Effects of Low-dose Prednisolone on Endothelial Function, Atherosclerosis, and Traditional Risk Factors for Atherosclerosis in Patients with Rheumatoid Arthritis — A Randomized Study

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ABSTRACT. ***Objective.*** To determine the influence of low-dose prednisolone on atherosclerosis, endothelial function, and risk factors for atherosclerosis in patients with early rheumatoid arthritis (RA).

Methods. At start of the first disease modifying antirheumatic drug, 67 patients with early, active RA were randomized to either 7.5 mg prednisolone daily (n = 34) or no prednisolone (n = 33). In the prednisolone group, 21 were treated for 2 years and 13 continuously. After a mean of 5 years intima-media thickness (IMT) and calculated intima-media area (cIMa) of the carotid arteries were determined by B-mode ultrasound. Endothelial function was determined by flow-mediated dilatation (FMD) of the brachial artery.

Results. IMT [median (interquartile range) 0.675 mm (0.58–0.82) vs 0.673 mm (0.62–0.80)], cIMa [13.7 mm^2 (11.45–20.37) vs 14.1 mm^2 (12.34–17.38)], prevalence of atherosclerotic plaques (82.3% vs 81.9%), and endothelial function [FMD% (mean ± SD) 3.88% ± 2.8 vs 3.74% ± 2.9] did not differ between patients treated with and those not treated with prednisolone. There were no differences in lumen diameter of carotid arteries, or levels of lipoproteins, glucose, and blood pressure. Patients treated for at least 4 years (and currently treated) with prednisolone had a trend to higher systolic blood pressure (157 ± 29 mm Hg) compared with untreated patients (141 ± 28 mm Hg; p = 0.06) and had higher cholesterol levels (5.6 mmol/L ± 1.39 vs 4.9 ± 28; p = 0.03). In the whole cohort, age and HDL were independently associated with IMT; age, HDL, and blood pressure with cIMa; and age and serum creatinine with presence of atherosclerotic plaques.

Conclusion. Low-dose prednisolone did not influence endothelial function and atherosclerosis in patients with RA. However, total cholesterol was higher in patients treated with prednisolone. (First Release August 1 2007; J Rheumatol 2007;34:1810–6)

Key Indexing Terms:
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In recent years it has become clear that atherosclerosis, the main cause of cardiovascular disease (CVD), is an inflammatory disease, with activated immune-competent cells and production of proinflammatory cytokines in atherosclerotic lesions[1-4].

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The risk of CVD is very high in systemic lupus erythematosus (SLE) and is also elevated in rheumatoid arthritis (RA)[5-9]. In young women with RA, the risk of death in coronary artery disease is increased more than 3-fold[6]. However, although still elevated, the risk of CVD in RA appears to be lower than in SLE[10]. As in SLE, the underlying mechanisms causing this increased risk are not well characterized, but a combination of traditional and nontraditional risk factors including inflammation appear to be of importance[6-8,11-16]. As well, complications like extraarticular manifestations have been reported in RA-related CVD[15].

Several recent studies indicate an increased prevalence not only of CVD but also of atherosclerosis as determined by ultrasound of carotid arteries in patients with RA[11,12,14,17-20]. However, there are also negative findings, and thus the exact role of atherosclerosis in RA-related and SLE-related CVD remains to be elucidated[11]. Even though atherosclerosis is the main cause of CVD, it is mainly when atherosclerotic plaques rupture that they cause clinical events like myocardial infarc-

tion and stroke[21]. However, it is not known if atherosclerotic plaques in RA are more prone to rupture; if so, atherosclerosis could still be a major cause of CVD in RA, even though methods such as ultrasound do not detect large differences. Studies of endothelial function, in addition to determinations of atherosclerosis, are of importance because endothelial dysfunction may precede later development of atherosclerosis and CVD[22].

The role of glucocorticoid (GC) in treatment of RA has been discussed, and recently we reported that daily prednisolone added to the first disease modifying antirheumatic drug (DMARD) retards the progression of radiological damage after 2 years in patients with early RA, and also had a positive effect on remission rate and function[23]. To date, there are only a few studies of the effects of GC on CVD and atherosclerosis in RA, although the topic has been discussed for years. Thus, multivariate analyses show that use of prednisone is a risk factor for mortality in RA[24]. Further, in a retrospective study, GC treatment early in the disease increased the risk of CVD, possibly indicating an aggressive disease, whereas in patients with any CVD event during followup, GC treatment for at least one year seemed to delay the event[25]. Possibly the deleterious effects of GC on lipids, glucose metabolism, and blood pressure could be balanced by its control of inflammation. Further, in findings from a cross-sectional study, lifetime GC treatment was associated with carotid plaque and arterial incompressibility in patients with RA; however, treatment was given by indication[26]. To determine the issue of GC treatment and its risk for atherosclerosis the need for study of inception cohorts has been addressed, including patients with early RA[27].

In this prospective, randomized study, we report that low-dose prednisolone treatment in early RA was not related to atherosclerosis and did not influence endothelial function. The implications of these findings are discussed.

MATERIALS AND METHODS

Study group. Sixty-seven patients with RA were recruited from Karolinska University Hospital, Huddinge, as part of the 6-center BARFOT (Better Anti-Rheumatic FarmacO-Therapy) study, a Swedish multicenter study designed to investigate clinical and therapeutic aspects of early RA[28]. Details of the study protocol have been described[28]. With the BARFOT study as a basis, we recently investigated how low-dose prednisolone in addition to DMARD affects clinical variables and radiological signs of disease progression[23]. In the present study we investigated the effects of low-dose prednisolone on atherosclerosis measured by ultrasound, endothelial function, and traditional risk factors.

All patients in our study participated in the main BARFOT glucocorticoid study, which included 250 patients with early RA, who were randomized to evaluate treatment with 7.5 mg prednisolone in addition to their first DMARD therapy versus DMARD-only over a period of 2 years. Briefly, these patients had a diagnosis of RA according to American College of Rheumatology criteria[29], were between 18 and 80 years of age, had disease duration less than one year, and had active disease defined as a Disease Activity Score (DAS28) > 3.0. Exclusion criteria were earlier treatment with GC for RA or other diseases, previous treatment with DMARD, or contraindication for GC therapy. Of the total 250 patients, 81 were recruited from the Karolinska Huddinge Rheumatology Department and thus were eligible for the present study. Of these 81 patients, 14 did not take part, as 4 had died, 2 had moved, 3 were severely ill, and 5 did not want to participate. Of the 67 participating patients, 34 had been randomized to treatment with prednisolone 7.5 mg daily for the first 2 years of the disease, the prednisolone group. At the 2-year control, 13 among these were randomized according to the trial protocol to continue the prednisolone treatment for at least another 2 years, in fact the whole study period, and 21 to stop this treatment. Thirty-three of the 67 patients were randomized at baseline to nontreatment with prednisolone during the whole study period, the no-prednisolone group. DMARD was chosen by the treating physicians, in accord with the treatment strategy recommended in Sweden at the time of the study. Treatment with nonsteroidal antiinflammatory drugs (NSAID) was permitted and intraarticular steroid treatment was allowed. Four patients randomized to prednisolone treatment were taking antihypertensive drugs compared to 6 patients randomized to no-prednisolone. None had lipid-lowering therapy.

After a mean of 5.3 years (SD 0.6) cardiovascular variables were studied as described below, and blood was drawn after overnight fasting for analysis of risk and other factors. The investigation also included a written questionnaire, an interview and physical examination, and assessments of disease activity and function.

The study was approved by the Karolinska University Hospital Ethics Committee and was performed in accord with the Helsinki Declaration.

Assessment of carotid atherosclerosis. In all patients, the right and left carotid arteries were examined with a duplex scanner (Aspen, Acuson, Mountain View, CA, USA) using a 7 MHz linear array transducer. The patient was investigated in supine position with the head slightly turned away from the sonographer. The same trained sonographer performed all scans. The carotid arteries were carefully examined with regard to wall changes. The far wall of the common carotid artery (CCA) 0.5 to 1.0 cm proximal to the beginning of the carotid bulb was used for measurements of the intima-media thickness (IMT) and lumen diameter. IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. Lumen diameter was defined as the distance between the leading edge of the intima-lumen echo of the near wall and the leading edge of the lumen-intima echo of the far wall. The examinations were videotaped for subsequent analyses by a computer system[30] with automated tracing of echo interfaces and measurements of distances between the wall echoes within a 10 mm-long section of CCA in late diastole, defined by a simultaneous electrocardiographic recording. The mean values of IMT and lumen diameter within the 10-mm section were calculated. When a plaque was observed in the region of the CCA measurements, the IMT was not measured.

Carotid plaque was defined as a localized intima-media thickening > 1 mm and at least a 100% increase in thickness compared with adjacent wall segments. Plaque was screened for in the common, internal, and external carotid arteries. Plaque occurrence was scored as absence of plaque, presence of unilateral plaque, and presence of bilateral plaque. The differences between repeated measurements of IMT and lumen diameter, using the automated analyzing system, were 3.2% and 0.6% (coefficient of variation), respectively (with IMT of 0.48 to 1.04 mm and lumen diameter 4.34 to 7.91 mm). To compensate for the stretching effect of arterial distension (secondary to increased arterial pressure) on the wall thickness, the cross-sectional intima-media area was calculated using the formula 3.14 [(lumen diameter/2 + IMT)^2 – (lumen diameter/2)^2]. This calculated intima-media area (cIMa), but not the IMT, has been shown to be unaffected by variations in artery distension secondary to changes in blood pressure[31]. The ultrasonography methods have been described in detail[32,33].

Endothelial function. Ultrasound procedures for assessing endothelium-dependent flow-mediated dilatation (FMD) were performed in 59 patients by the same assessor (MR) as described in the international guidelines[34]. Patients were examined in the morning after an overnight fast and cessation of cigarette smoking. Patients were told not to use long-acting nitroglycerin or calcium channel-blocker drugs 36 hours before the examination. A high-resolution ultrasound scanner (System Five, GE Vingmed, Horten, Norway) with a 10.0 MHz linear array transducer was used. After a 10 minute equilibration

period at rest in recumbent position, a single dedicated ultrasonographer performed measurements of left brachial artery FMD. Scans of the brachial artery were taken proximal to the antecubital fossa and recorded on videotape. Baseline diameter recordings were obtained, then arterial occlusion was performed by inflating a forearm blood pressure cuff (12.5 cm wide) to 250 mm Hg for 4.5 min. After cuff release, diameter recordings were repeated during the postocclusive increase in brachial artery blood flow. The complete experimental sequence was performed twice with a 30 minute interval. Images were acquired digitally from the videotape and measured in random order by a single observer blinded to the ultrasonography conditions. Measurement of the brachial artery diameter was defined as the distance from the leading edge of the near wall intima-lumen echo to the leading edge of the far wall lumen-intima echo along a line perpendicular to the artery's long axis. A computer system with automated tracing of echo interfaces was used to measure distances between the wall echoes within a 5 mm-long section of the brachial artery. Brachial artery diameter was calculated in diastolic frames taken coincidentally with the R-wave on the electrocardiogram, twice at rest and then 45, 60, and 75 seconds after cuff deflation. A mean of the diameters after 45, 60, and 75 seconds was calculated. Diameter changes were expressed as percentage change relative to the mean baseline value. The mean of 2 FMD examinations was used. The difference between repeated measurements of FMD, using the automated analyzing system, was 5.5% (coefficient of variation).

Disease assessments. Disease activity was measured by the Disease Activity Score composite index (DAS28), calculated on 28 joints[35], which includes number of swollen joints, number of tender joints, patient's assessment of global disease activity, and erythrocyte sedimentation rate (ESR). Functional disability was assessed using the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[36]. The HAQ score ranges from 0 to 3, a higher score indicating a higher degree of disability.

Blood pressure was measured in both arms after 10 minutes of rest by a specially trained nurse (MW). Hypertension was defined as blood pressure > 140/90 or treatment with antihypertensive drugs.

The questionnaire and interview, for which the research nurse was responsible, included information about smoking history, previous and present cardiovascular morbidity, and presence of diabetes mellitus.

Laboratory tests. Blood samples were taken between 8:00 and 9:30 AM, after 8 to 12 hours of fasting. Levels of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured enzymatically (Modular Analytics P, Roche Diagnostics). Serum low-density lipoprotein (LDL) cholesterol was calculated using the Friedewalds equation (LDH = total cholesterol – HDL cholesterol – 0.45 × triglyceride). Lipoprotein(a) [Lp(a)] levels were determined by a turbidimetric method (Modular Analytics P, Roche Diagnostics). Plasma homocysteine was determined by fluorescence-polarization immunoassay (Abbot).

Fibrinogen, homocysteine, ESR, and high-sensitivity C-reactive protein (CRP) levels were determined by routine techniques at the Department of Clinical Chemistry, Karolinska University Hospital.

Statistics. Statistical data were computed using StatView software (SAS Institute AB, Göteborg, Sweden). Skewed continuous variables were logarithmically transformed to attain normal distribution. Study groups were compared using ANOVA for continuous variables and chi-square for categorical variables. Fisher's PLSD was used as post-hoc test. Correlation analysis was performed using simple and multiple regression for normally distributed variables, and Spearman correlation analysis for non-normally distributed variables. The significance level was put at $p < 0.05$.

RESULTS

Baseline characteristics of the study group are given in Table 1. There were no significant differences between treatment groups at enrolment into the BARFOT program. Of note, disease activity determined as DAS28 and HAQ score did not differ between groups. These baseline characteristics for 67 patients did not differ from the rest of the patients in the main study (data not shown). There were no significant differences in smoking habits or incidence of previous ischemic cardiovascular diseases between the 2 groups.

All 13 patients randomized to continue prednisolone at Year 2 were taking that drug at completion of the study. Of those randomized to stop prednisolone treatment after 2 years, one started that treatment at Year 3. No patient in the no-prednisolone group started with prednisolone during the study. In both treatment groups, no patient received more than 5 intraarticular steroid injections per year.

Following the study protocol, DMARD were given to all patients at baseline; most patients were prescribed methotrexate including folic acid supplementation followed by sulfasalazine, with no difference between the study groups. At 1, 2, and 4 years as well as at the time for the present atherosclerosis assessments, treatment with DMARD was comparable between groups (Table 2). Those treated with prednisolone were more often not treated with NSAID (12 vs 20; $p = 0.05$). A few patients in each group started antihypertensive drugs during the study, but none started lipid-lowering drugs.

As described in Table 3, there were no significant differences between the prednisolone group and the no-prednisolone group in IMT, lumen diameter, cIMa, prevalence of plaques, and endothelial function. Nor were there any differences in those variables between patients treated with prednisolone for the whole study period and those not treated at all (Table 3). Similarly, there was no difference in levels of biomarkers including lipoproteins, CRP, ESR, creatinine, and glucose or in blood pressure between the 2 treatment groups (Table 4).

However, patients treated for at least 4 years (and currently treated) with prednisolone had a trend to higher systolic blood pressure (157 ± 29 mm Hg) as compared with those never treated with prednisolone (141 ± 28 mm Hg; $p = 0.060$). Further, in this subgroup of patients treated with prednisolone the whole time, the systolic but not the diastolic blood pressure increased from disease onset to the time of our investigation, from 136/79 to 155/85 mm Hg ($p = 0.011$). Also, the patients treated constantly with prednisolone had significantly higher total cholesterol levels (5.6 mmol/L ± 1.39) compared to nontreated patients (4.9 mmol/L ± 1.28; $p = 0.03$). Other factors did not differ between these subgroups.

In a simple regression model, mean IMT was significantly associated with systolic blood pressure ($R = 0.59$, $p < 0.001$), HDL ($R = –0.34$, $p = 0.008$), triglycerides ($R = 0.37$, $p = 0.005$), creatinine ($R = 0.39$, $p < 0.02$), age ($R = 0.65$, $p < 0.001$), and cigarette pack-years ($R = 0.40$, $p < 0.004$). In contrast, LDL, glucose, homocysteine, ESR, CRP, DAS28, fibrinogen, Lp(a), and body mass index (BMI) were found not to be significantly associated with IMT.

However, in a stepwise multiple regression model, only age and HDL remained significant in the model if the whole group was analyzed ($F = 46.2$ and 19.9, respectively; $p <$

Table 1. Baseline characteristics of the study group at enrolment in the BARFOT program, separated into those randomized to prednisolone or no prednisolone from onset of disease. Results are presented as means (SD) or percentage.

	Prednisolone, N = 34	No Prednisolone, N = 33	p
Age, yrs	55 (25)	55 (10)	NS
Sex, % male	38.2	33.3	NS
Patients with nodules, n	1	4	NS
HAQ score	1.1 (0.58)	1.2 (0.56)	NS
DAS28	5.4 (1.0)	5.3 (1.1)	NS
CRP	38.6 (36.9)	43.4 (45.1)	NS
ESR, mm	45.1 (25.2)	45.6 (28.9)	NS
Blood pressure, mm	136 (20)/79 (10)	142 (21)/82 (9)	NS
Smoking status, n			
Nonsmoker	14	8	NS
Current smoker	12	15	NS
Ex-smoker	8	10	NS
Diabetes mellitus, n	2	2	NS
Ischemic cardiovascular disease, n	5	4	NS

NS: not significant.

Table 2. Number of patients treated with DMARD, biologics, and NSAID in the 2 groups at the time of atherosclerosis assessment for this study.

	Prednisolone, N = 34	No Prednisolone, N = 33	p
DMARD			
Methotrexate	14	11	NS
Sulfasalazine	2	4	NS
Others	5	6	NS
MTX combinations	5	7	NS
Other combinations	1	1	NS
No DMARD	7	3	NS
TNF inhibitors	0	1	NS
NSAID	12	20	0.05

NS: no significance.

0.05).

In a simple regression model, mean cIMa was significantly associated with systolic blood pressure ($R = 0.60$, $p < 0.001$), HDL ($R = -0.36$, $p = 0.004$), triglycerides ($R = 0.39$, $p = 0.0012$), age ($R = 0.59$, $p < 0.001$), and BMI ($R = 0.26$, $p < 0.0034$). In contrast, LDL, glucose, homocysteine, ESR, CRP, DAS28, fibrinogen, Lp(a), and cigarette pack-years were not significantly associated with cIMa.

In a stepwise multiple regression model, age, systolic blood pressure, and HDL remained significant in the model ($F = 8.5$, 10.6, and 13.2, respectively; $p < 0.05$).

In the whole study group, only age and creatinine were associated with presence of atherosclerotic plaques in a univariate analysis, but only age remained significant in a logistic regression model (chi-square 5.1, $p = 0.02$). FMD% was not associated with any of the variables tested.

During the whole observation period only one patient, in the prednisolone group, had a CVD event, namely, a coronary revascularization procedure.

DISCUSSION

We report that low-dose prednisolone treatment did not influence atherosclerosis, determined as IMT, cIMa, lumen diameter, and presence of atherosclerotic plaques in carotid arteries, or endothelial function. The role of prednisolone in development of atherosclerosis in patients with autoimmune disorders has been much discussed, as prednisolone (or other types of GC) is — in addition to other side effects — atherogenic, due to its well-known effects on metabolic factors, for example, by reducing insulin sensitivity in RA[37] and by triggering diabetes[5].

The beneficial short-term effect of GC in the treatment of RA has been known for a long time, but it is only recently that low doses of prednisolone for 2 years have been found to have a positive effect on outcome in RA[23]. It is therefore even more important to determine the effects of prednisolone on atherosclerosis in order to prevent negative side effects. Since atherosclerosis is an inflammatory disease and the main cause of CVD, it could be hypothesized that prednisolone may ameliorate disease development by inhibiting inflammation in the artery wall. This possibility is supported by experimental studies in atherosclerosis-prone rabbit models, where cortisone acetate decreased the progression of atherosclerosis by 60%, but also raised cholesterol levels[38]. Dexamethasone had a similar effect in another rabbit model, by decreasing atherosclerosis in parallel with induction of hyperlipidemia[39]. On the other hand, when high-dose GC were used in another rabbit model, atherogenesis was increased in the treatment group[40].

It is plausible to assume that the different effects of GC for risk factors such as hyperlipidemia, diabetes, and hypertension on the one hand and the antiinflammatory effects on the other have opposite effects on atherogenesis, and the final outcome may depend on which of these effects dominates. The

Table 3. Atherosclerosis measurements of the prednisolone (Pred) and no-prednisolone patients, a mean of 5 years after enrolment into the study.

	All Patients, N = 34*	Prednisolone Patients Treated 2 yrs, N = 21	Patients Treated Whole Study Period, N = 13	No Prednisolone, All Patients, N = 33*	p, All Pred vs No-pred	p, Pred Whole Period vs no-pred
IMT left, mm	0.690 (0.54–0.91)	0.640 (0.54–0.95)	0.710 (0.59–0.91)	0.696 (0.61–0.87)	NS	NS
IMT right, mm	0.636 (0.57–0.74)	0.650 (0.57–0.80)	0.600 (0.57–0.72)	0.653 (0.58–0.80)	NS	NS
IMT mean, mm	0.675 (0.58–0.82)	0.660 (0.56–0.86)	0.681 (0.58–0.80)	0.673 (0.62–0.80)	NS	NS
Carotid artery lumen, left diameter, mm	6.16 (5.60–6.64)	6.17 (5.70–6.80)	6.12 (5.60–6.60)	6.00 (5.84–6.59)	NS	NS
Carotid artery lumen, right diameter, mm	6.01 (5.57–6.68)	6.06 (5.49–6.57)	6.00 (5.57–6.86)	5.89 (5.49–6.48)	NS	NS
Carotid artery lumen, mean diameter, mm	6.14 (5.57–6.63)	6.20 (5.58–6.53)	6.06 (5.68–6.76)	5.89 (5.55–6.55)	NS	NS
cIMa left, mm^2	14.0 (11.61–23.16)	13.2 (11.14–23.50)	15.3 (11.61–21.86)	14.4 (12.25–17.25)	NS	NS
cIMa right, mm^2	13.6 (11.05–18.43)	14.3 (10.94–20.37)	12.2 (11.40–17.31)	13.3 (11.86–17.24)	NS	NS
cIMa mean, mm^2	13.7 (11.45–20.37)	13.7 (11.48–21.56)	14.9 (11.45–18.43)	14.1 (12.34–17.38)	NS	NS
Plaque prevalence, %	82.3	85.1	71.4	81.9	NS	NS
Brachial artery diameter, mm	3.68 ± 1.2	3.50 ± 1.2	3.96 ± 1.5	3.53 ± 0.93	NS	NS
FMD %	3.88 ± 2.8	4.17 ± 3.2	3.44 ± 2.08	3.74 ± 2.9	NS	NS

Data are mean ± SD for normally distributed variables, median (interquartile range) for nonparametric variables. * Brachial artery diameter and FMD% were only measured in 33 patients in the prednisolone group and 26 patients in the no-prednisolone group. IMT: intima-media thickness, cIMa: calculated intima-media area, FMD: flow-mediated dilatation of brachial artery.

Table 4. Atherosclerosis risk factors and disease activity in the 2 treatment groups at time of atherosclerosis measurements.

	Prednisolone, N = 34	No Prednisolone, N = 33	p
BMI	25.7 ± 4.2	25.6 ± 4.8	NS
Total cholesterol	5.2 ± 1.2	4.9 ± 0.9	NS
HDL	1.6 ± 0.57	1.6 ± 0.42	NS
LDL	3.1 ± 1.0	2.8 ± 0.7	NS
Triglycerides	1.1 (0.67)	1.0 (0.50)	NS
Lp(a)	281 (598)	184.5 (323)	NS
Homocysteine	12.9 ± 4.9	12.7 ± 3.7	NS
Fibrinogen	3.4 ± 0.75	3.7 ± 1.0	NS
Creatinine	71 (21.7)	69 (27.2)	NS
Glucose	4.9 (0.7)	5.05 (1.0)	NS
Blood pressure			
Systolic	143.8 ± 25.3	140.8 ± 27.8	NS
Diastolic	80.0 ± 6.9	80.0 ± 14.0	NS
HAQ score	0.45 ± 0.49	0.81 ± 0.62	0.012
ESR, mm	15.0 (18)	16.0 (23.2)	NS
CRP, mg/L	4.0 (10.3)	4.7 (18.6)	NS
DAS28	3.0 ± 1.3	3.3 ± 1.5	NS

Data are mean ± SD for normally distributed variables, median (interquartile range) for nonparametric variables. BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, Lp(a): lipoprotein(a).

dose of prednisolone may therefore be a crucial factor that determines the outcome of treatment in atherosclerosis and CVD.

We recently reported a weak but significant association between total prednisolone dose and CVD in patients with SLE in a nested case-control study to investigate risk factors and underlying mechanisms of the very high risk of CVD in SLE[41]. However, prednisolone is given to patients with active disease and signs of systemic inflammation, and an association between prednisolone dose and CVD may also reflect the role of inflammation for development of CVD. Doses in patients with active SLE are typically higher than those used in our study. Furthermore, the SLE study was not prospective[41].

To our knowledge the role of prednisolone in atherosclerosis and CVD in rheumatic diseases has not been studied in randomized prospective studies before. The evidence from other diseases is also very scarce. However, one study indicates that low-dose inhaled steroids in patients with asthma is associated with a decreased risk of myocardial infarction[42]. In Cushing's disease, where cortisone levels are high, the risk of CVD is elevated, and this increased risk also persists when the underlying disease is cured[43]. Available evidence is therefore compatible with the possibility that the effects of GC on atherosclerosis and CVD may depend on dose, and that lower doses as in our study are at least not atherogenic.

It is still possible that the treatment with prednisolone for 2 or at least 4 years was not enough to elicit increased atherosclerosis that would have developed at a later stage. This possibility is not supported by our findings, as flow-mediated dilatation of the brachial artery, an early sign of endothelial dysfunction, was not different between those who received prednisolone and those who did not. Endothelial dysfunction precedes development of atherosclerosis and has been reported by several investigators to be a sign of early changes that may later lead to increased atherosclerosis and CVD[22]. Endothelial dysfunction is an early measurement of arterial changes, and is more prevalent in patients with RA compared

to controls[44]. Our data indicate that low-dose prednisolone does not promote a further increase in endothelial dysfunction.

Mechanisms other than the metabolic and antiinflammatory properties of GC may influence atherosclerosis and risk for CVD, since GC has proapoptotic, antiproliferative, and antifibrotic effects. These could theoretically inhibit plaque growth, but on the other hand could also destabilize plaque, leading to plaque rupture and ensuing myocardial infarction or stroke. Further, functional resistance to GC may contribute to excessive wound repair in atherosclerosis and restenosis[45].

We observed that current low-dose prednisolone, in the subgroup that was treated for at least 4 years, was associated with higher systolic blood pressure, a reported risk factor for atherosclerosis in patients with RA[46]. This finding indicates that close monitoring of blood pressure is important during low-dose prednisolone treatment. This potentially atherogenic effect of prednisolone could be counterbalanced by treatment with antihypertensive drugs. Prednisolone was also associated with higher total cholesterol levels in the smaller group treated for at least 4 years. This may indicate that monitoring of lipids is important during low-dose prednisolone treatment.

The exact role of atherosclerosis as determined by IMT and cIMa in RA-related CVD is not clear. Most studies report greater IMT or at least increased prevalence of atherosclerotic plaques in RA patients compared to controls; but negative findings have also been reported[11,12,14,17-20]. It may be that even ultrasound does not always allow discrimination between lesions in RA patients and controls — there may still be important differences in the local inflammatory process leading to plaque rupture[47].

Our findings indicate that low-dose prednisolone does not appear to have an adverse effect on atherosclerosis and endothelial function, at low concentrations (7.5 mg). However, prednisolone still may have an adverse effect on systolic blood pressure and cholesterol level in the group treated for at least 4 years. Larger, prospective studies are needed to investigate whether low-dose prednisolone influences clinical events like myocardial infarction and stroke.

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