Review

Macrovascular disease and atherosclerosis in SSc

M. E. Hettema, H. Bootsma and C. G. M. Kallenberg

Atherosclerosis is considered to be 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 athrogenesis. 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 SSc. 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 a 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, vasoospasm and endothelial dysfunction. Moreover, markers of vascular damage in atherosclerosis, like antibodies to oxidized 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.

KEY WORDS: Macrovascular disease, Atherosclerosis, 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 ischaemia 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 [1, 2]. Several autoimmune diseases, including RA [3–7], SLE [8–13] and WG [14], are characterized by an increased prevalence of atherosclerosis, and consequently, increased cardiovascular morbidity and mortality.

SSc is an autoimmune disorder characterized by widespread vascular involvement. Microvascular abnormalities and RP are well-known as major sites of pathology [15–18], 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, such as heart, lungs and kidneys, was found to be an independent adverse predictor of mortality [19].

In this review, we discuss data on the prevalence and aetiology 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 [20–25]. We searched for original articles in PubMed and Medline published between 1950 and 2007 with the search strategy ‘atherosclerosis OR macrovascular’ in association with ‘systemic sclerosis’. We also used relevant papers retrieved from references of articles found by the search strategy.

Evidence for macrovascular disease and atherosclerosis in SSc

The prevalence of vascular abnormalities in SSc has been considered to be inversely proportional to the size of blood vessels studied [26]. Macrovascular disease was considered extremely rare. Although the heart is one of the major organs involved in SSc [27], coronary arteries were rarely involved in histopathological material [28–31] or in coronary angiography [32]. Even so, in SSc patients admitted to the hospital because of acute myocardial infarction, the odds ratio of having normal coronary arteries was 33.89 compared with the patients admitted from the general population, suggesting microvascular and not macrovascular disease in these patients [33]. Also, cerebrovascular involvement in SSc has rarely been documented, although the opposite has been stated [34]. 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% CI of 0.5, 3.3) [35]. More studies are available regarding peripheral atherosclerotic vascular disease. An increased prevalence of peripheral vascular disease in SSc patients compared with healthy controls (21.7 vs 4.6%) has been observed by Veale et al. [36], using a questionnaire for intermittent claudication, and by Youssef et al. [35], using data available from angiography, Doppler ultrasound or physical examination (prevalence 58 vs 10%, RR 6.0 with 95% CI 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 [37]. 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 [38–41]. As...
a consequence, digital ischaemia, ulceration or amputation is a well-known, but feared manifestation in SSC [42–44]. Several groups have studied subclinical, early atherosclerosis in SSC. Using 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 [45–48], while others found significantly increased IMT values or increased prevalence of carotid artery disease in SSC patients (Table 1) [49–53]. IMT values of the femoral artery in SSC patients and healthy controls were comparable [25, 45]. 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 [45, 54–59]. 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 [60–62]. ABPI has been used in asymptomatic SSC patients. Ho et al. [50] 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 [49, 51, 60]. Several other non-invasive tests have been used for the assessment of subclinical early atherosclerosis. Evaluation 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 non-arrhythmic cardiac events [63]. The latter can be explained by the influence of heart rate variability on haemodynamic factors, leading to changes in the vascular wall. Evaluation of heart rate variability showed a reduced variability, indicating the presence of autonomic cardiac neuropathy in SSC patients without known cardiac disease [64–67].

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.

Aetiology

Traditional risk factors were equally distributed between SSC patients and controls in the aforementioned 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.

Lipoprotein profile

Dyslipidaemia, 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. Increased HDL levels have been detected in patients with limited cutaneous SSC (lcSSc) compared with 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 remodelling, endothelial dysfunction and even vasospasm [71, 72]. Another cardiovascular pathogenic factor is lipoprotein(a) [Lp(a)] [73]. Its exact mechanism is unknown, but [Lp(a)] counterbalances the pro- and anti-coagulant, pro- and anti-inflammatory and vasorelaxing and vasocostricting 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 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].

aPLs are present in the APS. APS is clinically characterized by recurrent arterial and venous thrombosis as well as pregnancy losses. These antibodies have pro-coagulant activity and are pro-atherogenic, as has been shown by increased prevalence of cardiovascular disease in patients with APS and SLE [91]. The role of aPLs in vascular manifestations in SSC is unclear. A prevalence of aCLs and anti-β2-glycoprotein-1 antibodies (anti-β2GPI) of 0–40% has been reported in SSC, but no relation of the antibodies with clinical manifestations of the APS was seen [92–99]. However, some studies found an association with pulmonary hypertension, endothelial dysfunction and myocardial ischaemia or necrosis [92, 95, 96]. No association with digital ischaemia was found [97].

Other antibodies present in diseases with vascular damage are the AECAs. These antibodies have been reported in various diseases, such as coronary atherosclerosis, diabetes mellitus, hypertension and autoimmune diseases [100–106]. In WG and SLE, a relation between AECAs 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.

Table 1. Carotid ultrasound studies in SSC

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of SSC patients</th>
<th>lcSSc vs dcSSc</th>
<th>Mean age of SSC patients (yrs)</th>
<th>No. of controls</th>
<th>Mean age of controls (yrs)</th>
<th>IMT values of the CCA (and bulb) in SSC patients compared with controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lekakis et al. [52]</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>Cheng et al. [46]</td>
<td>53</td>
<td>NA</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>Cheng et al. [49]</td>
<td>52</td>
<td>33:19</td>
<td>lcSSc 66; dcSSc 55</td>
<td>52</td>
<td>50</td>
<td>0.68 ± 0.27 mm (lcSSc) and 0.62 ± 0.20 mm (dcSSc) vs 0.63 ± 0.20 mm; P = 0.090</td>
</tr>
<tr>
<td>Szuica et al. [47]</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>Kaloudis et al. [51]</td>
<td>66</td>
<td>55:11</td>
<td>lcSSc 62; dcSSc 53</td>
<td>66</td>
<td>58</td>
<td>0.90 ± 0.036 mm (lcSSc) and 0.87 ± 0.043 mm (dcSSc) vs 0.69 ± 0.013 mm; P &lt; 0.01</td>
</tr>
<tr>
<td>Bartoli et al. [49]</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>Bartoli et al. [53]</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>

NA: not available.
In the presence of normal coronary arteries in SSc, even in patients subclinical early atherosclerosis in SSc, and to explain differences in accelerated atherosclerosis between SSc and other autoimmune rheumatic diseases.


coronary artery stenosis was found in seven asymptomatic SSc patients using a myocardial multidetector CT [147]. 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 and structural abnormalities as underlying factors [148–150]. Improvement of myocardial perfusion after administration of oral nifedipine supports the hypothesis of myocardial RP in SSc [151–153]. 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 [154]. 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 [40]. 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 [155].

Summary

The immune system is involved in the pathogenesis of atherosclerosis that 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 with healthy controls. SSc also is an autoimmune disease, and vascular involvement is frequent. RP 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.

Rheumatology key messages

- Unlike other autoimmune rheumatic diseases, no increased prevalence of clinically manifest or subclinical early atherosclerosis is apparent in SSc, though increasing evidence suggests macrovascular involvement.
- Microvascular involvement is a primary characteristic of SSc.

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References

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