Accelerated Atherosclerosis in Autoimmune Rheumatic Diseases

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Atherosclerosis is a multifactorial process that commences in childhood but manifests clinically later in life. Atherosclerosis is increasingly considered an immune system–mediated process of the vascular system. The presence of macrophages and activated lymphocytes within atherosclerotic plaques supports the concept of atherosclerosis as an immune system–mediated inflammatory disorder.1,2 Inflammation can aggravate atherosclerosis via different mechanisms secondary to autoimmunity, infectious diseases, and other proatherogenic changes that occur during the inflammatory state.

Autoimmune rheumatic diseases (AIRDs) are associated with higher rates of cardiovascular morbidity and mortality, primarily secondary to accelerated atherosclerosis. This phenomenon can be attributed to traditional risk factors for atherosclerosis and use of specific drugs, such as corticosteroids, but also might be the result of other autoimmune and inflammatory mechanisms that are aggravated in AIRDs. Several AIRDs exhibit increased overt cardiovascular disease (CVD) prevalence as well as findings of advanced subclinical atherosclerosis, which may precede the appearance of a clinical disease and thus be a target of early identification and preventive therapy.

Cells of the immune system can be found within atherosclerotic plaques, which suggests that they have a role in the atherogenic process. Their migration and activation within the plaques can be secondary to various stimuli, including infectious agents.3 These cells probably aggravate atherosclerosis, because CD4+ and CD8+ T-cell depletion reduced fatty streak formation in C57BL/6 mice. In addition, after crossing of apolipoprotein E (ApoE)-knockout mice with immunodeficient mice, they increased lesion area in the latter by 164%.4 It is therefore not surprising that as in autoimmune diseases, the cellular components within atherosclerotic plaques secrete various cytokines, including many interleukins as well as tumor necrosis factor-α and platelet-derived growth factor.

A cellular immune response specifically directed against heat-shock proteins (HSPs), oxidized low-density lipoprotein (oxLDL), and β₂-glycoprotein-I (β2GPI) has been reported, suggesting a direct involvement of these molecules in atherosclerosis.1 β2GPI can be found in human atherosclerotic lesions obtained from carotid endarterectomies, it abundantly expressed within the subendothelial regions and the intimal-medial border of human atherosclerotic plaques, and it colocalizes with CD4+ lymphocytes.5 On transfer of lymphocytes obtained from β2GPI-immunized LDL-receptor–deficient mice into syngeneic mice, the recipients exhibited larger fatty streaks compared with mice that received lymphocytes from control mice. However, T-cell depletion of lymphocytes failed to induce this effect.6 Therefore, T cells specific for β2GPI are capable of increasing atherosclerosis, suggesting that β2GPI is a target autoantigen in atherosclerosis. There are probably many more such specific cell lines reacting with specific antigens that can modulate atherosclerosis by either aggravating or decreasing its extent (proatherogenic or antiatherogenic).

Several autoantibodies are associated with atherosclerosis and its manifestations in humans. Animals provide good models for studying the effect of these autoantibodies on atherosclerosis. Active immunization of LDL-receptor–deficient mice with anti-cardiolipin (aCL) antibodies resulted in development of high titers of mouse aCL and increased atherosclerosis compared with control subjects.7 Immunization of mice with β2GPI resulted in pronounced cellular and humoral responses to β2GPI, with high titers of anti-β2GPI

Received October 16, 2004; revision received June 4, 2005; accepted June 7, 2005.

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(Circulation. 2005;112:3337-3347.)

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/CIRCULATIONAHA.104.507996

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Accelerated Atherosclerosis in Rheumatoid Arthritis

Patients with rheumatoid arthritis (RA) have a reduced life expectancy, with standardized mortality ratios ranging from 0.87 to 3.0.11,12 CVDs represent the main cause of death in both clinical and community-based cohorts of RA populations.11,12 In addition, there is evidence that mechanisms determining enhanced CVD mortality in RA are present very early during the natural history of the disease. Several types of cardiac involvement can occur in RA. However, ischemic heart disease secondary to atherosclerosis seems to represent the main cause of CVD deaths in RA populations.11,13 Cigarette smoking is a risk factor for development of RA and has a dose-dependent relationship with both disease severity and rheumatoid factor production.14 However, different studies failed to identify smoking as a predictor of CVD mortality in seropositive RA and inflammatory polyarthritis.15 RA treatment and lifestyle of RA patients may favor physical inactivity, hypertension, diabetes mellitus, and obesity, but there is no clear evidence that these factors are implicated in accelerated atherosclerosis in RA.15,11 Methotrexate, widely used to treat RA, increases plasma levels of homocysteine, which is a novel, and potentially modifiable, risk factor for CVD in the general population.16 Comorbidities such as obesity, hypertension, diabetes mellitus, and smoking increase the risk of developing CVD in RA.17–19 Numerous factors contribute to increased CVD risk in RA.20–22

Although this may support a role for rheumatoid vasculitis in promoting atherosclerosis, there are several lines of evidence suggesting that a dysfunction, rather than a full-blown “vasculitic phenotype,” is the leading event to early endothelial damage in RA. Functional abnormalities of the endothelium have been found in distinct cohorts of RA patients, independently of patients’ age, duration of the disease, degree of disease activity, or seropositivity.20,21 Despite the fact that different factors could alter endothelium homeostasis, prevalent data support the view that abnormal endothelial function in RA is essentially linked to inflammation. In a recent evaluation of young RA patients with low disease activity, endothelial dysfunction, assessed by brachial flow-mediated vasodilatation, was predicted independently by LDL cholesterol and by the mean levels of C-reactive protein (CRP), as evaluated at different time points (Figure 1). Persistent endothelial dysfunction predisposes to organic damage of the vascular wall that, in a preclinical stage, before overt disease, can be detectable by ultrasound measurement of carotid intimal-medial thickness (IMT). Many investigations provided evidence of increased carotid IMT in RA.20–22 This finding could not be explained by corticosteroid treatment but appeared to be essentially associated with markers of systemic inflammation and disease duration, thereby emphasizing the importance of RA as a risk factor for atherosclerosis.

Among the immunological factors shared by the pathogenic processes of atherosclerosis and RA, a particular subset of CD4+ T cells that lacks surface CD28 molecule (CD4+CD28−) has given rise to a great concern in recent years. These cells are expanded, probably stimulated by endothelial autoantigens,22 in the peripheral blood of unstable angina pectoris patients and a subgroup of RA patients. Furthermore, they infiltrate the atherosclerotic plaques and display a high proinflammatory and tissue-damaging potential that promotes vascular injury.23 The role of these cells in contributing to early development of atherosclerosis in RA has been confirmed in a recent study showing that RA patients with CD4+CD28− cell expansion have a higher degree of endothelial dysfunction and a higher carotid IMT than patients without expansion of these cells.21
diabetes mellitus as well.25,26 Clinical evidence that it is accelerated in these patients in the general population, but there is also epidemiological and atherosclerosis was observed in more than 50% of deceased patients in postmortem studies, a significant extent of atherosclerosis confirmed in more recent studies as well. Moreover, in SLE patients with a prevalence ranging from 6% to 10%, and the risk of developing this manifestation is 4 to 8 times higher than normal.25,26 Moreover, acute myocardial infarction was the cause of death in 3% to 25% of SLE patients.25,26 The traditional risk factors that were the most common predictors of clinical events were older age at disease diagnosis, hypercholesterolemia, and hypertension. However, atherosclerosis cannot be explained by Framingham risk factors alone, and it has been attributed to complex interactions between traditional risk factors and factors associated with the disease per se or its treatment. Among the nontraditional risk factors, cumulative dosage and/or longer duration of corticosteroid therapy and longer duration of disease seem to be the major predictors of atherosclerosis in SLE studies.25,26 Some novel risk factors that could contribute to atherosclerosis development have been reported recently. These include inflammatory markers: CRP, fibrinogen, interleukin-6, CD40/CD40L, adhesion molecules; immunological factors: aCL, anti-β2GPI, anti-oxLDL, and anti-HSP antibodies; abnormal coagulation factors: Fibrinogen, plasminogen activator inhibitor-1, and homocysteine; and lipoprotein and modified lipids: Lipoprotein(a) and HDL.

Diagnostic investigations can reveal a higher prevalence of cardiovascular lesions, because they allow the detection of subclinical atherosclerosis. Abnormalities of the coronary circulation have been reported in 40% of SLE patients by use of single photon emission computed tomography (SPECT) and dual isotope myocardial perfusion imaging (DIMPI)23 and an even higher percentage (27 of 33 patients) by use of 99mTc-SPECT.33 Coronary artery calcifications were detected by electron beam CT in 31% of SLE patients, and the extent of calcification was particularly high in SLE patients compared with control subjects.34 The most commonly used method for the detection of subclinical atherosclerosis is carotid B-mode ultrasound. By use of ultrasound, carotid plaques were found with a frequency ranging between 17% and 65% of SLE patients.35–39 Although carotid ultrasound directly investigates only the carotid artery, this technique provides an accurate measurement of subclinical atherosclerosis (Figure 2).

The evaluation of risk factors for clinical atherosclerosis is difficult in SLE because there is a low number of observed cardiovascular events because of low prevalence of the disease. The study of subclinical atherosclerosis has the advantage of providing a higher number of lesions leading to a more suitable evaluation of risk factors. The following studies, summarized in Table 1, evaluated the extent and clinical associations of subclinical atherosclerosis in SLE. Using the B-mode ultrasound, Manzi et al35 observed focal atherosclerotic plaques in 40% of 175 SLE women. They found an inverse relationship between disease activity measured by SLAM score and the plaque. Svenungsson et al36 performed ultrasound measurements of common carotid artery in 26 SLE patients with previous CVDs (SLE cases), 26 SLE patients without previous CVD (SLE control subjects) and 26 population control subjects. They found plaques in 65% of SLE cases, 38% of SLE control subjects, and 11% of patients, the mean number of modifiable traditional risk factors for atherosclerosis (ie, hypercholesterolemia, arterial hypertension, diabetes mellitus, obesity, smoking, and sedentary lifestyle) is higher than that expected in an age-, sex-, and race-matched normal population.30 In the major clinical studies on atherosclerosis, performed in Toronto,31 Baltimore,25 and Pittsburgh,26 the traditional risk factors that were the most common predictors of clinical events were older age at disease diagnosis, hypercholesterolemia, and hypertension. Moreover, atherosclerosis was described in SLE patients with a prevalence ranging from 6% to 10%, and the risk of developing this manifestation is 4 to 8 times higher than normal.25,26 Although atherosclerosis develops early in the course of the disease, younger age at diagnosis seems to be the major determinant of atherosclerosis in SLE.25,26 Moreover, in SLE

Figure 1. Brachial flow–mediated vasodilatation (FMV) assessed on the brachial artery by ultrasonography in a normal control subject (A) and in a patient with RA (B). FMV, expressed as the relative increase in brachial artery diameter during hyperemia and defined as 100×(posthyperemia diameter−basal diameter)/basal diameter], was 12% in the normal subject and 3% in the RA patient.
the control subjects. Factors found more often in SLE cases compared with SLE control subjects (factors associated with overt CVD) were osteoporosis, lupus anticoagulant, higher steroid cumulative dosage, high levels of triglycerides, α1-antitrypsin, oxLDL, anti-oxLDL, lipoprotein(a), homocysteine, and low levels of HDL cholesterol. These authors found no relationship between plaque and disease variables, including renal involvement.

Roman et al37 performed a case-control study using carotid ultrasound in 197 SLE patients and 197 control subjects. They found plaques in 37% of SLE patients and in only 15% of the control subjects. In the multivariate analysis of risk factors, 2 variables were associated with plaque: Age and the diagnosis of SLE. Older age at diagnosis, longer duration of disease, higher damage-index score, absence of the use of cyclophosphamide and hydroxychloroquine, and absence of anti-Sm antibody were associated with plaque in SLE patients. The authors suggested that patients with less severe disease leading to a lower use of corticosteroid or immunosuppressants have a higher likelihood of plaque. However, in that study, patients with less severe disease were older than those with more severe disease. Therefore, the higher prevalence of plaque in this group could be related not to milder disease but rather to age itself, a factor not considered by the authors in the multiple regression analysis for disease-related factors. Selzer et al39 performed a study in 214 female SLE patients without clinical CVD using B-mode carotid ultrasound for assessing mean IMT and plaque and Doppler flow probes for measuring aortic PWV. Plaques were found in 32% of patients. Using logistic regression analysis, determinants of plaques included older age, higher systolic blood pressure, lower level of HDL-3, and use of antidepressants.

Doria et al38 performed a study to prospectively evaluate the role of traditional and nontraditional factors associated with subclinical atherosclerosis in SLE. The authors studied 78 SLE patients without overt CVD (mean age, 31 years; mean follow-up, 60±9 months). SLE clinical and laboratory parameters, disease activity (ECLAM score) and damage, treatment, and traditional risk factors for atherosclerosis were evaluated. At the baseline (T0) and after a 5-year follow-up (T1), the serum levels of anti–oxidized palmitoyl arachidonoxyll phosphocholine (oxPAPC), anti-HSP65, and anti-β2GPI antibodies, and CRP were tested. OxPAPC is an important antigenic epitope of oxidize LDL. A thickened intima (IMT >0.9 mm) was found in 22 patients (28.2%) and plaque (IMT >1.3 mm) in 13 of them (16.6%). Maximum IMT and mean IMT were (mean±SD) 0.71±0.10 mm, respectively. The prevalence of carotid plaques observed in patients was lower than that found in other carotid ultrasound

<table>
<thead>
<tr>
<th>TABLE 1. Carotid Ultrasound Studies in SLE</th>
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<td>Svenungsson et al36</td>
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<td>No. of Patients</td>
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<td>Plaque, %</td>
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<td>Mean IMT, mm</td>
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<td>Healthy control subjects*</td>
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<td>Risk factor evaluation</td>
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*In the 2 studies including healthy control subjects, the control group had significantly decreased IMT and plaque prevalence compared with the SLE study group.
studies. In multivariate analysis, age and cumulative prednisone intake were associated with carotid abnormalities; age, hypertension, and anti-oxPAPC at T1 were correlated with higher maximum IMT and mean IMT. The conclusion of the study was that an interaction between traditional risk factors, particularly age, and nontraditional risk factors, the most important of which was cumulative prednisone intake, seemed to be relevant for atherosclerosis in SLE patients. Age, as a predictor of atherosclerosis, seemed to be even more important in SLE than in the general population, probably because disease activity/severity as well as its treatment had particularly deleterious effects in older patients.

Accelerated Atherosclerosis in Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is a prothrombotic state characterized by recurrent arterial and venous thrombosis, recurrent pregnancy loss, and the presence of circulating antiphospholipid antibodies (aPL). Thrombophilia may be associated with premature atherosclerosis, and accelerated atherosclerosis was suggested as an additional clinical feature of APS. This pathological process may be mediated by the direct proinflammatory and procoagulant activity that aPLs exert on endothelial cells or indirectly, via the inflammatory/immune mechanisms that have been implicated in autoantibody-mediated thrombosis. In 1993, Vaarala et al provided the first evidence that some IgG monoclonal antibodies may be involved in atherosclerosis. This study also suggested that some aPLs were capable of cross-reacting with oxLDL in SLE. Hypercholesterolemia, diabetes mellitus, smoking, obesity, arterial hypertension, and sedentary lifestyle in APS appear to be similar to those in the general population. Therefore, the pathogenesis of accelerated atherosclerosis in APS may be a result of an interaction between traditional and nontraditional risk factors.

Premature atherosclerosis of the lower limbs as the first symptom of the APS has been reported previously. Three patients were described with severe systemic atherosclerosis, including aortic occlusion, associated with high levels of aCL and hyperhomocysteinemia and other risk factors without other features of SLE or primary APS. A prospective study of 116 consecutive new patients with intermittent claudication has been performed to determine the prevalence of prothrombotic factors in that setting. Some kind of thrombophilia was demonstrated in almost one quarter of patients; these autoantibodies were significantly higher in APS patients with arterial thrombosis than in patients with venous thrombosis and pregnancy morbidity. These results suggest that autoantibodies against β2GPI/oxLDL complexes are pathogenetically important in arterial atherosclerosis.

A humoral response to the atherosclerotic plaque components β2GPI and HSP might also be involved in the pathogenesis of stroke. A case-control study in 93 patients with acute ischemic stroke and 93 control subjects showed that elevated IgA anti-β2GPI and IgG anti-HSP 60/65 antibodies are independently associated with increased risk for ischemic stroke. This humoral response might link autoimmune thrombophilia and atherosclerosis in stroke patients. However, although some studies have shown that the occurrence of high aPL titers can be considered independent risk factors for myocardial infarction and stroke, some others failed to demonstrate such an association. Romero et al reported on the existence of autoantibodies against malondialdehyde-modified lipoprotein(a) (a molecule that exhibits behavioral similarities to malondialdehyde-modified LDL) in 104 patients with APS (61 with primary APS and 43 with secondary APS). The high prevalence of these antibodies in APS patients supports the presence of oxidative processes in the pathogenesis of APS and their potential role in atherosclerosis. aPLs seem to play an important role in atherosclerosis development by inducing nitric oxide and superoxide production. Furthermore, direct interference of these antibodies with the activity of paraoxonase, an HDL-related antioxidant enzyme, would contribute to the accelerated process of atherogenesis in APS. In contrast, recent studies suggest that passive administration of some IgG monoclonal antibody against phospholipid and LDL antigens may protect against atherosclerosis in atherosclerosis-prone LDLR−/− mice. This apparent clash was suggested to be the result of the presence of different types of autoantibodies, namely “protective” and “pathogenic,” which are all measured together.

B-mode ultrasound can help measure arterial IMT and degree of atherosclerotic plaque in the carotid and femoral arteries. IMT is regarded as a sensitive marker for the earliest stages of atherosclerosis. Unfortunately, such studies in humans having APS are scarce (Table 2). Ames et al analyzed the relationship between aPL and IMT in 42 subjects with aPL (29 with primary APS). In a stepwise multiple regression analysis, IgG aCL titer independently predicted the extent of IMT at all carotid segments examined.
These data strongly support an atherogenic role for IgG aCL. In another study, atherosclerosis in premenopausal women with APS and SLE was investigated by ultrasound and evaluated as carotid and femoral artery IMT and as the presence of plaques. Premenopausal women with APS and SLE had an increased prevalence of carotid and femoral plaque that was not accounted for by other predictors of atherosclerosis, including age, lipid parameters, and cumulative steroid dose. However, in this study, the aPLs tested were not associated with atherosclerosis, and there were no significant differences between the IMT values of patients and control subjects.

The role of aPL and/or APS as independent risk factors for atherosclerosis is unclear, in part because the majority of studies include patients with secondary APS. Medina et al investigated the prevalence and clinical significance of carotid artery IMT in 28 patients with primary APS and 28 healthy subjects matched by age and sex. The results of this study demonstrated a significantly increased IMT with lumen diameter decrease in patients with primary APS compared with normal control subjects. In addition, patients with primary APS and higher IMT had a 3-fold higher risk for stroke than those without IMT. Using transcranial Doppler ultrasound, the authors found that the majority of primary APS patients with thickened IMT also displayed abnormal transcranial Doppler. Another recent study also provides additional evidence for enhanced atherosclerosis in APS, because carotid IMT, both at the carotid bifurcation and at the internal carotid artery, was higher among 20 primary APS patients compared with 20 control subjects, primarily in patients >40 years old.

The issue of primary versus secondary APS in terms of atherosclerosis extent has recently been addressed by Jimenez et al. They have consecutively studied 70 SLE patients, 25 primary APS patients, and 40 healthy women for carotid artery atherosclerosis. Whereas the IMT levels were similar among the 3 study groups, the prevalence of carotid plaques was higher and appeared earlier in SLE patients than in the primary APS or the control groups. SLE patients having secondary APS had a higher prevalence of carotid plaque than primary APS patients. Of note is that SLE patients also had a higher prevalence of traditional risk factors for CVDs than patients with primary APS.

These data suggest a potential proatherogenic role for aPL in patients having APS, and it should be kept in mind that certain subgroups of aPL may actually be protective against atherosclerosis. New biological markers and imaging/functional studies are useful in defining APS patients with high vascular risk. Regarding atherosclerosis treatment strategies in APS, an aggressive treatment of all traditional risk factors for atherosclerosis should be taken, including hypercholesterolemia, diabetes mellitus, smoking, obesity, arterial hypertension, and sedentary lifestyle. In addition to antiplatelet and anticoagulant therapy aimed at avoiding recurrent thrombosis, the use of folic acid, B vitamins, cholesterol-lowering agents (preferably statins), and hydroxychloroquine should also be considered. Even though these agents might modify atherosclerosis in APS, no firm data currently exist to support this view.

### Macrovascular Disease and Atherosclerosis in Systemic Sclerosis

SSc affects the microcirculation and injures the endothelium, leading eventually to vessel occlusion and tissue anoxia. In addition, SSc significantly accelerates the suffering of the vessel wall of the macrocirculation, increasing the risk of vascular occlusive diseases. The link between SSc and atherosclerosis was identified in some cases of patients with SSc who underwent amputation of the lower limbs because of peripheral macrovascular disease. Four SSc patients were reported with severe macrovascular involvement of the lower or upper limbs, characterized by the presence of very low vascular risk factors. In the biopsy of the ulnar artery of these patients, only a marked vessel narrowing without plaques was detected. In limited cutaneous SSc, macrovascular disease was detected in 18 of 31 patients (58%), and amputation was performed in 5 patients: Biopsies showed marked intimal thickening, proliferation with destruction of the internal elastic lamina, and transmural lymphocytic and plasmacellular infiltrate. In 10 of 53 SSc patients, intermittent claudication (21.7%) and coexistent ischemic heart disease (15.2%) and cerebrovascular disease (6.5%) were detected. Doppler
study of the main arteries of the limbs, neck, and abdomen
demonstrated that primarily the ulnar artery was affected,
with stenosis also confirmed by subtraction angiography in 9
of 26 patients and by angiography in 15 SSc patients.
Angiography demonstrated an increased rigidity of the radial
artery and lower-limb involvement.65 The carotid artery was
involved in approximately 64% of SSc patients, compared
with 35% of control subjects. The involvement of the
carotid artery was also recently confirmed in 53 SSc patients,
because the IMT of the common carotid artery, evaluated by
ultrasound, was significantly increased and correlated with
the presence of the D allele of the ACE gene, which is
associated with accelerated atherosclerosis (M.M.C., unpub-
lished data, 2004). An increased frequency of the D allele has
been demonstrated as correlating with the presence of SSc.67
These findings suggest that significantly higher IMT and
DD/ID ACE polymorphism are correlated with and predis-
pose to macrovascular involvement in SSc.

The diffuse involvement of the vascular tree in SSc,
ranging from the microcirculation to the macrocirculation,
may be linked primarily to 2 factors: The disease pathogen-
esis and the predisposition of the single subject to atheroscle-
rosis. These 2 elements can thus overlap, jeopardizing the
integrity of the vessel wall. In genetically predisposed SSc
patients, characterized by ischemia and oxidative stress, with
raised levels of LDL undergoing oxidation, triggering vessel wall inflammation, the overlap with SSc-dependent
endothelial injury creates a noxious loop involving the
microcirculation and macrocirculation. In this scenario,
pathogenetic factors participating in endothelial suffera-
tion, such as anti–endothelial cell antibodies, dysfunction of
the fibrinolytic and coagulation system, and an increase of
circulating levels of homocysteine, soluble intercellular
adhesion molecule-1, and CRP may contribute significantly
to increased risk of developing accelerated macrovascular
disease.70–73 In the future, drugs protecting the vessel wall,
such as statins and antioxidants, might become potential tools
for the management of microvascular and macrovascular
involvement in SSc. The extent of enhanced atherosclerosis
in SSc, if any at all, is not yet clear, because fewer studies
(compared with those of RA, SLE, and APS) addressed this
specific question.

### Primary Systemic Vasculitis and Accelerated Atherosclerosis

Primary systemic vasculitides (PSVs) are immune system-
mediated diseases of the blood vessels characterized by a
systemic inflammatory reaction and multiple lesions occur-
ing in specific districts of the vascular bed. These features
might be involved in favoring or accelerating atherogenesis in
PSV. Many similarities exist between atherosclerosis and
PSV with respect to the initial localization, the role of
multiple causal factors and pathogenetic mechanisms, and
some clinical manifestations and possible future treatment
strategies. Vessel intima is the site at which inflammation
develops in atherosclerosis and in most types of PSV; in both
cases, endothelial cell (EC) activation and damage may occur
not only by the action of exogenous or biochemical stimuli
(bacterial and viral infections, toxins, smoke, hyperglycemia,
hyperlipidemia/dyslipidemia, etc) but also as a result of an in
situ immune response.74,75 Such immune responses can be
triggered by exogenous antigens, probably more importantly
in the initial phases, and by autoantigens. In fact, PSV and
atherosclerosis are now considered autoimmune diseases,
because in both cases, autoantibodies, autoantigens, and/or
autoactive cells have been identified, and active immuni-
zation or passive transfer of immune elements have repro-
duced the diseases in experimental models.1 Once activated,
ECs expose adhesion molecules, secrete cytokines, chemo-
kines, growth factors, and metalloproteinases and assume
procoagulant properties. The molecular and cellular medi-
ators of inflammation and vascular lesions then differ between
atherosclerosis and vasculitis and between various PSV
diseases. For example, cell infiltrates in atherosclerotic plaques include T lymphocytes and mononuclear/macrophages
but not neutrophils, and fibrinoid necrosis does not occur; the
formation of foam cells and smooth muscle cell activation are

### TABLE 3. Enhanced Atherosclerosis and Associated Factors in Autoimmune Rheumatic Diseases

<table>
<thead>
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<th>Disease</th>
<th>Evidence for Enhanced Atherosclerosis</th>
<th>Factors Involved in Enhanced Atherosclerosis</th>
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<tr>
<td>RA</td>
<td>High prevalence of CAD, increased extent of subclinical atherosclerosis [ultrasound studies of carotid IMT]</td>
<td>High prevalence of classic risk factors for atherosclerosis, drugs used for treatment [methotrexate increase homocysteine]</td>
</tr>
<tr>
<td>SLE</td>
<td>High prevalence of CAD, increased extent of subclinical atherosclerosis [ultrasound studies of carotid IMT, coronary artery calcifications, abnormalities in cardiac scintigraphy]</td>
<td>High prevalence of classic risk factors for atherosclerosis, corticosteroid therapy, long disease duration</td>
</tr>
<tr>
<td>APS</td>
<td>Thrombosis is a main feature of the syndrome, increased extent of subclinical atherosclerosis [ultrasound studies of carotid IMT], aPLs are prevalent in patients with macrovascular diseases, aPLs predict future CVD in the general population</td>
<td>Animal models support a proatherogenic role of aPL</td>
</tr>
<tr>
<td>SSc</td>
<td>High prevalence of macrovascular disease (65, 66). Few studies on atherosclerosis.</td>
<td>Oxidative stress, AECA</td>
</tr>
<tr>
<td>PSV</td>
<td>Increased extent of subclinical atherosclerosis (ultrasound studies of carotid IMT) in Wegener’s granulomatosis. Not studied in other diseases.</td>
<td>Enhanced inflammation and excessive vascular remodeling</td>
</tr>
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</table>

AECA indicates anti–endothelial cell antibody; CAD, coronary artery disease.
Vasculitis lesions, conversely, have an important neutrophil component and fibrinoid necrosis, as in Wegner’s granulomatosis (WG) or microscopic polyangiitis, or include granulomas, as in WG, Churg-Strauss disease, and giant-cell arteritis.

The increase in systemic and local secretion of soluble mediators of inflammation and the enhanced adhesion between ECs and monocytes during vasculitis may favor plaque formation and generalized endothelial dysfunction. For example, endothelium-dependent vasodilatation of brachial arteries is impaired in patients having WG, a PSV typically involving small vessels. A recent study by de Leeuw et al77 provides the first direct evidence for enhanced atherosclerosis in PSV. In this study, common carotid artery IMT was compared between 29 patients having inactive WG and 26 control subjects. IMT was found to be significantly increased among WG patients compared with control subjects. No differences in traditional risk factors and endothelial activation markers (thrombomodulin, vascular cell adhesion molecule-1, von Willebrand factor) was found between WG patients and control subjects. Nonetheless, levels of high-sensitivity CRP, matrix metalloproteinases-3 and -9, and tissue inhibitor of metalloproteinase-1 were increased among patients, supporting a role for enhanced inflammation and excessive vascular remodeling as contributing factors to enhanced atherosclerosis in WG patients.77

EC activation may be induced in PSV by specific pathological autoantibodies, such as anti–endothelial cell antibodies and anti-neutrophil cytoplasmic antibodies.78,79 Vasculitis may trigger or favor not only inflammatory but also immune reactions associated with atherogenesis, for example, increasing the expression of autoantigens (e.g., HSP 60/65) on activated ECs. Strong experimental evidence points to a role for an immune response directed toward HSP60/65 in atherogenesis, and anti-HSP60 antibodies are considered an independent risk factor for coronary and carotid atherosclerosis.80 Moreover, typical “vasculitic” EC changes may result in increased oxidation of circulating LDL81 and accumulation of oxLDL in the subendothelial region. OxLDL aggravates the proinflammatory changes of ECs, monocyte/macrophage activation, and foam cell formation. In the vasculitis named Bechet’s disease, an increased oxidation of LDL and EC activation have been reported, together with anti-oxLDL antibody production82; these autoantibodies, reported in other PSV83 and rheumatic diseases characterized by accelerated atherosclerosis, correlate with myocardial infarction, cerebrovascular accidents, progression of coronary atherosclerosis, and coronary artery restenosis after angioplasty.

Atherosclerosis in Sjogren’s Syndrome

Sjogren’s syndrome (SS) is an autoimmune disease characterized by autoantibody production and chronic mononuclear cell infiltration of exocrine gland tissues. The disease is manifested by sicca syndrome and systemic involvement that includes musculoskeletal, pulmonary, gastric, renal, and nervous system disease. Cardiac involvement is very rare among patients having SS. In a recent review of patients with primary SS and those with SS secondary to SLE, none of the patients had cardiac disease.84 A literature review has failed to identify even a single article that examined the risk and occurrence of atherosclerosis among patients with primary SS. In addition, the development of atherosclerotic plaques in patients with RA and SLE was not associated with the presence of secondary SS.85

Few case reports describe the occurrence of stroke among young patients with SS. However, those strokes were attributed to vasculitis and not secondary to accelerated atherosclerosis.86,87 In a recent study, patients with primary SS were found to have a lower frequency of autoantibodies to lipoprotein lipase compared with patients with SLE or RA and normal control subjects. Anti–lipoprotein lipase antibodies have been associated with elevated levels of triglycerides and possibly accelerated atherosclerosis.88 Taken together, the data suggest that further studies are indicated to determine the risk of atherosclerosis and CVD among patients with primary SS. Currently there is no available data suggesting that this common autoimmune condition is associated with enhanced atherosclerosis.

Conclusions

Enhanced and premature atherosclerosis is a feature of some AIRDs and a possible feature of others because of inflammation and more specific immune mechanisms (Table 3). RA, SLE, and APS carry an increased risk for CVD. RA and SLE are characterized by an increased risk of coronary artery disease and prevalence of typical risk factors for these diseases and an increased extent of subclinical atherosclerosis. However, other factors attributed to disease activity, inflammation, and therapeutic interventions are also implicated in the higher prevalence of atherosclerosis and its complications in both diseases. APS is a prothrombotic state characterized by thrombosis of any vessel; however, the association of aPL with CVDs in the general population, the findings of enhanced subclinical atherosclerosis in APS patients, and the proatherogenic effect of aPL in animal models support a possible proatherogenic (in addition to prothrombotic) role of these autoantibodies. In these 3 conditions, premature atherosclerosis can be detected in some patients in its preclinical stage. Physicians thus should attempt to minimize the presence of conventional CVD risk factors in their patients and treat their patients as belonging to a group having a high risk for CVD. In SSc and PSV, although there is a high prevalence of macrovascular disease, there are few data supporting enhanced atherosclerosis in these conditions. In addition, no data yet exist to support enhanced atherosclerosis in SS. Future research is needed to determine whether these AIRDs are also associated with accelerated atherosclerosis and its manifestations.

Acknowledgments

This study was supported in part by a Freda and Leon Schaller (O.B.E.), Ilford, UK, Grant for Research in Autoimmunity (2004) (to Dr Shoenfeld) and in part by Ricerca Corrente, IRCCS, Istituto Auxologico Italiano 2004, and by Progetti di Ricerche Fianalizzate, Italian Ministry of Health (2003) (to Dr Meroni).

References


Key Words: atherosclerosis | cardiovascular diseases | myocardial infarction | vasculature
Accelerated Atherosclerosis in Autoimmune Rheumatic Diseases
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_Circulation_. 2005;112:3337-3347
doi: 10.1161/CIRCULATIONAHA.104.507996
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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