

# Preclinical Carotid Atherosclerosis in Patients with Rheumatoid Arthritis

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**Background:** Rheumatoid arthritis is associated with increased morbidity and mortality because of cardiovascular disease, independent of traditional risk factors.

**Objective:** To determine the prevalence of preclinical atherosclerosis in patients with rheumatoid arthritis and to identify clinical and biological markers for atherosclerotic disease in this patient population.

**Design:** Matched, cross-sectional study.

**Setting:** Hospital for Special Surgery in New York City.

**Patients:** 98 consecutive outpatients with rheumatoid arthritis who were followed by rheumatologists and 98 controls matched on age, sex, and ethnicity.

**Measurements:** Cardiovascular risk factor ascertainment and carotid ultrasonography in all participants; disease severity, disease treatment, and inflammatory markers in patients with rheumatoid arthritis.

**Results:** Despite a more favorable risk factor profile, patients with rheumatoid arthritis had a 3-fold increase in carotid atherosclerotic

plaque (44% vs. 15%;  $P < 0.001$ ). The relationship between rheumatoid arthritis and carotid atherosclerotic plaque remained after accounting for age, serum cholesterol levels, smoking history, and hypertensive status; adjusted predicted prevalence was 7.4% (95% CI, 3.4% to 15.2%) for the control group and 38.5% (CI, 25.4% to 53.5%) for patients with rheumatoid arthritis. Age ( $P < 0.001$ ) and current cigarette use ( $P < 0.014$ ) were also significantly associated with carotid atherosclerotic plaque. Among patients with rheumatoid arthritis, atherosclerosis was related to age, hypertension status, and use of tumor necrosis factor- $\alpha$  inhibitors (a possible marker of disease severity).

**Limitations:** The study had a cross-sectional design, and inflammatory markers were determined only once.

**Conclusions:** Patients with rheumatoid arthritis have a high prevalence of preclinical atherosclerosis independent of traditional risk factors, suggesting that chronic inflammation and, possibly, disease severity are atherogenic in this population.

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Compared with the general population, patients with rheumatoid arthritis die prematurely (1, 2), primarily because of cardiovascular disease (1–3). Women with this disease have high rates of nonfatal myocardial infarction (4–6), even in the absence of traditional risk factors for atherosclerosis (4, 5, 7). Although markers of disease severity have been linked to an increase in overall mortality rates (1), researchers have not been able to clearly identify specific aspects of rheumatoid arthritis or its treatment that might heighten the risk for cardiovascular disease. Use of corticosteroids or disease-modifying antirheumatic drugs does not appear to increase the risk for cardiovascular events (2). In fact, a large longitudinal study recently reported that death rates from myocardial infarction among North American patients with rheumatoid arthritis had declined to the level seen in the general population (thereby yielding a greater magnitude of decline) in the setting of increased methotrexate use (8). In another U.S. study, methotrexate use was associated with lower all-cause mortality rates in rheumatoid arthritis, mostly because cardiovascular mortality rates were decreased (9).

Early diagnosis of atherosclerosis in this population might trigger more aggressive prophylaxis, but we have not determined the prevalence of preclinical atherosclerosis or identified markers for the disease. In this study, we examined the prevalence of atherosclerosis in patients with rheumatoid arthritis by using ultrasonogram-defined carotid ar-

tery plaque as a direct measure and proxy for generalized atherosclerosis and as a surrogate for coronary atherosclerosis; we also examined those features of rheumatoid arthritis that predict plaque presence. Previous studies reported that plaque prevalence in rheumatoid arthritis is statistically similar to that of control populations (10, 11). However, in systemic lupus erythematosus, another autoimmune disease characterized by chronic inflammation, cross-sectional studies that were conducted by us and by others showed a marked increase in plaque compared with that seen in carefully matched controls (12, 13). The increased plaque rate in systemic lupus erythematosus is associated with chronic inflammation (not with treatment or with traditional atherosclerosis risk factors), suggesting that similar factors may be at work in rheumatoid arthritis.

Preclinical disease may also be identified by using ultrasonography to determine carotid intima-media thick-

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**Context**

Patients with rheumatoid arthritis are prone to premature death from coronary heart disease despite few risk factors. Researchers have wondered if chronic inflammation is a trigger.

**Content**

The authors measured inflammatory markers and risk factors for coronary heart disease in 98 matched case-patients and controls (mean age, 48 years). Carotid ultrasonography revealed that 44% of case-patients and 15% of controls had atherosclerotic plaque. Independent predictors of plaque were age, smoking, and rheumatoid arthritis. In patients with rheumatoid arthritis, inflammatory mediators did not predict plaque.

**Limitations**

This cross-sectional study cannot prove that rheumatoid arthritis accelerates atherosclerosis.

**Interpretation**

Carotid atherosclerotic plaque is much more common in patients with rheumatoid arthritis than in controls. The mechanism remains unknown.

—The Editors

ness, an indirect measure of atherosclerosis. Intima-media thickness was increased in 2 studies of East Asian patients with rheumatoid arthritis (14, 15) but not in a U.S. study (11). Intima-media thickness varied more with disease duration (14, 15), but an association with serum C-reactive protein levels and erythrocyte sedimentation rate (2 markers of inflammation) has not been established because of conflicting reports (11, 15). Intima-media thickness does not always correlate with atherosclerosis, particularly in relatively young individuals with chronic inflammatory disease (12, 13), and it may measure other aspects of vascular disease. Discrete atherosclerotic plaque is a potent independent predictor of incident cardiovascular disease, whereas intima-media thickness in areas free of discrete plaque has limited value as a marker after traditional risk factors for cardiovascular disease are considered (16–18).

Because of conflicting data regarding premature preclinical atherosclerosis in rheumatoid arthritis, we chose to use the direct measure of plaque to examine the prevalence of carotid atherosclerosis in consecutive unselected, non-hospitalized patients with rheumatoid arthritis and matched controls. For our other primary outcome, we sought to determine those clinical and biological measures that best predict the presence of plaque.

**METHODS****Study Sample**

We consecutively recruited patients who met the American College of Rheumatology's classification cri-

teria for a diagnosis (possessing at least 4 of 7 criteria) of rheumatoid arthritis (19) and who were enrolled in the Rheumatoid Arthritis Registry at the Hospital for Special Surgery in New York. Patients were recruited at regular visits with their rheumatologists during a 15-month period (participation rate, 94%). Exclusion criteria were age younger than 18 years, serum creatinine level of 270  $\mu\text{mol/L}$  or greater ( $\geq 3.0$  mg/dL) or creatinine clearance of 0.50 mL/s or less ( $\leq 30$  mL/min), or current or recent (within the past 3 months) pregnancy. We quantified extent of disease by recording extra-articular manifestations (for example, the Sjögren syndrome, leg ulcers, and evidence of vasculitis, such as nail fold infarcts, splinter hemorrhages, and motor neuropathy), active joint count (number of tender or swollen joints), number of joints irreversibly damaged (fixed deformity or surgical replacement) (20), and the patient's score on the Multidimensional Health Assessment Questionnaire (21). We recorded treatment by patient interview and chart review. Because treatment is often intermittent or at varying dosages, we tabulated medication use as "never," "former," or "current." An 83-year-old woman had a previous stroke that was documented by magnetic resonance imaging, and a 45-year-old man had had coronary artery bypass surgery; we calculated our results both including and excluding these 2 patients.

Patients were matched to controls on the basis of age (within 5 years), sex, and ethnicity. Controls were normotensive and hypertensive individuals who participated in longitudinal studies funded by the National Institutes of Health (22, 23) at the Hypertension Center of The New York Hospital and who underwent similar imaging protocols.

We assessed patients for traditional cardiovascular disease risk factors: family history of myocardial infarction in first-degree male relatives younger than 55 years of age or first-degree female relatives younger than 65 years of age, smoking, hypertension (defined as blood pressure of 140/90 mm Hg or higher or the prescribed use of antihypertensive medications), diabetes mellitus (self-reported diagnosis), and fasting serum cholesterol levels. Hypertensive controls were studied after antihypertensive medications had been withheld for 3 or more weeks, whereas antihypertensive medications were not systematically withheld in hypertensive patients with rheumatoid arthritis. Brachial blood pressure was obtained at the end of the ultrasonographic studies after patients had remained in the supine position for 45 to 60 minutes in a quiet, darkened room. Of 100 patients with rheumatoid arthritis, a 74-year-old man was unable to be matched to a suitable control and a woman was excluded because she met diagnostic criteria for systemic lupus erythematosus. The institutional review board approved the study protocol, and all participants gave written informed consent.

## Carotid Ultrasonography

All study participants underwent carotid ultrasonography, which was performed by experienced research sonographers who used an identical protocol. A single cardiologist, who was blinded to the identity of the study participants, interpreted the results. In brief, as previously described (22, 23), participants were studied in the supine position with slight hyperextension of the neck. Both extracranial carotid arterial systems were extensively scanned in multiple planes to optimize identification of atherosclerosis, which was defined as discrete plaque protruding into the lumen at least 50% beyond the diameter of the surrounding wall. Doppler interrogation was performed to evaluate the presence of significant ( $\geq 50\%$  diameter reduction) obstruction. Intima-media thickness was measured from end-diastolic (minimum dimension) M-mode images of the far wall of the distal common carotid artery. Intima-media thickness was not measured in a location containing plaque. Mean values of right and left intima-media thicknesses are presented. Reproducibility of intima-media thickness and detection of plaque has been well documented (24–26). Carotid ultrasonographic studies were performed in the control group before 1999, whereas studies in the patients with rheumatoid arthritis were performed between 2000 and 2002.

## Laboratory Assessment

Laboratory assessment of the patients with rheumatoid arthritis included routine chemistries and serum rheumatoid factor level. A high-sensitivity assay to determine serum levels of C-reactive protein was analyzed with a Cobas Integra system (Roche Diagnostics, Basel, Switzerland). Serum lipoprotein(a) levels were measured with an immunoturbidometric reagent (Diasorin, Stillwater, Minnesota) on a Roche Diagnostics Cobas Fara II system. Serum interleukin-6 levels were measured by automated enzyme immunoassay (Biosource International, Camarillo, California) on a Roche Diagnostics Cobas Core II analyzer. Serum levels of soluble intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 were measured by enzyme-linked immunosorbent assay (Caltag, Burlingame, California, and R&D Systems, Minneapolis, Minnesota, respectively). Gas chromatography and mass spectrometry were used to measure fasting serum homocysteine levels.

## Statistical Analysis

Continuous variables are presented as mean values with SDs or median values and quartiles. Comparisons between groups were made with Student *t*-tests for independent samples for continuous variables and with chi-square tests for categorical variables. The Mann-Whitney test was used for comparison of variables that were highly skewed. We used multivariable logistic regression analysis to assess the independence of associations with atherosclerosis. Results are reported as predicted prevalence rates and their 95% CIs for each level of a factor, controlling for differences on all other factors in the analysis. Statistical

analyses were performed with SPSS for Windows, version 11.0 (SPSS Inc., Chicago, Illinois), and SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

## Role of the Funding Sources

The National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Heart, Lung, and Blood Institute of the National Institutes of Health provided funding for the study. The funding sources had no role in the design, conduct, or reporting of the study.

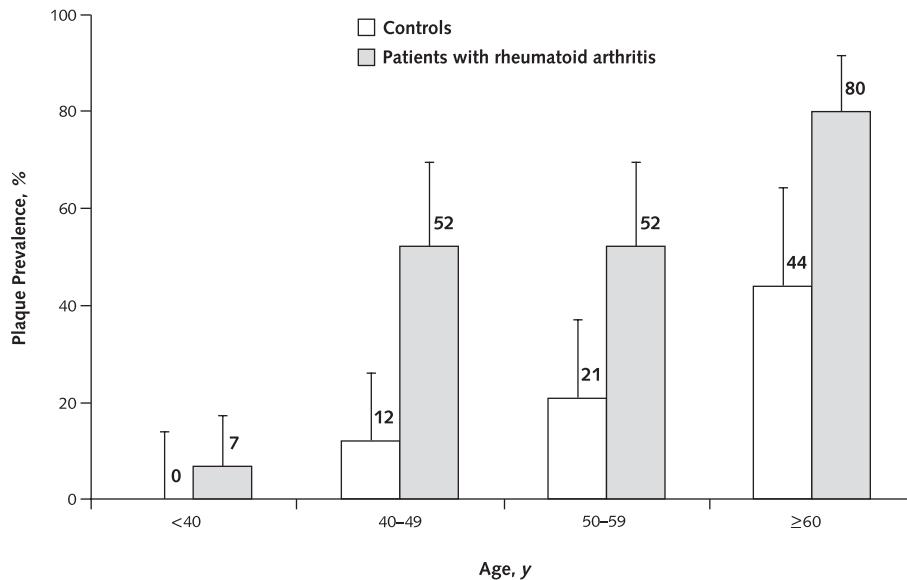
## RESULTS

The 98 patients with rheumatoid arthritis ranged in age from 20 to 83 years; mean age at diagnosis was 35 years, and mean duration of disease was 12 years. Rheumatoid factor was present in 56 patients (57%), and anticyclic citrullinated peptide antibodies were present in 49 patients (50%). The mean number of irreversibly damaged joints was 8 per patient, and 26 (27%) patients had undergone joint replacement. The Sjögren syndrome was present in

**Table 1. Demographic Variables, Cardiovascular Disease Risk Factors, and Carotid Ultrasonography Findings in Participants**

Variable	Patients with Rheumatoid Arthritis (n = 98)	Controls (n = 98)	P Value
<b>Demographic characteristic</b>			
Mean age (SD), y	48 (13)	47 (13)	
Women, %	98	98	
White, %	72	70	
<b>Comorbid condition, %</b>			
Hypertension	18	22	0.48
Diabetes mellitus	1	1	0.99
<b>Body mass index (SD), kg/m<sup>2</sup></b>	24.9 (5.7)	25.4 (4.5)	0.51
<b>Systolic blood pressure (SD), mm Hg*</b>			
Normotensive	106 (15)	110 (14)	0.124
Hypertensive	120 (20)	153 (22)	<0.001
<b>Diastolic blood pressure (SD), mm Hg*</b>			
Normotensive	68 (8)	69 (8)	0.60
Hypertensive	73 (10)	91 (11)	<0.001
<b>Current cigarette use, %</b>	5	17	0.007
<b>Serum total cholesterol level (SD)</b>			
mmol/L	5.35 (1.14)	5.46 (1.19)	0.49
mg/dL	207 (44)	212 (46)	
<b>Carotid plaque, %</b>	44	15	<0.001
<b>Common carotid artery intima-media thickness (SD), mm</b>	0.64 (0.17)	0.70 (0.17)	0.011

\* Antihypertensive medications were systematically withheld in controls.

**Figure.** Prevalence of atherosclerotic plaque in controls and in patients with rheumatoid arthritis, subdivided according to age.

Error bars indicate 95th percentiles.

23 patients, 5 of whom also had vasculitis and 1 of whom had leg ulcers. A total of 71% of patients were receiving prednisone therapy or had received it in the past; 63% and 46% of patients were receiving therapy (or had received therapy in the past) with methotrexate or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors, respectively. Additional demographic and cardiovascular risk factor variables are described in **Table 1**.

By design, patients and controls were similar in number, age, sex, and ethnicity (**Table 1**). Participants in the control group had slightly higher, albeit normal, blood pressure measurements at the time of the study, probably because their antihypertensive medications had been systematically discontinued in anticipation of the study. Mean blood pressure levels were statistically similar between patients with rheumatoid arthritis (106/68 mm Hg) and the controls (110/69 mm Hg) when hypertensive participants were eliminated from the analysis. The control group had a higher percentage of current smokers and lower serum high-density lipoprotein cholesterol levels (but similar serum total cholesterol levels).

Despite the more adverse risk profile in the controls, carotid atherosclerosis was 3-fold more prevalent in the patients with rheumatoid arthritis (44% vs. 15%;  $P < 0.001$ ). The prevalence of atherosclerosis was higher in patients with rheumatoid arthritis in all decades of life, particularly among the younger patients (**Figure**). Mean intima-media thickness was significantly greater in the control group.

A multivariable logistic regression analysis was performed to predict the presence of plaque from disease status, age, hypertension status, current cigarette use, and se-

rum total cholesterol level. Our analysis identified the presence of rheumatoid arthritis as an independent risk factor associated with the presence of atherosclerosis; the adjusted predicted prevalence of disease for controls was 7.4% (95% CI, 3.4% to 15.2%) compared with 38.5% (CI, 25.4% to 53.5%) for patients with rheumatoid arthritis ( $P < 0.001$ ). In addition, age ( $P < 0.001$ ), cigarette use ( $P < 0.014$ ), and possibly serum total cholesterol level ( $P < 0.097$ ) were independent factors associated with the presence of plaque; hypertension did not seem to be independently associated (**Table 2**). Diabetes mellitus was present in only 1 individual in each group and did not affect the results, nor did exclusion of the 2 patients with clinical cardiovascular disease and their controls.

Compared with patients who had rheumatoid arthritis without plaque, those with plaque were older at the time of the study; were older at onset of disease; had higher serum total cholesterol, low-density lipoprotein cholesterol, and baseline homocysteine levels and higher systolic blood pressure; and were more often hypertensive (**Tables 3 and 4**). The prevalence of cigarette use and family history of premature myocardial infarction and diabetes mellitus did not differ between the 2 groups, nor did serum levels of high-density lipoprotein cholesterol or lipoprotein(a). Women with atherosclerosis were more likely to be postmenopausal than were those without (71% vs. 27%;  $P < 0.001$ ); however, this relationship was eliminated when age was taken into consideration. Patients with plaque tended to have longer duration of disease, higher scores on the Multidimensional Health Assessment Questionnaire, and more joint replacements (**Table 4**). Disease treatment was similar between the 2 groups except that TNF- $\alpha$  inhibitor

therapy was used more frequently in patients with atherosclerosis. Of note, plaque presence did not differ according to use of cyclooxygenase-2 inhibitor therapy. Use of lipid-lowering agents was uncommon (5% in each group) at the time of the study.

Levels of inflammatory mediators did not differ between rheumatoid arthritis patients without and with atherosclerosis but were increased in comparison with the normal range (55% of all patients had serum high-sensitivity C-reactive protein levels >30.0 mg/L, and 33% of all patients had erythrocyte sedimentation rates >27 mm/h). Median serum high-sensitivity C-reactive protein levels were 40.0 mg/L (interquartile range, 12.0 to 109.0 mg/L) and 26.0 mg/L (interquartile range, 15.0 to 65.0 mg/L) ( $P = 0.51$ ) and median erythrocyte sedimentation rates were 19 mm/h (interquartile range, 7 to 37 mm/h) and 19 mm/h (interquartile range, 11 to 39 mm/h) ( $P = 0.64$ ) in patients without and with atherosclerosis, respectively. Serum levels of interleukin-6, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1 were also similar in the 2 groups (data not shown).

Because age is so strongly correlated with plaque levels, those factors that exhibited a significant bivariate association with plaque in Tables 3 and 4 were reevaluated after adjusting for age. The only factor that remained statistically significant after controlling for age was the use of TNF- $\alpha$  inhibitor therapy. The possibility that this type of therapy was a surrogate marker for disease severity is supported by a higher number of fulfilled diagnostic criteria

**Table 2. Predicted Prevalence of Atherosclerosis in Participants\***

Variable	Predicted Prevalence (95% CI), % <sup>†</sup>	P Value
<b>Age</b>		<0.001
≤39 y	2.6 (0.6–10.4)	
40–49 y	28.4 (16.1–45.2)	
50–59 y	29.3 (17.0–45.5)	
≥60 y	61.5 (41.6–78.2)	
<b>Serum total cholesterol level</b>		0.097
<5.18 mmol/L (<200 mg/dL)	12.5 (6.3–23.3)	
5.18–6.20 mmol/L (200–239 mg/dL)	28.8 (16.0–46.2)	
>6.20 mmol/L (>240 mg/dL)	22.1 (10.5–40.8)	
<b>Hypertension</b>		0.37
No	17.3 (10.4–27.3)	
Yes	24.3 (11.4–44.4)	
<b>Current cigarette use</b>		0.014
No	15.8 (9.4–25.5)	
Yes	51.4 (23.3–78.6)	
<b>Participant group</b>		<0.001
Control	7.4 (3.4–15.2)	
Patient with rheumatoid arthritis	38.5 (25.4–53.5)	

\* As determined by multivariable logistic regression.

<sup>†</sup> Predicted prevalence rates are adjusted for all other factors in the analysis.

**Table 3. Demographic Variables and Cardiovascular Disease Risk Factors in Patients with Rheumatoid Arthritis with and without Plaque**

Variable	Patients with No Plaque (n = 55)	Patients with Plaque (n = 43)	P Value
<b>Demographic characteristic</b>			
Age (SD), y	41 (11)	56 (11)	<0.001
White, %	69	77	0.30
<b>Body mass index (SD), kg/m<sup>2</sup></b>	24.2 (5.2)	25.7 (6.1)	0.152
<b>Blood pressure (SD), mm Hg</b>			
Systolic	102 (11)	116 (19)	<0.001
Diastolic	68 (9)	70 (8)	0.126
<b>Current smoker, %</b>	1.8	9.3	0.095
<b>Comorbid condition, %</b>			
Hypertension	9	30	0.007
Diabetes mellitus	1.8	0	0.37
<b>Family history, %</b>	11.1	14.3	0.64
<b>Serum total cholesterol level (SD)</b>			<0.001
mmol/L	4.97 (1.11)	5.84 (1.01)	
mg/dL	192 (43)	226 (39)	
<b>Serum low-density lipoprotein cholesterol level (SD)</b>			<0.001
mmol/L	2.56 (0.83)	3.31 (0.93)	
mg/dL	99 (32)	128 (36)	
<b>Serum high-density lipoprotein cholesterol level (SD)</b>			0.38
mmol/L	1.76 (0.52)	1.84 (0.47)	
mg/dL	68 (20)	71 (18)	
<b>Serum lipoprotein(a) level (SD)</b>			0.56
mmol/L	1.11 (1.34)	0.67 (0.67)	
mg/dL	43 (52)	26 (26)	
<b>Serum homocysteine level (SD), μmol/L</b>	4.44 (0.15)	5.03 (0.22)	0.035

for rheumatoid arthritis in patients who had received TNF- $\alpha$  inhibitor therapy compared with those who had not (5.2 [SD, 1.0] vs. 4.8 [SD, 0.8];  $P = 0.029$ ). Patients who had received therapy with these agents also had higher scores on the Multidimensional Health Assessment Questionnaire than those who had not (0.68 [SD, 0.49] vs. 0.48 [SD, 0.50];  $P = 0.050$ ).

## DISCUSSION

Our study documents a prevalence of preclinical atherosclerosis that was 3-fold greater in patients with rheumatoid arthritis than that seen in controls who were matched for age, sex, and ethnicity. The increased risk

**Table 4. Measures of Disease Severity and Disease Treatment in Patients with Rheumatoid Arthritis with and without Plaque**

Variable	Patients with No Plaque (n = 55)	Patients with Plaque (n = 43)	P Value
Age at diagnosis (SD), y	30 (12)	42 (13)	<0.001
Duration of disease (SD), mo	134 (119)	165 (123)	0.162
Rheumatoid arthritis criteria (SD), n	5.0 (0.9)	5.1 (1.0)	0.87
Joint count (SD), n*	12 (16)	13 (15)	0.72
Irreversible joint damage (SD), n†	6 (8)	10 (12)	0.40
Joint replacement, %	21	35	0.135
Multidimensional Health Assessment Questionnaire score (SD)	0.52 (0.48)	0.64 (0.54)	0.36
Therapy, %‡			
Methotrexate	67	57	0.34
Cyclooxygenase-2 inhibitor	62	50	0.23
Prednisone	69	74	0.56
Leflunomide	15	21	0.40
Etanercept	33	51	0.065
Infliximab	4	21	0.009
Tumor necrosis factor- $\alpha$ inhibitor	35	58	0.020
Gold	41	51	0.31
Hydroxychloroquine	72	70	0.79

\* Joint count (number of tender or swollen joints) out of 68 joints bilaterally.

† Joints irreversibly damaged (fixed deformity) out of 94 joints bilaterally.

‡ Indicates current or former use for each medication.

occurred independently of traditional risk factors (such as hypertension, smoking, and low serum high-density lipoprotein cholesterol level) even though these factors were slightly more adverse in the control group. The increased risk was similar to the risk we previously found in patients with systemic lupus erythematosus (12) and was also similar to that seen in patients of similar ages who had diabetes mellitus (Roman MJ. Unpublished observations from the Strong Heart Study). This leads us to speculate that early onset of atherosclerosis may be a characteristic of other chronic inflammatory diseases. Plaque is an unequivocal manifestation of atherosclerosis and is a more potent predictor of adverse cardiovascular outcome than is intima-media thickness (16, 27, 28). Intima-media thickness, which was larger in our control population, probably results from increased blood pressure. Studies of relatively young individuals (approximate mean age, 45 years) with systemic lupus erythematosus also showed no increase in carotid intima-media thickness compared with controls but clearly demonstrated a presence of excess plaque (12, 13). In our study on systemic lupus erythematosus, more vigorous treatment of patients was associated with lower plaque prevalence; in patients with rheumatoid arthritis, however, the use of TNF- $\alpha$  inhibitor therapy was associated with higher plaque prevalence. Our patients' initial diagnoses of rheumatoid arthritis antedated the availability of these agents, which were added later to their treatment

regimens because the disease did not respond to conventional treatment. It is therefore possible that use of TNF- $\alpha$  inhibitor therapy represents a surrogate marker of disease activity and damage in our study.

Data from the Nurses' Health Study (4) support our observation of an association between disease duration and atherosclerosis. The adjusted relative risk for myocardial infarction among nurses who had had rheumatoid arthritis for less than 10 years matched that of controls, whereas women who had had rheumatoid arthritis for 10 or more years had a 3-fold increase in risk for myocardial infarction. Few of our patients received statin therapy (which may alleviate the inflammation of rheumatoid arthritis in addition to reducing serum cholesterol levels); therefore, we were unable to assess the effect of these drugs on inflammation or atherosclerosis (29). Similar to the findings in our study of systemic lupus erythematosus (12), we found no relationship between atherosclerosis and the use of corticosteroid therapy.

The mechanism by which premature atherosclerosis develops in rheumatoid arthritis is not known. The lack of an association between inflammatory mediators and atherosclerosis does not exclude the possibility that chronic inflammation is atherogenic because the cross-sectional design of this study does not permit an estimate of lifelong inflammatory burden. A recent Italian study of patients with rheumatoid arthritis found that common carotid artery intima-media thickness was increased in patients in whom 15% or more T cells expressed the CD4<sup>+</sup>CD28<sup>-</sup> phenotype (the 90th percentile of distribution in a normal population). This increase was not seen in those patients with less than 15% of their T cells expressing this phenotype (30), suggesting a relationship between this specific lymphocyte subset and 1 form of carotid disease (no data are provided regarding the relationship of this subset of T cells to plaque).

Previous studies that failed to show an increase in carotid atherosclerosis in rheumatoid arthritis were relatively small and used varying methods. A Swedish case-control study of 39 patients and controls evaluated only the right carotid and femoral arteries and reported both together (10). A Korean case-control study of 53 postmenopausal patients and 53 controls (mean age, 55 years) found carotid plaque (focal protrusion  $\geq 1.5$  mm) in only 1 patient and in no controls (14). The authors of the latter study attributed the virtual absence of carotid atherosclerosis in their sample to substantially lower rates of atherosclerosis and ischemic heart disease in Korea. A larger Japanese study of 138 patients with rheumatoid arthritis and 94 controls showed carotid plaque (focal protrusion  $\geq 2.0$  mm) in only 3.6% of patients and 4.3% of controls.

The only other U.S. study of rheumatoid arthritis that used carotid ultrasonography involved 204 patients and 102 controls (11). Carotid intima-media thickness (a composite of common and internal carotid intima-media thicknesses) did not differ between patients and controls.

Carotid plaque (reported per artery rather than per person) was increased in patients (30% vs. 25% of arteries in controls), but the difference did not achieve statistical significance. Multivariate analyses were not performed in the patients with rheumatoid arthritis alone. Other methodologic differences included a study sample that was older (mean age, 60 years), included more men (11%), excluded smokers, had higher blood pressure, and had a greater prevalence of diabetes mellitus (18%) and hypercholesterolemia (13%).

Limitations of our study include its cross-sectional design and inherent inability to establish probable causality as opposed to documentation of associations. Single determinations of serum cholesterol levels and inflammatory markers in particular may not accurately represent concentrations over time and cumulative burden of exposure. In addition, we were unable to precisely quantify lifetime dosages of medications to examine more fully the effect of pharmacologic therapy on development of atherosclerosis.

In conclusion, patients with rheumatoid arthritis have a marked increase in carotid atherosclerosis independent of traditional risk factors, including age. In patients, plaque presence is associated with age; hypertension status; and the use of TNF- $\alpha$  inhibitor therapy, a possible marker of disease severity. Carotid ultrasonography is a simple and inexpensive way of identifying preclinical atherosclerosis in this highly vulnerable population. In addition to prospective management of traditional cardiac risk factors, we emphasize the need for aggressive control of rheumatoid arthritis disease activity because chronic inflammation is probably a driving force for premature atherosclerosis. Future research efforts should seek to define more precisely the mechanisms whereby atherosclerosis is accelerated in persons with rheumatoid arthritis and to identify interventional strategies that will slow the development of clinical cardiovascular disease in this group.

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