Subclinical Coronary Artery Calcification and Relationship to Disease Duration in Women with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine the association between disease duration of rheumatoid arthritis (RA) and the presence and extent of coronary artery calcification (CAC) in women with RA.

Methods. In this cross-sectional study, 185 women with RA duration of at least 2 years and no clinical cardiovascular disease completed electron-beam tomography (EBT) scans and risk factor assessment. Multivariable logistic regression was used to associate RA duration quartiles with subclinical CAC and extent of CAC.

Results. Age was similar across the quartiles of RA duration. Patients with RA > 23 years had significant increased odds (unadjusted OR 2.60, 95% CI 1.21–5.53) of having more extensive CAC compared to the referent group, those with RA for 2–7 years. This association remained significant after adjustment for traditional coronary heart disease (CHD) risk factors and RA-related covariates. Patients with intermediate RA duration (8–13 yrs) were more likely to have presence of any CAC (OR 3.03, 95% CI 1.06–8.66) compared to the referent group only after adjusting for age, race, and traditional CHD risk factors. Patients with longer RA duration were more likely to have cumulative joint damage, manifested as prior joint surgery, joint deformity, and greater functional disability. Lower body mass index also was associated with longer RA duration.

Conclusion. Patients with longstanding RA have more extensive subclinical atherosclerosis or CAC compared to patients of the same age, independent of other CHD risk factors. RA duration may be a surrogate for factors related to the disease process or its treatment that may promote coronary atherogenesis. (First Release Nov 15 2007; J Rheumatol 2008;35:61–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CORONARY ARTERY CALCIFICATION RISK FACTORS
DISEASE DURATION ELECTRON BEAM TOMOGRAPHY CARDIOVASCULAR DISEASE

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Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased morbidity and mortality from cardiovascular events[1-4], particularly ischemic heart disease[5]. Patients with RA have higher prevalence and severity of surrogate measures of coronary atherosclerosis compared to controls[6-8]. Disease duration in RA has been reported as an independent risk factor for myocardial infarction[9] and indicators of subclinical atherosclerosis detected by noninvasive testing. Specifically, the associations of arterial stiffness[7], presence of carotid plaque[10], more extensive carotid plaque[11], increased carotid intima-media thickness[12,13], and increase in coronary artery calcification (CAC)[14] with increasing RA duration suggest that the cumulative effect of the disease process and/or its treatment may potentiate cardiovascular risk.

Electron-beam computed tomography (EBT) is a surrogate measure of atherosclerosis. This noninvasive technique has a high degree of accuracy and reproducibility and can assess the presence and extent of CAC, reflecting calcium deposits in atherosclerotic plaque[15,16]. CAC as measured by EBT has been shown to be a strong predictor of subsequent coronary

heart disease (CHD) events[17,18]. In asymptomatic women with low to moderate cardiac risk, presence of CAC (relative risk 2.6, 95% CI 1.1–6.2) is an independent predictor of CHD events; whereas in asymptomatic men, the relative risk for CHD events in those with presence of CAC is much higher (RR 10.5, 95% CI 3.9–28.4)[17]. Asymptomatic individuals with higher CAC scores (≥ 100) have a relative risk of 13 (95% CI 5.7–29.6) for all atherosclerotic CHD events compared to those with lower CAC scores (< 100)[18]. In addition, a greater 2-year change in CAC score was independently associated with subsequent CHD events.

One study describes noninvasive imaging of the coronary arteries in RA[14]. Chung, *et al* reported CAC scores in men and women with RA and in controls, grouping patients with RA duration < 5 years (early disease) and patients with disease for at least 10 years (established disease)[14]. This included subjects with prior coronary artery procedures such as stenting, and those with intermediate disease duration were not evaluated. After adjusting for traditional risk factors, including age but not prior CHD or C-reactive protein (CRP) level, those with established disease were more likely to have extensive CAC than those with early disease (OR 2.52, 95% CI 1.05–5.13)[14].

We tested the hypothesis that patients with increasing RA duration have more extensive coronary atherosclerosis as measured by CAC, independent of traditional risk factors for CHD and markers of inflammation measured at the time of EBT imaging. Using a sample of similar-age women with RA, the relationship between RA duration and the presence and extent of subclinical CAC was determined. Finally, factors associated with prolonged RA duration, such as functional status, joint damage, and treatment, were examined in relation to CAC.

MATERIALS AND METHODS

Study population. Women with RA were recruited for a cross-sectional evaluation of RA disease features, cardiovascular risk factors, and EBT of the coronary arteries and aorta (2000-2004). All RA participants were diagnosed after age 16 years according to 1987 revised American College of Rheumatology criteria[19], with disease duration ≥ 2 years, and were recruited from the University of Pittsburgh Medical Center Arthritis Network outpatient practices. The first 200 women with RA fulfilling entry criteria and providing written informed consent were enrolled. Four patients did not complete the EBT scans, and one patient was excluded due to diagnosis misclassification. Of the remaining 195 patients, 10 patients with a prior cardiovascular event (myocardial infarction, angina, or stroke) were excluded from this analysis.

This study was approved by the Institutional Review Board of the University of Pittsburgh.

Variable measurements. Information on patient demographics and potential risk factors was collected at the time of EBT scan.

Traditional cardiovascular risk factors. The study visit included anthropomorphic measurements (height, weight, waist and hip circumferences), 2 consecutive blood pressure readings (with patients seated), and a fasting blood draw. Total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured at the Lipid Laboratory, University of Pittsburgh Graduate School of Public Health, which has been certified by the US Centers for Disease Control and Prevention. Low-density lipoprotein (LDL) cholesterol was calculated from measured total cholesterol, HDL, and triglycerides (Friedewald equation)[20]. Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as [insulin (mU/l) × glucose (mmol/l)]/22.5, and the homeostatic model assessment of beta-cell function (HOMA-B) was calculated as [20 × insulin (mU/l)]/[glucose (mmol/l) – 3.5][21,22]. Hypertension was defined as a previous physician diagnosis of hypertension, measured mean blood pressure ≥ 140/90 mm Hg, or use of antihypertensive medication. Dyslipidemia was defined as total cholesterol ≥ 200 or LDL cholesterol ≥ 130 or HDL cholesterol < 40 or use of lipid-lowering medication. These cut-points for total, LDL, and HDL cholesterol were based on the Adult Treatment Panel III classification for borderline high total and LDL cholesterols, and low HDL cholesterol. Diabetes mellitus was defined as use of hypoglycemic agent or measured fasting blood glucose > 126 mg/dl. Other information was also collected regarding family history of premature CHD (first relative having myocardial infarction before age 60 yrs), cigarette smoking (current, past, or never), and menopausal status (when menopausal status was uncertain, follicle-stimulating hormone levels were measured).

Disease-related factors. Patients with RA were also evaluated for the following: age of disease diagnosis, disease duration, physician's assessment of disease activity and severity by visual analog scale (VAS), morning stiffness, rheumatoid nodules, joint deformity, history of joint surgery, and modified Health Assessment Questionnaire Disability Index (mHAQ)[23]. Disease severity was a composite assessment (by VAS) by the evaluating physician based on clinical features and examination of the patients. All individuals in the study were HLA-typed using DNA typing technology as described[24]. Polymerase chain reaction amplification of the DRB1-chain genes was performed and the typing carried out using digoxygenin-labeled probes as described[24]. Patients were classified as DR4-positive or negative based on the presence of at least one of the DR4 alleles DRB1*0401, 0404, 0405, or 0408 associated with RA susceptibility and severity in Caucasians[25,26]. RA duration was defined as the time interval between the date of RA diagnosis and the date of evaluation and EBT scan. Patients were stratified into quartiles of RA duration based on the distribution of RA duration in this study sample (2 to 7, 8 to 13, 14 to 23, and > 23 yrs).

Inflammatory markers and biomarkers of endothelial activation. Fibrinogen was measured using a modified clot-rate assay, and latex immunonephelometry was used for determination of high sensitivity CRP (mg/dl). Erythrocyte sedimentation rate (ESR, mm/h) was measured by Westergren method. Soluble E-selectin (sE-selectin) and soluble intercellular adhesion molecule-1 (sICAM-1) were measured using commercial assays (Parameter Human sE-Selectin Immunoassay and sICAM-1 Immunoassay; R&D Systems, Minneapolis, MN, USA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA).

Medications. Data by self-report regarding corticosteroid treatment (ever use, current use, and daily dosage) and current use of nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, disease modifying antirheumatic drugs (DMARD), anti-tumor necrosis factor-α (TNF-α) agents, aspirin, hormonal therapy, and lipid-lowering medications were recorded.

EBT scanning protocol. EBT scans were performed using an Imatron C-150 scanner (Imatron, San Francisco, CA, USA) using standard imaging procedures. For CAC, 3-mm slices were scanned at the same point in diastole (at 80% of the patient's RR interval in electrocardiogram) during a single breathhold, starting at the aortic root to the apex of the heart. All EBT scans were read by the same cardiologist (DE). All pixels > 130 Hounsfield units and > 1 mm^2 within the coronary arteries were considered to represent calcium. A calcium score was calculated for each region of interest multiplying the area of all significant pixels by a grade number (1, 2, 3, or 4) indicative of the peak computed tomography number (Hounsfield units). The individual region of interest scores were summed for a total Agatston calcium score[27]. The analysis was based on the total Agatston calcium scores as described[28].

Statistical analysis. Baseline characteristics of subjects were compared based

on quartiles of RA duration. The distribution of calcium scores in the coronary arteries was highly skewed and could not be normalized by standard transformations. Thus, the calcium scores were stratified as discrete rather than continuous variables. In the multivariable logistic regressions, the outcome or dependent variables were the calcium scores, which were categorized using described classification schemes: (1) any CAC (CAC score > 0)[14] and (2) extent of CAC (0, 1–100 = mild, 101–400 = moderate, > 400 = severe). Classification scheme 2 is modified[29] using CAC score of 0 instead of ≤ 10 for consistency with scheme 1.

The trend across RA duration quartiles was evaluated using the test for log odds. Associations between RA duration quartiles and presence of CAC and the extent of CAC were determined using a series of binary and polychotomous logistic regression models, with adjustment of covariates that included race, CHD risk factors, and RA-related factors. Before adding the variable of interest, RA duration, all variables that were univariately associated with the CAC outcome variables ($p < 0.20$), had known association with CHD risk, and were not highly correlated with RA duration were included in the stepwise multivariate logistic regression analyses. As RA-related factors were highly correlated with each other, the association of each one of these RA-related factors with the CAC outcome was tested separately in age-adjusted models. All tests used a 2-tailed significance level of 0.05. All first-order 2-way interactions were tested. Analyses were performed using the Stata/SE version 9.0 for Windows (Stata Corp., College Station, TX, USA).

RESULTS

Table 1 shows the characteristics of the 185 RA women according to quartiles of RA duration. Mean age was not significantly different across the 4 groups. Patients in the highest quartile were diagnosed with RA at a much younger age (mean 28.2 yrs) and had a diagnosis of RA for at least 23 years at the time of study. These patients were more likely to have had rheumatoid nodules and indicators of cumulative RA-related damage: joint surgery, joint deformity, greater disease severity by physician VAS, and greater functional disability by mHAQ. Median daily prednisone dosage was slightly higher in patients with longer RA duration ($p = 0.01$ for trend). Patients in the highest quartile of RA duration had significantly lower body mass index (BMI; $p = 0.002$). There were no differences across RA duration quartiles for traditional CHD risk factors, other metabolic characteristics, RA-related factors, inflammatory markers, and markers of endothelial activation.

Overall, the median CAC score was 1.4 (IQR 0–65.9), and 58% of the patients had CAC (score > 0). Patients with RA for 2–7 years (the first quartile; Figure 1A) appeared to have the lowest prevalence of any CAC, although no significant trend for greater prevalence of any CAC was present in the RA duration quartile groups overall. There was no significant interaction between age and RA duration. There was a significant trend for longer RA duration in patients with higher quartile of CAC score ($p = 0.02$; Figure 1B). Patients with RA duration > 7 years were 2-fold more likely to have more extensive CAC than the referent group (RA 2–7 yrs), as shown in Table 2.

We reexamined the association of RA duration with CAC outcome variables by testing the following models to avoid both saturation of the multivariable regression models and introduction of highly correlated variables. The RA-related variables that were univariately associated with CAC outcomes and highly correlated with RA duration were "ever had rheumatoid nodule," disease severity by VAS, mHAQ, history of joint surgery, and joint deformity. Therefore, these variables did not enter into the stepwise selection. This resulted in the following multivariable regression models: (1) age and race; (2) age, race, and CHD risk factors (smoking history, hypertension, and HOMA-IR); and (3) age, race, CHD risk factors, and ESR as an inflammatory marker/RA-related factor at study. Since ESR, high-sensitivity (hs) CRP, and fibrinogen were highly correlated with one another, hsCRP and fibrinogen were substituted separately for ESR to determine their influence on the final model. Among the RA-related factors that were not associated with RA duration, ESR alone continued to be significantly associated with the CAC outcomes.

After adjusting for covariates in model 2 (Table 3), patients in the second quartile of RA duration (8–13 yrs) had a 3-fold increase in odds for any CAC when compared to the referent group. While patients in the third and fourth quartiles of RA duration appeared to have around 2-fold increase in risk for any CAC compared to the referent group, this association did not reach statistical significance. Similarly, after adjusting for covariates, patients in the second and third RA-duration quartiles were more likely to have more extensive CAC compared to the referent group (Table 4). Nonetheless, patients with RA duration > 23 years, the highest quartile, continued to have significant odds of having more extensive CAC compared to the referent group after adjustment of covariates. Substitution of hsCRP or fibrinogen for ESR in model 3 did not change the results. There was no incremental increase in odds of having any CAC or more extensive CAC associated with more prolonged RA-duration quartiles, since patients in the third RA-duration quartile appeared to have overall lower odds than those in the second and fourth RA-duration quartiles.

Risk factors univariately associated with any CAC were older age, postmenopausal status, smoking history, hypertension, greater BMI, greater waist circumference, greater disease severity by VAS, higher mHAQ score, joint deformity, and higher levels of insulin, ESR, fibrinogen and sICAM ($p < 0.05$). Using multivariable logistic regression with forward stepwise selection (variables with $p < 0.20$), the independent risk factors for having any CAC were older age, longer RA duration, greater BMI, smoking history, and higher ESR; the independent risk factors for having more extensive CAC were similar, as shown in Table 5. The RA-duration variable lost its significant association with CAC and more extensive CAC when RA-related factors such as joint deformity and mHAQ score were added to the multivariable models.

DISCUSSION

In this cross-sectional study, patients with the most recent diagnosis of RA appeared to have the lowest prevalence of any CAC compared to those with longer RA duration,

Table 1. Clinical and biological variables by quartiles of rheumatoid arthritis (RA) duration. Continuous variables presented as mean (standard deviation) or median (interquartile range: 25th to 75th percentile). Categorical variables presented as frequency (percentage).

Characteristic	Quartile of RA Duration, years 1st (2–7), n = 51	2nd (8–13), n = 43	3rd (14–23), n = 46	4th (> 23), n = 45	p for Trend
Demographics					
Age, yrs	58.3 (8.6)	57.1 (13.3)	59.3 (10.4)	59.5 (8.7)	0.45
Race Caucasian, %	51 (100)	36 (83.7)	44 (95.7)	44 (97.8)	0.91
Postmenopausal, %	42 (82.4)	32 (74.4)	38 (82.6)	35 (77.8)	0.80
College education, %	22 (43.1)	18 (41.9)	20 (43.5)	13 (28.9)	0.21
CHD risk factors					
Family history of CHD, %	15 (31.9)	12 (30)	17 (37.8)	18 (43.9)	0.19
Smoking history					
Ever smoker, %	24 (47.1)	23 (53.5)	23 (50)	19 (42.2)	0.62
Current smoker, %	5 (9.8)	8 (18.6)	1 (2.2)	3 (6.7)	0.21
Metabolic features					
Diabetes mellitus	3 (5.9)	2 (4.7)	0	3 (6.8)	0.81
Hypertension	21 (41.2)	11 (25.6)	22 (47.8)	20 (44.4)	0.36
Dyslipidemia	37 (72.6)	26 (60.5)	31 (67.4)	29 (64.4)	0.53
Body mass index	29.7 (7.6)	28 (5.4)	27.4 (4.6)	26.1 (5)	0.002
Waist-hip ratio	0.87 (0.11)	0.83 (0.09)	0.86 (0.08)	0.89 (0.15)	0.76
HOMA-IR	2.8 (2–3.7)	2.6 (1.8–3.3)	2.2 (1.7–3.1)	2.4 (1.6–2.9)	0.23
HOMA-B	162 (113–262)	157 (108–209)	169 (125–232)	144 (87–671)	0.36
RA features					
Age at RA diagnosis, yrs	52.8 (11.5)	46.9 (13.9)	40.9 (10.9)	28.2 (9.2)	< 0.001
Rheumatoid factor	29 (58)	32 (78.1)	39 (88.6)	31 (70.5)	0.06
HLA-DR4	34 (68)	27 (62.8)	32 (71.1)	33 (73.3)	0.45
Rheumatoid nodule, ever	18 (35.3)	23/40 (57.5)	31/43 (72.1)	31/43 (72.1)	< 0.001
Disease activity VAS (0–10 cm)	1.5 (0.4–3.5)	1.8 (0.5–3.4)	2 (1.2–3.9)	2.1 (1.2–3.1)	0.09
Disease severity VAS (0–10 cm)	2.4 (0.4–5.5)	3 (1.3–6.2)	5.9 (3.3–8.3)	7.3 (4.8–8.7)	< 0.001
mHAQ	0.38 (0.13–0.75)	0.63 (0.38–0.88)	0.63 (0.38–1.13)	1 (0.5–1.5)	< 0.001
Disease damage					
Joint surgery	12 (23.5)	17 (39.5)	27 (58.7)	38 (84.4)	< 0.001
Joint deformity	24 (47.1)	30 (71.4)	42 (91.3)	40 (88.9)	< 0.001
Current treatment (%)					
NSAID	29 (56.9)	30 (69.8)	37 (80.4)	31 (68.9)	0.09
DMARD	29 (56.9)	32 (74.4)	30 (65.2)	25 (55.6)	0.77
Methotrexate	29 (56.9)	30 (69.8)	30 (65.2)	24 (53.3)	0.71
Hydroxychloroquine	15 (29.4)	3 (7)	10 (21.7)	5 (11.1)	0.07
TNF-α blocker	14 (27.5)	13 (30.2)	18 (39.1)	12 (26.7)	0.80
Corticosteroid					
Ever use	43 (86)	41 (95.4)	41 (89.1)	37 (82.2)	0.90
Continuous use for > 6 mo	30 (70)	29 (70.7)	30 (73.2)	29 (78.4)	0.38
Current use	18 (35.3)	15 (34.9)	21 (45.7)	23 (51.1)	0.07
Median daily use, mg	0 (0–2.5)	0 (0–2.5)	0 (0–5)	1.2 (0–5)	0.01
Acute-phase reactants					
Median hsCRP	5 (1.1–9.7)	4.5 (2.2–7.8)	6.5 (1.9–15.3)	5 (1.8–16.3)	0.22
Median ESR	8 (5–18)	14 (7–26)	12.5 (7–24)	11 (4–27.5)	0.41
Median fibrinogen	331 (265–379)	317 (253–393)	308 (267–357)	320 (253–374)	0.73
Markers of endothelial activation					
Median sE-selectin ng/ml	45.3 (28.6–67.3)	38.4 (30.7–62.4)	50.8 (33.9–82.7)	44.1 (31.4–60.1)	0.47
Median sICAM-1, ng/ml	288 (238–339)	269 (233–382)	313 (255–392)	282 (240–361)	0.60
Homocysteine, mg/dl	11.0 (9.9–12.3)	11.4 (9.6–13.4)	11.4 (9.5–15.5)	11.4 (9.3–13.7)	0.86

CHD: coronary heart disease; HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-B: homeostatic model assessment of beta-cell function; VAS: visual analog scale by physician (1–10 cm, 10 being most severe); mHAQ: modified Health Assessment Questionnaire (higher score associated with lower function); NSAID: nonsteroidal antiinflammatory drug; DMARD: disease modifying antirheumatic drug; TNF-α: tumor necrosis factor-α; hsCRP: high sensitivity C-reactive protein; ESR: Westergren erythrocyte sedimentation rate; sE-selectin: soluble E-selectin; sICAM-1: soluble intracellular adhesion molecule-1.

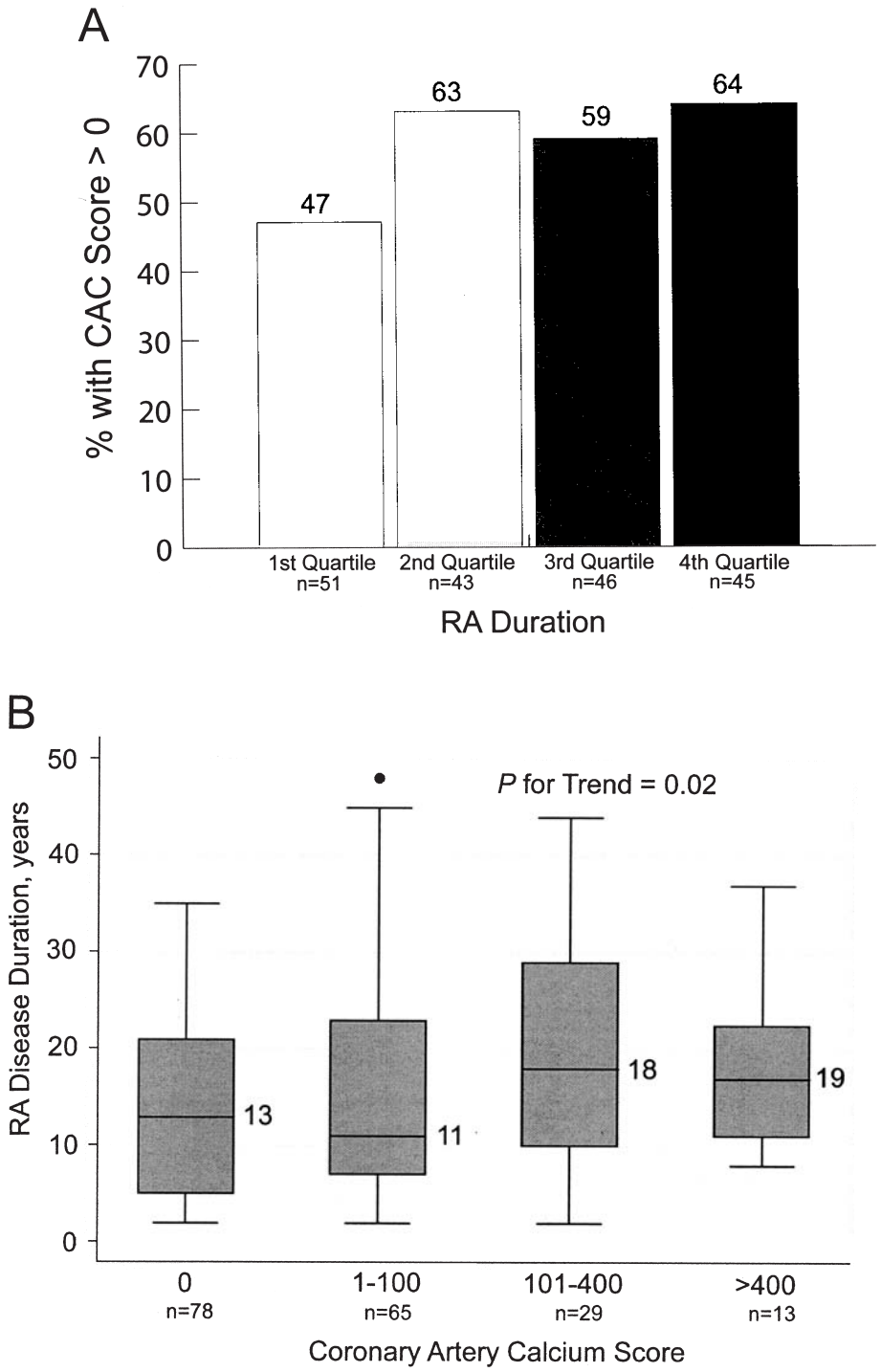

Figure 1. A. Prevalence of coronary artery calcification by quartiles of RA disease duration. B. Median RA disease duration by increasing coronary artery calcium score. Boxes indicate 25th and 75th percentiles; lines show 5th and 95th percentiles for the data.

although this finding was not statistically significant. In addition, those with more extensive CAC were likely to have more longstanding RA. Given the similar mean age of the women across quartiles of RA duration, this result supports the hypothesis that atherosclerosis of the coronary arteries, as measured by CAC, is more extensive in RA patients with well established disease. Whether a higher CAC score indicates greater CHD risk in women with RA is not known, and this cross-sectional analysis did not allow us to address this critical question.

Similar observations of relationship between RA duration and noninvasive imaging for atherosclerosis have been reported in studies of carotid intima-media thickness, presence or severity of carotid plaque, and prevalence and severity of CAC in patients with RA[10-12,14]. Our findings are consistent with those of Chung, *et al* of at least a 2-fold increase in likelihood of having more severe CAC in patients with established RA (> 10 yrs) compared to those with early RA (< 5 yrs)[14]. However, cut-points for quartiles of RA duration in the results reported here were based on a sampling of women with disease duration of at least 2 years but not otherwise specified. Women with prior clinical CHD also were excluded from this study based on the very high correlation of cardiovascular events with arterial plaque calcification, with calcification scores being used to predict risk for events[18,29]. Our results cannot be explained simply by age differences related to RA duration, as the mean age by quartiles of patients in this study were comparable. However, demographic and traditional risk differences among the 4 quartiles were present, although not necessarily statistically significant, and other differences across groups that were not identified in our analysis may con-

Table 2. Unadjusted odds ratio of presence of coronary artery calcification (CAC) (score > 0) and more extensive CAC, according to RA-duration group, in 185 women with RA.

RA Duration (yrs)	Any CAC		More Extensive CAC	
	OR	95% CI	OR	95% CI
1st quartile (2–7)	Referent	—	Referent	—
2nd quartile (8–13)	1.90	0.83–4.34	2.20	1.03–4.72
3rd quartile (14–23)	1.60	0.72–3.57	2.12	1.00–4.52
4th quartile (> 23)	2.04	0.90–4.64	2.60	1.21–5.53

Table 3. Multivariable adjusted odds ratio of presence of coronary artery calcification (score > 0), according to RA-duration group, in 185 women with RA.

RA Duration (years)	Adjusted for Age and Race		Adjusted for Age, Race, CHD, and Metabolic Risk Factors*		Adjusted for Age, Race, CHD/Metabolic Risk Factors, RA-Related Factor†	
	OR	95% CI	OR	95% CI	OR	95% CI
1st quartile (2–7)	Referent	—	Referent	—	Referent	—
2nd quartile (8–13)	2.29	0.84–6.21	3.03	1.06–8.66	2.25	0.78–6.44
3rd quartile (14–23)	1.59	0.65–3.88	1.93	0.73–5.08	1.40	0.54–3.63
4th quartile (> 23)	2.01	0.82–4.96	2.62	1.00–6.88	2.16	0.83–5.58

Variables in the models that were not highly correlated with RA duration and that were therefore included: CHD and metabolic risk factors (hypertension, smoking history, and HOMA-IR); RA-related factor (ESR). * CHD and metabolic risk factors that did not enter the model: college education, family history of CHD, dyslipidemia, and waist-hip ratio. † RA-related factors that did not enter the model: rheumatoid nodule, disease severity (VAS), mHAQ score, joint deformity, and joint surgery.

Table 4. Multivariable adjusted odds ratio of more extensive coronary artery calcification, according to RA-duration group, in 185 women with RA.

RA Duration (years)	Adjusted for Age and Race		Adjusted for Age, Race, CHD, and Metabolic Risk Factors*		Adjusted for Age, Race, CHD/Metabolic Risk Factors, RA-Related Factor†	
	OR	95% CI	OR	95% CI	OR	95% CI
1st quartile (2–7)	Referent	—	Referent	—	Referent	—
2nd quartile (8–13)	2.22	0.96–5.18	2.89	1.21–6.91	2.76	1.15–6.66
3rd quartile (14–23)	2.08	0.94–4.60	2.45	1.06–5.67	2.35	1.01–5.46
4th quartile (> 23)	2.57	1.14–5.75	2.94	1.30–6.62	3.14	1.38–7.17

Variables in the models that were not highly correlated with RA duration and that were therefore included: CHD and metabolic risk factors (hypertension, smoking history, and HOMA-IR); RA-related factor (ESR). * CHD and metabolic risk factors that did not enter the model: college education, family history of CHD, dyslipidemia, and waist-hip ratio. † RA-related factors that did not enter the model: rheumatoid nodule, disease severity (VAS), mHAQ score, joint deformity, and joint surgery.

Table 5. Risk factors associated with presence and more extensive coronary artery calcification (CAC) among RA women without clinical CHD using multivariable logistic regressions.

Any CAC	OR	95% CI	More Extensive CAC	OR	95% CI
Age	1.12	1.07–1.17	Age	1.10	1.07–1.15
RA duration (quartiles)	1.39	1.02–1.90	RA duration (quartiles)	1.37	1.06–1.78
ESR (every 10 mm/h)	1.30	1.03–1.63	ESR (every 10 mm/h)	1.25	1.07–1.45
Body mass index	1.10	1.03–1.18	Hypertension	2.02	1.09–3.76
Smoking history	2.07	1.02–4.20	Smoking history	2.48	1.36–4.52

tribute to the observed variability in presence of calcification and scores across the quartiles.

A significant trend for longer RA duration in those with more extensive CAC, although no incremental or stepwise increase in likelihood for more extensive CAC, was seen in those with longer RA duration. Those patients with the longest RA duration or youngest age at onset of RA had consistently significant increased odds for more extensive CAC compared to those with the most recent onset of RA or older age at onset. This raises the question of early exposure to systemic effects of a chronic inflammatory state that may trigger or promote early initiation of atherogenesis in women with RA whose disease began at younger age.

It is not surprising that patients with the shortest RA duration (2–7 yrs) in our study had the lowest prevalence of CAC, as calcification of plaque tends to occur later in more established atheroma in response to a chronic pathological process[30-32]. However, these patients with RA duration < 7 years are not necessarily risk-free nor at lower risk for CHD. Maradit-Kremers, *et al* have reported an increased risk of unrecognized myocardial infarction in subjects over the 2 years prior to fulfillment of criteria for RA, suggesting that a smoldering inflammatory state prior to the diagnosis of RA may play a role in such events[4].

While EBT measures calcified plaque in the coronary arteries, it is not an infallible tool for detection of clinically significant atherosclerosis in these vessels. Unstable atherosclerotic plaque is prone to rupture, resulting in acute coronary syndrome, but unstable plaque may not be calcified[33]. Thus, the measurement of CAC by EBT assesses the overall coronary atherosclerotic burden but neither the quality nor the stability of the atherosclerotic plaque. The correlation of EBT scores with subsequent CHD risk is undetermined in patients with RA, but followup of these subjects will help determine the positive predictive value of CAC for cardiovascular events in this high-risk group.

An incremental increase in odds for more extensive CAC associated with increasing RA duration was observed. Patients with longer RA duration/younger onset of RA also were more likely to have had rheumatoid nodules, joint deformity, joint surgery, and greater functional disability (higher mHAQ score) in our sample, reflecting greater cumulative damage with increasing duration of RA. While those patients with more remote onset of RA might have had a more aggressive disease course or received less aggressive treatment than those with RA onset later in life, the current literature suggests the opposite. Increasing age at symptom-onset was found to be associated with more radiological damage at presentation[34]. Additionally, patients with elderly-onset RA appeared to receive less aggressive treatment than those with younger-onset RA of comparable disease duration, severity and activity; however, these patients had mean RA duration of only 5.3 years[35]. Alternatively, RA treatment may alter atherogenesis and plaque calcification either favorably or detrimentally, as drug-related antiinflammatory effects are offset by metabolic risk factors for atherosclerosis. No significant difference in the current use of DMARD or TNF-α blockers across RA-duration quartiles was observed in this study. Cumulative drug exposure over duration of RA likely is a very important determinant of vascular health, including arterial plaque formation and calcification, but unfortunately this information was not available in this study sample. As we refine RA treatment options to minimize cardiovascular risk, caregivers must continue to focus on managing traditional CHD risk factors by promoting smoking cessation and optimal blood pressure in patients with RA.

Interestingly, patients with longer RA duration had lower BMI, even though the waist-hip ratios were not different across RA-duration quartiles. Lower BMI has been observed in patients with increasing RA duration[12]. In addition, low BMI is associated with mortality and cardiovascular death in RA[36,37]. Low BMI without a concomitant low waist-hip ratio likely reflects sarcopenia or muscle-wasting while maintaining truncal fat, as might be expected in rheumatoid cachexia. Thus, low BMI may be a surrogate indicator of prolonged exposure to circulating proinflammatory cytokines such as TNF-α, with its known muscle-wasting effects[38]. However, even though our patients in the highest quartile of RA duration had the lowest BMI, their mean BMI of 26 did not suggest low body weight. Further, we found a significant association of higher BMI with presence of CAC, as seen in a non-RA population[39], although neither high nor low BMI has been reported as an independent risk factor for carotid atherosclerosis or higher CAC scores in patients with RA[10,14].

Limitations of this study include the cross-sectional design of our data collection and the demographics of the RA patients, who were all female, primarily postmenopausal, and predominantly Caucasian, reflecting the ethnicity of our location. While the subjects appeared similar across groups, it is possible that the patients in different quartiles of RA duration varied in other ways, such as cardiovascular fitness or dietary intake, that might affect atherosclerosis risk and thus affect CAC risk. Because historic data on prior RA treatment and disease course were not available, we cannot determine if CAC patterns reported here were more a function of these factors or disease duration itself. Because CAC was not determined in patients with early RA (duration < 2 yrs), we cannot comment on CAC across the entire spectrum of RA duration. In spite of these limitations, the relatively homogeneous feature of this sample, with characteristics representing a large proportion of patients seen with RA, allows our findings to be extrapolated to many female RA patients seen for routine care. Longitudinal followup is necessary to determine the significance of our findings with regard to risk for clinical CHD events.

We describe the relationship between RA duration and RA-related factors on coronary artery calcification without age and sex as major confounders. Our results indicate that

women with RA with greater disease duration appeared to have more extensive coronary artery calcification than those with more recent RA onset and similar age. Whether this reflects less aggressive early treatment in patients diagnosed more remotely or cumulative effects of RA and/or its treatment is not clear. As the burden of chronic systemic inflammation is reduced in RA with increasingly effective treatment options, cardiovascular disease risk may diminish accordingly. The utility of noninvasive measures of atherosclerosis such as EBT will be important in detecting subclinical CHD disease to identify subjects likely to be at high risk for subsequent events, as these patients should ultimately be targeted for aggressive risk-factor reduction.

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