CHAPTER 6

MACROVASCULAR DISEASE AND
ATHEROSCLEROSIS IN SYSTEMIC SCLEROSIS

M.E. Hettema
H. Bootsma
C.G.M. Kallenberga

Rheumatology 2008; 47: 578-83
ABSTRACT

Atherosclerosis is considered a chronic inflammatory disorder. Several autoimmune rheumatic diseases are characterized by premature and accelerated atherosclerosis in which both classical and non-classical risk factors contribute to atherogenesis. Systemic sclerosis (SSc) is characterized by vasculopathy, and microvascular involvement is common. Macrovascular involvement is considered rare, although increased prevalence of macrovascular disease has been reported as well. Here, we review the literature regarding coronary artery disease, cerebrovascular disease and peripheral arterial disease in systemic sclerosis. An increased prevalence of distal peripheral artery disease in the digits has been found. The prevalence of coronary artery disease and cerebrovascular disease is not increased, although studies using intima-media thickness of the carotid artery as marker of early atherosclerosis showed discrepant results. Besides traditional risk factors, as present in the general population, non-traditional risk factors are present in SSc as well, such as increased lipoprotein[a], oxidized LDL, inflammation, vasospasm and endothelial dysfunction. Moreover, markers of vascular damage in atherosclerosis, like antibodies to oxidised LDL, and increased levels of soluble vascular adhesion molecules, have been described in association with vascular damage in SSc. Nevertheless, generalized premature atherosclerosis has not been detected in SSc. Therefore, further research is necessary to assess the prevalence of clinically manifest or subclinical early atherosclerosis in SSc.
INTRODUCTION

Atherosclerosis underlying cardiovascular mortality is the leading cause of death in developed countries (WHO Statistical Information System, www.who.int/whosis). Atherosclerosis is a disease of large and medium-sized arteries and can result in ischemia and infarction. Clinical manifestations include coronary heart disease, stroke and peripheral vascular disease. Atherosclerosis is considered an inflammatory disease, in which, amongst others, monocytes, macrophages, and T-cells as well as autoantibodies, autoantigens, and cytokines play a role. Several autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Wegener’s granulomatosis (WG), are characterized by an increased prevalence of atherosclerosis, and, consequently, increased cardiovascular morbidity and mortality.

Systemic sclerosis (SSc) is an autoimmune disorder characterized by widespread vascular involvement. Microvascular abnormalities and Raynaud’s phenomenon (RP) are well-known as major sites of pathology, but less attention has been paid to macrovascular abnormalities. Although survival in SSc has improved during the last decades, a recently performed meta-analysis still showed increased standardized mortality ratios. Involvement of major organs, as heart, lungs and kidneys, was found to be an independent adverse predictor of mortality.

In this review, we discuss data on the prevalence and etiology of macrovascular disease and atherosclerosis in SSc. Evaluation of the prevalence of clinically manifest atherosclerosis in SSc is difficult, as both the prevalence of SSc in the general population and the number of observed cardiovascular events are low. However, early atherosclerosis can be studied in cohorts of patients using standardized techniques. Therefore, we will also review studies describing subclinical, early atherosclerotic changes as assessed by measuring intima media thickness (IMT) of the carotid artery.

Evidence for macrovascular disease and atherosclerosis in systemic sclerosis

The prevalence of vascular abnormalities in SSc has been considered to be inversely proportional to the size of blood vessels studied. Macrovascular disease was considered extremely rare. Although the heart is one of the major organs involved in SSc, coronary arteries were rarely involved in histopathologic material or at coronary angiography. Even so, in SSc patients admitted to a hospital because of acute myocardial infarction, the odds ratio of having normal coronary arteries was 33.89 compared to the patients admitted from the general population, suggesting microvascular and not macrovascular disease in these patients. Also, cerebrovascular involvement in SSc has rarely been documented, although the opposite has been stated. Only one retrospective cohort study is available, showing no increased prevalence of cerebrovascular disease in 31 female SSc patients compared with matched controls (prevalence 26% vs 19%, RR 1.3 with 95% confidence interval of 0.5-3.3). More studies are available regarding peripheral atherosclerotic vascular disease. An increased prevalence of peripheral vascular disease in SSc patients compared to healthy controls (21.7% vs 4.6%) has been observed by Veale et al, using a
questionnaire for intermittent claudication, and by Youssef et al, using data available from angiography, Doppler ultrasound or physical examination (prevalence 58% vs 10%, RR 6.0 with 95% confidence interval of 2.0-18). When angiographic findings of the lower and upper limb in SSc patients were related to cardiovascular risk factors an association was observed between these risk factors and proximal peripheral artery disease, but not distal peripheral artery disease. Distal peripheral artery disease is present in the digits of many SSc patients, showing a high frequency of digital stenosis and occlusions in the digital arteries of patients. Lesions were most frequently found in the 2nd to 5th proper palmar digital artery, the ulnar artery and the superficial palmar arch. As a consequence, digital ischaemia, ulceration or amputation is a well-known, but feared manifestation in SSc.

Several groups have studied subclinical, early atherosclerosis in SSc. Using intima-media thickness (IMT) of the carotid artery as a marker of early atherosclerosis discrepant results were reported. No differences in IMT or intraluminal diameter of the common carotid artery (CCA) between SSc patients and controls were noted by some authors, while others found significantly increased IMT values or increased prevalence of carotid artery disease in SSc patients (Table 1). IMT values of the femoral artery in SSc patients and healthy controls were comparable. Nevertheless, large vessel involvement has been suggested in SSc since altered elastic properties of the carotid artery, increased stiffness of the aorta, and decreased arterial distensibility have all been reported in SSc patients.

Another method to assess subclinical atherosclerosis is by means of ankle brachial pressure index (ABPI), which is also the usual non-invasive assessment approach of patients with symptomatic peripheral vascular disease. This technique can also be used to predict cardiovascular disease and mortality. ABPI has been used in asymptomatic SSc patients. Ho et al reported a significantly increased prevalence of peripheral artery disease, but in other studies no differences in ABPI between SSc patients and healthy controls were found. Several other non-invasive tests have been used for the assessment of subclinical early atherosclerosis. Evaluating of heart rate variability has been used for assessing cardiovascular autonomic function, and is found to be a predictor of sudden arrhythmic death, but also of nonarrhythmic cardiac events. The latter can be explained by the influence of heart rate variability on hemodynamic factors, leading to changes in the vascular wall. Evaluating heart rate variability showed a reduced variability, indicating the presence of autonomic cardiac neuropathy in SSc patients without known cardiac disease.

In conclusion, an increased prevalence of distal peripheral artery disease is present in SSc. Conflicting results regarding early signs of atherosclerosis are present, but can be explained by methodological differences, such as differences in patients included in the study, comorbidity, and non-invasive techniques used.

**Etiology**

Traditional risk factors were equally distributed between SSc patients and controls in the above mentioned studies. Hence, other factors beyond traditional cardiovascular risk factors may contribute to any putatively increased prevalence of cardiovascular, cerebrovascular and peripheral vascular disease in SSc.
Macrovascular disease and atherosclerosis in systemic sclerosis

Table 1 Carotid ultrasound studies in SSc

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of SSc patients</th>
<th>lcSSc: dcSSc</th>
<th>Mean age SSc patients, years</th>
<th>No. of controls</th>
<th>Mean age controls, years</th>
<th>IMT values of the CCA (and bulb) in SSc patients compared to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lekakis52</td>
<td>12</td>
<td>0:12</td>
<td>49</td>
<td>12</td>
<td>49</td>
<td>0.83 ± 0.3 mm vs 0.46 ± 0.2 mm, p=0.002</td>
</tr>
<tr>
<td>Cheng46</td>
<td>53</td>
<td>N.A.</td>
<td>43</td>
<td>53</td>
<td>55</td>
<td>0.65 ± 0.24 mm vs 0.63 ± 0.20 mm, p=0.74</td>
</tr>
<tr>
<td>Cheng45</td>
<td>52</td>
<td>33:19</td>
<td>lcSSc 56</td>
<td>dcSSc 55</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Szucs47</td>
<td>29</td>
<td>19:10</td>
<td>52</td>
<td>29</td>
<td>49</td>
<td>0.67 ± 0.26 mm vs 0.57 ± 0.09 mm, p=0.067</td>
</tr>
<tr>
<td>Kaloudi 51</td>
<td>66</td>
<td>55:11</td>
<td>lcSSc 62</td>
<td>dcSSc 53</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>Bartoli49</td>
<td>53</td>
<td>45:8</td>
<td>60</td>
<td>53</td>
<td>56</td>
<td>0.85 ± 0.03 mm vs 0.68 ± 0.01 mm, p&lt;0.03</td>
</tr>
<tr>
<td>Bartoli53</td>
<td>35</td>
<td>24:11</td>
<td>61</td>
<td>20</td>
<td>“matched”</td>
<td>0.93 ± 0.29 mm vs 0.77 ± 0.13 mm, p&lt;0.003</td>
</tr>
</tbody>
</table>

Abbreviations: No., number; lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; IMT, intima-media thickness; CCA, common carotid artery; N.A., not available

Lipoprotein profile

Dyslipidemia, i.e. increased levels of low density lipoprotein (LDL) cholesterol and triglycerides, and decreased high density lipoprotein (HDL) cholesterol,68 is an important traditional risk factor for cardiovascular disease. Decreased HDL levels have been detected in patients with limited cutaneous SSc (lcSSc) compared to healthy controls.69 No studies are available on LDL levels in SSc. However, patients with SSc showed increased susceptibility to oxidation of LDL, a process in which oxidized LDL (OxLDL) is formed.70 OxLDL is a proatherogenic lipoprotein, which, amongst others, promotes foam cell formation, vascular oxygen radical formation, tissue remodeling, endothelial dysfunction, and even vasospasm.71;72 Another cardiovascular pathogenic factor is lipoprotein[a].73 Its exact mechanism is unknown, but lipoprotein[a] (Lp[a]) counterbalances the pro- and anticoagulant, pro- and anti-inflammatory, and vasorelaxing and vasoconstricting properties of the endothelium, in which raised concentrations are linked with atherosclerosis and thrombosis.74;75 In patients with SSc, increased concentrations of Lp[a] without further differences in lipid profile in comparison with healthy controls have been found, both in limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc).76;77
**Autoantibodies**

Increased concentration of antibodies to OxLDL (aOxLDL) have been described in atherosclerosis.\(^78-82\) In young individuals or in early stages of atherosclerosis low aOxLDL levels have been found.\(^83;84\) Immunization with OxLDL in experimental animals resulted in a protective effect on the process of atherogenesis leading to increased aOxLDL levels and a reduction in atherosclerosis.\(^85-89\) Increased concentrations of aOxLDL have been found in patients with SSc, particularly in dcSSc.\(^77;90\)

Antiphospholipid antibodies are present in the antiphospholipid syndrome (APS). APS is clinically characterized by recurrent arterial and venous thrombosis as well as pregnancy losses. These antibodies have procoagulant activity and are proatherogenic, as has been shown by increased prevalence of cardiovascular disease in patients with APS and SLE.\(^91\) The role of antiphospholipid antibodies in vascular manifestations in SSc is unclear. A prevalence of anticardiolipin antibodies (aCL) and anti-beta2-glycoprotein-I antibodies (anti-beta2GPI) of 0-40% has been reported in SSc, but no relation of the antibodies with clinical manifestations of the antiphospholipid syndrome was seen.\(^92-99\) However, some studies found an association with pulmonary hypertension, endothelial dysfunction and myocardial ischemia or necrosis.\(^92;95;96\) No association with digital ischemia was found.\(^97\)

Other antibodies present in diseases with vascular damage are the antiendothelial cell antibodies (aECA). These antibodies have been reported in various diseases, such as coronary atherosclerosis, diabetes mellitus, hypertension, and autoimmune diseases.\(^100-106\) In Wegener’s granulomatosis and SLE a relation between aECA and disease activity has been found. However, the precise role of aECAs is unclear. It is possible that aECAs are an epiphenomenon of vascular damage, or are pathogenic antibodies.\(^107\) AECAs have been detected in 22-85% of SSc patients.\(^108;110\) Differences in detection of AECAs may be ascribed to patient selection and technique used in the laboratory. AECAs are also associated with vascular damage in SSc, such as digital ischemia, pulmonary hypertension and nailfold capillary abnormalities.\(^111-114\)

**Inflammation**

Inflammation is a hallmark of systemic autoimmune diseases. Also in SSc inflammation is present when the disease is active. Disease activity in SSc can be assessed by using the preliminary European Scleroderma Study Group (EScSG) activity indices (a score ranging from 0-10). A score higher than 3 denotes active disease.\(^115;116\) One of the items of this scale is C-reactive protein (CRP), found to be a strong marker of cardiovascular risk in asymptomatic subjects and subjects with a history of a cardiovascular event.\(^117-122\) Elevated acute phase reactants have been found especially in dcSSc (41.8%) compared to lcSSc (24.6%), as have been described in the large EULAR Scleroderma Trials and Research (EUSTAR) group database.\(^123\) Therefore, inflammation might play a role in vascular abnormalities in SSc. No data are available concerning acute phase reactants and atherosclerosis in SSc.
**Endothelial dysfunction**

Inflammation, auto-antibodies, oxLDL, and other stimuli allow the endothelium to undergo changes resulting in endothelial cell activation. Endothelial cell activation is an initiating step in atherogenesis. Endothelial function can be assessed non-invasively by means of several methods, based on the inability of dysfunctional endothelium to cause vasodilation of the vessels by its inability to release endothelium-derived vasodilatory mediators. Acetylcholine is used in most studies studying endothelium-dependent vasodilation, as acetylcholine cannot exert its effects in the absence of functional endothelial cells. Endothelium-independent vasodilation can be studied by using glyceryl nitrate, causing vasodilation by direct action on the smooth muscle.

Measurement of flow mediated dilation (FMD, endothelium-dependent) and endothelium-independent vasodilation via high-ultrasound techniques allowed the detection of endothelial dysfunction in children and adults with risk factors for atherosclerosis. A relationship between endothelial dysfunction, intima media thickness and cardiovascular risk factors has been established. Studies using laser Doppler flowmetry, studies using brachial reactivity via ultrasound, and studies using venous occlusion plethysmography show evidence both in favor of, but also against impaired endothelial-dependent as well as endothelial-independent vasodilation in SSc. This might be explained by methodological differences between studies, like differences in sites of measurements or use of a different protocol. Also, endothelial function of conduit arteries has been studied by the assessment of ultrasound-derived FMD of the brachial artery, while LDF has been used for measurement of flow in the microcirculation. Comparison between these two different non-invasive methods has revealed conflicting results. Interestingly, an association between impairments of FMD and increased IMT was found in some but not all studies.

Expression of vascular adhesion molecules, such as P-selectin, L-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, is increased in atherosclerosis, but their role in the recruitment, regulation of transmigration and retention of immune cells to atherosclerotic lesions still needs to be clarified. Increased levels of soluble forms of various adhesion molecules in combination with endothelial dysfunction has also been described in SSc, but not in relation to atherosclerosis or macrovascular disease.

**Vasospasm**

Autopsy studies of the heart showed focal areas of acute and subacute necrosis in combination with contraction band necrosis in the presence of normal coronary arteries in SSc, even in patients who, prior to death, were known with signs of ischemic heart disease. Bulkley et al stated that contraction band necrosis was the result of a reperfusion lesion, suggesting that the lesions found at autopsy were the consequence of transient nonperfusion due to arrhythmias or Raynaud’s phenomenon (RP) of the coronary arteries. Cold provocation in patients with SSc resulted in reversible myocardial perfusion abnormalities in a significant proportion of patients. Indeed, severe impairment of coronary blood flow, not due to coronary artery stenosis, was found in 7 asymptomatic SSc patients using a myocardial multidetector computed tomography. Coronary flow reserve (CFR), a marker of the coronary circulation, is used to evaluate the effects of coronary artery stenosis on coronary microvasculature and myocardial perfusion.
Impaired CFR has been found in SSc patients, but no differentiation could be made between vasospasm or structural abnormalities as underlying factors. Improvement of myocardial perfusion after administration of oral nifedipine supports the hypothesis of myocardial RP in SSc. Coronary vasospasm is also known in the general population as variant angina or Prinzmetal angina. Endothelial dysfunction as well as local hyperreactivity play a role in its pathogenesis. Vasospasm with or without the presence of structural vascular abnormalities was also seen during digital arteriography in patients with SSc, in whom RP is a common manifestation. Vasospasm has also been observed in patients with SLE, with and without RP, and SSc in cerebral blood flow after a cooling test of the hand.

SUMMARY
The immune system is involved in the pathogenesis of atherosclerosis, which is considered to be an inflammatory disease. Atherosclerosis is more prevalent and the risk of coronary vascular disease is increased in patients with various autoimmune diseases compared to healthy controls. Systemic sclerosis also is an autoimmune disease, and vascular involvement is frequent. Raynaud’s phenomenon is often the first manifestation. The disease is mainly characterized by microvascular involvement, and increasing evidence suggests also macrovascular involvement. Besides traditional risk factors, as in the general population, non-traditional risk factors are present in SSc, such as increased Lp[a], OxLDL, inflammation, vasospasm and endothelial dysfunction. Moreover, markers of vascular damage, like aOxLDL, aECA and increased levels of vascular adhesion molecules are present in SSc. However, clinically manifest atherosclerosis was found to be rare, and studies assessing subclinical, early atherosclerosis showed conflicting results. Cardiovascular involvement is most likely the result of vasospasm of the coronary arteries. Further research is necessary to assess the prevalence of clinically manifest or subclinically early atherosclerosis in SSc, and to explain differences in accelerated atherosclerosis between SSc and other autoimmune rheumatic diseases.
REFERENCES

Macrovascular disease and atherosclerosis in systemic sclerosis


74. Koschinsky ML. Lipoprotein(a) and the link between atherosclerosis and thrombosis. Can.J.Cardiol. 2004;20 Suppl B:37B-43B.


Macrovascular disease and atherosclerosis in systemic sclerosis


