

Increased Coronary-Artery Atherosclerosis in Rheumatoid Arthritis: Relationship with Disease
Duration and Cardiovascular Risk Factors

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ABSTRACT

Background Rheumatoid arthritis, a chronic inflammatory disease, is associated with increased cardiovascular mortality but little is known about the prevalence and severity of coronary-artery atherosclerosis.

Methods We used electron-beam computed tomography to measure the extent of coronary-artery calcification as a marker of atherosclerosis in 227 subjects. Of these, 70 had early rheumatoid arthritis, 71 established rheumatoid arthritis, and 86 were controls. The extent of coronary-artery calcification was compared in patients and controls and the relation between the patients' clinical characteristics and the extent of coronary-artery calcification was examined.

Results Coronary-artery calcification scores were higher in patients with established rheumatoid arthritis (305.5 ± 899.4) compared with those with early disease (104.9 ± 283.5) and controls (174.9 ± 621.2) ($P=0.001$). Coronary calcification was more frequent in patients with established rheumatoid arthritis (43 of 71 patients, 60.6 percent) than in patients with early rheumatoid arthritis (30 of 70 patients, 42.9 percent) and control subjects (33 of 86 subjects, 38.4 percent) ($P=0.016$). The odds ratio for having more severe coronary calcification in patients with established disease was 2.73 (95% CI 1.4-5.5, $P=0.005$) compared to control subjects after adjustment for age and sex. Among patients with rheumatoid arthritis, cumulative pack-years of smoking ($P=0.04$) and a higher erythrocyte sedimentation rate ($P=0.05$) were associated with more severe coronary-artery calcification after statistical adjustment for age and sex.

Conclusion The prevalence and severity of coronary calcification is increased in patients with established rheumatoid arthritis and is related in part to smoking and an increased erythrocyte sedimentation rate.

Rheumatoid arthritis is a common inflammatory disease that affects 0.5 to 1 percent of the population (1) and is associated with increased mortality rates. (2-4) Epidemiological studies have shown that this increased mortality is largely attributable to cardiovascular disease, primarily coronary heart disease. (3;4) Considerable evidence suggests that inflammation plays a role in the pathogenesis of atherosclerosis. (5-7) In several animal models that were genetically modified to produce higher levels of inflammatory mediators, atherosclerosis was more severe. (8;9) Also, inflammatory cells and mediators are present in human atherosclerotic plaque, (10) and furthermore, higher concentrations of markers of inflammation such as C-reactive protein (CRP) (11) and interleukin-6 (12) predict coronary heart disease risk. Therefore, premature atherosclerosis could represent a consequence of chronic inflammation, such as occurs with rheumatoid arthritis.

Some studies that have used indirect indicators of coronary atherosclerosis such as carotid artery intima-media thickness suggest that atherosclerosis is more prevalent in patients with rheumatoid arthritis than controls,(13-15) however the prevalence of coronary-artery atherosclerosis and the mechanisms underlying the increased risk of ischemic heart disease in rheumatoid arthritis are not known. The presence and extent of coronary-artery calcification can be determined by computed tomography (CT) (16) and correlates with the severity of atherosclerosis measured in pathological specimens (17) or by angiography.(18;19) Furthermore, it predicts the risk of myocardial infarction (20) or death due to coronary heart disease.(21) Recently, we used electron-beam CT to show that the prevalence of atherosclerosis is markedly increased in patients with systemic lupus erythematosus.(22) Rheumatoid arthritis and systemic lupus erythematosus are both characterized by chronic inflammation, but their pathogenesis

differs. These differences may provide insight into the relationship between chronic inflammation and the pathogenesis of atherosclerosis.

In addition, structural damage to joints occurs early in the course of rheumatoid arthritis, usually within the first few years of disease (23) and thus structural changes in the coronary artery vasculature could also occur early. We tested the hypothesis that patients with rheumatoid arthritis have more severe coronary artery atherosclerosis than control subjects of similar age, race and sex and that this is related to the clinical characteristics of the patients.

PATIENTS AND METHODS

Subjects

We studied 141 patients with rheumatoid arthritis and 86 control subjects. Consecutive eligible patients older than 18 years of age who met the classification criteria for rheumatoid arthritis (24) and had duration of disease less than 5 years (early rheumatoid arthritis) or more than 10 years (established rheumatoid arthritis) were enrolled. Controls did not meet classification criteria for rheumatoid arthritis or any other inflammatory disease. Control subjects were frequency matched for age, sex and race with the entire group of rheumatoid arthritis patients so as to ensure that the control group would not differ markedly from either the early or established rheumatoid arthritis groups with respect to these variables. Recruitment continued until a minimum of 70 patients has been enrolled in each group.

Patients were recruited from a registry of patients with early rheumatoid arthritis, (25) local rheumatologists and by advertisements. Control subjects were recruited from patients' acquaintances, by advertisement, and from a database of volunteers maintained by the General Clinical Research Center. The study was approved by the Institutional Review Board

of Vanderbilt University Hospital and all subjects gave written informed consent.

Information was obtained through a structured interview, self-reported questionnaires, physical examination, laboratory tests, and electron-beam CT, and in patients, review of medical records. Current and cumulative medication use was determined from both the information provided by patients and medical records. A family history of coronary-artery disease was defined as a first-degree relative having a myocardial infarction or stroke before the age of 55 in males, and before the age of 65 in females. Height and weight were measured and body mass index was calculated. Blood pressure was determined as the average of two measurements obtained 5 minutes apart after subjects had rested in supine position for at least 10 minutes. Subjects were considered hypertensive if they were taking anti-hypertensive agents or if they had a systolic blood pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg. In patients, disease activity was measured using the Disease Activity Score based on evaluation of 28 joints (DAS28). (26) The DAS28 score is a validated composite index containing a 28-joint count for tenderness, a 28-joint count for swelling, erythrocyte sedimentation rate (ESR), and the patient's overall assessment of well-being. Ability to perform activities of daily living was measured using the modified Health Assessment Questionnaire (0-3) with a score of 0 representing no impairment of function. (27)

Blood was collected after an overnight fast for the measurement of a complete blood count, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, lipoprotein(a) [Lp(a)], and homocysteine. In patients with rheumatoid arthritis, CRP and Westergren ESR were measured and medical records were reviewed to determine the presence or absence of rheumatoid factor.

Imaging Procedures

All subjects underwent imaging with an Imatron C-150 scanner (GE/Imatron, South San Francisco, CA). Imaging was performed with a 100-msec scanning time and a single-slice thickness of 3 mm. A total of 40 slices were obtained during a single breath-holding period starting at the aortic arch and proceeding to the level of the diaphragm. Tomographic imaging was electrocardiographically triggered at 60 percent of the interval between R waves. All areas of calcification within the borders of a coronary artery with a minimal attenuation of 130 Hounsfield units were computed. A calcified coronary plaque was considered present if at least three contiguous pixels were detected (voxel size: 1.03mm^3). If a patient had undergone prior coronary artery stenting or by-pass surgery, the stent and all metal clips were excluded from the computation of the calcium score. The acquired images were reviewed at the core electron-beam CT laboratory on a NetraMD workstation (ScImage, Los Altos, CA). Subjects were included in this study only if complete data were available from their scans, without misregistration of slices due to artifacts of motion, respiration, or asynchronous electrocardiographic triggering. To ensure the continuity and consistency of the interpretation of scores, a single expert investigator (PR), unaware of the subjects' clinical status, read all the scans.

Calculation of Calcium Scores

The degree of coronary-artery calcification was calculated as described by Agatston et al.(16) The sum of the scores for all coronary arterial lesions provides an overall score for each individual. The correlation between this score and other variables, such as coronary risk factors, inflammatory markers, and rheumatoid arthritis disease activity, was determined.

Statistical Analysis

Assuming that the frequency of coronary-artery calcification in control subjects would be approximately 44 percent, (28) in order to achieve 85 percent power with a two-sided significance level of 5 percent the study required 70 subjects in each of the three groups to detect a 25 percent relative increase (55% for early and 69% for established rheumatoid arthritis). Sample size calculations were performed using a chi-squared test for the trend of three proportions using nQuery Advisor version 4.0 (Statistical Solutions, Saugus, MA).

Baseline characteristics among control subjects and patients with early and established rheumatoid arthritis were described using mean \pm standard deviation (SD) for continuous variables and proportions for categorical variables.

Statistical analyses were performed in two phases. First, the prevalence of coronary-artery calcification and coronary risk factors were compared in control subjects and patients with early and established rheumatoid arthritis using Kruskal-Wallis tests for continuous variables and Fisher's exact tests or chi-square tests for categorical variables. Proportional odds logistic regression was used to test the independent relationship between disease status and severity of coronary calcification. Coronary calcification [graded as none (calcium score = 0), mild (calcium score = 1-109) or moderate-to-severe (calcium score > 109) based on the median Agatston score of 109 for all individuals with a calcification score >0] was treated as the dependent variable and disease status (none, early disease and established disease) was treated as the independent variable using two indicator variables for comparing each disease status versus none (dummy variables). Since the prevalence and extent of coronary-calcification in the general population is greater in men and increases with age (19) we

adjusted for these variables. Further adjustment was performed for hypertension and cumulative pack-years of smoking because of their clinical relevance.

Second, we analyzed only patients with rheumatoid arthritis. Continuous variables were compared using the Mann-Whitney U test and categorical variables using Fisher's exact test. Characteristics of patients within the three categories of calcification scores (none, mild and moderate-to-severe) were compared using Kruskal-Wallis tests and Fisher's exact tests. Unadjusted and adjusted odds ratios were calculated using the proportional odds logistic regression model to determine the independent associations with the three ordinal categories of calcium score.

All analyses used a two-sided significance level of 5 percent and were conducted using SAS software version 8.02 (SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of patient and control groups

Patients with rheumatoid arthritis (n=141) and control subjects (n=86) were of similar age (54.9 ± 11.7 years and 52.8 ± 11.5 years, respectively), sex (68.8 and 65.1 percent female) and race (89.4 and 86.1 percent Caucasian). Study subjects were predominantly well-educated, with 87 percent of subjects having 12 or more years of education. The mean (\pm SD) duration of disease from the time of first symptom was 2.1 ± 1.2 years for patients with early rheumatoid arthritis and 20.6 ± 8.6 years for those with established disease.

The demographic characteristics and cardiovascular risk factors of the 70 patients with early rheumatoid arthritis, 71 patients with established rheumatoid arthritis and 86 controls are shown in Table 1. A coronary-artery procedure (angioplasty, stent, or bypass graft) had been performed in 5.8 percent of control subjects and 5.7 and 9.9 percent of patients with early and established rheumatoid arthritis, respectively. The prevalence of hypertension was 67.6 percent in patients with established rheumatoid arthritis, 38.6 percent in those with early rheumatoid arthritis and 38.4 percent in control subjects ($P < 0.001$). Of the control subjects 9.3 percent currently smoked, whereas 22.9 percent and 29.6 percent of patients with early and established rheumatoid arthritis, respectively, did ($P = 0.002$); exposure to smoking in pack-years was similar in the three groups. Serum concentrations of total, HDL, and LDL cholesterol and Lp(a), and triglycerides were similar among patients and controls (Table 1).

Coronary-artery calcification

The prevalence of coronary-artery calcification and the average score in controls and patients with early and established rheumatoid arthritis are shown in Table 2. Coronary-artery calcium scores averaged 305.5 ± 899.4 in patients with established rheumatoid arthritis

compared with 104.9 ± 283.5 in those with early disease and 174.9 ± 621.2 in controls ($P=0.001$). Coronary-artery calcification was more prevalent in patients with established rheumatoid arthritis (60.6 percent) than in those with early rheumatoid arthritis (42.9 percent) and controls (38.4 percent) (overall $P=0.016$, early RA compared to controls $P=0.57$, established RA compared to controls $P=0.006$) (Table 2, Figure 1). Figure 2 illustrates the frequency of coronary-calcification scores of 0, 1-109 and >109 in controls and patients with rheumatoid arthritis younger than 50 years of age, 50-59 years, and 60 years and older.

Coronary-calcification in patients with early rheumatoid arthritis and control subjects did not differ significantly (odds ratio 1.21, 95% CI 0.65–2.26) but was increased in patients with established rheumatoid arthritis compared to controls (odds ratio 3.03 (95% CI 1.65-5.57, $P<0.001$) (Table 2). After adjustment for age and sex the severity of coronary calcification remained significantly elevated in patients with established rheumatoid arthritis compared to controls (odds ratio 2.73, 95% CI 1.36-5.47, $P=0.005$). The association remained significant after further adjusting for age, sex, hypertension and cumulative pack-years of smoking (odds ratio 2.26, 95% CI 1.10-4.63, $P=0.026$).

Relationship between disease characteristics and coronary-artery calcification among patients

Clinical characteristics differed in patients with early and established rheumatoid arthritis (Table 3). As expected, cumulative exposure to medications used to treat rheumatoid arthritis was greater in patients with established disease. Patients with early and established rheumatoid arthritis had similar disease activity scores (DAS28) but the modified Health Assessment Questionnaire score ($P=0.02$) and ESR ($P=0.04$) were higher in patients with established disease. The average number of swollen joints was 5.0 ± 5.7 in early and 5.2 ± 5.6 in

established rheumatoid arthritis. Approximately 17 percent of patients in both groups were receiving treatment with therapy that blocked tumor necrosis factor.

The characteristics of rheumatoid arthritis patients with no, mild, and moderate-to-severe coronary-artery calcification are shown in Table 4. Older age, male sex, longer disease duration, higher systolic blood pressure, more total pack-years of smoking and higher homocysteine concentrations were more common in patients with rheumatoid arthritis with coronary calcification than those without. After adjusting for age and sex only pack-years of smoking and erythrocyte sedimentation rate remained significantly associated with coronary calcification in patients with rheumatoid arthritis (Table 4).

DISCUSSION

Our results show that coronary-artery atherosclerosis, as detected by the presence of coronary-artery calcification on electron-beam CT, is more severe and more prevalent in patients with established rheumatoid arthritis than in those with early disease or control subjects. Patients with established rheumatoid arthritis had an average age of approximately 58 years and were older than controls (average age 53 years) and patients with early rheumatoid arthritis (average age 51 years). Nevertheless, the increase in coronary calcification remained significant after statistical adjustment for age and sex (odds ratio 2.73, $P=0.005$), and after adjustment for age, sex, hypertension and pack-years of smoking (odds ratio 2.26, $P=0.026$). Thus, atherosclerosis is frequently present in patients with established rheumatoid arthritis and cannot be predicted by the presence of classical cardiovascular risk factors.

Previous studies have reported that the prevalence of subclinical atherosclerosis, detected as an increase in the intima-media thickness of the carotid artery, is higher in patients with rheumatoid arthritis than controls. (13;14;29). But it has been recognized that the association between increased carotid artery intima-media thickness and coronary-artery atherosclerosis is weak, (30) and the prevalence of coronary atherosclerosis in patients with rheumatoid arthritis, and its relationship to disease duration and activity, has remained unclear.

In the present study we measured coronary-artery calcification by electron-beam CT, a technique that provides a reproducible and quantitative method for the detection of subclinical coronary artery atherosclerosis and yields information about the risk of future cardiovascular risk additional to that provided by other risk factors.(31;32) The finding of increased severity

and higher prevalence of coronary-artery calcification indicates that coronary atherosclerosis and cardiovascular risk are increased in patients with established rheumatoid arthritis. Our data also show that the prevalence and severity of coronary-artery calcification was not increased significantly in patients with early rheumatoid arthritis. This suggests that structural coronary artery disease, as detected by electron-beam CT, may occur later than structural joint damage since, for example, 32 percent of patients with rheumatoid arthritis had bone erosions at the time of diagnosis and 70 percent after 3 years.(33)

The cause of increased atherosclerosis in patients with rheumatoid arthritis is not known and therefore comparison among patients with coronary-artery calcification of different severity may be informative. As occurs in the general population, traditional cardiovascular risk factors such as age, smoking and male sex were more frequent among rheumatoid arthritis patients with coronary-artery calcification. By contrast, other traditional cardiovascular risk factors such as LDL and HDL cholesterol and other risk factors such as homocysteine, were not associated with the severity of coronary-artery calcification in patients with rheumatoid arthritis. After statistical adjustment for age and sex, only pack-years of smoking and ESR remained statistically significantly associated with calcification. This finding suggests that smoking and inflammation, two risk factors for atherosclerosis in the general population, may be particularly important risk factors in patients with rheumatoid arthritis.

Substantial evidence suggests that individuals who smoke are more likely to develop rheumatoid arthritis, and that patients with rheumatoid arthritis who smoke are more likely to have more severe disease.(34) Thus, it is possible that smoking, a potent risk factor for atherosclerosis, interacts with rheumatoid arthritis to accelerate atherosclerosis to a greater

degree in patients with this disease. Substantial evidence also indicates that inflammation can accelerate atherosclerosis,(5;35) and markers of inflammation such as CRP are elevated in patients with coronary artery disease. We did not measure CRP concentrations in control subjects, but the average concentrations of CRP in patients with rheumatoid arthritis (9.8 ± 13.1 mg/l) were substantially higher than the average concentration found in the general population without cardiovascular disease (approximately 1.1 mg/l).(11) Nevertheless, elevated concentrations of CRP in the patients with rheumatoid arthritis were not associated with coronary-artery calcification. In contrast, the ESR was associated with coronary-artery calcification. This difference may be informative since the ESR and CRP, both acute-phase reactants, are generally correlated, as they were in this study ($\rho=0.56$, $P<0.001$). The fact that the ESR is particularly affected by concentrations of fibrinogen, an independent risk factor for coronary heart disease (36), could theoretically explain the finding that ESR but not CRP was associated with coronary calcification. However, it would be more informative to have serial measures of inflammation rather than a single cross-sectional measure.

Recently, we used electron-beam CT to establish that the prevalence of atherosclerosis is markedly increased in patients with systemic lupus erythematosus.(22) The unadjusted odds ratio for coronary-artery calcification in that population was approximately 5, higher than the odds ratio of approximately 3 in patients with established rheumatoid arthritis. Rheumatoid arthritis and systemic lupus erythematosus are both chronic inflammatory conditions but lupus is characterized by more B-cell activation and deposition of immune complexes. Both lupus and rheumatoid arthritis increase the risk of coronary-artery calcification, but understanding why lupus appears to impart a greater risk may elucidate aspects of inflammation that are particularly important in the pathogenesis of atherosclerosis.

In conclusion, our results indicate that coronary-artery atherosclerosis, detected as calcification of the coronary arteries on electron-beam CT, is more severe and more prevalent in patients with established rheumatoid arthritis than patients with early disease and control subjects. Coronary atherosclerosis is associated with smoking and an increased erythrocyte sedimentation rate in patients with rheumatoid arthritis. Rheumatoid arthritis, a chronic inflammatory disease should be added to the list of conditions associated with increased coronary-artery atherosclerosis; better control of inflammation and avoidance of smoking could decrease such risk.

Authors' Contributions

Cecilia P. Chung: Performed data entry and analysis, wrote the first draft

Annette Oeser: Collected and entered data, responsible for performance of the study, assisted with study design

Paolo Raggi: Analyzed the electron beam CT scans, assisted with study design

Tebeb Gebretsadik: Performed statistical analysis

Ayumi K. Shintani: Performed statistical analysis, assisted with study design

Tuulikki Sokka: Recruited patients, assisted with study design and analysis

Theodore Pincus: Recruited patients, assisted with study design and analysis

Ingrid Avalos: Performed data entry and analysis

C. Michael Stein: Designed and supervised the study

All authors contributed to the writing and editing of the paper

Conflict of Interest and Source of Funding

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Table 1. Clinical characteristics of patients with rheumatoid arthritis and control subjects*

Characteristic	Control subjects (N=86)	Early rheumatoid arthritis (N=70)	Established rheumatoid arthritis (N=71)	P- Value†
Age (yrs)	52.8±11.5	51.4±10.6	58.3±11.8	<0.001‡
Female sex (%)	65.1	61.4	76.1	0.15
White race (%)	86.1	94.3	84.5	0.14
Duration of disease (yrs)	NA	2.1±1.2	20.6±8.6	<0.001
Total pack-yr of smoking	10.6±22.2	12.9±22.8	14.0±22.8	0.37
Hypertension (%)	38.4	38.6	67.6	<0.001‡
Family history of coronary heart disease (%)	27.9	28.6	27.1	0.98
Body mass index	27.7±5.9	29.1±5.9	28.4±5.9	0.33
Coronary-artery procedure (%)	5.8	5.7	9.9	0.65
Glucose (mg/dl)	92.3±34.9	88.8±15.3	93.4±20.0	0.31
Creatinine (mg/dl)	0.8±0.2	0.8±0.2	0.8±0.3	0.64
Total Cholesterol (mg/dl)	194.1±36.0	187.3±39.4	187±38.4	0.34
High-density lipoprotein (mg/dl)	46.9±12.4	44.1±13.3	48.3±14.9	0.07
Low-density lipoprotein (mg/dl)	123.4±31.6	115.6±29.3	112±35.2	0.10
Lp (a) lipoprotein	23.7±33.3	14.4±17.2	17.2±18.6	0.20
Triglycerides (mg/dl)	118.5±62.5	155.8±253.7	143.4±104.7	0.30
Current use of statins (%)	11.6	14.3	11.3	0.85
Homocysteine (umol/L)	10.6±10.0	10.0±2.5	11.4±4.1	<0.001‡

* Plus-minus values are means ± SD

† P-values are for Kruskal-Wallis test or for Fisher's two-tailed exact test, as appropriate, for comparisons among groups.

‡ Denotes a statistically significant difference between established rheumatoid arthritis and control subjects

Table 2: Coronary-artery calcification prevalence and scores in patients with early and established rheumatoid arthritis and in control subjects.*

	Control subjects (N=86)	Early rheumatoid arthritis (N=70)	Established rheumatoid arthritis (N=71)	P-Value†
Agatston score	174.9±621.2	104.9±283.5	305.5±899.4	0.001
Prevalence of any coronary calcium	38.4%	42.9%	60.6%	0.016
Calcium score				
1-109	24.4%	25.7%	19.7%	
>109	14.0%	17.1%	40.9%	
Unadjusted OR (95% CI) ‡	1	1.21 (0.65-2.26) P=0.55	3.03 (1.65-5.57) P<0.001	
Adjusted for age and sex OR (95% CI) ‡	1	1.31 (0.65-2.64) P=0.45	2.73 (1.36-5.47) P=0.005	
Adjusted for age, sex, hypertension and pack-years OR (95% CI) ‡	1	1.22 (0.60-2.49) P=0.58	2.26 (1.10-4.63) P=0.026	

* Plus-minus values are means \pm SD

† P-values are for Kruskal-Wallis test or for Fisher's two-tailed exact test, as appropriate, for comparisons among groups.

‡ Proportional odds logistic regression was used to obtain unadjusted and adjusted odds ratios for the severity of coronary calcification

Table 3. Characteristics of patients with early and established rheumatoid arthritis*

Characteristic	Early rheumatoid arthritis (N=70)	Established rheumatoid arthritis (N=71)	P Value†
Rheumatoid factor ‡‡ (%)	68.7	77.3	0.27‡
Erythrocyte sedimentation rate (mm/hr)	18.8±18.1	27.1±22.3	0.04
C-reactive protein (mg/l)	9.1±13.8	10.4±12.4	0.66
Number of swollen joints (0-28)	5.0±5.7	5.2±5.6	0.75
Number of tender joints (0-28)	4.6±6.2	4.8±6.5	0.99
Disease activity visual analogue scale (0-10 cm)§	3.2±2.4	3.9±2.6	0.10
Modified health assessment questionnaire (0-3)¶	0.4±0.4	0.6±0.6	0.02
Pain visual analogue scale (0-10 cm) ††	3.7±2.5	4.2±2.4	0.15
Disease activity score (DAS28)	3.2±1.5	3.5±1.4	0.15
Cumulative dose of prednisone (g)	2.8±3.3	17.2±24.1	<0.001
Cumulative dose of methotrexate (g)	1.3±2.0	8.4±28.5	<0.001
Cumulative dose of hydroxychloroquine (g)	45.4±98.1	292.3±556.7	0.004

* Plus-minus values are means ±SD

† Unless otherwise noted Mann-Whitney U tests were used for comparisons between groups.

‡ Fisher's two-tailed exact test was used

§ Higher scores for the disease activity score and the disease activity visual analogue scale indicate greater disease activity.

¶ Higher scores for the modified Health Assessment Questionnaire indicate more difficulty in performing activities of daily life.

†† Higher scores on the pain visual analogue scale indicate a higher level of pain.

‡‡ Rheumatoid factor was available for 133 patients.

Table 4. Characteristics of patients with rheumatoid arthritis according to different categories of coronary-artery calcification score. *

CHARACTERISTIC	NO CALCIFICAT ION	CALCIUM SCORE 1-109	CALCIUM SCORE >109	UNADJUSTED †		ADJUSTED FOR AGE AND SEX†	
				OR (95% CI)	P Value	OR (95% CI)	P Value
	N=68	N=32	N=41				
Age (yr)	48.7±10.1	56.7±9.8	63.7±9.3	1.12 (1.08-1.16)	<0.001	NA	NA
Male sex (%)	19.1	43.7	41.5	2.48 (1.26-4.86)	0.008	NA	NA
White race (%)	86.8	96.9	87.8	1.32 (0.47-3.68)	0.60	0.84 (0.26-2.7)	0.77
Duration of disease (yr)	8.8±9.4	11.8±13.5	15.5±10.7	1.04 (1.01-1.07)	0.005	1.02 (0.99-1.06)	0.20
Systolic blood pressure (mm Hg)	128.8±18.1	131.1±20.7	143.2±22.0	1.03 (1.01-1.04)	0.001	1.00 (0.98-1.02)	0.70
Diastolic blood pressure (mmHg)	74.5±10.2	76.9±11.8	75.7±10.7	1.01 (0.98-1.04)	0.47	1.00 (0.96-1.03)	0.85
Family history of coronary heart disease (%)	25.0	38.7	24.4	1.08 (0.54-2.16)	0.83	1.16 (0.54-2.51)	0.71
Total pack-yrs of smoking	6.6±11.7	21.6±28.8	18.5±27.8	1.01 (1.00-1.04)	0.009	1.02 (1.00-1.04)	0.04
Body mass index, kg/m ²	28.9±6.3	29.5±7.0	28.1±4.1	0.99 (0.94-1.04)	0.63	0.96 (0.91-1.02)	0.20
Creatinine (mg/dl)	0.77±0.22	0.87±0.23	0.85±0.23	4.58 (1.12-18.70)	0.03	0.59 (0.12-2.87)	0.51
Total cholesterol (mg/dl)	185.5±40.7	185.4±32.9	191.1±40.3	1.00 (0.99-1.01)	0.48	1.00 (1.00-1.01)	0.30
High density lipoprotein (mg/dl)	47.0±14.4	48.3±15.9	43.2±12.3	0.99 (0.97-1.01)	0.27	0.99 (0.96-1.01)	0.32

Low density lipoprotein (mg/dl)	111.1±31.1	112.8±28.4	118.9±36.9	1.01 (1.00-1.02)	0.21	1.01(1.00-1.02)	0.14
Triglycerides (mg/dl)	151.3±255.1	130.0±92.2	162.2±125.1	1.00 (1.00-1.00)	0.86	1.00 (1.00-1.00)	0.86
Lp(a) lipoprotein (mg/dl)	14.7±17.9	15.8±17.5	17.6±18.6	1.01 (1.00-1.03)	0.41	1.00 (0.98-1.02)	0.99
Homocysteine, (µmol/L)	9.9±3.0	11.6±3.4	11.4±3.9	1.12 (1.02-1.23)	0.02	1.02 (0.91-1.13)	0.78
Erythrocyte sedimentation rate (mm/hr)	20.2±18.0	19.6±20.8	30.2±23.3	1.02 (1.00-1.03)	0.03	1.02 (1.00-1.04)	0.05
C-reactive protein (mg/l)	9.3±13.3	8.4±10.0	11.7±14.9	1.01(0.99-1.03)	0.41	1.01 (0.99-1.04)	0.41
Rheumatoid factor‡	69.8%	75.0%	76.3%	1.32 (0.64-2.73)	0.45	1.63 (0.71-3.71)	0.25
Modified health assessment questionnaire (0-3) ¶	0.46±0.47	0.53±0.48	0.58±0.56	1.53 (0.82-2.84)	0.18	1.77 (0.88-3.57)	0.11
Disease activity DAS28§	3.1±1.4	3.4±1.6	3.6±1.4	1.17 (0.95-1.45)	0.14	1.19 (0.94-1.51)	0.16
Glucose (mg/dl)	87.7±13.9	91.9±15.9	96.2±23.6	1.02 (1.00-1.04)	0.02	1.01 (0.99-1.03)	0.24
Cumulative dose of hydroxychloroquine (g)	191.3±499.1	110.8±245.5	180.0±380.8	1.00 (1.00-1.00)	0.73	1.00 (1.00-1.00)	0.71
Cumulative dose of methotrexate (g)	5.9±28.6	4.9±10.7	3.2±3.5	1.00 (1.00-1.00)	0.53	1.00 (1.00-1.00)	0.27
Cumulative dose of prednisone (g)	7.1±11.6	16.7±31.3	9.9±13.6	1.00 (1.00-1.00)	0.37	1.00 (1.00-1.00)	0.79

* Plus-minus values are means ± SD

† Proportional odds logistic regression was used to obtain unadjusted and age-and sex-adjusted odds ratios for the severity of coronary calcification

§ Higher scores for the disease activity score indicate greater disease activity.

¶ Higher scores for the modified health assessment questionnaire indicate more difficulty in performing activities of daily life.

‡ Rheumatoid factor was available for 133 patients.

Figure Legends

Figure 1. The frequency of coronary-artery calcium scores in patients with rheumatoid arthritis and control subjects

Figure 2. The prevalence of coronary-artery calcification among patients with rheumatoid arthritis and control subjects, according to age.

Figure 1. The frequency of coronary-artery calcium scores in patients with rheumatoid arthritis and control subjects.

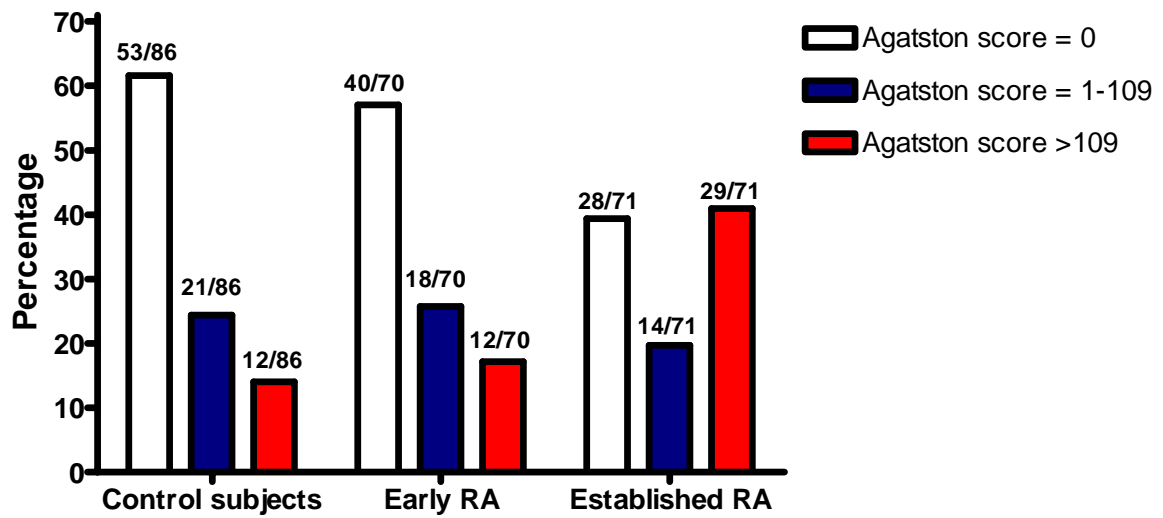


Figure 2. The prevalence of coronary-artery calcification among patients with rheumatoid arthritis and control subjects, according to age.

