

Do Carotid Artery Diameters Manifest Early Evidence of Atherosclerosis in Women with Rheumatoid Arthritis?

Laura L. Schott, Ph.D.,¹ Amy H. Kao, M.D., M.P.H.,² Amy Cunningham,² Rachel P. Wildman, Ph.D.,³ Lewis H. Kuller, M.D., Dr.P.H.,¹ Kim Sutton-Tyrrell, Dr.P.H.,¹ and Mary Chester M. Wasko, M.D., M.Sc.²

Abstract

Objective: Given the high incidence of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA), we examined the associations between RA diagnosis and characteristics and evidence of carotid atherosclerosis. We take a unique approach by evaluating lumen and interadventitial diameters in addition to intima-media thickness and plaque.

Methods: Ninety-three women with RA were matched with 93 healthy women by age, race, and menopause status. In cross-sectional analyses, we compared common carotid artery measures between groups and examined their relationships with measures of RA severity and activity.

Results: Mean age was 53.3 years, and median RA duration was 14 years. Lumen diameter in patients was significantly greater than in healthy women (5.50 vs. 5.19 mm, $p < 0.001$), as was interadventitial diameter (6.92 vs. 6.61 mm, $p < 0.001$). Having RA also was independently associated with greater lumen ($\beta = 0.256$, $p < 0.01$) and interadventitial ($\beta = 0.261$, $p < 0.01$) diameters, after controlling for cardiovascular risk factors and intima-media thickness. Carotid intima-media thickness (0.70 vs. 0.71 mm) was similar, and the prevalence of carotid plaque in patients (21%) was higher but not statistically different from healthy women (15%). In patients with RA, we found positive associations between methotrexate dose and interadventitial diameter, between hypothyroidism and intima-media thickness, and between hypothyroidism and soluble endothelial adhesion molecule and plaque, independent of cardiovascular risk factors.

Conclusions: Women with RA have increased carotid artery diameters compared with healthy women. This may reflect premature vascular aging and may be an early indicator of increased cardiovascular risk.

Introduction

RHEUMATOID ARTHRITIS (RA) IS A CHRONIC, inflammatory autoimmune disorder that affects 1% of the U.S. population, particularly women of childbearing age and early menopausal age, with a 2.5:1 female/male ratio.¹ In patients with RA, cardiovascular disease (CVD) is a major determinant of morbidity and is the leading cause of death.^{2,3} To detect the burden of CVD in RA, noninvasive measures, such as carotid ultrasound, have been promoted to identify subjects with preclinical atherosclerosis.⁴⁻¹⁹ Serum markers of inflammation also are being explored, given their link with CVD in the general population and in patients with RA.^{6,9,14,20-26}

Carotid ultrasound measures of lumen diameter, interadventitial diameter, intima-media thickness (IMT), and plaque

have been evaluated as early indicators of systemic atherosclerosis in non-RA populations and are informative measures of vascular health.²⁷⁻²⁹ Changes in these four measures are interdependent,³⁰ occurring as both part of the natural aging process and in response to insult or injury. Arterial dilatation (i.e., vascular remodeling) begins as an adaptive response to changes in wall shear stress concomitant with increased wall thickness,^{27,28,31-34} but ultimately, larger carotid diameter is a marker of vascular aging and is associated with cardiovascular risk factors, plaque rupture, inflammatory activity, and increased risk of myocardial infarction (MI).^{28,30,35-38} IMT is increased in individuals with coronary heart disease (CHD) and MI, is associated with numerous cardiovascular risk factors, and predicts risk of cardiovascular events.³⁹⁻⁴² Carotid plaque has been linked with cardiovascular risk factors and ischemic stroke.^{43,44} Although

¹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

²University of Pittsburgh Department of Medicine, Division of Rheumatology and Clinical Immunology, Pittsburgh, Pennsylvania.

³Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York.

IMT and plaque are typically used to assess atherosclerosis, lumen diameter is a critical indicator of arterial remodeling, thus providing adjunct information.^{30,35}

Thus far, carotid ultrasound findings in RA patients have generally not included measures of lumen or interadventitial diameter. Although studies typically find common carotid IMT to be higher in RA patients compared with controls,^{4–12} other studies (particularly those in the United States) have found no difference^{13–16} or the opposite results.¹⁸ To provide insight into these discrepancies and likely better understand the effect of RA disease severity and activity on vascular aging, it may be necessary to examine carotid diameters in conjunction with IMT and plaque.

The purpose of our study was twofold. We sought to (1) compare carotid arterial diameters, IMT, and plaque in women with RA with matched healthy women and (2) evaluate the associations between RA-related factors and indicators of early carotid disease in patients.

Materials and Methods

Participants

Women with RA consecutively seen at a university-based outpatient rheumatology practice and the University of Pittsburgh Medical Center (UPMC) Arthritis Network Disease Registry volunteered for a prospective study of CVD prevalence and risk factor assessment.⁴⁵ Registry participants, who gave informed consent to be notified in writing of research opportunities, comprised RA patients from the university-based practices (approximately one third) and two university-affiliated, community-based practices (approximately two thirds). Eligibility criteria, including age >30 years, American College of Rheumatology criteria for RA⁴⁶ for at least 2 years, and completion of a carotid scan, were met by 104 women.

Healthy participants were selected from 535 women who participated in the Women's Healthy Lifestyle Project, an intervention trial examining cardiovascular risk factors during menopause.^{47,48} At enrollment, these women were aged 44–50 years, with no indication of CVD. As part of an ancillary study, 85% of participants had carotid ultrasound scans an average of 5 years after enrollment, during which some changes in health status developed (e.g., hypertension). Healthy participants eligible for the current retrospective analysis completed a scan ($n = 453$) and were randomized to the nonintervention arm of the study ($n = 275$).

Patients with RA and healthy participants were individually matched retrospectively by age (± 5 years), menopause status, and race. Arterial diameter measures were not available on all eligible participants because this protocol component was not initially included during scanning and was unobtainable *post hoc*. The final sample consisted of 93 patients with RA and 93 healthy women with IMT and plaque measures, and of these, 78 patients and 90 healthy women with diameter measures.

The RA cardiovascular study, intervention trial, and carotid scan protocols were approved annually by the Institutional Review Board of the University of Pittsburgh. All participants provided informed written consent.

Clinical measures

Clinical data and cardiovascular risk factors were obtained through patient interview and physical examination. Fasting

blood samples were assayed at the Department of Epidemiology Nutrition Laboratory. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were averaged from two seated measurements⁴⁹; height and weight were used to calculate body mass index (BMI, kg/m²). Women were assessed for hormone therapy use (any in the prior year), hypertension (SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg,⁵⁰ and/or antihypertensive drugs), diabetes (glucose ≥ 6.99 mmol/L [126 mg/dL]⁵¹ and/or medication), and hypercholesterolemia (cholesterol ≥ 5.17 mmol/L [200 mg/dL]⁵² and/or lipid-lowering drugs). Menopause status was based on participant self-report, plus endogenous hormone levels in patients with RA. For analysis, menopause status was dichotomized as postmenopausal (no bleeding cycle or taking hormone therapy for ≥ 12 consecutive cycles, or hysterectomy with bilateral oophorectomy) vs. not (i.e., premenopausal or perimenopausal). Measures were collected within approximately 1 month of the ultrasound scan for RA patients and within 1 year for healthy participants because protocols regarding timing of visits varied for the two studies.

RA characteristics

Patients with RA were also evaluated for RA-related and inflammatory markers (Table 2). Soluble endothelial adhesion molecule (sE-selectin) was measured using a high sensitivity quantitative sandwich enzyme assay and determined colorimetrically; soluble intercellular adhesion molecule (sICAM-1) was measured by an ELISA assay and determined by colorimetric reaction (assays from R&D Systems, Minneapolis, MN); high sensitivity C-reactive protein (hsCRP) was determined using latex immunonephelometry (all completed at Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington, VT). Additional laboratory variables were measured by routine methods as described previously.⁴⁵

Carotid ultrasound measures

Arteries were examined using an ultrasound scanner (Toshiba SSA-270A, Tustin, CA) equipped with a 5-MHz linear array imaging probe. With participant in the supine position, left and right arteries were viewed at end diastole in transverse and longitudinal projections. Common carotid near and far walls were examined 2 cm proximal to the bifurcation. Digitized images were used to trace the media-adventitial and intima-lumen interfaces across 1-cm lengths, and IMT was computed as the average of both arteries. Lumen diameter was measured as the distance between the lumen-intima interfaces of the left common carotid artery, where the walls were parallel and there was no evidence of plaque. Interadventitial diameter was calculated as the distance between the adventitia-media interfaces.

Carotid arteries were evaluated for the presence of eccentric focal plaque in the bifurcation, internal, and common areas. Plaque was defined as a distinct area protruding into the vessel lumen with $\geq 50\%$ thickness than the surrounding area. Presence of plaque was categorized as no/small plaque ($< 30\%$ stenosis) and medium/large/multiple plaques ($\geq 30\%$ stenosis). This categorization captured the severity distinction of our sample more appropriately than either dichotomizing as plaque "any versus none" or totaling the number of plaques.

All scans were completed by trained technicians in the same laboratory and read later by technicians blinded to study group. The laboratory has shown IMT, plaque, and diameters to be reliable measures of carotid atherosclerosis. For each measure (IMT,⁵³ plaque,⁵⁴ and diameter), the reproducibility coefficient was ≥ 0.78 , and the intraclass correlation coefficient was ≥ 0.84 in this laboratory.

Statistics

In this cross-sectional study, patients with RA and healthy women were compared using unpaired *t* tests and chi-square tests. Univariate associations between clinical measures and carotid outcomes were examined via Pearson/Spearman correlation. Because of their skewed distribution, inflammatory markers were both log transformed and divided into quartiles.

In multivariable analyses, dependent (outcome) measures were IMT, lumen diameter, interadventitial diameter (all linear regression), and plaque (logistic), with RA diagnosis as the independent variable. Models were adjusted for cardiovascular risk factors determined via univariate associations. In diameter models, height was included to account for body size, which is positively correlated with arterial size. To control for potential confounding between the two groups, diameter models controlled for IMT, and the IMT model was adjusted for interadventitial diameter. For RA-only regression, each RA characteristic (listed in Table 2) was individually added to the multivariable cardiovascular risk factor model for each outcome. Analyses were also run using only Caucasian women, and as there were no differences, results are reported on the full sample.

All analyses were implemented using the SAS system for Windows version 8.2 (SAS Institute, Cary, NC). Values of $p \leq 0.05$ were considered significant.

Results

The combined group was 97% Caucasian, 68% postmenopausal, and 53.3 ± 3.9 years old. Patients with RA had higher BMI, blood pressure, and triglycerides and were more likely to be never smokers and have been diagnosed with hypertension, whereas healthy women had higher fasting glucose levels (Table 1). Patients with RA had larger lumen and interadventitial diameters than did healthy participants, but there was no difference in IMT. Presence of plaque in RA patients (21%) was higher but was not statistically different from that in healthy women (15%).

For patients, average age at RA diagnosis was 37 years, with a median disease duration of 14 years, and 71% reported experiencing morning stiffness, lasting 1 hour on average (Table 2). Patients with RA who had diameter measures available were generally similar to patients who did not have diameter measures with respect to all characteristics reported in Table 2. The two exceptions were that patients without diameter measures were all rheumatoid factor positive and were less likely to have hypertension than those with diameter measures.

Regression models

Based on univariate analyses, covariates included in multivariable models were hypertension (significantly, positively associated with all carotid outcomes), hypercholesterolemia (w/plaque), glucose (w/IMT), age (w/IMT), and race (w/IMT). In regression analyses adjusted for these risk factors and IMT, RA diagnosis was positively associated with wider lumen and interadventitial diameters (Table 3). On average, diameters for patients with RA were 0.27 mm wider than those of controls. These results did not change if

TABLE 1. COMPARISON OF HEALTHY PARTICIPANTS AND PATIENTS WITH RHEUMATOID ARTHRITIS^a

Characteristic	Healthy participants (n = 93)	Patients with RA (n = 93)	p value
Clinical measures			
Mean age, range (years)	53.2, 46.7–58.7	52.9, 42.0–60.2	0.62
Current/former/never smokers (%)	7/51/35	12/31/50	0.01
Diabetes	2 (2%)	3 (3%)	0.65
Glucose (mmol/L)	5.61 ± 0.578	4.98 ± 1.07	<0.001
Body mass index (kg/m ²)	25.8 ± 3.4	28.4 ± 6.5	0.001
Hypertension	11 (12%)	27 (29%)	0.004
Systolic blood pressure (mm Hg)	110.5 ± 12.7	120.5 ± 17.9	<0.001
Diastolic blood pressure (mm Hg)	70.8 ± 7.9	77.3 ± 10.4	<0.001
Hypercholesterolemia	51 (55%)	59 (63%)	0.23
Total cholesterol (mmol/L)	5.38 ± 0.78	5.30 ± 0.83	0.26
High-density lipoproteins (mmol/L)	1.61 ± 0.36	1.52 ± 0.36	0.12
Low-density lipoproteins (mmol/L)	3.22 ± 0.69	3.11 ± 0.78	0.34
Triglycerides (mmol/L)	0.94 [0.77, 1.39]	1.32 [0.98, 1.70]	<0.001
Current hormone therapy	36 (44%)	35 (38%)	0.36
Carotid ultrasound measures			
Lumen diameter (mm)	5.19 ± 0.47	5.50 ± 0.60	<0.001
Interadventitial diameter (mm)	6.61 ± 0.54	6.92 ± 0.67	<0.001
Intima-media thickness (mm)	0.71 ± 0.08	0.70 ± 0.10	0.94
Presence of plaque ^b	14 (15%)	19 (21%)	0.29

^aFor Tables 1 and 2, characteristics are summarized as *N*(%), mean \pm standard deviation (SD), or median [interquartile range] unless otherwise indicated.

^bPresence of plaque, medium, large, or multiple plaques.

TABLE 2. ADDITIONAL CHARACTERISTICS FOR WOMEN WITH RHEUMATOID ARTHRITIS

Characteristic	
Age at rheumatoid arthritis diagnosis (years)	37.3 ± 10.9
Disease duration since diagnosis (years)	14 [7, 23]
Rheumatoid factor positive	64 (73%)
Morning stiffness	65 (71%)
Extraarticular disease	73 (78%)
Health Assessment Questionnaire Disability Index ⁵⁵	0.75 ± 0.57
Number of prior disease-modifying antirheumatic drugs (DMARDs) (ever)	3.5 ± 1.9
Current nonsteroidal anti-inflammatory drug use	69 (75%)
Current prednisone use	38 (41%)
Daily prednisone dose (mg)	5.4 ± 3.5
Current methotrexate use	57 (61%)
Weekly methotrexate dose (mg)	14.5 ± 5.1
Current tumor necrosis factor inhibitor use	35 (38%)
Hypothyroidism ^a	12 (13%)
Erythrocyte sedimentation rate (ESR) (mm/h)	10.0 [5.0, 24.5]
High sensitivity C-reactive protein (hsCRP) (mg/L)	5.6 [2.2, 13.0]
Fibrinogen (μmol/L)	9.3 [7.6, 10.8]
Plasminogen activator inhibitor type 1 (PAI-1) (μg/L)	19.3 [10.4, 45.0]
Soluble intercellular adhesion molecule [sICAM-1] (ng/mL)	271 [232, 335]
Soluble endothelial adhesion molecule [sE-selectin] (ng/mL)	40.3 [29.7, 64.5]

^aHypothyroidism was indicated by self-report, including treatment with medications.

IMT was omitted from the models. In contrast, IMT was similar between groups whether or not diameter was in the model. RA diagnosis was not associated with the presence of plaque in multivariable models. Results were essentially the same when other risk factors were considered as covariates, such as substituting SBP for hypertension, substituting BMI for height, or adding smoking, menopausal status, or hormone therapy to the models. Hypertension was the only cardiovascular risk factor associated with diameters, and African American race (plus age when interadventitial diameter was omitted) was associated with IMT. Age and hy-

percholesterolemia were positively associated with presence of plaque.

RA characteristics

Unadjusted analyses in RA patients showed that RA duration was positively associated with IMT (Spearman's $r = 0.21$, $p = 0.04$), but this relationship disappeared after controlling for age. Average daily dose of prednisone was positively associated with lumen and interadventitial diameters (Spearman's $r = 0.46$, $p = 0.008$, and $r = 0.47$, $p = 0.006$, re-

TABLE 3. MULTIVARIABLE REGRESSION MODELS OF CAROTID ARTERY OUTCOMES OF ALL SUBJECTS^a

Risk factor	Dependent outcomes			
	Lumen diameter (mm) n = 168 β^b	Interadventitial diameter (mm) n = 168 β	Intima-media thickness (mm) n = 186 β	Presence of plaque n = 186 OR
Rheumatoid arthritis diagnosis	0.270**	0.275**	-0.015	1.66
Age (years)	0.012	0.010	0.002	1.12*
African American race	-0.199	-0.168	0.088*	2.61
Hypertension	0.274**	0.290**	-0.013	1.23
Hypercholesterolemia	-0.013	0.003	0.005	2.46*
Glucose (mmol/L)	-0.022	-0.027	0.014*	1.37
Height (cm)	0.017**	0.017**	—	—
Intima-media thickness (mm)	1.021*	3.084***	—	—
Interadventitial diameter (mm)	—	—	0.071***	—

^aThe first six risk factors were included in the model for each dependent outcome; additionally, height and intima-media thickness were included in the diameter models, and interadventitial diameter was included in the intima-media thickness model.

^b β , regression coefficient; OR, odds ratio.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

spectively). Average weekly dose of methotrexate was positively associated with interadventitial diameter and IMT (Spearman's $r = 0.33$, $p = 0.02$, and $r = 0.33$, $p = 0.01$, respectively). The highest quartile of levels of hsCRP, sE-selectin and plasminogen activator inhibitor type 1 (PAI-1) were associated with a small but nonsignificant increase in diameter and plaque measures. There was a significant negative association between continuous sICAM-1 and IMT (Spearman's $r = -0.23$, $p = 0.03$). None of the other listed RA characteristics showed significant univariate associations with the carotid outcomes.

In multivariable models in women with RA, no RA characteristic was associated with lumen diameter when individually added to the model controlling for cardiovascular risk factors. For those currently taking methotrexate, weekly dose was positively associated with interadventitial diameter (Table 4); however, this association was no longer significant when age was replaced with RA duration and age at diagnosis or when IMT was added to the model. Current prednisone use was associated with decreased IMT, whereas hypothyroidism was associated with increased IMT in separate models. These associations remained when interadventitial diameter was included or when RA duration and age at diagnosis were substituted for age. Plaque was positively associated with sE-selectin and hypothyroidism in individual models after controlling for cardiovascular risk factors. No other RA characteristics were significantly associated with carotid outcomes in multivariable models of patients with RA.

Discussion

This study is the first to describe wider carotid artery lumen and interadventitial diameters in women with RA com-

pared with healthy women, independent of cardiovascular risk factors and IMT. In the women with RA, positive associations were found between methotrexate dose and interadventitial diameter, between hypothyroidism and IMT, and between sE-selectin and hypothyroidism and plaque, each independent of cardiovascular risk factors. Diameters were positively associated with prednisone dose, whereas in multivariable models, IMT was negatively associated with current prednisone use. These findings may indicate evidence of accelerated vascular aging and early atherosclerotic risk among women with RA.

Vascular adaptation?

Vascular remodeling is a dynamic, early response to risk factors, wall thickening, and increased wall shear stress.^{27,28,31-34} Concomitant increase of carotid diameters (i.e., outward radial enlargement) allows lumen cross-sectional area and arterial flow to be kept constant and maintains or decreases IMT/plaque by distributing it over a larger area.³⁰ Because the artery has a limited capacity to dilate, however, continued formation of IMT and plaque ultimately causes reduction of blood flow.^{27,34,35,56} Arterial remodeling also suggests inflammatory cells and protease activities and may be indicative of lesser vessel elasticity and plaque rupture.^{30,35} Thus, enlarged diameters can be considered a sign of vascular adaptation and a marker for early atherosclerosis.

Alternatively, our results may reflect a unique, RA-related atherogenic effect on arterial diameters that is specific to RA itself rather than a result of remodeling in response to thickened IMT. Perhaps the underlying autoimmune disease process, its treatment, or an interplay between the two accounts for a change in the evolution of atherosclerotic vascular dis-

TABLE 4. MULTIVARIABLE REGRESSION MODELS OF SIGNIFICANT RHEUMATOID ARTHRITIS FACTORS ASSOCIATED WITH CAROTID OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS^a

Risk factor	Dependent outcomes				
	Interadventitial diameter (mm) n = 57 β^b	Intima-media thickness (mm) n = 93 β		Presence of plaque n = 93 OR	
Age (years)	0.022	0.004	0.003	1.29	1.16
African American race ^c	0.818	0.101	0.121*	3.65	—
Hypertension	0.166	0.013	0.008	0.98	1.43
Hypercholesterolemia	0.120	0.018	0.026	2.23	2.68
Glucose (mmol/L)	0.023	0.010	0.011	1.19	1.23
Height (cm)	0.019	—	—	—	—
Weekly methotrexate dose (mg)	0.040*	—	—	—	—
Prednisone user	—	0.057**	—	—	—
Hypothyroidism	—	—	0.085**	7.25*	—
Log of sE-selectin (ng/mL)	—	—	—	—	3.09*

^aThe first five risk factors were included in each individual model, plus height for diameter; the remaining factors were individually added in respective models for each outcome (interadventitial diameter, intima-media thickness, and plaque). All significant associations are displayed, resulting in varying number of columns per outcome.

^b β , regression coefficient; OR, odds ratio; sE-selectin, soluble endothelial adhesion molecule.

^cTo maintain model fit, race was dropped from the plaque model listed in the final column because of missing data ($n = 84$).

* $p < 0.05$.

** $p < 0.01$.

ease in these patients. In contrast, diameter differences were not found among treatment groups or compared with controls in separate studies.^{15,57} Others have suggested that chronic systemic inflammation leads to endothelial dysfunction and accelerated atherogenesis in patients with RA.^{22,23,25}

Literature comparisons

Our finding of similar common carotid IMT between groups is consistent with studies of RA patients in the United States and two Italian studies.^{13–16} Another study found IMT in RA patients to be less than in controls.¹⁸ Other investigators have found higher common carotid wall thickness in RA patients compared with controls.^{4–12} In contrast to the subjects we described, these studies generally report on slightly older patients with a wider age spectrum, enrolled both men and women, and used non-United States samples. Research indicates that IMT increases with age,^{28,58} and is greater in men.⁴⁰

Based on patient ages, results suggest a U-shaped relationship, where IMT may be similar between patients and controls at younger and older ages (e.g., <50 or >60 years old^{13–16}). Thus, younger samples may have been studied at an earlier point on an arterial remodeling continuum, with RA patients having vessel wall dilatation and thus preserved IMT.

Ethnicity and control characteristics may also be influencing results, given that results of greater IMT in RA patients occurred outside the United States.^{4–12} Interestingly, carotid IMT in our healthy women (mean 0.71 mm) was much higher when compared with several previous studies (common carotid IMT 0.58–0.68 mm), whereas IMT in our RA patients was similar to that in other studies (range 0.64–0.77 mm).^{4–6}

It cannot be said with certainty that all RA patients have greater IMT than controls or if this difference is only observed in patients of certain ages or ethnicities, at particular time points in the course of disease (RA or atherosclerosis), or in conjunction with health and population of controls. A study of IMT progression in women with RA found an accelerated rate of annual wall thickening when compared with healthy controls.¹⁷ Thus, although there is evidence that IMT may differ between RA patients and controls, the course of progression may be distinct from other conditions where increased IMT is seen at a very early stage of atherogenesis.

Regarding carotid plaque, several studies reported no difference in plaque prevalence,^{4–6,9,14} whereas others have found increased carotid plaque in RA patients.^{8,10–13,15,18} Sample size may have limited our ability to detect statistically significant differences in plaque, which was clinically higher in our women with RA. Plaque frequently occurs in areas of transition or turbulence (e.g., internal carotid artery or bifurcation).³⁴ Therefore, variations in methodology (i.e., area of plaque assessment, plaque characterization) may be influencing results.

RA-related characteristics

We found several RA characteristics associated with measures of carotid atherosclerosis. The positive association between duration of disease and IMT is typically reported.^{5,6,10,12,20,59,60} As was found here, RA medications

may be positively^{18,61} or negatively²¹ associated with atherosclerosis. Incongruencies exist because pharmacological treatment can be a marker for RA severity, contributing adversely to cardiovascular risk (e.g., hyperlipidemia) or, conversely, exerting a protective effect by reducing RA-related systemic inflammation.^{26,62–65} Additionally, medication types, effectiveness, and side effects influence when and how they are prescribed, and studies vary on whether current, cumulative, or multiple medication exposure is considered. Previous studies have linked hypothyroidism with IMT and plaque in patients with RA^{59,60} and with accelerated atherosclerosis in non-RA subjects.⁶⁶ Impaired lipid metabolism/profiles, obesity, high homocysteine levels, and effects of thyroid hormones on vascular cells are all potential pathways for this link.

Studies show inconsistent relationships between inflammatory markers and atherosclerosis in RA patients. The cross-sectional nature of our study and others does not capture the changing inflammatory milieu over time in RA patients. Further, the clinical course of RA is exceedingly variable, ranging from mild, self-limiting arthritis to rapidly progressing, multisystem inflammation.¹ As others,^{5,16,18} we did not find a relationship between either CRP or erythrocyte sedimentation rate (ESR) and carotid atherosclerosis, although a positive association between these and IMT or plaque has been noted elsewhere.^{14,17,20,22} Others have reported a positive association between sICAM-1 and IMT and between sE-selectin and plaque.²¹ Similarly, we found a positive association between sE-selectin and plaque. Our patients showed a high degree of extraarticular disease, which is indicative of significant systemic inflammation and consistent with their disease duration and high proportion of rheumatoid factor positivity. Inflammation in RA has been most consistently linked to endothelial function, another early marker of atherosclerosis.²² Thus, certain RA characteristics and markers of inflammation support a link between RA and early atherosclerosis.

Limitations

The strength of our study was the use of ultrasound measures novel for patients with RA, namely, lumen and interadventitial diameters, and it was unfortunate that 18 subjects were missing these measures. This was a cross-sectional study presented without correction for multiple comparisons; thus, care should be taken when interpreting and generalizing results. Using a convenience sample of controls who were recruited as part of another study and matched retrospectively is another limitation of our study. Nonetheless, by examining carotid diameter, we were able to demonstrate early signs of vascular aging and atherosclerotic risk in women with RA.

Conclusions

Our study of patients with RA is unique and noteworthy. We used a carotid ultrasound technique not typically reported for detecting vascular aging in an RA sample. We found greater carotid arterial diameters in women with RA compared with matched healthy women, whereas IMT was similar. We propose that lumen and interadventitial diameters may be more sensitive measures of early atherosclerosis in women with RA than ultrasound measurement of IMT

and plaque and may explain previous discrepancies. Carotid diameter vascular remodeling may be an important step in atherogenesis in this autoimmune disease and should be included in measures of early atherosclerotic CVD in patients with RA.

Acknowledgments

We gratefully acknowledge the important contributions of the staff and study participants in time, data collection, and dedication to research. We thank Susan Manzi, M.D., M.P.H., for her helpful input in study concept, design, and manuscript review. We also would like to acknowledge the University of Pittsburgh Medical Center's Arthritis Network physicians who developed the Network Diseases Registry, our primary source of RA participants.

The study involving women with RA was funded by the NIH/NCRR/GCRC grant MO1-RR000056, American Heart Association Established Investigator Award 0040149N, Arthritis Foundation Western PA Chapter, NIH 1 K23 AR47571, and American College of Rheumatology/ Research and Education Foundation Physician Scientist Development Award. Research involving the healthy women was funded by American Heart Association Grant-in-Aid Award 0050236N and NIH grant HL-45167.

Disclosure Statement

The authors have no conflicts of interest to report.

References

- Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001; 358:903–911.
- Solomon DH, Goodson NJ, Katz JN, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1608–1612.
- Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997;24:445–451.
- Alkaabi JK, Ho M, Levison R, Pullar T, Belch JJ. Rheumatoid arthritis and macrovascular disease. *Rheumatology* 2003;42:292–297.
- Kumeda Y, Inaba M, Goto H, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46: 1489–1497.
- Park YB, Ahn CW, Choi HK, et al. Atherosclerosis in rheumatoid arthritis: Morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002;46:1714–1719.
- Daza L, Aguirre M, Jimenez M, Herrera R, Bollain JJ. Common carotid intima-media thickness and von Willebrand factor serum levels in rheumatoid arthritis female patients without cardiovascular risk factors. *Clin Rheumatol* 2007;26: 533–537.
- Pamuk ON, Unlu E, Cakir N. Role of insulin resistance in increased frequency of atherosclerosis detected by carotid ultrasonography in rheumatoid arthritis. *J Rheumatol* 2006; 33:2447–2452.
- Jonsson SW, Backman C, Johnson O, et al. Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. *J Rheumatol* 2001;28:2597–2602.
- Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porra C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine* 2003;82:407–413.
- Pahor A, Hojs R, Gorenjak M, Rozman B. Accelerated atherosclerosis in pre-menopausal female patients with rheumatoid arthritis. *Rheumatol Int* 2006;27:119–123.
- Ciftci O, Yilmaz S, Topcu S, et al. Impaired coronary microvascular function and increased intima-media thickness in rheumatoid arthritis. *Atherosclerosis* 2008;198:332–337.
- Rodriguez G, Sulli A, Cutolo M, Vitali P, Nobili F. Carotid atherosclerosis in patients with rheumatoid arthritis: a preliminary case-control study. *Ann NY Acad Sci* 2002;966:478–482.
- del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003;48:1833–1840.
- Roman MJ, Devereux RB, Schwartz JE, et al. Arterial stiffness in chronic inflammatory diseases. *Hypertension* 2005; 46:194–199.
- Gerli R, Sherer Y, Vaudo G, et al. Early atherosclerosis in rheumatoid arthritis: Effects of smoking on thickness of the carotid artery intima media. *Ann NY Acad Sci* 2005;1051: 281–290.
- Nagata-Sakurai M, Inaba M, Goto H, et al. Inflammation and bone resorption as independent factors of accelerated arterial wall thickening in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;48:3061–3067.
- Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;144:249–256.
- Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, et al. HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. *Am J Med* 2003;114:647–652.
- del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. *Arthritis Rheum* 2005;52:3413–3423.
- Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? *Scand J Rheumatol* 2004;33:373–379.
- Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: A disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005;35:8–17.
- Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: Potential mechanisms and solutions. *Curr Opin Rheumatol* 2005;17:286–292.
- Hwang SJ, Ballantyne CM, Sharrett AR, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: The Atherosclerosis Risk In Communities (ARIC) study. *Circulation* 1997;96:4219–4225.
- Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005;112:3337–3347.
- Chung CP, Avalos I, Raggi P, Stein CM. Atherosclerosis and inflammation: Insights from rheumatoid arthritis. *Clin Rheumatol* 2007;26:1228–1233.
- Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness. Adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. *Stroke* 1997;28:2442–2447.
- Kiechl S, Willeit J. The natural course of atherosclerosis. Part II: Vascular remodeling. Bruneck Study Group. *Arteriosclerosis Thromb Vasc Biol* 1999;19:1491–1498.

29. Schmidt-Trucksass AS, Grathwohl D, Frey I, et al. Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. *Atherosclerosis* 1999;145:107–114.
30. Ward MR, Pasterkamp G, Yeung AC, Borst C. Arterial remodeling. Mechanisms and clinical implications. *Circulation* 2000;102:1186–1191.
31. Labropoulos N, Zarge J, Mansour MA, Kang SS, Baker WH. Compensatory arterial enlargement is a common pathobiologic response in early atherosclerosis. *Am J Surg* 1998;176:140–143.
32. Polak JF, Kronmal RA, Tell GS, et al. Compensatory increase in common carotid artery diameter. Relation to blood pressure and artery intima-media thickness in older adults. *Cardiovascular Health Study*. *Stroke* 1996;27:2012–2015.
33. Samijo SK, Willigers JM, Barkhuysen R, et al. Wall shear stress in the human common carotid artery as function of age and gender. *Cardiovasc Res* 1998;39:515–522.
34. Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* 1988;112:1018–1031.
35. Pasterkamp G, Galis ZS, de Kleijn DPV. Expansive arterial remodeling: Location, location, location. *Arteriosclerosis Thromb Vasc Biol* 2004;24:650–657.
36. Mannami T, Baba S, Ogata J. Potential of carotid enlargement as a useful indicator affected by high blood pressure in a large general population of a Japanese city: The Suita study. *Stroke* 2000;31:2958–2965.
37. Jensen-Urstad K, Jensen-Urstad M, Johansson J. Carotid artery diameter correlates with risk factors for cardiovascular disease in a population of 55-year-old subjects. *Stroke* 1999;30:1572–1576.
38. Bots ML, Grobbee DE, Hofman A, Witteman JC. Common carotid intima-media thickness and risk of acute myocardial infarction: The role of lumen diameter. *Stroke* 2005;36:762–767.
39. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: The Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 2000;151:478–487.
40. Dobs AS, Nieto FJ, Szklo M, Barnes R, Sharrett AR, Ko WJ. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 1999;150:1055–1067.
41. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;128:262–269.
42. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* 2007;115:459–467.
43. Spagnoli LG, Mauriello A, Sangiorgi G, et al. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA* 2004;292:1845–1852.
44. Wilson PW, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997;337:516–522.
45. Kao AH, Krishnaswami S, Cunningham A, et al. Subclinical coronary artery calcification and relationship to disease duration in women with rheumatoid arthritis. *J Rheumatol* 2008;35:61–69.
46. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–324.
47. Simkin-Silverman L, Wing RR, Hansen DH, et al. Prevention of cardiovascular risk factor elevations in healthy premenopausal women. *Prev Med* 1995;24:509–517.
48. Kuller LH, Simkin-Silverman LR, Wing RR, Meilahn EN, Ives DG. Women's Healthy Lifestyle Project: A randomized clinical trial: Results at 54 months. *Circulation* 2001;103:32–37.
49. Dischinger P, DuChene AG, Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. *Controlled Clin Trials* 1986;7:137S–157S.
50. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252.
51. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197.
52. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.
53. Thompson T, Sutton-Tyrrell K, Wildman R. Continuous quality assessment programs can improve carotid duplex scan quality. *J Vasc Technol* 2001;25:33–39.
54. Sutton-Tyrrell K, Wolfson SKJ, Thompson T, Kelsey SF. Measurement variability in duplex scan assessment of carotid atherosclerosis. *Stroke* 1992;23:215–220.
55. Pincus T, Summey JA, Soraci SA Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346–1353.
56. Kazmierski R, Watala C, Lukasik M, Kozubski W. Common carotid artery remodeling studied by sonomorphological criteria. *J Neuroimaging* 2004;14:258–264.
57. Hafstrom I, Rohani M, Deneberg S, Wornert M, Jogestrand T, Frostegard J. Effects of low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis—A randomized study. *J Rheumatol* 2007;34:1810–1816.
58. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke* 1992;23:1752–1760.
59. Dessein PH, Joffe BI, Veller MG, et al. Traditional and non-traditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2005;32:435–442.
60. Dessein PH, Norton GR, Woodiwiss AJ, Joffe BI, Wolfe F. Influence of nonclassical cardiovascular risk factors on the accuracy of predicting subclinical atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2007;34:943–951.
61. del Rincon I, O'Leary DH, Haas RW, Escalante A. Effect of glucocorticoids on the arteries in rheumatoid arthritis. *Arthritis Rheum* 2004;50:3813–3822.
62. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: Back to the future?. *Arthritis Rheum* 2002;46:2553–2563.
63. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;46:862–873.

64. Gerli R, Goodson NJ. Cardiovascular involvement in rheumatoid arthritis. *Lupus* 2005;14:679–682.
65. Raynauld JP. Cardiovascular mortality in rheumatoid arthritis: How harmful are corticosteroids? *J Rheumatol* 1997;24:415–416.
66. Nagasaki T, Inaba M, Henmi Y, et al. Decrease in carotid intima-media thickness in hypothyroid patients after normalization of thyroid function. *Clin Endocrinol* 2003;59:607–612.

Address reprint requests to:
Laura L. Schott, Ph.D.
Department of Epidemiology
University of Pittsburgh
130 DeSoto Street, A546
Pittsburgh, PA 15261
E-mail: schottll@upmc.edu