The Extent of Subclinical Atherosclerosis Is Partially Predicted by the Inflammatory Load: A Prospective Study over 5 Years in Patients with Rheumatoid Arthritis and Matched Controls

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ABSTRACT. ***Objective***. This prospective followup study investigated subclinical atherosclerosis in relation to traditional cardiovascular disease (CVD) risk factors and inflammation in patients with rheumatoid arthritis (RA) recruited at diagnosis compared with controls.

Methods. Patients diagnosed with early RA were consecutively recruited into a prospective study. From these, a subgroup aged ≤ 60 years (n = 71) was consecutively included for ultrasound measurement of intima-media thickness (IMT) and flow-mediated dilation (FMD) at inclusion (T0) and after 5 years (T5). Age- and sex-matched controls (n = 40) were also included.

Results. In the Wilcoxon signed-rank test, both IMT and FMD were significantly aggravated at T5 compared to baseline in patients with RA, whereas only IMT was significantly increased in controls. In univariate linear regression analyses among patients with RA, the IMT at T5 was significantly associated with age, systolic blood pressure (BP), cholesterol, triglycerides, Systematic Coronary Risk Evaluation (SCORE), and Reynolds Risk Score at baseline ($p < 0.05$). Similarly, FMD at T5 was significantly inversely associated with age, smoking, systolic BP, SCORE, and Reynolds Risk Score ($p < 0.05$). A model with standardized predictive value from multiple linear regression models including age, smoking, BP, and blood lipids at baseline significantly predicted the observed value of IMT after 5 years. When also including the area under the curve for the 28-joint Disease Activity Score over 5 years, the observed value of IMT was predicted to a large extent.

Conclusion. This prospective study identified an increased subclinical atherosclerosis in patients with RA. In the patients with RA, several traditional CVD risk factors at baseline significantly predicted the extent of subclinical atherosclerosis 5 years later. The inflammatory load over time augmented this prediction. (J Rheumatol First Release April 15 2015; doi:10.3899/jrheum.140694)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CARDIOVASCULAR DISEASE INFLAMMATION
ATHEROSCLEROSIS PROSPECTIVE

Patients with rheumatoid arthritis (RA) have an increased mortality and morbidity because of cardiovascular disease (CVD) compared with the general population[1,2,3,4]. We, and others, have previously shown that patients with established RA have a premature atherosclerosis as measured by an increased intima-media thickness (IMT) of the common carotid artery compared with controls[5,6,7]. An increased IMT, measured by ultrasonography (US), is regarded to be an early indicator of a generalized atherosclerosis[8], and several studies in the general population have shown a relationship between an increased IMT and a future CV event[9,10,11]. This observation has now been confirmed among patients with RA[12,13].

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Moreover, endothelial dysfunction, a sign of very early atherosclerosis, can be indicated by an impaired flow-mediated vascular dilation (FMD) of peripheral arteries measured by US[14]. In the general population, FMD has been associated with other risk factors for CVD and shown to be predictive of a future CV event[14,15,16].

In our study of patients with very early RA, there were no significant differences in the measurements of subclinical atherosclerosis (i.e., IMT and FMD) between patients with RA at the time of diagnosis and matched control subjects[17]. However, a significant increase in IMT after 18 months of disease was found among the patients with RA. In other studies of patients with RA, an increased IMT has been shown in patients with recent disease onset as well as longstanding disease, albeit there are some contradictory reports[5,6,7,18,19,20]. Previous studies of FMD in patients with RA have involved small cohorts, and nearly all were composed of patients with longstanding disease[18,19,21,22,23], with only a few studies evaluating patients with early RA[24,25]. A few prospective studies regarding subclinical atherosclerosis among patients with early RA have been published, but none involves a prospective inception cohort from the onset of RA disease compared with controls as investigated in our study[7,26].

From our ongoing prospective case-control study[17], we present data after 5 years of followup from the first measurements. We hypothesized that the progression of atherosclerosis was already established early in the pathogenesis of RA, and was related to inflammatory activity over time. Thus, our primary aim was to investigate whether the progression of atherosclerosis, as measured by IMT and FMD, was more rapid in patients with RA compared with controls during the first 5 years of disease following a diagnosis of RA. The second aim was to identify which traditional risk factors for CVD or factors related to rheumatic disease, assessed at baseline and during 5 years of followup, could predict the atherosclerotic load among such individuals.

MATERIAL AND METHODS

Patients and controls. Our study is part of a continuing structured program involving patients with early RA for the prospective analysis of the development of CVD using the nationwide Swedish Rheumatoid Arthritis Registry. All eligible patients with newly diagnosed RA (i.e., fulfilling the American College of Rheumatology criteria)[27] and being symptomatic for no longer than 12 months were continuously enrolled into the register. The inclusion of patients with RA and controls has been described[17]. Five years after inclusion into the study (T5), 71 of the 79 patients with RA who were originally included were willing to participate in the followup study, and 40 of the original 44 controls were reassessed. The controls (1 control for 2 patients, but in 13 cases, 1 control per patient) were matched for age (± 5 yrs) and sex. All individuals gave their written consent in accordance with the Declaration of Helsinki. The study was approved by the Regional Ethics Committee of Umeå University, Umeå, Sweden.

Physical examination and surveys. All patients were examined clinically at their inclusion into the study (T0) and regularly thereafter at 3, 6, 12, 18, and 60 months after diagnosis. The number of swollen and tender joints (28-joint count) and the patient's global assessment were recorded, and a Disease Activity Score at 28 joints (DAS28) including the erythrocyte sedimentation rate (ESR) was calculated[28]. All participants were requested to complete a survey on comorbidity, and a survey of CVD risk factors and lifestyle[29], both at inclusion and after 5 years. Any previous CV events were verified by analysis of medical records (codes according to International Classification of Diseases, 10th ed: I21–23, I61–64, I74, I80–82). Blood pressure (BP) was measured at the time of the US measurements. Body mass index (BMI), European Systematic Coronary Risk Evaluation (SCORE)[30], and Reynolds Risk Score[31] were calculated at both T0 and T5. These compound measures of CVD risk factors indicate the risk of death because of CVD (SCORE) and the risk of a CV event during the next 10 years (Reynolds Risk Score). In addition to the traditional CVD risk factors, the Reynolds Risk Score also includes C-reactive protein (CRP). When calculating the Reynolds Risk Score, all patients were regarded as being non-diabetic because of a lack of information regarding hemoglobin A1c concentrations.

US investigations. The patients with RA were included as soon as possible following a diagnosis of RA (T0). They were examined by US, a mean (SD) of 16.2 months (6.6), after the primary symptom of RA. The US examinations at the followup (T5) were performed, a mean (and median) of 60 months (SD 1.2, range 55–64), after the initial examination. All examinations were performed by the same experienced investigator with the subject in a supine position in a quiet, temperature-controlled room. A Sequoia 512 US system (Siemens, Acuson Corp) was used with a 15L8 transducer for the brachial artery and an 8L5 transducer for carotid artery studies. All investigations were digitally stored for analyses to be performed by a single observer (EL; intraobserver variability for IMT r = 0.988). The same observer (EL) performed all analyses at all timepoints during followup. The observer (EL) could not remain unaware of the health status of the participants. The investigations have been described in detail[17].

Blood sampling. Rheumatoid factor, soluble CRP (mg/l), and ESR (mm/h) were measured according to routine methods. Whenever several analyses of DAS28, CRP, or ESR were performed, the assessment closest to the US measurement was used in the statistical analysis. Blood was also drawn after an overnight fast for measurement of blood lipids, i.e., cholesterol (mmol/l), high-density lipoproteins (HDL; mmol/l), and triglycerides (mmol/l), using routine methods at each of the participating hospitals.

Statistics. Differences in variables between patients with RA and matched controls were analyzed using simple conditional logistic regression analyses. Comparisons over time within the RA group or the control group were performed using the Wilcoxon signed-rank test. Simple (univariate) and multiple linear regression analyses were used to identify variables associated with FMD or IMT. Results from simple linear regression (variables with $p < 0.05$), together with clinical assumptions based on previous published data on atherosclerosis in patients with RA as well as in the general population, determined which covariates were included in the multiple linear regression models. Standardized predictive value from multiple linear regression models was used in evaluation of predictive models. Correlations between standardized predictive value and observed values were tested with Spearman rank correlation. Area under the curve (AUC) was calculated for DAS28 when repeated measurements were available[32]. Data from measurements 0, 6, 12, and 60 months after diagnosis were used for this calculation. Progression of US measurements between T0 and T5 are given as percentage. Based on results from previous publications[33], calculations showed that a sample size of 26 in each group would render 95% power to detect a difference in IMT of 0.1 mm and SD of 0.1 mm. In some of the descriptive statistics, there were occasional values missing that were regarded as random. In the tables regarding the simple regressions, the numbers of patients that could be included in each regression analysis are given. For the multiple linear regression models, model evaluations were performed that showed some interaction between the variables in the model; however, these interactions were of minor importance and the model clinically interesting. P values < 0.05 were considered statistically significant. All calculations were made using SPSS 18.0 (SPSS Inc.).

RESULTS

Our study included 71 patients with RA and 40 controls. Descriptive data are presented in Table 1. Regarding medication, 58 of the patients with RA (82%) had ever been treated with methotrexate, 32 with sulfasalazine (45%), 44 with other disease-modifying antirheumatic drugs (62%; i.e., oral gold, hydroxychloroquine phosphate, azathioprine, leflunomide, cyclosporine, mycophenolate mofetil), and 9 with biologics (13%). Eight of the patients with RA (11%) had ever experienced a CV event (3 acute myocardial infarctions, 3 strokes, 2 thromboembolic events), of which 1 was a new event between T0 and T5 (Table 1). Among the controls, 2 (5%) had ever experienced a CV event, of which 1 was during the period of our study (Table 1).

T5 compared with T0. The patients with RA had both a significantly higher IMT and a poorer FMD at T5 compared with at T0 (Figure 1, Table 1). Systolic BP was significantly increased among the patients with RA during the 5 years of followup. The disease activity decreased significantly at T5 compared with T0. The worsening of the US measurements in the control group was only significant with regard to IMT (Figure 1, Table 1).

Patients with RA compared with controls. There were no significant differences in the US measurements among the patients with RA compared with controls, either at T0 or at T5 (Table 1).

Progression of US measurements. There were no significant differences in the progression of the US measurements between the patients with RA and controls [mean (SD) in percent progression of IMT in RA vs controls was 14.2 (15.6) vs 13.4 (12.7), p value > 0.05; and mean (SD) percentage progression FMD in RA vs controls was –10.1 (122.2) vs 23.5 (142.2), p > 0.05]. In simple regression models for both the patients with RA and the control cohort, the progression of the IMT was not significantly associated with any measures of disease activity or any other of the measured variables (data not shown). In the corresponding simple regression models among the patients with RA, the progression of impairment of FMD was significantly associated with the disease duration (β –0.05, 95% CI –0.1 – –0.01) and ever smoking (β –0.02, 95% CI –0.04 – –0.001). None of the measures of disease activity were significantly associated with the changes in FMD (data not shown). None of the measured variables were significantly associated with the progression of impairment of FMD in the control cohort (data not shown).

Simple regression models for the US measurements. In simple regression models among the patients with RA, the IMT at

Table 1. IMT, FMD, traditional CVD risk factors, and disease activity in patients with early RA, and age- and sex-matched controls evaluated at both T0 and T5. Values are mean (SD) unless otherwise specified.

Characteristics	RA at T0, n = 71	At T5	Controls at T0, n = 40	At T5
Female, n (%)	61 (86)		32 (80)	
Age, yrs	51.5 (10.7)		48.1 (10.9)	
Symptom duration, mos	16.1 (6.7)		—	
RF, n (%)	48 (67)		—	
IMT, mm	0.52 (0.13)	0.58 (0.13)***	0.54 (0.13)	0.60 (0.12)***
Endothelium dependent flow-mediated vasodilation, %	109.2 (4.7)	107.0 (4.7)***	107.2 (4.5)	106.0 (4.6)
Systolic BP, mmHg	123.5 (14.4)	126.3 (13.9)*	117.7 (11.3)	124.1 (12.1)***
Diastolic BP, mmHg	77.0 (8.2)	76.4 (7.4)	76.4 (8.2)	77.5 (7.1)
Cholesterol, mmol/l	5.5 (0.9)	5.3 (1.0)	5.3 (1.1)	5.6 (1.1)
HDL, mmol/l	1.6 (0.5)	1.6 (0.5)	1.5 (0.4)	1.7 (0.5)
Triglycerides, mmol/l	1.3 (0.5)	1.2 (0.5)	1.1 (0.3)	1.0 (0.5)
BMI, kg/m^2	25.8 (4.0)	25.7 (4.5)	25.1 (4.9)	25.2 (4.2)
ESR, mm/h	17.5 (16.2)	15.6 (11.9)	—	—
CRP, mg/l	11.9 (10.8)	7.7 (7.2)**	—	—
DAS28	3.5 (1.4)	3.1 (1.5)†	—	—
SCORE[30]	0.9 (1.3)	1.4 (1.7)***	0.6 (0.7)	1.6 (1.9)***
Reynolds Risk Score[31]	2.2 (3.3)	2.7 (3.3)	—	—
Previous CVD event, n (%)	5 (7)	8 (11)	1 (3)	2 (5)
Diabetes mellitus, n (%)	3 (4)	3 (4)	0 (0)	0 (0)
Statin use, ever, n (%)	2 (3)	6 (9)	1 (3)	5 (13)
Antihypertensives use, n (%)	NA	17 (24)	NA	11 (28)
NSAID use, ever, (%)	47 (72)	65 (93)	2 (5)	1 (3)

* p < 0.05. ** p < 0.01. *** p < 0.0001. † p = 0.061 compared with T0. IMT: intima-media thickness; FMD: flow-mediated dilation; CVD: cardiovascular disease; RA: rheumatoid arthritis; T0: baseline; T5: after 5 years; RF: rheumatoid factor; BP: blood pressure; HDL: high-density lipoproteins; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; SCORE: Systematic Coronary Risk Evaluation; NSAID: nonsteroidal antiinflammatory drugs; NA: not available.

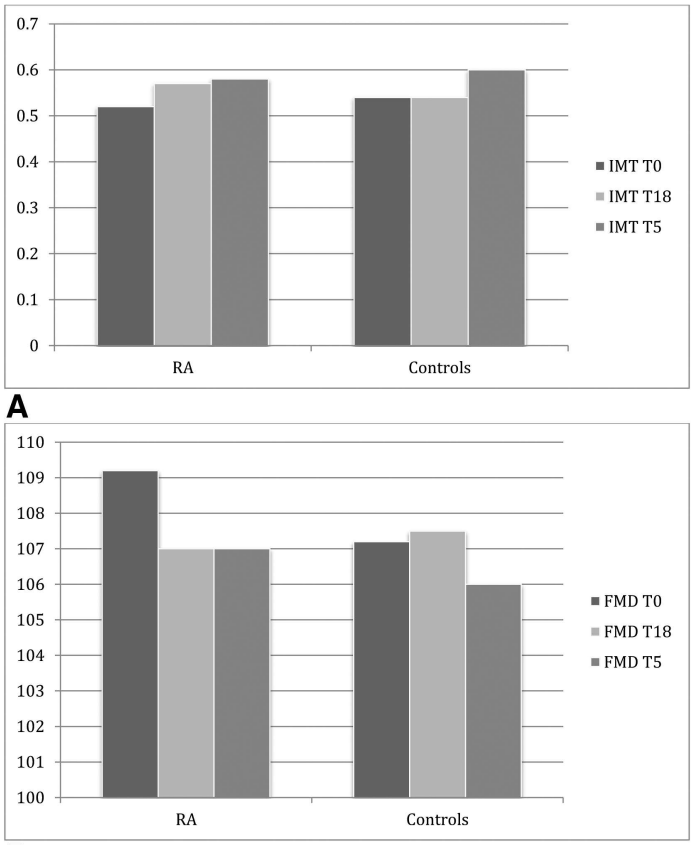

Figure 1. (A) IMT and (B) FMD in 71 patients with RA and 40 controls at baseline and after 5 years of followup. The measurements at T18 of followup are in a subgroup of 27 patients with RA and the corresponding 27 controls. IMT: intima-media thickness; FMD: flow-mediated dilatation; RA: rheumatoid arthritis; T18: after 18 months.

T5 was significantly associated with age and systolic BP both at T0 and T5. This was also true for some of the blood lipids, SCORE, and the Reynolds Risk Score, whereas BMI was only associated significantly at T5 (Table 2). Among the controls, the same traditional CVD risk factors at T0 and T5 were significantly associated with IMT at T5 in addition to relationships with sex and HDL cholesterol (Table 2).

In the same simple regression models among the patients with RA, but with FMD at T5 as the dependent variable, age, systolic BP at T5, ever smoking as well as SCORE at T0 and T5, and Reynolds Risk Score at T0 were significantly inversely associated with FMD (Table 3). Among the controls, none of the traditional CVD risk factors were significantly associated with FMD at T5 (data not shown).

Multiple regression models for the US measurements. In a multiple regression model among patients with RA, with IMT at T5 as the dependent variable, and age, smoking, systolic BP, triglycerides, cholesterol, and HDL all at T0 as independent variables, the US measurement was significantly associated with age (Table 4, Model 1). Model 1 explained 30% of the variance in IMT at T5. When adjusting this model for the AUC for DAS28 over 60 months, IMT at T5 was significantly associated with BP and cholesterol (Table 4, Model 2); Model 2 explained 71% of the variance in IMT at T5.

The calculated standardized predictive values according to Model 1, including age, smoking, BP, and blood lipids, were significantly correlated with the observed values of IMT T5 ($r = 0.59$, $p < 0.01$ for RA, and $r = 0.74$, $p < 0.01$ for controls). Also, the calculated standardized predictive values according to Model 2, including the same variables as Model 1 as well as AUC DAS28 over 60 months, were significantly correlated with the observed values of IMT T5 ($r = 0.97$, $p < 0.01$ for RA; Figure 2).

DISCUSSION

In this prospective followup study from disease onset in patients with RA, subclinical atherosclerosis, measured as IMT and FMD, had exacerbated significantly during the first 5 years of the disease. Only atherosclerosis, measured as IMT, increased significantly in the matched controls followed in parallel.

Table 2. Simple regression models among 71 patients with early RA, and 40 age- and sex-matched controls with IMT after 5 years of followup as the dependent variable.

Characteristics	RA			Controls		
	β	95% CI	p	β	95% CI	p
Female	–0.7/+, n = 71	–1.6–0.2	> 0.1	–1.7/+, n = 40	–2.4 – –0.9	< 0.001
Age, yrs	0.08, n = 71	0.05–0.09	< 0.001	0.07, n = 40	0.04–0.09	< 0.001
Systolic BP, T0, mmHg	0.03, n = 71	0.008–0.05	0.006	0.05, n = 40	0.02–0.08	0.002
Cholesterol, T0, mmol/l^{-1}	0.3, n = 57	–0.04–0.7	0.08	0.4, n = 39	0.03–0.7	0.04
HDL, T0, mmol/l^{-1}	0.1, n = 66	–0.6–0.8	> 0.1	–1.0, n = 40	–2.0 – –0.1	0.03
Triglycerides, T0, mmol/l^{-1}	0.6, n = 66	–0.06–1.3	0.07	0.7, n = 40	–0.1–1.5	0.05
BMI, T0	0.04, n = 70	–0.05–0.1	> 0.1	0.09, n = 38	0.02–0.2	0.01
SCORE, T0	0.5, n = 54	0.2–0.7	< 0.001	1.0, n = 39	0.6–1.5	< 0.001
Reynolds Risk Score, T0	0.2, n = 38	0.1–0.3	< 0.001			—
Systolic BP, T5, mmHg	0.04, n = 67	0.02–0.06	0.001	0.05, n = 40	0.02–0.07	0.003
Cholesterol, T5, mmol/l^{-1}	0.3, n = 66	0.02–0.7	0.04	0.4, n = 40	0.05–0.7	0.03
Triglycerides, T5, mmol/l^{-1}	0.6, n = 66	–0.06–1.3	0.07	0.7, n = 40	–0.1–1.5	0.05
BMI, T5	0.07, n = 48	–0.004–0.1	0.07	0.1, n = 37	0.01–0.2	0.03
AUC DAS28, 60 mos	–0.01, n = 33	–0.01–0.03	> 0.1			—
SCORE, T5	0.4, n = 66	0.2–0.5	< 0.001	0.4, n = 39	0.2–0.5	< 0.001
Reynolds Risk Score, T5	0.2, n = 42	0.1–0.3	< 0.001			—

RA: rheumatoid arthritis; IMT: intima-media thickness; BP: blood pressure; T0: baseline; HDL: high-density lipoproteins; T5: after 5 years; BMI: body mass index; SCORE: Systematic Coronary Risk Evaluation; AUC: area under the curve; DAS28: 28-joint Disease Activity Score.

Table 3. Simple regression models among 71 patients with early RA with FMD after 5 years of followup as dependent variable.

Characteristics	β	95% CI	p
Age, yrs	–0.2, n = 71	–0.3 – –0.05	0.003
SCORE, T0	–1.7, n = 54	–2.6 – –0.8	0.001
Reynolds Risk Score, T0	–0.5, n = 38	–1.0 – –0.05	0.03
Systolic BP, T5, mmHg	–0.09, n = 71	–0.2 – –0.006	0.034
Smoking ever, yrs	–0.1, n = 60	–0.2 – –0.04	0.002
SCORE, T5	–1.1, n = 66	–1.8 – –0.5	0.001

RA: rheumatoid arthritis; FMD: flow-mediated dilation; SCORE: Systematic Coronary Risk Evaluation; T0: baseline; BP blood pressure; T5: after 5 years.

Several theories have been proposed to explain the increased atherosclerosis in patients with RA[34]. In the present study, a higher burden of traditional CVD risk factors at inclusion into the study (i.e., at diagnosis of RA) was significantly associated with the extent of atherosclerosis 5 years later. The combined measurement SCORE indicates the risk of death in CVD during the following 10 years while taking sex, smoking, systolic BP, and cholesterol concentration into account[30]. Ridker, *et al* have developed an algorithm for assessing the risk of CVD (i.e., the Reynolds Risk Score) that also includes inflammation measured as CRP[31]. In our study, we identified a strong relationship between these risk scores,

Table 4. Multiple regression models among 71 patients with early RA who had IMT after 5 years of followup as dependent variable.

Characteristics	Model 1			Model 2		
	β	95% CI	p	β	95% CI	p
Age, yrs	0.05	0.005–0.1	0.03	0.81	–0.02–0.2	0.1
Smoking ever, yrs	–0.004	–0.03–0.03	0.8	–0.02	–0.08–0.04	0.4
Systolic BP, T0, mmHg	0.2	–0.01–0.6	0.2	0.09	0.01–0.2	0.03
Triglycerides, T0, mmol/l^{-1}	0.8	–0.08–1.7	0.07	0.4	–1.1–1.8	0.6
Cholesterol, T0, mmol/l^{-1}	0.05	–0.3–0.4	0.8	–0.7	–1.4–0.02	0.05
HDL, T0, mmol/l^{-1}	0.5	–0.4–1.5	0.3	1.8	–0.2–3.7	0.07
AUC DAS28, 60 mos			—	–0.001	–0.01–0.01	0.9

Adjusted R^2 for Model 1 = 0.30. Adjusted R^2 for Model 2 = 0.71. RA: rheumatoid arthritis; IMT: intima-media thickness; BP: blood pressure; HDL: high-density lipoproteins; AUC: area under the curve; DAS28: 28-joint Disease Activity Score.

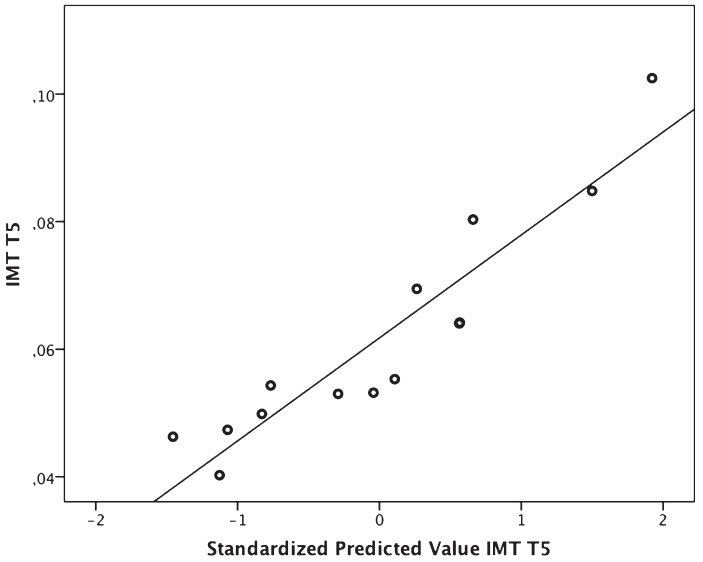

Figure 2. Relation between observed values of IMT T5 and standardized predictive values for the multiple regression model in Table 4, Model 2, including age, smoking, BP, and blood lipids at baseline, as well as inflammatory load over time in patients with RA. IMT: intima-media thickness; T5: after 5 years of followup; BP: blood pressure; RA: rheumatoid arthritis.

both at baseline and at the 5-year followup, and subclinical atherosclerosis. These results indicate that the interplay between disparate traditional CVD risk factors might be important among patients with RA, and that this interplay aggravates the development of atherosclerosis over time.

In 2010, the European League Against Rheumatism published recommendations for the management of the risk of CVD in patients with RA that included multiplying the SCORE value by 1.5 if the patient had 2 or more of the following: (1) a disease duration of more than 10 years, (2) persistent high inflammation, and/or (3) extraarticular manifestations[35]. Thereafter, some studies evaluated not only this multiplied SCORE, but also other CV risk scores in patients with RA, finding that the risk scores overestimate or underestimate the risk of CVD among these patients[36,37]. Further, 1 study found a better prediction of the CVD risk by adding IMT to the SCORE among patients with RA[38]. In our present study, we were unable to evaluate the risk score because of a low number of CV events. However, the best fitting model to explain the increase in IMT at T5 in patients with RA included the accumulated disease activity, measured by DAS28, over the 5 years. When only traditional CVD risk factors at baseline were included, the best fitting model explained only 30% of the variance in IMT after 5 years of followup. When adding the variable representing accumulated disease activity (i.e., AUC DAS28 over 5 years), the level of explanation increased to 71%, and both systolic BP and variables reflecting blood lipids increased their explanatory strength. None of the other variables assessed in our study increased the level of explanation to any significant extent. Ajeganova, *et al* showed that patients with high inflammation, both at diagnosis of RA and over the first 2 years, had a higher risk of a CV event[39]. In a prospective study from northern Sweden with 700 patients, we found that the occurrence of a CV event was explained by traditional CVD risk factors and potentiated by high disease activity over time[40]. This indicates that patients with RA with several traditional CVD risk factors at the time of diagnosis can be predicted to have an accelerated atherosclerosis 5 years later. If the patient with RA also has a sustained high level of inflammation, the degree of atherosclerosis after 5 years could be predicted to be even more accelerated.

In our study, we found no difference in the IMT between patients with RA and control subjects; however, this only measures the thickness of the arterial wall in a limited region. A maladaptive outward remodeling of the arterial wall has been observed in patients with RA, with an increased risk of plaque rupture[41]. We did not evaluate this mechanism in our present study, but it may explain the lack of difference between patients with RA and controls, and may also indicate an increased risk of CV event(s) among patients with RA despite a seemingly normal IMT.

In our present study, the results regarding FMD were not as definitive as those regarding IMT, neither among the patients with RA, nor among the controls. There are several possible underlying causes to this. First, after the initiation of our study, it has been described that the measurements of FMD should be standardized in several recommended aspects to get reproducible results[14]. Further, other studies using several measurements of subclinical atherosclerosis in

patients with RA have been unable to show FMD results as distinct as the measurement of other variables[19,42]. Compared with IMT, FMD is influenced more by the immediate effects of the patient's disease, and it has even been speculated that a higher CRP level could have a direct protective effect on the endothelium[19]. Our present study, however, revealed no association between disease activity and FMD, whether protective or deleterious. Further, there was a lack of significant associations between disease activity and the progression rate, both for IMT and FMD. Most probably this was because of small numerical progressions. Two previous studies have shown several variables to be associated with the progression of IMT[7,26]. However, these studies did not include inception cohorts, and the individuals had a rheumatic disease of longer duration, and consequently a greater progression of atherosclerosis than the individuals in our study.

The main strength of our present study is its prospective design from disease onset. Data on traditional CVD risk factors, as well as variables related to the RA disease, were collected from the onset of disease and then continuously during 5 years of followup, making it possible to find models associated with the prospective values of IMT and FMD. In northern Sweden, practically all of the patients with newly diagnosed RA are included in a structured followup program. Of these patients, all those aged ≤ 60 years were invited to participate in our present study within 12 months of their diagnosis. Because inflammation is considered to be of relatively higher importance for the atherosclerotic progression in younger patients[2,26], this cohort is ideal for unmasking any difference prospectively. Another strength of our study was that the same person (EL) undertook all of the US measurements, thereby eliminating any interpersonal variation.

The main limitation is the number of controls, but unfortunately it was not possible to include more. The associations between the measurements of subclinical atherosclerosis and the traditional CVD risk factors were not as apparent within the control cohort as among the patients with RA; this is most probably due to the small number of individuals in the control group not providing sufficient power to detect such relationships. However, the associations between these measurements and traditional CVD risk factors are well studied in the general population and the results in our study were consistent with published results[9]. Further, in our study, no measured variables of inflammation among the controls were available, and therefore, some of the statistical analyses were not possible. However, our study was directed at the interplay between inflammation and other CVD risk factors among the patients with RA. Inflammation as a risk factor for atherosclerosis in the general population was not the object of our study and has been well studied by others[43].

This prospective study demonstrated an increased progression of subclinical atherosclerosis in patients with RA over the first 5 years following diagnosis. In patients with RA, several traditional CVD risk factors at the onset of RA disease were strongly associated with the measurements of atherosclerosis both at baseline and 5 years later. Additionally, the inflammatory load over time augmented the atherosclerotic load. A model including age, smoking, BP, blood lipids at baseline, and inflammatory load over time predicted the observed IMT after 5 years of followup to a very large extent. SCORE, a composite measurement of the load of traditional CVD risk factors, was one of the strongest variables associated with atherosclerosis at baseline as well as after 5 years. This indicates that, in patients with RA, traditional CVD risk factors should be screened for, and if indicated, intervention should be initiated at the time of diagnosis to prevent an accelerated progression of atherosclerosis. Further, the inflammatory load over time has to be diminished by aggressive and effective treatment of the RA disease; that will also diminish any accelerated atherosclerosis.

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