA testing using a panel of 17 citrullinated antibodies and 3 native proteins/peptides (12). For the RHYTHM patients, an expanded panel of 30 citrullinated and 5 native proteins/peptides was used (13), of which 16 citrullinated and 2 native proteins/peptides overlapped with the panel used for the ESCAPE RA cohort.

Assessment of covariates. *Clinical characteristics.* Demographics and smoking history were self-reported and collected from standardized study questionnaires. Body mass index, blood pressure, hypertension, and diabetes mellitus were defined and measured as previously described (8,9).

RA-specific covariates. RA disease duration was calculated from the time of physician diagnosis. RA disease activity was calculated with the Disease Activity Score in 28 joints using the C-reactive protein (CRP) level (8,9). The use of glucocorticoids, biologic and nonbiologic disease-modifying antirheumatic drugs, aspirin, and cholesterol medications was ascertained by patient interview.

Laboratory covariates. Serum and plasma were separated by centrifugation and stored at −70°C. High-sensitivity CRP, interleukin-6 (IL-6), cholesterol levels, rheumatoid factor (RF), and IgM and anti–cyclic citrullinated peptide (anti-CCP) antibodies were assessed as previously described (8,9). RF and anti-CCP antibodies were defined as positive if ≥40 units and ≥60 units, respectively.

Statistical methods. Baseline characteristics were summarized and expressed as the mean ± SD or median (interquartile range) for continuous variables. Numbers and percentages were calculated for categorical variables. CAC was analyzed as a linear variable: log-transformed CAC score + 1. ACPA levels were dichotomized at the 75th percentile. The association between seroreactivity to a panel of citrullinated and native (noncitrullinated) proteins/peptides with CAC was assessed using linear regression with adjustment for confounders and variables significantly associated with CAC. The association of CAC with ACPAs that were measured in only 1 of the cohorts was examined in a similar manner. An alpha value of 0.05 was defined as statistically significant. Statistical calculations were performed using SAS, version 9.4.

Results

Clinical characteristics. Patient characteristics are summarized in Table 1. RHYTHM patients were more likely than the ESCAPE RA participants to be nonwhite and to have diabetes mellitus. In the ESCAPE RA cohort, current smoking, ever smoking, and having a CAC score >0 were more common than in the RHYTHM cohort.

Association between ACPAs and CAC. No statistically significant association between ACPAs and CAC score was identified in the ESCAPE RA cohort, although a trend was noted with high levels of anti-Cit-histone H2B (Table 2). In the RHYTHM cohort, high levels of seroreactivities targeting Cit-vimentin, Cit-histone H2A, and Cit-histone H2B were associated with CAC score in univariable T2

Table 1. Characteristics of patients in the ESCAPE RA and RHYTHM cohorts*

Characteristic	ESCAPE RA (n = 195)	RHYTHM (n = 75)	Total (n = 270)
Demographics			
Age, years	59 ± 9	54 ± 13	58 ± 10
Female, no. (%)	118 (60)	64 (85)	182 (68)
White, no. (%)	170 (87)	27 (37)	197 (73)
RA characteristics			
Disease duration, median (IQR) years	9 (4–17)	7 (3–17)	8 (4–17)
DAS28-CRP	3.6 ± 1.1	3.7 ± 1.2	3.7 ± 1.1
RF or anti-CCP positivity, no. (%)	126 (65)	56 (79)	182 (68)
Any HLA–DRB1 shared epitope alleles, no. (%)	134 (68)	43 (61)	177 (67)
IL-6, median (IQR) pg/ml	3.8 (1.7–7.7)	2.8 (1.4–8.7)	3.6 (1.7–8.2)
CRP level, median (IQR) mg/liter	2.4 (1.1–7.2)	2.7 (0.6–6.7)	2.6 (1–6)
HAQ score (range 0–3), median (IQR)	0.6 (0.1–1.2)	1.0 (0.5–1.7)	0.7 (0.2–1.3)
Nonbiologic DMARD use, no. (%)	164 (84)	52 (73)	216 (80)
Biologic DMARD use (current), no. (%)	89 (46)	23 (32)	112 (42)
TNF inhibitor use (current), no. (%)	85 (44)	19 (27)	104 (39)
Glucocorticoids (current), no. (%)	75 (38)	25 (35)	100 (37)
Current prednisone dose, median (IQR) mg	0 (0–5)	5 (4–10)	0 (0–5)
Cardiovascular risk factors			
Diabetes mellitus, no. (%)	13 (7)	9 (13)	22 (8)
Systolic blood pressure, mm Hg	128 ± 19	118 ± 19	125 ± 19
Diastolic blood pressure, mm Hg	76 ± 9	70 ± 10	74 ± 10
Hypertension, no. (%)	79 (40)	31 (41)	110 (41)
Total cholesterol, mg/dl	195 ± 38	192 ± 39	194 ± 39
LDL cholesterol, mg/dl	116 ± 31	107 ± 35	113 ± 32
HDL cholesterol, mg/dl	55 ± 19	61 ± 20	56 ± 19
Triglycerides, median (IQR) mg/dl	107 (68–151)	93 (77–140)	100 (74–148)
Current smoking, no. (%)	23 (12)	5 (7)	28 (11)
Ever smoking history, no. (%)	116 (59)	30 (43)	146 (55)
Body mass index, kg/m^2	28 ± 5	28 ± 6	28 ± 5
Any CAC, no. (%)	106 (54)	25 (33)	131 (49)

* Values are the mean ± SD unless otherwise indicated. ESCAPE RA = Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis; RHYTHM = Rheumatoid Arthritis Study of the Myocardium; RA = rheumatoid arthritis; IQR = interquartile range; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; IL-6 = interleukin-6; HAQ = Health Assessment Questionnaire; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CAC = coronary artery calcium.

analysis; however, statistical significance was lost in the adjusted analysis (Table 2). In the analysis of the combined cohorts, high levels of anti-Cit-histone H2B antibodies were significantly associated with higher CAC scores in unadjusted ($P = 0.001$), and adjusted ($P = 0.03$) analyses (Figure 1). No association was seen between CAC and levels of the noncitrullinated control proteins in either cohort or in the pooled analysis (Table 2).

The association of ACPAs with CAC progression over 3 years was also investigated. Although no association was found ($P = 0.09$), only the ESCAPE RA cohort had repeated CAC measurements, and, of those, the number of progressors was small (n = 92). The total number of high-level ACPAs present per patient was also not associated with either baseline CAC or CAC progression (data not shown).

Association of ACPAs and CAC per strata of patient characteristics. The association between CAC and high levels of ACPAs targeting Cit-Apo E$^{277–296}$, Cit-biglycan$^{247–266}$, and Cit-filaggrin$^{48–65}$ varied by sex (interaction term P value less than 0.05 for each). However, although these 3 ACPAs were associated with CAC in univariable analysis, statistical significance was lost in multivariable models (data not shown). In addition, there was an interaction between ever-smoking history and CAC, with higher CAC scores seen in ever smokers with higher ACPA levels, but significance was lost in adjusted analyses (data not shown). No difference in the association of high levels of ACPAs with CAC was noted by race, shared epitope status, and/or RF or anti-CCP positivity (data not shown).

Discussion

This study shows that in RA patients without clinical CVD, high levels of ACPAs targeting Cit- histone H2B proteins, but not ACPAs targeting other citrullinated and noncitrullinated antigens, were significantly associated with higher CAC scores when compared with lower levels of these antibodies.

RA patients have an increased risk of atherosclerosis and CHD that is only partially explained by traditional

Table 2. Association between CAC and APCA reactivity: linear regression parameter estimates of the log-transformed coronary artery calcium score (CAC)+1 per category of ACPA reactivity (dichotomized at the 75th percentile) in ESCAPE RA, RHYTHM, and combination cohorts*

	ESCAPE RA (n = 195)		RHYTHM (n = 75)				Combined cohorts total (n = 270)			
	Univariate Coefficient	*P*	Univariate Coefficient	*P*	Multivariate Coefficient†	*P*	Univariate Coefficient	*P*	Multivariate Coefficient‡	*P*
Autoantigens										
Anti-Cit-fibrinogen	0.30	0.50	0.43	0.52	–	–	0.30	0.42	–	–
Cit-fibrinogen $A^{41–60}$	0.68	0.13	1.17	0.08	–	–	0.79	0.03§	0.22	0.54
Cit-fibrinogen $A^{556–575}$	0.32	0.48	0.63	0.35	–	–	0.36	0.33	–	–
Cit-fibrinogen $A^{211–230}$	0.44	0.33	1.01	0.13	–	–	0.50	0.19	–	–
Cit-fibrinogen $A^{616–635}$	0.44	0.33	0.49	0.46	–	–	0.53	0.16	–	–
Cit-fibrinogen $A^{582–599}$	–	–	0.54	0.42	–	–	–	–	–	–
Cit-fibrinogen $A^{27–43}$	–	–	0.54	0.42	–	–	–	–	–	–
Cit-fibrinogen $B^{36–52}$	–	–	0.88	0.18	–	–	–	–	–	–
Cit-fibrinogen $B^{54–72}$	–	–	0.15	0.82	–	–	–	–	–	–
Cit-fibrinogen $B^{246–267}$	–	–	0.15	0.82	–	–	–	–	–	–
Cit-vimentin	−0.05	0.92	1.37	0.04§	0.96	0.08	0.56	0.14	–	–
Cit-vimentin$^{58–77}$	0.12	0.79	1.31	0.05§	0.94	0.11	0.07	0.86	–	–
Cit-vimentin$^{1—16}$	–	–	1.13	0.09	–	–	–	–	–	–
Cit-apolipoprotein A1	−0.43	0.34	0.79	0.24	–	–	0.26	0.50	–	–
Cit-apolipoprotein $A1^{231–248}$	–	–	−0.74	0.26	–	–	–	–	–	–
Cit-apolipoprotein E	0.01	0.97	0.04	0.95	–	–	0.41	0.33	–	–
Cit-apolipoprotein $E^{277–296}$	0.61	0.18	0.61	0.36	–	–	0.38	0.31	–	–
Cit-filaggrin$^{48–65}$	0.62	0.17	0.85	0.20	–	–	0.63	0.09	–	–
Cyclic Cit-filaggrin$^{48–65}$	–	–	−0.34	0.59	–	–	–	–	–	–
Cit-biglycan$^{247–266}$	0.58	0.20	0.66	0.32	–	–	0.47	0.21	–	–
Cit-histone H2A	–	–	1.28	0.05§	0.90	0.14	–	–	–	–
Cit-histone $H2A^{1–20}$	0.38	0.40	0.94	0.16	–	–	0.77	0.04§	0.33	0.32
Cit-sm-histone $H2A^{1–20}$	–	–	0.46	0.50	–	–	–	–	–	–
Cit-histone H2B	0.80	0.08	1.34¶	0.05§	0.84	0.15	1.21	0.001§	0.74	0.03§
Cit-histone $H2B^{62–81}$	0.07	0.88	1.45	0.03§	0.52	0.38	0.60	0.11	–	–
Cit-clusterin$^{231–250}$	0.09	0.83	1.26	0.06	–	–	0.44	0.24	–	–
Cit-clusterin$^{221–240}$	–	–	0.99	0.14	–	–	–	–	–	–
Cit-enolase	0.16	0.72	–	–	–	–	–	–	–	–
Cit-enolase $A^{5–21}$	–	–	0.76	0.26	–	–	–	–	–	–
Cit-fibronectin	–	–	−0.17	0.80	–	–	–	–	–	–
Cit-fibronectin$^{1029–1042}$	–	–	0.03	0.97	–	–	–	–	–	–
Noncitrullinated controls										
Fibrinogen	0.37	0.41	−0.16	0.80	–	–	0.38	0.31	–	–
Apo A1	0.29	0.47	−0.64	0.33	–	–	0.59	0.11	–	–
Apo E	0.06	0.89	–	–	–	–	–	–	–	–
Vimentin	–	–	−0.36	0.59	–	–	–	–	–	–
Histone H2A	–	–	−0.22	0.72	–	–	–	–	–	–
Histone H2B	–	–	−0.17	0.80	–	–	–	–	–	–

* CAC = coronary artery calcium; ACPA = anti–citrullinated protein antibody; ESCAPE RA = Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis; RHYTHM = Rheumatoid Arthritis Study of the Myocardium.
† Adjusted for age, rheumatoid arthritis disease duration, hypertension, diabetes mellitus, and tumor necrosis factor inhibitor use.
‡ Adjusted for age, sex, rheumatoid arthritis disease duration, ever smoking, hypertension, body mass index, high-density lipoprotein cholesterol, triglycerides, lipid medication, and aspirin use.
¶ Adjusted for antihistone H2B.

cardiovascular risk factors (1–3). RA itself is an independent risk factor for this excess risk (2,3), and although autoimmunity has been proposed as the possible link, the exact pathogenesis remains poorly understood.

Citrullination is a posttranslational protein modification that occurs as part of inflammation within the atherosclerotic plaque, as it does in the synovium (4). Recent data suggest a role for ACPAs in atherosclerosis: anti-Cit-vimentin antibodies correlated with subclinical atherosclerosis in early RA (13); Cit-fibrinogen and co-localizing peptidylarginine deiminase type 4 enzyme were identified within the atherosclerotic plaque of autopsied non-RA patients, and ACPAs in RA subjects targeting Cit-fibrinogen and Cit-vimentin were associated with an increase in aortic plaque burden (4). However, a study by Montes et al found no association between 3 different measures of atherosclerosis, including CAC, and ACPAs targeting Cit-fibrinogen and its $B^{36–52}$ peptide (5). Our

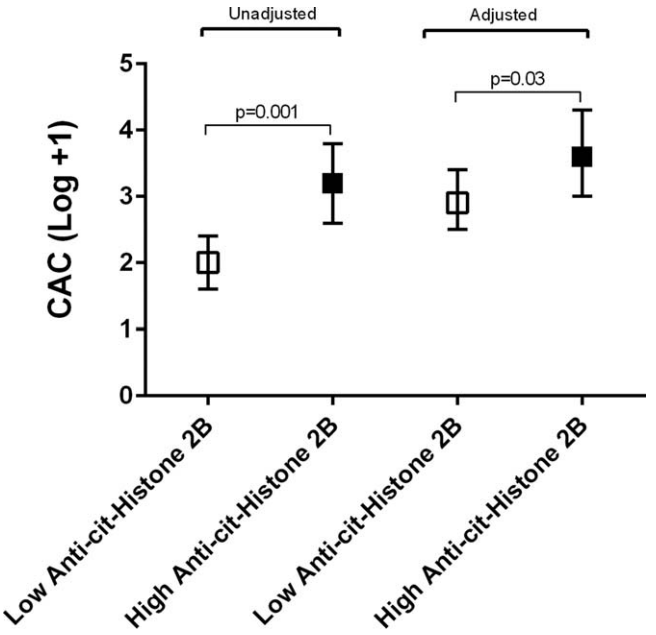

Figure 1. Association of coronary artery calcium (CAC) with levels of anti–citrullinated histone H2B antibody. Linear regression of the association of the log transformation of CAC score (CAC)+1 and anti–citrullinated histone H2B antibody level (75th percentile versus lower percentiles). Adjusted model adjusted for age, sex, rheumatoid arthritis disease duration, ever smoking, hypertension, body mass index, high-density lipoprotein cholesterol, triglycerides, lipid medication, and aspirin use.

study examined a much broader array of autoantigens than the prior studies and in a larger combined cohort. We failed to find an association between anti-Cit-fibrinogen or anti-Cit-vimentin antibodies with CAC, but identified a strong association with ACPAs targeting Cit-histone H2B. Several factors could account for these differences. Sokolove studied aortic calcification and exclusively in females with RA (4), while El-Barbary evaluated the association between anti-Cit-vimentin antibodies with carotid intima-media thickness, in contrast to our study, which utilized CAC, a direct measure of coronary artery disease (6). Montes also investigated CAC in addition to carotid artery measures but limited the ACPA investigations to anti-Cit-fibrinogen and its $B^{36–52}$ peptide (5), while our study addressed a much broader array of citrullinated autoantigens.

Histones, DNA-packaging nuclear proteins released during inflammation, are thought to be proatherogenic, at least in part by promoting the aggregation and uptake of low-density lipoproteins into foam cells (14). Although this relates to noncitrullinated histones, it is tempting to speculate a role in the citrullinated forms of these proteins in atherosclerosis. In support of this, Cit-histones are considered to be a biomarker for netosis. Netosis is a neutrophil extracellular aggregate (trap) consisting of DNA segments wound in a mixture of nuclear and cytoplasmic proteins including histones, myeloperoxidase, and neutrophil elastase, known to have potent proinflammatory, cytotoxic, and prothrombotic effects that are independently associated with coronary atherosclerosis and ischemic cardiac events (15). Moreover, immune complexes containing citrullinated histone H2B have the capacity to initiate inflammation, including inducing neutrophil activation (16). Our data extend these findings by suggesting a potential role of anti-Cit-histone antibodies in the evolution of atherosclerosis in RA. Interestingly, no additive effect was seen in the number of high-level ACPAs and their association with CAC, supporting specificity in the association with anti-Cit-histone H2B antibodies. Although anti-Cit-histone reactivity was not associated with the progression of CAC, the number of progressors in the ESCAPE RA cohort was small.

The strengths of this study include its sample size, derived from 2 independent cohorts of RA patients without clinical CVD who were well phenotyped for CV risk. Furthermore, the expanded panel of ACPAs allowed for the testing of additional seroreactivities of potential interest in atherosclerosis. Study limitations include using an ACPA panel that consisted of candidate autoantigens identified through synovial analysis; thus, potential additional autoantigens more relevant in atherosclerosis were conceivably missed.

In conclusion, high levels of anti-Cit-histone H2B antibodies were associated with a higher burden of atherosclerosis, measured by CAC, in RA patients without CVD. Future studies to explain their role in the pathogenesis of atherosclerosis in RA are warranted.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Geraldino-Pardilla had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Geraldino-Pardilla, Giles, Bathon.
Acquisition of data. Geraldino-Pardilla, Giles, Sokolove, Zartoshti, Robinson, Budoff, Detrano, Bokhari, Bathon.
Analysis and interpretation of data. Geraldino-Pardilla, Giles, Sokolove, Zartoshti, Robinson, Budoff, Detrano, Bokhari, Bathon.

REFERENCES

1. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303–7.
2. Szekanez Z, Kerekes G, Der H, Sandor Z, Shoenfeld Y, Soltesz P, et al. Accelerated atherosclerosis in rheumatoid arthritis. Ann NY Acad Sci 2007;1108:349–58.
3. Bartoloni E, Alunno A, Bistoni O, Gerli R. Cardiovascular risk in rheumatoid arthritis and systemic autoimmune rheumatic disorders: a suggested model of preventive strategy. Clin Rev Allergy Inmmunol 2013;44:14–22.
4. Sokolove J, Brennan MJ, Sharpe O, Lahey LJ, Kao AH, Krishnan E, et al. Citrullination within the atherosclerotic plaque: a potential target for the anti–citrullinated protein antibody response in rheumatoid arthritis. Arthritis Rheum 2013;65:1719–24.
5. Montes A, Corrales A, Calaza M, Lopez-Mejias R, Parra JA, Gonzalez-Gay MA, et al. Lack of replication of an association between anti–citrullinated fibrinogen and subclinical atherosclerosis in patients with rheumatoid arthritis. Arthritis Rheumatol 2015; 67:2861–5.

6. El-Barbary AM, Kassem EM, El-Sergany MA, Essa SA, Eltomey MA. Association of anti-modified citrullinated vimentin with subclinical atherosclerosis in early rheumatoid arthritis compared with anti-cyclic citrullinated peptide. J Rheumatol 2011;38:828–34.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
8. Chung CP, Giles JT, Kronmal RA, Post WS, Gelber AC, Bathon JM, et al. Progression of coronary artery atherosclerosis in rheumatoid arthritis: comparison with participants from the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther 2013;15:R134.
9. Winchester R, Giles JT, Nativ S, Downer K, Zhang HZ, Bag-Ozbek A, et al. Association of elevations of specific T cell and monocyte subpopulations in rheumatoid arthritis with subclinical coronary artery atherosclerosis. Arthritis Rheumatol 2016;68:92–102.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Vimonte M, Detrano R. Quantification of coronary artery calcium from electron beam tomograms. J Am Coll Cardiol 1990;15:827–32.
11. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Kronmal RA, et al. Coronary artery calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008; 358:1336–45.
12. Solow EB, Yu F, Thiele GM, Sokolove J, Robinson WH, Mikuls TR, et al. Vascular calcifications on hand radiographs in rheumatoid arthritis and associations with autoantibodies, cardiovascular risk factors and mortality. Rheumatology (Oxford) 2015;54:1587–95.
13. Sokolove J, Johnson DS, Lahey LJ, Wagner CA, Cheng D, Thiele GM, et al. Rheumatoid factor as a potentiator of anti–citrullinated protein antibody–mediated inflammation in rheumatoid arthritis. Arthritis Rheumatol 2014;66:813–21.
14. Pemberton AD, Brown JK. In vitro interactions of extracellular histones with LDL suggest a potential pro-atherogenic role. PLoS One 2010;5:e9884.
15. Borissoff JI, Joosen IA, Versteylen MO, Brill A, Fuchs TA, Kietselaer BL, et al. Elevated levels of circulating DNA and chromatin are independently associated with severe coronary atherosclerosis and a prothrombotic state. Arterioscler Thromb Vasc Biol 2013;33:2032–40.
16. Sohn DH, Rhodes C, Onuma K, Zhao X, Sharpe O, Sokolove J, et al. Local joint inflammation and histone citrullination in a murine model of the transition from preclinical autoimmunity to inflammatory arthritis. Arthritis Rheumatol 2015; 67:2877–87.