# Increased Prevalence of Atherosclerosis in Patients with Medium Term Rheumatoid Arthritis

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*ABSTRACT*. ***Objective.*** To measure the extent of atherosclerosis in patients with rheumatoid arthritis (RA) with a disease duration of considerable length, and in age and sex matched individuals.

***Methods.*** Thirty-nine patients with RA (30 women, 9 men) with disease onset occurring between 1974 and 1978, and less than 65 years of age at the time of investigation, were enrolled together with 39 sex and age matched controls. Quantitative measurement of intima-media thickness (IMT) and semiquantitative assessment of the presence of plaque were undertaken by B-mode ultrasound of the common carotid artery (CCA-IMT) and the common femoral artery on the right-hand side. Echo Doppler cardiography was performed with an Accuson Aspen. The results were related to disease activity variables and accumulated disease activity, to lipid levels [i.e., cholesterol, high density lipoproteins, low density lipoproteins, triglycerides (TG)], to hemostatic factors [tissue plasminogen activator antigen (tPAag), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF)], and to soluble adhesion molecules (sICAM-1 and sE-selectin).

***Results.*** Patients with RA had higher maximal and mean IMT values compared with controls. The difference concerning mean CCA-IMT reached statistical significance in patients with RA and correlated significantly with lipids (cholesterol, LDL, LDL/HDL ratio, TG) and tPAag. The prevalence of plaques, as well as of aortic cusp sclerosis, was higher in RA but only the difference in aortic cusp sclerosis was statistically significant. Patients with plaques had significantly higher levels of lipids (cholesterol, LDL, LDL/HDL ratio) than patients without plaques, while patients with cusp sclerosis had significantly higher cholesterol and TG levels. sICAM-1 was significantly higher both in patients with plaques and in those with aortic cusp sclerosis compared to patients without.

***Conclusion***. Our results suggest an accelerated atherosclerosis in patients with RA that is related mainly to lipid levels. (J Rheumatol 2001;28:2597–602).

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS ATHEROSCLEROSIS B-MODE ULTRASOUND LIPIDS ECHOCARDIOGRAPHY SOLUBLE INTRACELLULAR ADHESION MOLECULE 1

Increased cardiovascular mortality in rheumatoid arthritis (RA) has been described in several reports[1-4]. Further, increased cardiovascular morbidity in RA has been suggested in clinical[5] and interview based[6,7] reports. We and others have reported altered levels of factors important for thrombogenesis, as well as for atherogenesis, in RA[8-11]. We have also identified the inflammatory activity in RA to be of importance for the development of cardiovascular disease (CVD)[12]. The prevalence of atherosclerosis and its interaction with inflammation in RA is, however, unknown.

B-mode ultrasound provides reliable noninvasive measurement of atherosclerosis during its subclinical stage[13]. It allows detection and quantitative measurement of the intima-media wall thickness (IMT)[14] and semiquantitative scoring of the size of atherosclerotic plaques in the carotid and femoral arteries[15,16]. The IMT of the carotid arteries is considered a marker of generalized atherosclerosis[16,17]. Aortic cusp sclerosis can be identified by echocardiography and has been suggested to be another manifestation of atherosclerotic disease[18].

We evaluated the presence and the extent of atherosclerosis, as measured by ultrasonography of the large superficial arteries and the heart, in patients with medium term RA and thus with a considerable accumulated disease burden, compared with the general population. In patients with RA, the results were related to markers of inflammatory activity, including accumulated disease activity score, markers of endothelial activation, lipid levels, and factors associated with atherothrombogenesis.

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## MATERIALS AND METHODS

*Subjects*. All patients registered at our Department of Rheumatology between 1974 and 1979 (n = 211) who had early (i.e., duration of ≤ 1 year) seropositive RA[19] were included in an earlier study[12]. Of these, all patients younger than 65 years at the time of the present study were enrolled for investigation. Seven patients declined to participate in the study, in most cases because they had moved from this region. Another 3 patients of the original cohort had died before sampling; one of these had suffered a known cardiovascular event (myocardial infarction). Thirty-nine patients (30 women, 9 men) (mean age 51.6 yrs, range 38–65) with a disease duration of 19–23 yrs remained for the present study. Controls were 39 age and sex matched individuals selected at random from the population register of the same region.

At the time of the investigation, 10 of the patients were being treated with corticosteroids and 26 with disease modifying antirheumatic drugs (DMARD), i.e., methotrexate (8), sulfasalazine (4), myocrisine (7), chloroquine/hydroxychloroquine phosphate (5), azathioprine (5), penicillamine (1). Ten patients had no therapy with DMARD nor with corticosteroids for their RA. Seven patients in the RA cohort and 4 of the controls were receiving hormone replacement therapy. No patient or control had known hyperlipidemia and none were treated with lipid lowering therapy.

The presence of established cardiovascular risk factors in the patient and control groups is presented in Table 1.

Accumulated disease activity was assessed retrospectively according to recorded information as described by Baecklund[20]. This accumulated disease activity score considers the number of swollen and tender joints, erythrocyte sedimentation rate (ESR), and global disease activity as judged by the examining clinician. Variables were assessed at presentation, after one year, and subsequently every 2 years after disease onset.

*Blood sampling and analytic procedures*. All sampling was done between 8:00 and 11:00 AM within a 6 week period. Blood was drawn for ESR. Non-anticoagulated blood was collected, after an overnight fast, for analysis of cholesterol and triglycerides (TG), while EDTA plasma was collected for protein analysis by electrophoresis, without prior freezing. Blood was collected into Stabilyte tubes for tissue plasminogen activator antigen (tPAag) and into citrate tubes for analysis of von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1) mass, and D-dimer. Serum was used for the other analyses. After centrifugation at 2000 × g for 20 min plasma and sera were stored at –80°C until assayed.

ELISA methods were used for analysis of PAI mass and tPAag (Immulite PAI-1 and TintElize tPA, respectively; Biopool, Umeå, Sweden), of vWF using primary antibody and second antibody conjugate purchased from Dako (Gentofte, Denmark), and of the fibrin split product D-dimer (NycoCard D-dimer; Nycomed, Lidingö, Sweden). C-reactive protein (CRP), haptoglobin, orosomucoid, and fibrinogen were determined by immunoturbidimetry. Soluble intercellular adhesion molecule 1 (sICAM-1) and soluble E-selectin (sE-selectin) were measured using ELISA (R&D Systems, Natick, MA, USA). Cholesterol, TG, and, after precipitation, high density lipoprotein cholesterol (HDL) were determined by dry chemistry on Vitros 950 IRC multianalyzer (Johnson & Johnson Clinical Diagnostics Inc., New York, NY, USA). Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Lipoprotein (a) was analyzed by ELISA (TintElize, Biopool).

*Table 1*. Established cardiovascular risk factors in 39 RA patients with 19–23 years of disease duration, and 39 age and sex matched controls.

| Variable | RA | Controls | p |
|---|---|---|---|
| Hypertension, treated | 9 | 5 | NS |
| Diabetes mellitus | 1 | 0 | NS |
| Smoking, ever | 18 | 22 | NS |
| Cardiovascular event ever | 1 | 1 | NS |
| Body mass index* | 22.68 (4.17) | 23.74 (5.24) | NS |

*Results presented as median (interquartile range). NS: not significant.

*Vascular disease measurements*. B-mode ultrasound of the right carotid and femoral arteries was carried out with an Accuson Aspen or Sequoia ultrasound system using a 7 MHz transducer. The examinations were carried out by the same sonographer. The sonographer scanned the right common carotid artery (CCA), the carotid bulbs, and the proximal internal and external carotid arteries. The right common femoral artery (CFA) and the proximal superficial and deep femoral arteries were also scanned. For each location, the vessel was imaged in multiple longitudinal planes for the best resolution of the intima-media wall thickness (IMT) of the far wall. For grading of focal plaques longitudinal and cross sectional images were used. Still frames were stored on MO-discs for later IMT measurements and the scans were recorded on SVHS videotapes. The IMT was recorded on a single image along centimeter-long longitudinal segments of CCA just proximal to the carotid bulb (on average 8 mm in patients vs 7.9 mm in controls) and just proximal to the bifurcation of the CFA (on average 9.2 vs 9.1 mm). The maximal thickness as well as the mean thickness of the registered segment were reported. A semiquantitative subjective scale (grade 0–3)[16] was used to grade the size of plaques of the same regions.

*Echocardiographic examination*. Echocardiography was performed using an Accuson Aspen or Sequoia for registration of standard 2-D and M-mode scans. All registrations were recorded on SVHS videotape for subsequent analysis. Asynergy was evaluated according to Hennan, *et al*[21].

*Statistics*. Statistical differences between patients and controls in terms of laboratory data were tested with the Wilcoxon signed rank test. Differences in echocardiographic and IMT data were tested with chi-square and Student's paired t test, respectively. Differences between subgroups within the RA group were tested with the Mann-Whitney U test. Chi-square was used when testing differences in nominal data. Correlations between variables were tested using the Spearman rank correlation test.

## RESULTS

Data on inflammatory variables, lipid levels, hemostatic factors and adhesion molecules in the patient and control groups are presented in Table 2.

*B-Mode registration. Intima-media thickness*. When comparing patients with RA and their controls, the thickness of the intima-media was generally greater in the RA group in terms of both maximal and mean thickness; however, only the difference of the mean thickness of the CCA (CCA-IMT) reached significance (Table 3).

*Plaque scoring*. Numerically more patients than controls had plaques (grade 1 + 2) of their right common carotid and/or common femoral arteries (Table 4). Plaques of grade 2 were almost twice as common in patients with RA compared with controls, but the difference did not reach the statistical significance level.

*Echocardiographic examination*. Aortic cusp sclerosis/stenosis was evident in 11 patients, including one patient who had undergone an operation for placement of an aortic valve prosthesis, and in 3 controls. The difference was significant ($p < 0.05$). Presence of asynergy of the left ventricular wall did not differ significantly between the groups (2 and one patients, respectively).

*Relation to established cardiovascular risk factors*. The mean CCA-IMT correlated significantly with the cholesterol level, with LDL-cholesterol, with the LDL/HDL ratio,

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*Table 2*. Levels of lipids, homocysteine, adhesion molecules, hemostatic factors, and markers of disease activity in 39 RA patients with 19–23 years of disease duration, and 39 age and sex matched controls. Results are presented as medians (interquartile range).

| | RA | Controls | p |
|---|---|---|---|
| ESR, mm/h | 22.0 (21.0) | 6.0 (6.0) | < 0.001 |
| Haptoglobin, g/l | 1.56 (1.1) | 1.01 (0.5) | <0.001 |
| Accumulated disease activity score* | 4.5 (1.2) | Not applicable | — |
| Cholesterol, mmol/l | 5.20 (1.9) | 5.80 (1.1) | NS |
| HDL cholesterol, mmol/l | 1.33 (0.5) | 1.46 (0.6) | NS |
| LDL cholesterol, mmol/l | 3.2 (1.6) | 3.8 (0.8) | NS |
| LDL/ HDL | 2.7 (1.5) | 2.7 (1.2) | NS |
| Triglycerides, mmol/l | 1.21 (1.0) | 1.05 (0.8) | NS |
| Lp(a) mg/l | 104.5 (157.0) | 101.5 (224.0) | NS |
| PAI-1 mass, ng/ml | 34.5 (89.0) | 17.8 (18.3) | < 0.01 |
| tPA antigen, ng/ml | 7.9 (4.4) | 8.8 (4.1) | NS |
| D-dimer, mg/l | 0.30 (0.5) | 0.10 (0.0) | <0.001 |
| vWF, IE/ml | 1.34 (0.6) | 1.23 (0.3) | NS |
| sICAM-1, ng/ml | 364 (210.3) | 247 (68.0) | <0.001 |
| sE-selectin, ng/ml | 67.1 (33.6) | 53.7 (22.8) | <0.01 |

*according to Baecklund, *et al*[20]. ESR: erythrocyte sedimentation rate; HDL: high density lipoproteins; LDL: low density lipoproteins; Lp(a); lipoprotein(a); PAI: plasminogen activator inhibitor; tPA: tissue plasminogen activator; vWF: von Willebrand factor; sICAM; soluble intercellular adhesion molecule; sE-selectin: soluble E- selectin.

*Table 3*. Intima-media thickness in 39 patients with RA and 39 age and sex matched controls. Results presented as mean values (SEM).

| Variable | RA | Controls | p |
|---|---|---|---|
| CCAdx | | | |
| Max, mm | 0.93 (0.05) | 0.88 (0.03) | NS |
| mean, mm | 0.79 (0.04) | 0.70 (0.03) | 0.05 |
| CFAdx | | | |
| Max, mm | 1.26 (0.14) | 1.15 (0.12) | NS |
| mean, mm | 0.97 (0.07) | 0.87 (0.08) | NS |

CCA: common carotid artery, CFA: common femoral artery, Max: maximal thickness along the examined cm-long part of the far wall; Mean: mean thickness along the examined cm-long segments of the far wall; dx:right.

*Table 4*. Presence of atherosclerotic plaques in the common carotid artery and/or the common femoral artery in 38 patients with RA and 38 controls. Values in parentheses are percentages.

| | RA | Controls | p |
|---|---|---|---|
| Grade 0 | 20 (52.6) | 22 (57.9) | NS |
| Grade 1 | 6 (15.8) | 9 (23.7) | NS |
| Grade 2 | 12 (31.6) | 7 (18.4) | NS |
| Grade 1 + 2 | 18 (47.4) | 16 (42.1) | NS |

Plaque: Intima-media wall thickness > 50% thicker than the neighboring sites: Grade 0: No plaques; Grade 1: One or more small plaques (each < about 10 $mm^2$); Grade 2: Moderate to large plaques as judged subjectively; Grade 3: Large plaques that cause a hemodynamic change in blood flow.

and with TG in the patients with RA (Table 5). CCA-IMT also correlated with tPAag, but with none of the other hemostatic factors (Table 5). The CCA-IMT correlated with age in both patients and controls ($p < 0.05$ for both groups).

Patients with plaques had significantly higher levels of cholesterol ($p < 0.05$), LDL cholesterol, and the LDL/HDL ratio compared to patients without plaques ($p < 0.01$ for both; Table 6). Patients with aortic cusp sclerosis had significantly higher levels of cholesterol and TG than patients without. Patients with plaques or aortic cusp sclerosis also had a significantly higher level of sICAM-1 ($p < 0.05$; Table 6). RA patients with plaques were significantly older compared with patients without plaques ($p < 0.01$), and there was a tendency toward more smokers in this group ($p = 0.05$). There were no significant differences in hypertension or corticosteroid use at the time of sampling between patients with and without plaques (data not shown).

*Relation to inflammatory activity*. In the RA group, CCA-IMT did not correlate with any inflammatory variables nor with accumulated disease activity (Table 5). In patients with cholesterol levels below the median value (i.e., ≤ 5.2 mmol/l) there was an evident negative correlation between the cholesterol level and measures of inflammatory activity (i.e., CRP, orosomucoid, fibrinogen; data not shown). However, in this low cholesterol group, no correlation between markers of inflammatory activity and CCA-IMT could be identified either. Nor were there any differences between inflammatory measures in patients with or without plaques, or aortic cusp sclerosis (data not shown).

*Table 5*. Correlations between mean intima-media wall thickness of right common carotid artery (CCA-IMT) and hemostatic factors, lipid levels, adhesion molecules, and markers of disease activity in 39 patients with RA and controls.

| | CCA-IMT | |
|---|---|---|
| | RA | Controls |
| Accumulated disease activity† | 0.13 | — |
| ESR | 0.09 | –0.11 |
| Haptoglobin | 0.23 | –0.27 |
| PAI mass | 0.25 | –0.18 |
| tPAag | 0.43* | 0.14 |
| D-dimer | 0.11 | –0.37* |
| vWF | 0.17 | 0.35 |
| Cholesterol (total) | 0.37* | 0.03 |
| HDL cholesterol | –0.26 | 0.02 |
| LDL cholesterol | 0.57** | 0.09 |
| LDL/HDL | 0.43* | 0.04 |
| Triglycerides | 0.41* | –0.02 |
| Lp(a) | 0.01 | 0.20 |
| sICAM-1 | 0.20 | –0.14 |
| sE-selectin | 0.25 | –0.18 |

†According to Baeckman, *et al*[20]; *$p < 0.05$, **$p < 0.01$. For definitions see Table 2.

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*Table 6.* Lipid and sICAM-1 levels in RA patients with versus patients without atherosclerotic plaque (grade 1 + 2) in the common carotid artery and/or the common femoral artery of the right side and in patients with versus without aortic cusp sclerosis. Results are presented as median values (interquartile range).

| Variable | Plaques | No Plaques | p | Aortic cusp sclerosis | No cusp sclerosis | p |
|---|---|---|---|---|---|---|
| Cholesterol, mmol/l | 6.6 (2.0) | 5.0 (0.7) | < 0.05 | 6.7 (1.9) | 5.0 (1.0) | < 0.01 |
| LDL cholesterol, mmol/l | 4.2 (2.1) | 3.0 (0.7) | < 0.01 | 4.4 (2.4) | 3.2 (0.8) | 0.078 |
| LDL/HDL | 3.1 (1.8) | 2.2 (1.5) | < 0.01 | 3.9 (3.4) | 2.5 (1.1) | NS |
| Triglycerides, mmol/l | 1.28 (0.8) | 0.99 (0.8) | = 0.085 | 1.96 (1.2) | 1.16 (0.7) | 0.05 |
| sICAM-1, ng/ml | 415.5 (266.0) | 297.5 (130.0) | < 0.05 | 481.0 (268.0) | 305.5 (138.0) | <0.05 |

For definitions see Table 2.

## DISCUSSION

We found indications of increased progression of atherosclerotic manifestations in patients with RA compared with age and sex matched controls. Somewhat unexpectedly, atherosclerosis was only weakly related to measures of inflammatory activity, but correlated mainly to lipid levels in this study.

Intima-media thickness (IMT) is regarded as a sensitive marker of the early subclinical phase of atherosclerosis[16,17,22]. Recorded maximal and mean values of IMT showed numerically higher values of the carotid as well as the femoral arteries in RA. However, probably due to the small number of the cohort, only mean IMT of the right CCA reached significant difference. Atherosclerotic plaques represent more manifest changes of the vessel wall. In line with the findings on IMT, numerically more patients than controls had atherosclerotic plaques in CCA and/or CFA. Further, significantly more patients had evidence of aortic cusp sclerosis, which has been suggested to be another reflection of the atherosclerotic process[18,23]. The groups were statistically equivalent with respect to presence of CVD, as measured by an earlier cardiovascular event and other traditional cardiovascular risk factors. An association has been established between smoking and IMT[24,25]. We found no such correlation in our group of patients with RA, but there was a tendency toward more of the patients with plaques to be smokers.

There have been attempts to evaluate the prevalence of atherosclerosis in RA. Increased peripheral atherosclerosis has been reported as measured radiologically[26], while autopsy studies have revealed divergent results[5,27,28]. However, these studies comprise mainly hospital based materials and describe findings on manifest atherosclerosis but give no information on early, subclinical changes. Despite the small number of patients, our results suggest an increased atherosclerotic progression in patients with RA of medium disease duration compared with non-rheumatoid individuals of the same age and sex with comparable established cardiovascular risk factors. The patient cohort comprises virtually all patients with RA aged 65 years or less in our region with disease onset during 1974-78, and therefore a disease duration of 18–22 years at the time of the present investigation. Only 3 patients of the original cohort had died, and the exclusions can be regarded as random. Consequently, although the power of the study is limited, the present cohort, comprising the whole spectrum of patients from those in total remission to those with a highly active disease, should reflect the true presence of atherosclerosis in patients with RA with a medium term disease burden, but still not influenced by the progressive atherosclerosis of the senium.

We found positive correlations between CCA-IMT and the levels of cholesterol and TG as well as LDL cholesterol and the LDL/HDL ratio. The presence of atherosclerotic plaque, as well as aortic cusp sclerosis, was also related to higher lipid levels. We and others have reported patients with RA to have decreased levels of total cholesterol and of HDL and LDL cholesterol[29,30], which were inversely related to their inflammatory status[29]. However, the low cholesterol levels in inflammatory active RA do not seem to protect against atherogenesis. In an earlier study, we actually found that a low cholesterol level — probably due to a high disease activity — showed a tendency to predict CVD[9]. The present study suggests that patients with RA and with raised levels of lipids seem to be more prone to atherogenesis, as is the general population. The relationship between lipid levels and CCA-IMT and plaques, respectively, was in fact more prominent in RA patients than in controls without clinical vascular disease. The lack of correlation between IMT and lipid levels in our controls may be due to a small sample of younger subjects comprising mainly women, but also to few prominent atherosclerotic manifestations. Another interpretation could be that the patients with RA and 20 years of disease burden have developed a more aged vascular bed with relatively more arterial and valvular sclerosis. RA patients with plaques also seemed to be somewhat more likely to carry other established cardiovascular risk factors, for example smoking. Thus, it seems urgent that in addition to the treatment of their arthritis these patients should be screened, and adequately treated for, other cardiovascular risk factors, particularly presence of hyperlipidemia, even when not at extreme levels.

In the general population, several prospective studies have shown that CRP is a predictor of increased risk for

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myocardial infarction, stroke, and peripheral vascular disease[31-34]. We have reported a predictive effect of the inflammatory reaction on the development of cardiovascular event[12]. Despite these findings, the inflammatory reaction did not appear to have a major effect on atherogenesis in the present RA group. However, the level of the adhesion molecule sICAM-1, shown to predict myocardial infarction in healthy males[35], was significantly higher in patients with plaques and in patients with aortic cusp sclerosis. The exact cellular origin of the increased sICAM-1 levels is not known. A tentative interpretation is that the increased sICAM-1 levels represent an upregulation of ICAM-1 on endothelial cells by inflammatory cytokines such as tumor necrosis factor-α, interferon-γ, and interleukin 1 (IL-1)[36], leading to increased recruitment of monocytes to the vascular intima. This reasoning is supported by the increased IL-1α expression found in the endothelium of muscle vessels in RA with extraarticular manifestations[37]. Thus, the atherosclerotic process in RA may not be directly associated with the acute phase reaction, which is strongly correlated to IL-6. One may speculate on an increased endothelial sensitivity leading to increased atherogenesis in patients with RA despite the low lipid levels in inflammatory active RA. Treatment with glucocorticoids might actually have a beneficial effect on atherosclerosis in this context through downregulation of ICAM-1 expression on endothelial cells[36]. Our collected knowledge suggests a complex situation in which the inflammation in RA may have greater influence on other mechanisms involved in the atherothrombotic process and a subsequent cardiovascular event. These mechanisms need to be further elucidated.

Our results suggest an increased atherosclerotic progression in patients with RA of medium term disease duration compared with the general population. This may be the result of continuous endothelial activation leading to a prematurely aging, dysfunctional vasculature that may be more susceptible to traditional cardiovascular risk factors, e.g., cholesterol level, compared to the general population. The findings may contribute to the explanation of the increased cardiovascular death reported in RA.


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