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Scleroderma and Related Disorders
Cardiovascular Risk in Systemic Sclerosis: Micro- and Macro-vascular Involvement

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Abstract

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of multiple organs (kidney, heart, lung, gastrointestinal tract, and skin), endothelial damage leading to vascular disease, and autoantibody production. Although the microvascular disease is well-understood, mechanistic insights explaining the presence and extent of macrovascular disease in SSc patients has been a matter of intense debate, especially in the past few years. Patients with systemic sclerosis have an increased risk for atherosclerotic cardiovascular disease (CVD), possibly mediated by inflammatory and fibrotic mechanisms. The excess cardiovascular risk in SSc is suggested by increased arterial stiffness, carotid intima thickening, and reduced flow-mediated dilatation. Given the involvement of the microvasculature, the differentiation between primary and ischemic heart disease is difficult. There is a relative paucity of data regarding clinical and preclinical CVD in SSc. Therefore, large cohort studies are required to clarify whether CVD is predominantly associated with atherosclerosis or microvascular involvement. The aim of this review is to discuss primary and ischemic heart disease and their contribution to CVD in SSc.

Key Words: Cardiovascular disease, primary heart involvement, systemic sclerosis, vascular complications

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by diffuse fibrosis of the skin and the internal organs.¹² SSc is about 4 times more common in women than men (3:1–14:1), and usually is divided into two main types: (a) diffuse cutaneous systemic sclerosis (dcSSc) and (b) limited cutaneous systemic sclerosis (lSSc). Raynaud’s phenomenon may be present for years (up to 10 or more) before the manifestations of the disease. Lung and gastrointestinal tract involvement are observed almost in the same frequency in both forms of scleroderma, whistle myocardial fibrosis, and kidney-related complications are more common in dcSSc. Irrespective of disease subset, cardiopulmonary complications such as heart failure, pulmonary hypertension, and interstitial lung disease represent the leading cause of death in SSc subjects. Although the microvascular damage is the hallmark of SSc heart disease, it has been suggested that macrovascular involvement, namely, atherosclerotic coronary and/or cerebrovascular disease may also be more prevalent in SSc compared with healthy subjects. Accelerated atherosclerosis is an established entity underlying several systemic inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus, but it remains unknown whether it is associated with increased cardiovascular disease (CVD) in SSc. On the other hand, primary heart disease in the form of cardiac tissue fibrosis is hardly differentiated and difficult to be prevented. The aim of this review is to summarize the role of micro- and macrovascular involvement in CVD risk in this population and to discuss aspects of possible management strategies.

Pathophysiology of Vascular Disease in Systemic Sclerosis

Clinical and pathological features of vascular damage and
endothelial cell activation are both recognized to play an important role in scleroderma microvascular disease. It is clear that endothelial cell dysfunction is a key element in the pathogenesis of SSc, but the initial triggers for microvascular dysfunction remain uncharacterized.[8] The pathogenesis of SSc is complex and appears to involve endothelium, epithelium, fibroblasts, and immunological mediators, resulting in dysregulated vascular remodeling and ultimately, in obstructive vasculopathy.[9] Fibroblast proliferation and differentiation are triggered by mediators of the fibrotic process, such as transforming growth factor beta 1) and endothelin 1 which have a pivotal role in the excess matrix production and connective tissue accumulation characteristic of SSc. Platelet abnormalities also play an important role in the pathogenesis of vasculopathy by promoting fibroblast activation and enhancing aggregability of vasoactive substances. This latter group includes antiendothelial cell antibodies, which are estimated to occur in 44%–84% of SSc patients and may induce apoptosis.[4-7] Apoptosis of endothelial cells plays an important role in the pathogenesis of SSc. An in vitro study suggested that endothelial cell apoptosis in SSc is induced by antibody-dependent cell-mediated cytotoxicity through the Fas pathway.[8]

Besides endothelial activation, autoimmune dysregulation is also actively involved in derangement of vascular homeostasis. For example, antiendothelial cell antibodies, occurring in 44%–84% of SSc patients induce endothelial cell apoptosis, thus contributing to several CVD pathologies including atherosclerosis, thrombosis and connective tissue diseases.[4-7] Anticentromere antibody positivity has been associated with plaque formation and ischemic arterial events compared to anticentromere antibody-negative patients (67% vs. 39% and 32% vs. 11%; \( P = 0.006 \) and \( P = 0.01 \), respectively) and to controls (67% vs. 41% and 32% vs. 7%, \( P = 0.02 \) and \( P = 0.0003 \), respectively).[9] Last but not least, antiphospholipid antibodies have been also linked to the presence of pulmonary arterial hypertension (PAH) in a population of 940 SSc patients.[10]

**Cardiovascular Disease Burden in Systemic Sclerosis**

CVD and cerebrovascular mortality account for 20%–30% of deaths in SSc.[11] In a retrospective study in 5,860 SSc patients, pulmonary fibrosis, PAH, heart failure, and arrhythmias were the leading disease-related causes of mortality.[12] Man et al. performed a systematic review to evaluate the relationship between SSc and macrovascular disease in the coronary, carotid, cerebrovascular, and peripheral vasculature, and they found an increased prevalence of atherosclerosis in all vessels. More specifically, the incidence rates of myocardial infarction (MI), stroke and peripheral vascular disease in 865 SSc patients were 4.4, 4.8, and 7.6/1,000 person/years, respectively, vs. 2.5, 2.5, and 1.9 in the 8,643 controls.[13] Moreover, the occurrence of myocardial infarction or stroke was compared between 1239 SSc patients and 10 age- and sex-matched controls per case. It was found that patients with SSc had an increased risk for myocardial infarction (HR: 3.49 [95% confidence interval [CI]], 2.52–4.83) and stroke (HR: 2.35, 95% CI: 1.59–3.48). The risk was highest during the 1st year following diagnosis (HR: 8.95; 95% CI: 5.43–14.74 and HR: 5.25; 95% CI, 2.90–9.53 for MI and stroke, respectively).[14]

In SSc, multiple mechanisms may contribute to CVD including atherosclerosis, vasculopathy, and vasospasm. A retrospective cohort study investigating the prevalence of macrovascular disease in females with ISSc concluded that peripheral macrovascular disease occurred more often in SSc patients; although, there was no significant difference in the prevalence of CVD compared to controls.[15] Results from the Australian Scleroderma Cohort Study including 850 SSc patients, as well as 15,787 and 8,802 individuals as controls from the National Health Survey and the Australian Diabetes, Obesity, and Lifestyle Study respectively, presented almost a 3-fold higher prevalence of coronary artery disease defined as history of percutaneous coronary intervention, coronary artery bypass grafting, angina or MI among SSc individuals even after controlling for diabetes mellitus, obesity and hypercholesterolemia.[16] A nationwide population-based prospective study, including 1344 SSc patients and 13,440 age-, sex-, and comorbidity-matched controls indicated that SSc patients had a 2.45-fold risk for developing acute myocardial infarction compared with the general population independently of the presence of relevant risk factors.[17] These findings are in line with population-based studies in Australia and Sweden suggesting a higher prevalence of coronary artery disease in SSc patients. In conclusion, most of the recent data show higher rates of atherosclerotic coronary artery disease in the SSc population compared to controls which constitute a relatively novel observation. Given the heterogeneity of the studies regarding methodology, patient sample and size as well as predefined outcomes, the necessity of larger well-designed studies is required to assess whether macrovascular involvement has a significant input in increased CVD morbidity and mortality observed in these patients.

**Morphological and Functional Markers of Atherosclerosis in Systemic Sclerosis**

The utilization on noninvasive methods for the assessment of morphological and functional markers of vascular dysfunction has been proposed for CVD risk stratification in a number of conditions related to atherosclerosis such as rheumatoid arthritis and diabetes mellitus as well as the general population.[18] In the context of SSc numerous studies have investigated surrogate markers such as carotid intima-media thickness, pulse wave velocity
and analysis. No differences in intima-media thickness between SSc patients and controls were reported by some authors\cite{19,20} while others have found abnormally high thickness in SSc patients.\cite{21,22} In a study of 22 SSc patients and 20 controls, no difference was found in the CIMT between the two groups, although there was an association between stiffness parameters, anti-Scl-70 antibodies and anticentromere antibodies.\cite{23} A systematic review and meta-analysis found significantly higher CIMT in SSc compared to controls, indicating that atherosclerosis is increased in SSc.\cite{24} In SSc, high IMT was variably associated with age, oxidized low-density lipoprotein (LDL), angiotensin-converting enzyme (ACE) polymorphism, and antibodies against human heat shock protein (HSP)-60 and mycobacterial HSP-65\cite{22} and steroid treatment,\cite{25} but not with disease duration and clinical characteristics.\cite{26,27} A recent systematic review and meta-analysis including studies on carotid intima-media thickness, flow-or nitrate-induced vasodilatation (flow-mediated dilatation, nitroglycerine-mediated dilatation), pulse wave velocity, augmentation index, and ankle-brachial pressure index concluded that abnormalities leading to macrovascular dysfunction are more prevalent in SSc patients compared to controls.\cite{28} With regard to peripheral artery disease Youssef et al., showed a 6-fold increased prevalence of peripheral macrovascular disease, detected by angiography, Doppler ultrasound or physical examination, in 31 patients with iSSc compared to controls.\cite{15} In summary, current data from the noninvasive evaluation of vascular morphology and function do not clearly indicate that surrogate markers of atherosclerosis are more prominent in SSc; however, a couple of recent meta-analyses imply that macrovascular function may be impaired in this population.

**Traditional Cardiovascular Disease Risk Factors**

Traditional CVD risk factors such as arterial hypertension, dyslipidemia, obesity, smoking, etc., are significant contributors to CVD in the general population and various disease settings associated with increased CVD. Although the prevalence of such factors in SSc has not been assessed in large studies, it appears they have a minimal contribution to the development of atherosclerosis as the majority of recent data have demonstrated a similar distribution of classic CVD risk factors between SSc patients and controls. For example, no difference was recorded between 40 SSc patients and 45 controls during 24-hour blood pressure monitoring.\cite{29} However, a small cross-sectional study of 48 SSc patients and 46 healthy subjects was reported that SSc patients were more likely to be hypertensive and have a lower body mass index than controls. In this study, family history of coronary heart disease and current smoking habit did not differ between the two groups.\cite{30}

Similarly, results from studies investigating cholesterol levels in SSc subjects have been inconclusive. In a case–control study of 31 female SSc patients and 33 matched healthy controls SSc patients had statistically significant differences in lipoprotein and high-sensitivity C Reactive Protein (hs-CRP) levels compared with the control group.\cite{31} In another study, the lipoprotein profile of 24 female SSc patients and 24 healthy age- and sex-matched controls was determined. Significantly lower levels of high-density lipoprotein (HDL) cholesterol and total cholesterol were observed in SSc patients than in controls.\cite{32} To lend more support to this, Mok et al. showed that SSc patients had significantly lower low-density lipoprotein LDL cholesterol levels ($P = 0.001$), HDL levels ($P = 0.01$), and BMI, compared to controls.\cite{33} However, this study indicated that SSc is an independent risk factor for coronary calcification, as assessed by the coronary artery calcium score. Moreover, in a study of 52 SSc patients and 43 age- and sex-matched controls, there were no significant differences in the risk factors measured between patients and controls including cholesterol, HDL, triglyceride, and glucose concentrations, as well as systolic and diastolic blood pressures.\cite{34} The Australian Scleroderma Cohort Study showed that hypercholesterolemia, diabetes mellitus, and obesity were significantly less prevalent in SSc patients than in controls.\cite{35} Studies examining the association between biochemistry parameters and vascular outcomes of atherosclerosis in SSc patients are presented in Table 1.

Taking everything together there is no robust data to suggest that conventional CVD risk factors are more prevalent in SSc patients compared to controls and large cohorts are required to determine the precise contribution of these factors to increased cardiac morbidity and mortality in this population.

**Primary Heart Disease**

Scleroderma heart involvement (SHI) is classically subdivided into two types: primary SHI and SHI secondary to either lung or kidney involvement. SHI may be clinically silent, and it is commonly overlooked or not promptly diagnosed. Unfortunately, when heart involvement manifests clinically, it is usually associated with advanced heart failure and unfavorable prognosis.\cite{36}

Early and widespread subclinical cardiac dysfunction occurs in many SSc patients. Myocardial fibrosis is the hallmark of cardiac involvement in SSc, featured with patchy fibrotic deposits, distributed throughout left and right myocardium\cite{37} leading to abnormal vasoreactivity, with or without associated structural vascular disease. Disturbances in coronary microcirculation precipitated by fibrotic changes in cardiac tissue affect myocardial contractility resulting in reduced regional and global myocardial performance. In a case–control study of the EUSTAR database, including 7,073 patients only 5.4% of them had impaired left ventricular (LV) function defined as ejection fraction $< 55\%$.\cite{38} Age, sex, diffuse
cutaneous disease, disease duration, digital ulcerations, renal and muscle involvement, disease activity score, pulmonary fibrosis, and pulmonary arterial hypertension PAH were associated with LV dysfunction. A high prevalence of right-sided diastolic abnormalities, as expressed by the tricuspid E/A ratio inversion, has been reported in SSc patients unrelated to the SSc subset, and was independently associated with both pulmonary hypertension and LV diastolic dysfunction. Studies presenting demographic and serology characteristics associated with cardiac involvement in SSc patients are demonstrated in Table 2.

However, conventional echocardiographic methods are not sensitive enough to detect such abnormalities and LV ejection fraction is not considered a reliable marker of primary heart disease in this population. Modern and more sophisticated imaging modalities such as tissue Doppler echocardiography and cardiac magnetic resonance imaging can detect defects in myocardial function, structure, and morphology at early asymptomatic stages. Cardiac magnetic resonance appears to be a rapid and noninvasive method of determining subclinical right myocardial involvement that is otherwise undetected in patients with SSc. Left ventricular dysfunction and kinetic abnormalities, thinning of left ventricle myocardium, alterations in left and right ventricular ejection fractions as well as right ventricular dilatation due to PAH are revealed by cardiac magnetic resonance. Moreover, N-terminal pro-brain natriuretic peptide detected accurately patients with depressed myocardial contractility and overall cardiac involvement. While these methods should be encouraged for research purposes, we acknowledge that they may not be recommended yet for standard evaluation.

Arrhythmias and other conduction abnormalities are thought to result from conduction system fibrosis, myocardial scarring as well as autonomic cardiac neuropathy. Atrial and ventricular tachyarrhythmias result from myocardial fibrosis, whereas conduction defects and bradyarrhythmias are a consequence of conduction system fibrosis. Autopsy findings show that when fibrosis of the conduction system occurs, it most commonly affects the sinoatrial node. The most common clinical symptoms are dyspnea, palpitations, and syncope. Sudden death may also occur.

Pericardial disease is another cardiac manifestation, symptomatic in a low percentage of patients. Pathology of pericardial disease is clinically apparent in over 5%–16% of the cases. At echocardiography, pericardial effusion can be detected in up to 41% of patients, and in a larger proportion of cases, 33%–72%, at autopsy. Pericardial involvement in SSc is usually asymptomatic and benign. In the majority of cases, the presence of small pericardial effusion does not produce clinical symptoms and does not possess clinical significance. Large pericardial effusions, hemodynamically significant, are usually secondary to severe complications such as heart failure in the context of renal crisis and/or PAH.

### Pulmonary Arterial Hypertension

Pulmonary disease is a frequent complication of SSc. The incidence of systemic-sclerosis related PAH (SScPAH) is 5%–13% based on right catheterization studies and is associated with a worse prognosis compared to other forms of PAH. These differences cannot yet be fully explained, but it has been suggested that disease- and age-related factors combined with unique characteristics of the SSc pulmonary vasculopathy may play a role. Several aspects including obstructive proliferative changes of the medium-size and small vessels of the pulmonary arterial vasculature, chronic hypoxia due to advanced lung disease and pulmonary veno-occlusive disease are thought to be the major contributors of SScPAH.

The right ventricle is more impaired in SScPAH than in other types of PAH due to the stiffening of the vessels or the primary heart involvement.
Table 2: Overview of studies correlating demographic and laboratory parameters with primary heart involvement in systemic sclerosis

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Demographic</th>
<th>Serology</th>
<th>Cardiac involvement</th>
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<tbody>
<tr>
<td>Ferri et al.</td>
<td>30</td>
<td>Higher heart rate, lower circadian</td>
<td>Anti-Ku</td>
<td>Autonomic cardiac neuropathy</td>
</tr>
<tr>
<td>Rodriguez-Reyna et al.</td>
<td>139</td>
<td>Male gender</td>
<td>Anti-histone, Anti-RNA polymerase antibodies I, II, and III</td>
<td>LV systolic dysfunction</td>
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<tr>
<td>Hesselstrand et al.</td>
<td>276</td>
<td>Black race</td>
<td>Anti-RNA polymerase antibodies I, II, and III</td>
<td>Arrhythmia, conduction disturbances</td>
</tr>
<tr>
<td>Kuwana et al.</td>
<td>275</td>
<td>Older age</td>
<td>Anti-Scl70, anti-U3 RNP</td>
<td>LV systolic dysfunction</td>
</tr>
<tr>
<td>Steen[42]</td>
<td>963</td>
<td>N-terminal pro-brain natriuretic peptide</td>
<td>Anti-Scl70, anti-U3 RNP</td>
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</tr>
<tr>
<td>Lloyd-Jones et al.</td>
<td>514</td>
<td>Reduced myocardial contractility</td>
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<td>LV systolic dysfunction</td>
</tr>
<tr>
<td>Laing et al.</td>
<td>2084</td>
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<td>LV systolic dysfunction</td>
</tr>
<tr>
<td>Manno et al.</td>
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<td>LV systolic dysfunction</td>
<td>Anti-Scl70, anti-U3 RNP</td>
<td>LV systolic dysfunction</td>
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Anti-Scl70: Anti-topoisomerase I antibodies, LV: Left ventricular

Diastolic dysfunction is common in SSc patients, even in the presence of normal systolic pulmonary and LV function. The presence of isolated right ventricular involvement may suggest a latent pulmonary hypertension in this group of patients, as is revealed by stress echocardiography and tissue Doppler echocardiography.[52,53]

Worse outcomes and poorer response to targeted therapies in SSc-PAH are also driven by the presence of subclinical left heart disease.[54] An echocardiographic study was concluded that left atrial volume, as well as N-terminal pro b-type natriuretic peptide, are significant predictors of elevated PAH.[55] In a cohort study of 98 PAH-SSc and IPAH patients, it was shown that N-terminal pro b-type natriuretic peptide levels are significantly higher in PAH-SSc than IPAH and stronger predictors of survival in PAH-SSc.[56] Collectively, such observations highlight the significant variations in cardiac function and neurohumoral response in SSc-PAH secondary to coronary microvascular disease, cardiac tissue fibrosis, and myocardial dysfunction typically occurring in SSc heart involvement.

Therapeutic Intervention

Although survival in SSc has improved in recent years, CVD is still responsible for 20%–30% of the disease-related deaths.[11] Some studies in SSc patients have described the benefits of treatment with vasodilators, such as dihydropyridine type CCBs, angiotensin-converting enzyme inhibitors, and endothelin-1 receptor antagonists.[57] A large European League Against Rheumatism Scleroderma Trial registry database analysis concluded that treatment with CCBs may play a protective role against the development of LV dysfunction.[16] New vasodilator agents (e.g., phosphodiesterase type 5 inhibitors and riociguat)[58] that are beneficial in SSc-PAH and digital ulcers, may provide future-safe alternative therapies of SSc-related vasculopathy. Oxidative stress linked to nitric oxide synthase uncoupling is one of the major features during the transition from cardiac hypertrophy to overt heart failure. As it has been shown, nitric oxide synthase recoupling accompanied by increased nitric oxide bioavailability ameliorates cardiac hypertrophy and promotes right ventricular relaxation and improvement of right heart systolic and diastolic function in SSc-PAH.[52] PDE5 inhibitors, in addition to their basic role as a leading therapy for PAH and digital ulcers, may provide further benefit to SSc patients, improving coronary vasculature potency and ameliorating the myocardial ischemic damage.[35] Moreover, early diagnosis and treatment of SSc-PAH with novel targeted therapies can prevent the development of secondary heart disease.[59]

Equally important with the management of primary heart disease is the assessment and monitoring of traditional CVD risk factors, and treatment with lipid-lowering and/or antihypertensive agents, as per recommendations implemented in the general population. In this respect, lifestyle changes, such as physical activity and adopting a better diet, may also improve the overall quality of life and lead to a better management of CVD risk.

Conclusions

Recent advances have considerably improved our understanding of the distinct processes involved in SSc-related vasculopathy and heart disease. It remains unclear whether accelerated atherosclerosis contributes and to which extend in poor outcomes of SSc individuals particularly in view of CVD complications and events. More and better-designed studies are needed to clarify the exact mechanisms involved in micro- and macro-circulation in SSc patients and translate experimental and clinical findings into better care and prognosis of this devastating disease. The differentiation between primary SHI and macrovascular involvement and especially their contribution to overall CVD morbidity and
mortality rates is yet to be established. Prevention and surveillance of CVD disease can play an important role in improving long-term outcomes in SSc.

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There are no conflicts of interest.

**References**