Cardiovascular disease in systemic sclerosis

Francesca Cannarile*, Valentina Valentini*, Giulia Mirabelli, Alessia Alunno, Riccardo Terenzi, Filippo Luccioli, Roberto Gerli, Elena Bartoloni

Department of Medicine, Rheumatology Unit, University of Perugia, Via dal Pozzo 06132, Perugia, Italy
*These authors contributed equally to this work.
Correspondence to: Roberto Gerli. Department of Medicine, Rheumatology Unit, University of Perugia, Via dal Pozzo 06132, Perugia, Italy.
Email: roberto.gerli@unipg.it.

Abstract: Cardiovascular (CV) system involvement is a frequent complication of autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). It still remains unclear if a premature atherosclerosis (ATS) occurs even in systemic sclerosis (SSc). Although microvascular disease is a hallmark of SSc, in the last few years a number of studies highlighted a higher prevalence of macrovascular disease in SSc patients in comparison to healthy individuals and these data have been correlated with a poorer prognosis. The mechanisms promoting ATS in SSc are not fully understood, but it is believed to be secondary to multi-system organ inflammation, endothelial wall damage and vasculopathy. Both traditional risk factors and endothelial dysfunction have been proposed to participate to the onset and progression of ATS in such patients. In particular, endothelial cell injury induced by anti-endothelial antibodies, ischemia/reperfusion damage, immune-mediated cytotoxicity represent the main causes of vascular injury together with an impaired vascular repair mechanism that determine a defective vasculogenesis. Aim of this review is to analyse both causes and clinical manifestations of macrovascular involvement and ATS in SSc.

Keywords: Atherosclerosis (ATS); cardiovascular (CV) disease; systemic sclerosis (SSc)

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology characterized by three hallmarks: (I) vasculopathy with the pathognomonic microvascular involvement; (II) fibrosis of skin and visceral organs; (III) systemic inflammation characterized by the presence of circulating autoantibodies and pro-inflammatory cytokines (1,2).

Studies have consistently shown a substantially increased mortality in SSc with a pooled standardized mortality ratio ranging between 2.7 and 3.5. In particular, cardio-pulmonary complications, including pulmonary arterial hypertension and interstitial lung disease, represent the main causes of reduced life expectancy and death in these patients (3).

Indeed, it has been widely demonstrated that patients with autoimmune disease, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), present a higher mortality risk mainly for cardiovascular (CV) events. In this setting, acceleration of subclinical atherosclerotic damage has been advocated as the main mechanism leading to this increased risk. However, etiopathogenesis underlying atherosclerotic wall damage is still under investigation. A close interplay between traditional CV risk factors and inflammatory and autoimmune markers may contribute to both induction and progression of atherosclerosis (ATS) in these patients (4-8).

It remains still unclear whether accelerated ATS occurs even in SSc and studies aimed to investigate subclinical ATS risk in scleroderma patients produced contrasting data. In comparison to SLE and RA, accelerated ATS appears to have a different prevalence in SSc. Moreover, the inflammatory component seems to be less prominent and ATS less aggressive in SSc, making more difficult to demonstrated subclinical ATS in these patients.

Data derived from studies carried out in 60's and 70's, when the main cause of death was scleroderma renal crisis,

suggested that clinically manifested ATS was rare in SSc patients and that CV involvement was most likely the result of vasospasm of coronary arteries. Indeed, following recent advances in the treatment of scleroderma renal crisis and pulmonary arterial hypertension, causes of mortality in SSc changed and recent systematic reviews concluded that prevalence of ATS was increased in all vessels studied in SSc patients (9-11). Prevalence of CV and macrovascular disease has been demonstrated to be increased in SSc patients in comparison to healthy individuals and correlated with a poorer prognosis (9,12) and, actually, 20-30% of deaths in SSc patients are attribuitable to CV causes. In particular, the 2010 survey from the European League Against Reumatism Scleroderma Trials and Research (EUSTAR) database estimated that 26% of SSc-related causes of death were due to cardiac causes (mainly heart failure and arrhytmias) and 29% of non-SSc-related causes of death were due to CV causes (13). Interestingly, a recent cross-sectional analysis of a large United States hospitalization database [1993-2007] estimated that approximately 5.4% of 308,452 SSc hospitalizations were associated with atherosclerotic CV disease as a primary discharge diagnosis. This study represents the first evidence for higher in-hospital mortality associated with atherosclerotic CV disease in SSc compared to scleroderma patients free from atherosclerotic CV disease and to SLE and RA patients with atherosclerotic CV disease (14).

Primary cardiac involvement in SSc may manifest with different features, including myocardial damage, fibrosis of the conduction system, pericardial and, less frequently, valvular disease. In addition, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension and kidney pathology. The prevalence of primary cardiac involvement in SSc is variable and difficult to determine because of diversity of cardiac manifestations, presence of subclinical periods, type of applied diagnostic tools and differences in patient populations. Microvascular disease, characterized by both vasospasm and structural alterations, is a pathognomonic feature of SSc and Raynaud's phenomenon, pulmonary arterial hypertension and scleroderma renal crisis represent the main clinical manifestations. Of interest, microvascular involvement is thought to predict macrovascular ATS over time (15,16). Moreover, endothelial dysfunction contributes to the pathogenesis of atherosclerotic risk in SSc. It is well documented that, in an early stage of scleroderma, the endothelial cell layer of microcirculation is activated and/ or injured by unknown and different mechanisms, including infection-induced apoptosis, immunomediated cytotoxicity, anti-endothelial antibodies or ischemia-reperfusion injury. In addition, increased levels of endothelin, the most potent vasoconstrictive peptide released from endothelial layer, play a pivotal role in endothelial dysfunction in both SSc and ATS (17).

The main clinical features of atherosclerotic disease in SSc patients are represented by an involvement of peripheral, cerebrovascular, carotid and coronary arteries with consequent high risk of peripheral vascular disease, stroke and coronary heart disease.

In this review, we summarized recent evidences about ATS in SSc and discuss the question whether CV risk is increased in SSc patients as compared to the general population, given the potential relevant consequences on the management of such patients.

Etiopathogenesis of subclinical ateroslerosis

The etiology of ATS in SSc is unknown, but it may be secondary to concomitant multiple factors, including traditional CV risk factors, increased endothelial damage, and disease-specific immunologic and autoimmune factors (10).

Traditional CV risk factors

Although the prevalence of traditional CV risk factors in SSc has not been assessed in large studies, traditional CV risk factors alone do not seem be able to explain CV disease because the majority of these studies showed a similar distribution between patients and controls, thereby suggesting that other factors may contribute to the increased prevalence of CV disease in SSc (18). A Chinese study revealed a slight increase in blood pressure and fasting glucose and a lower BMI in SSc population (19), but other studies failed to show increased frequencies of obesity, hyperlipidaemia, hypertension and diabetes in SSc (9,20-22).

Results from studies on lipids are contradictory. Indeed, Lippi *et al.* reported high levels of lipoprotein (a), which are usually associated with increased CV risk (23), whereas Borba *et al.* depicted lower levels of high density lipoprotein and total cholesterol in SSc patients with respect to controls (24). Moreover, SSc patients may have increased levels of low density lipoproteins (LDL), as well as homocysteine and C-reactive protein (CRP), all associated with an increased risk of ATS (25). In addition, hypercholesterolaemia, diabetes mellitus and obesity were significantly less prevalent in SSc compared with the general population

in the Australian Scleroderma Cohort Study (18). Thus, further studies evaluating the role of traditional CV risk factors in determining CV risk in SSc are needed.

Mechanisms of endothelial damage

It is well recognized that clinical and pathological features of vascular damage and endothelial cell activation represent an important hallmark of scleroderma vasculopathy, even in absence of other concomitant risk factors. An impairment of endothelium-dependent vasodilation seems to occur before the onset of clinical ATS in SSc, highlighting the role of endothelial damage as one of the most important mechanisms involved in the pathogenesis of ATS itself (25). Vascular endothelium is a functionally remarkable organ regulating coagulation, fibrinolysis, permeability, vasomotion and inflammation. Different mechanisms have been demonstrated to induce and perpetuate endothelial dysfunction and progressive vasculopathy in scleroderma patients. Among these, dysregulation of vascular tone, as consequence of an imbalance between vasoconstrictor and vasodilator mediators, defective angiogenesis, endothelial injury/activation elicited by the activation of innate and adaptive immune response and functional defects of progenitor endothelial cells have been advocated as main pathogenic mechanisms underlying endothelial damage in SSc (26,27). Moreover, chronic endothelial cell perturbation and activation induced by ischemia and reperfusion lead to dysfunction and irreversible loss of integrity, with cell detachment and tissue injury. In scleroderma, indeed, the severe tissue hypoxia associated with chronic blood flow reduction represents a major stimulus for increased expression of vascular endothelial growth factors (VEGF) and abnormal angiogenesis. However, chronic tissue hypoxia and reduced flow circulation lead to a condition of defective vascularization (28). Up-regulation of VEGF also contributes to the development of fibrosis in both inflammatory and non-inflammatory stages of the disease (29). In particular, new blood vessels may form as consequence of an endothelial sprouting from pre-existing endothelial cells (angiogenesis) or peripheral recruitment of bone marrow-derived circulating endothelial progenitor cells (EPCs). Recent findings demonstrated that EPCs, in response to a condition of vascular injury or ischemia and in association with resident endothelial cells, contribute, at least in an early stage of the disease, to vascular healing by homing in the damaged endothelium, as demonstrated in other autoimmune diseases like Sjögren's syndrome (30). In

this setting, the reduced number of EPCs, their impaired differentiation in mature EPCs or reduced migratory ability may be considered indirect markers of subclinical ATS in many rheumatic diseases. Data concerning EPC levels in SSc seem to be conflicting mainly because of the different methods employed to detect EPCs. Moreover, disease duration represents an important factor to consider in the interpretation of available results. In this setting, a significantly increased number of EPCs has been demonstrated in patients with early stage of the disease, while patients with late SSc appear to be characterized by a reduced number of EPCs, suggesting a probable exhaustion of the precursor endothelial pool during disease course. Moreover, a low number of circulating EPCs seems to characterize a more active disease phenotype, identified by higher risk of digital vascular lesions and higher severity score (31-34). Moreover, SSc circulating EPCs are characterized by a defective functional phenotype with consequent defective migratory activity and impaired recruitment to ischemic damaged tissue. The presence of circulating antibodies with anti-endothelial activity in scleroderma patients may be considered an adjunctive mechanism associated with chronic endothelial damage (35,36). A novel marker of endothelial damage is the detection of circulating endothelial cells (CECs) released in the systemic circulation after detachment of cells from basement membrane in response to endothelial injury. Indeed, an increased number of circulating CECs has been demonstrated in patients with myocardial infarction (MI), unstable angina, peripheral vascular disease, but also in SSc, suggesting their role as marker of chronic endothelial damage (37,38).

Patterns of ATS in SSc

In consideration of the variability of expression of subclinical and functional atherosclerotic damage in SSc, ATS may be analyzed according to the type of vessels involved.

Peripheral arteries

Several observational studies have studied the prevalence of peripheral arterial disease (PAD) in SSc (39). Macrovascular disease, defined as involvement of blood vessels with an internal diameter >100 microns, has been recognized in conjunction with the more distal small vessel pathology (17). For example, a correlation between

morphology and bood flow of the proper palmar digital arteries and nailfold capillary morphology has been clearly demonstrated, providing evidence that progression of microvascular disease is linked to macrovascular disease. Scleroderma patients with low microvascular damage, which is with "early" capillaroscopic pattern, had a normal morphology of the proper palmar digital arteries with reduced blood flow and increased vascular resistance. The progression of microvascular damage can be identified by the evidence of an active and late capillaroscopic pattern and anti-topoisomerase I antibodies represented an independent predictive factor for macrovascular damage (40).

To elucidate the prevalence of PAD in SSc, several techniques other than physical examination (hystory of claudication or absence of pulses), have been employed. In particular, surrogate markers of atherosclerotic damage, including ankle brachial pressure index (ABPI) for arterial lower extremity involvement, blood pressure interarm difference (systolic/diastolic interarm difference) for proximal arterial disease of the upper extremities, pulse wave velocity (PWV) and pulse wave analysis (PWA) to evaluate arterial stiffness, have been demonstrated to be useful indicators of atherosclerotic wall damage. Youssef and colleges, showed a 6-times increased prevalence of peripheral macrovascular disease, detected by angiography, doppler ultrasound or physical examination, in 31 patients with limited SSc compared to controls (41). In a SSc cohort of young and mainly female patients, Veale and colleagues demonstrated a 22% prevalence of symptomatic PAD, as shown by the presence of intermittent lower limb claudication detected by Edinburgh Claudication questionnaire. This rate was almost five times greater than the 4.5% prevalence of symptomatic PAD in the general population, as reported by the similar WHO claudication questionnaire (42).

ABPI is a validated diagnostic tool for lower extremity PAD. In American College of Cardiologist/American Heart Association Practice Guidelines for Management of Patients with PAD, abnormal ABPI is defined as a continuous variable less than 0.90 and increasingly lower values reflect increased rate of arterial disease (19). A significantly increased prevalence of atherosclerotic PAD, defined by an ABPI cut off <0.99, has been demonstrated in 54 SSc patients with respect to controls in absence of difference of traditional CV risk factors between the two groups. In addition, two patients developed critical limb ischemia requiring surgery and, hystologically, the lesion resulted similar to an atheroma (43). These findings were

further confirmed by Wan *et al.*, who depicted ABPI values lower than 1.0% in 12% of 119 SSc patients examined without evidence of a significant difference between lcSSc and dcSSc. Circulating anti-centromere antibodies have been demonstrated to be more frequent in patients with symptomatic ischemic events (44). Anti-centromere positivity, in association with older age, smoking and limited cutaneous disease, resulted significantly associated with lower ABPI in a recent longitudinal study demonstrating that ABPI values remain stable in most SSc patients over time (45). Zeng and colleages showed that SSc patients are more likely to develop PAD, including upper and lower extremities arteries, as compared to healthy controls, being patients characterized by a lower ABPI and a higher blood pressure interarm difference (19). In addition, SSc itself resulted independent risk factor of PAD. In contrast with other studies, an increased PWV, marker of aortic wall stiffness, was not depicted in this Chinese population (19). Other two studies, however, failed to find differences in ABPI between SSc patients and healthy controls (46,47). Different inclusion criteria, such as different disease duration, may explain data discrepancy between studies. A recent study, performed in a small group of patients, suggested that the earliest endothelial changes in early diffuse SSc (<2 years from the first SSc symptoms) occur in smaller arterioles and microvascular beds, but not in medium or macrovascular beds (48). Other investigations showed a modest correlation between duration and arterial stiffness, suggesting that the macrovascular changes may progress over disease course (49,50), while others demonstrated that macrovascular dysfunction appears in early disease (25,51). Furthermore, angiographic findings of the lower and upper limb in SSc patients showed a correlation between CV risk factors and proximal, but not distal, PAD. Although with the limitation of the small sample size (26 angiograms), a retrospective study suggests that the microvasculopathy related to disease pathogenesis more than atherosclerotic damage may be considered the leading mechanism of peripheral vascular abnormalities in SSc (52). It has been recently shown that upper limb macrovascular arterial vasculopathy may occur in SSc female patients irrespective of the disease pattern and higher number of arterial vasculopathy was significantly associated with systolic pulmonary artery pressure (53).

Flow-mediated vasodilatation (FMD) is usually evaluated by ultrasonographic measurement of artery diameter at baseline and maximal vasodilatation following periodic ischemia, achieved by external cuff inflation. It is dependent

on the endothelium function following the release of endogenous substance from endothelium such as nitric oxide (16). A systematic review and meta-analysis (10) analyzed seven studies which evaluated the brachial artery FMD in SSc patients. In 57% of these studies (25,54-56), a significantly lower brachial artery FMD was observed in SSc compared to controls. Nytroglycerin-mediated dilatation (NMD) is usually measured by evaluating the percentage of change of arterial diameter from baseline following administration of 25-400 mcg sublingual nitroglicerin. Unlike FMD, this parameter is independent of endothelium function. Szucs *et al.* (25) investigated FMD and NMD in SSc patients compared with healthy controls demonstrating an impaired FMD in SSc, while NMD was preserved, as confirmed in a recent review (16).

Arterial stiffness is a well-validated surrogate marker of subclinical ATS and independent predictor of CV events and mortality (57). In a recent study, 40 SSc patients free from CV were demonstrated to have higher augmentation index (AIx), a composite measure of central aortic pressure enhancement by a reflected pulse wave, with respect to healthy controls. PWV, however, was not significantly increased. Interestingly, there was a paradoxical association between calcium channel blocker therapy and higher AIx. This correlation may reflect generalised vasculopathy rather than atherosclerotic disease (58). An elevated AIx in SSc suggests an increased prevalence of subclinical ATS. However, microvascular disease or myocardial dysfunction may also contribute to the observed abnormality, because AIx is a composite measure of arterial stiffness determined by PWV, arterial wave reflection and left ventricular ejection, thus providing additional information regarding vascular dysfunction in SSc in comparison to PWV alone (59). Other studies evaluating arterial stiffness in SSc showed different results, mainly because of small sample sizes. Some studies found higher AIx and PWV in diffuse SSc patients compared with controls (50,60-62), whilst Liu *et al.* found regional differences in PWV, with elevation at the forearm and arm, but no difference at the upper arm, aorta or leg (63). In contrast, several other studies found no elevation of arterial stiffness in SSc patients (19,64-66).

Taken together, these data suggest that SSc patients are more likely to develop PAD and scleroderma may be considered a risk factor of PAD.

Cerebrovascular vessels

Literature data aimed to estimate the prevalence of cerebrovascular disease in SSc and the relationship between disease and risk of ischaemic stroke is uncertain (67).

Cerebral involvement is currently not recognized as disease manifestation, although cerebral vascular involvement was described almost 50 years ago (68) and several studies suggested that cerebral disease may be underestimated (69-71). On the other hand, central nervous system may be affect by a microvascular damage as complication of systemic involvement (72). Patients with circulating anti-U1 RNP and anti-Scl70 antibodies have a higher risk of developing neurological complications (73). Intracerebral vascular calcifications, an independent risk factor of ischaemic stroke in the general population (74), were found by non contrast CT scan in 32% of asymptomatic SSc patients but in only 9% of controls (75). White matter hyperintensities on brain MRI, a known risk factor for future symtomatic stroke (76), were more common in asymptomatic SSc patients than in healthy controls (77,78). Furthermore, a single photon emission computed tomography (SPECT) investigation showed focal or diffuse hypoperfusion in mainly neurologically asymptomatic SSc patients, perhaps for microangiopatic damage of brain vessels (79). A retrospective small size cohort study found a not statistically significant increased prevalence (1.3 times) of cerebrovascular disease (transient ischemic attack, stroke, carotid or vertebral artery bruits, doppler evidence of carotid or vertebral artery disease, or angiographic evidence of carotid artery stenosis) in SSc patients with respect to controls (41). Interestingly, enhanced incidence of stroke has been reported in a large epidemiological study involving 865 scleroderma patients with a risk of 2.61 (20), while a nationwide cohort study conducted in Taiwan concluded that SSc is independently associated with a 43% increase in ischaemic stroke risk compared to healthy controls. Medications commonly employed in these patients, including calcium channel blockers, angiotensin-converting enzyme inhibitors, oral corticosteroids or immunosuppressants, did not modify the risk (67).

A significant increased prevalence of carotid artery stenosis, evaluated by B mode and color Doppler ultrasound, was demonstrated in 64% of patients with SSc with respect to controls without difference in the traditional CV risk factor profile between the two groups. Since carotid artery stenosis is a predictive factor of stroke, these findings suggest that SSc patients may have an increased risk of stroke (43). The increased ischaemic stroke risk in SSc may be due to different pathogenic mechanisms such as vascular injury, chronic inflammation and vasospasm (67). Cerebral vascular involvement may be

caused by endothelial dysfunction and ATS (80), but SSc is also associated with autoantibody production and, during disease course, patients develop functional and structural alterations in mutiple vascular beds with progressive visceral organ dysfunction secondary to fibrosis. Moreover, the apparent efficacy of immunosuppressive drugs in stroke treatment suggests a plausible association with inflammatory or immune mechanisms in these patients (81). Finally, cerebral vasospasm ("Raynaud's phenomenon-like") may be associated with transient ischaemic attacks or focal neurological defects and it is evidenced by reversibility of arterial lesions and absence of specific histologic findings (82).

Carotid arteries

Several groups have studied subclinical early ATS in SSc by ultrasound evaluation of carotid intima-media thickness (IMT) with conflicting results. Vessel IMT is calculated by measuring the avarage thickness of the intima-media complex, which is the distance between the first and the second echogenic lines from the lumen. It is widely recognized that IMT is a predictor of increased coronary artery disease (CAD), stroke and death in the general asymptomatic population. In SSc, some studies found no difference in IMT values between scleroderma patients and controls (63,66,83), while others depicted increased IMT in patients (55,84). These conflicting results have been further demonstrated in a recent review aimed to analyze studies reporting IMT in scleroderma patients in comparison to controls. Data interpretation may be hampered by small size of the cohorts enrolled and by variability of IMT ultrasonographic measurement between studies (9). No differences in IMT between SSc patients and controls were also demonstrated in a recent study where, on the other hand, significantly increased stiffness parameters were depicted in patients in comparison to controls (62). Moreover, a positive correlation of such parameters with anti-Scl-70 serum levels and an inverse correlation with anti-centromere antibodies were found in the same study. A 2011 systematic review and meta-analysis found significantly higher carotid IMT values in SSc patients compared to controls in 43% of 14 studies analyzed, demostrating increased risk of ATS. Of interest, IMT values, directly correlated with disease duration, was similar to those observed in patients with RA, diabetes mellitus or familial hypercolesterolemia (10). Similar findings were reported in a previous systematic and meta-analysis review involving six studies on scleroderma patients (85). Interestingly, a meta-analysis of longitudinal studies showed that increase

in carotid IMT (≥0.10 mm) was correlated with age- and sex-adjusted relative risk of 1.15 for myocardial infarction and 1.18 for stroke. Moreover, SSc patients were demonstrated to have enhanced risk of myocardial infarction and/or stroke compared to healthy subjects, in particular in late disease (86). In SSc, high IMT was variably associated with age, oxidized low-density lipoprotein (84), steroid treatment (87), angiotensin-converting enzyme polymorphism and antibodies against human heat shock protein (HSP)-60 and mycobacterial HSP-65 (84), but not with disease duration and clinical characteristics.

Finally, a recent study involving 46 SSc patients showed a significant higher prevalence of carotid plaque (45.6% vs. 19.5%) with similar carotid IMT in comparison to matched controls. Of interest, SSc patients with plaque were characterized by increased concentration of serum proteins implicated in both vasculopathy and fibrosis in comparison to patients without plaque (88).

Coronary arteries

The prevalence of ATS involving coronary vessels and its clinical manifestation, including angina, MI and sudden death, is difficult to evaluate in SSc. Indeed, primary cardiac involvement may depend on myocardial damage secondary to microvascular alterations (vasospastic events which result in areas of focal ischemia and recurrent ischemia-reperfusion injury), myocardial fibrosis with a 'mosaic' distribution (due to collagen accumulation), involvement of the conduction system with consequent arrhythmias and conduction defect, but also pericardial and valvular disease. Moreover, secondary heart disease due to renal vasculopathy, interstitial lung disease and pulmonary arterial hypertension, could adversely influence cardiac function and symptoms of cardiac complications could be not specific and overlapping with those of other comorbidities. Furthermore, hypertension, obesity, diabetes and other comorbidities may contribute to adversely influence cardiac function, mainly in older SSc patients (89). Of note, MI has been described in SSc patients with unaffected coronary arteries. In this setting, microvascular disease leading to ischemic events and contraction band necrosis, resulting from both occlusive vascular disease and intermittent vasospasm (the so called 'myocardial Raynaud's phenomenon'), has been demonstrated to be the main mechanism associated with myocardial ischemic events in these patients.

Two large cross-sectional cohort studies demonstrated

higher risk of coronary heart disease in SSc patients compared to the general population. The Australian Scleroderma cohort study investigated the prevalence of coronary heart disease, including MI, percutaneous coronary intervention, coronary artery bypass grafting, and CV risk factors in a wide cohort of SSc patients. An increased prevalence of about 3 times of coronary heart disease was found in the SSc group with respect to controls, even after controlling for diabetes mellitus, obesity and hypercholesterolemia (18). Similarly, a more recent study provided evidence that SSc is associated with increased risk of developing MI, stroke and peripheral vascular disease. The incidence rates of MI, stroke and peripheral vascular disease in 865 SSc patients were 4.4, 4.8 and 7.6 per 1,000 person/years, respectively, *vs.* 2.5, 2.5 and 1.9 in the 8,643 controls. These associations persisted after adjustment for CV risk factors, including BMI, smoking, hypertension, diabetes and hyperlipidaemia, suggesting that the increased risk of CV events in SSc may depend on both ATS and non-atherosclerotic factors, like vasospasm, SSc specific vasculopathy, vasculitis and thrombosis (20). Similar results were found in a recent nationwide population-based prospective study (90), showing that risk of acute MI was independently associated with SSc with a 2.45-fold greater risk in 1,344 SSc patients compared with 13,440 age-, sex- and comorbidity-matched controls. In addition, the impact of SSc on acute MI risk in this Japanese cohort resulted greater than hypertension (HR 2.08) and diabetes (HR 2.14), while immunosuppressants did not reduce this risk. Of note, only 1/3 of acute episodes of MI had CAD, confirming that MI may be caused by microvascular ischaemia and not only by coronary artery stenosis (90). A Swedish study showed that 111 SSc patients were at enhanced risk for ischemic heart disease and PAD, but not for ischemic cerebrovascular disease compared to controls. Moreover, patients with anti-centromere antibodies (ACA) had more plaques and more ischaemic arterial events compared to the other SSc patients, while anti-topoisomerase I-positive patients were characterized by fewer ischemic events. Such findings suggest that antibody profile and different disease subsets may contribute to macrovascular involvement. Moreover, in the whole SSc group, plaque occurence, IMT and ABI did not differ between patients and controls (91), in line with previous findings (83). In fact, several studies suggest that vasospasm, rather than ATS, is a major pathogenic mechanism of SSc-related heart disease. In addition, epicardial coronary arteries in SSc patients have been reported to be free of significant lesions even in the setting of

MI, congestive heart failure and sudden cardiac death (92).

Coronary vessel involvement has been ascertained invasively by coronarography in a few small studies. Akram *et al.* found that the prevalence of CAD in 172 SSc patients with suspected CAD was similar to that detected in controls (93). In addition, Derk *et al.* showed normal angiograms among 11 SSc patients hospital admitted because of acute myocardial disease. The odds ratio of having normal coronary arteries was 33.89 compared to patients from general population, further suggesting a microvascular involvement in these patients (92). In contrast, Tarek *et al.* assessed coronary arterial involvement in 14 asymptomatic female SSc patients free from CV risk factors, detecting 19 coronary angiographic abnormalities ranging from ectasia with slow flow, coronary stenosis, calcification, spasm and tortuosity. These findings suggest that coronary artery vasculopathy is common even in absence of classic CV risk factor, further supporting the role of disease as relevant risk factor for CAD (94). Easier and noninvasive methods such as transthoracic echocardiography with the evaluation of coronary flow reserve (CFR), a diagnostic marker of CAD, confirmed coronary vessels involvement. A reduction of CFR was found in 20 subjects with diffuse SSc and no signs or symptoms of CVD compared to controls (61). Subclinical coronary ATS may be also evaluated through multidetector computed tomography, a novel noninvasive procedure that provides a surrogate marker for coronary ATS by generating a coronary calcium score. Patients with SSc were found to have higher levels of coronary calcium and homocysteine than age-and sex-matched controls, but correlation between coronary calcification and angiographic data was not evaluated. However, another investigation showed that signs of coronary calcification by coronary CT were present in 56.2% of SSc patients and in only 18.8% of age-, sex-, and race-matched controls (95). The presence of coronary calcified plaques in SSc patients asymptomatic for angina was also demonstrated using computed tomography coronary angiography, confirming that subclinical ATS is not uncommon in SSc (96). The same group reported that SSc is an independent risk factor for increased coronary artery calcium deposition (21). Finally, a recent systematic meta-analysis review demonstrated a statistically significant increased CAD risk among SSc patients with a pooled risk ratio of 1.82 CAD, differently defined as acute MI, old MI, angina or coronary artery intervention (97).

In summary, angiographic, sonographic and computed tomography studies have provided conflicting data

regarding the presence of macrovascular coronary lesions and accelerated ATS in SSc. Screening for subclinical cardiac involvement provides an opportunity for early diagnosis and treatment, which is crucial for a positive outcome. Thus, SSc patients should be closely followed and modifiable risk factors should be treated at an early stage.

Conclusions

At the moment, the contribution of active inflammation, fibroproliferative vascular damage and traditional CV risk factors in accelerating ATS and consequent CVD is unclear as well as the morbidity and mortality associated with these conditions. However, since macrovascular disease seems to be more common in SSc, screening of SSc patients may allow to identify and treat patients at an early stage with the aim to lower the rate of CV mortality in these patients.

In addition, atherosclerotic mechanisms underlying CV events, such as MI, stroke and PAD, may be different. In this setting, other disease-specific factors, including medication use and lack of exercise may contribute to ATS disease.

In summary, CVD disease prevention and surveillance represent an opportunity to further reduce morbidity and mortality in SSc and, in consequence, modification of traditional CV risk factors should be part of standard care for these patients. However, additional research by large population-based studies is needed to determine mechanisms and prevalence of premature ATS in scleroderma patients.

Acknowledgements

References

1. Dumoitier N, Lofek S, Mouthon L. Pathophysiology of systemic sclerosis: state of the art in 2014. Presse Med 2014;43:e267-78.
2. Papagoras C, Achenbach K, Tsifetaki N, et al. Heart involvement in systemic sclerosis: a combined echocardiographic and scintigraphic study. Clin Rheumatol 2014;33:1105-11.
3. Rubio-Rivas M, Royo C, Simeón CP, et al. Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208-19.
4. Bartoloni Bocci E, Luccioli F, Angrisani C, et al. Accelerated atherosclerosis in systemic lupus erythematosus and other connective tissue diseases. Expert Rev Clin Immunol 2007;3:531-41.
5. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112:3337-47.
6. Bartoloni E, Alunno A, Bistoni O, et al. How early is the atherosclerotic risk in rheumatoid arthritis? Autoimmun Rev 2010;9:701-7.
7. Sarzi-Puttini P, Atzeni F, Gerli R, et al. Cardiac involvement in systemic rheumatic diseases: An update. Autoimmun Rev 2010;9:849-52.
8. Bartoloni E, Shoenfeld Y, Gerli R. Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. Arthritis Care Res (Hoboken) 2011;63:178-83.
9. Hettema ME, Bootsma H, Kallenberg CG. Macrovascular disease and atherosclerosis in SSc. Rheumatology (Oxford) 2008;47:578-83.
10. Au K, Singh MK, Bodukam V, et al. Atherosclerosis in systemic sclerosis: a systematic review and meta-analysis. Arthritis Rheum 2011;63:2078-90.
11. Soriano A, Afeltra A, Shoenfeld Y. Is atherosclerosis accelerated in systemic sclerosis? Novel insights. Curr Opin Rheumatol 2014;26:653-7.
12. Blagojevic J, Matucci Cerinic M. Macrovascular involvement in systemic sclerosis: comorbidity or accelerated atherosclerosis? Curr Rheumatol Rep 2007;9:181-2.
13. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15.
14. Dave AJ, Fiorentino D, Lingala B, et al. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: higher mortality than patients with lupus and rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:323-7.
15. Ngian GS, Sahhar J, Wicks IP, et al. Cardiovascular disease in systemic sclerosis--an emerging association? Arthritis Res Ther 2011;13:237.
16. Nussinovitch U, Shoenfeld Y. Atherosclerosis and macrovascular involvement in systemic sclerosis: myth or reality. Autoimmun Rev 2011;10:259-66.
17. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum 2013;65:1953-62.

18. Ngian GS, Sahhar J, Proudman SM, et al. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012;71:1980-3.

19. Zeng Y, Li M, Xu D, et al. Macrovascular involvement in systemic sclerosis: evidence of correlation with disease activity. Clin Exp Rheumatol 2012;30:S76-80.

20. Man A, Zhu Y, Zhang Y, et al. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. Ann Rheum Dis 2013;72:1188-93.

21. Mok MY, Lau CS, Chiu SS, et al. Systemic sclerosis is an independent risk factor for increased coronary artery calcium deposition. Arthritis Rheum 2011;63:1387-95.

22. Zakopoulos NA, Kotsis VT, Gialafos EJ, et al. Systemic sclerosis is not associated with clinical or ambulatory blood pressure. Clin Exp Rheumatol 2003;21:199-204.

23. Lippi G, Caramaschi P, Montagnana M, et al. Lipoprotein[a] and the lipid profile in patients with systemic sclerosis. Clin Chim Acta 2006;364:345-8.

24. Borba EF, Borges CT, Bonfá E. Lipoprotein profile in limited systemic sclerosis. Rheumatol Int 2005;25:379-83.

25. Szucs G, Tímár O, Szekanecz Z, et al. Endothelial dysfunction precedes atherosclerosis in systemic sclerosis--relevance for prevention of vascular complications. Rheumatology (Oxford) 2007;46:759-62.

26. Altorok N, Wang Y, Kahaleh B. Endothelial dysfunction in systemic sclerosis. Curr Opin Rheumatol 2014;26:615-20.

27. Fleming JN, Nash RA, Mahoney WM Jr, et al. Is scleroderma a vasculopathy? Curr Rheumatol Rep 2009;11:103-10.

28. Farouk HM, Hamza SH, El Bakry SA, et al. Dysregulation of angiogenic homeostasis in systemic sclerosis. Int J Rheum Dis 2013;16:448-54.

29. Maurer B, Distler A, Suliman YA, et al. Vascular endothelial growth factor aggravates fibrosis and vasculopathy in experimental models of systemic sclerosis. Ann Rheum Dis 2014;73:1880-7.

30. Bartoloni E, Alunno A, Bistoni O, et al. Characterization of circulating endothelial microparticles and endothelial progenitor cells in primary Sjögren's syndrome: new markers of chronic endothelial damage? Rheumatology (Oxford) 2014. [Epub ahead of print].

31. Del Papa N, Quirici N, Soligo D, et al. Bone marrow endothelial progenitors are defective in systemic sclerosis. Arthritis Rheum 2006;54:2605-15.

32. Kuwana M, Okazaki Y, Yasuoka H, et al. Defective vasculogenesis in systemic sclerosis. Lancet 2004;364:603-10.

33. Avouac J, Juin F, Wipff J, et al. Circulating endothelial progenitor cells in systemic sclerosis: association with disease severity. Ann Rheum Dis 2008;67:1455-60.

34. Allanore Y, Batteux F, Avouac J, et al. Levels of circulating endothelial progenitor cells in systemic sclerosis. Clin Exp Rheumatol 2007;25:60-6.

35. Kuwana M, Okazaki Y. Brief report: impaired in vivo neovascularization capacity of endothelial progenitor cells in patients with systemic sclerosis. Arthritis Rheumatol 2014;66:1300-5.

36. Del Papa N, Quirici N, Scavullo C, et al. Antiendothelial cell antibodies induce apoptosis of bone marrow endothelial progenitors in systemic sclerosis. J Rheumatol 2010;37:2053-63.

37. Erdbruegger U, Haubitz M, Woywodt A. Circulating endothelial cells: a novel marker of endothelial damage. Clin Chim Acta 2006;373:17-26.

38. Del Papa N, Colombo G, Fracchiolla N, et al. Circulating endothelial cells as a marker of ongoing vascular disease in systemic sclerosis. Arthritis Rheum 2004;50:1296-304.

39. Dimitroulas T, Giannakoulas G, Karvounis H, et al. Micro- and macrovascular treatment targets in scleroderma heart disease. Curr Pharm Des 2014;20:536-44.

40. Rosato E, Gigante A, Barbano B, et al. In systemic sclerosis macrovascular damage of hands digital arteries correlates with microvascular damage. Microvasc Res 2011;82:410-5.

41. Youssef P, Brama T, Englert H, et al. Limited scleroderma is associated with increased prevalence of macrovascular disease. J Rheumatol 1995;22:469-72.

42. Veale DJ, Collidge TA, Belch JJ. Increased prevalence of symptomatic macrovascular disease in systemic sclerosis. Ann Rheum Dis 1995;54:853-5.

43. Ho M, Veale D, Eastmond C, et al. Macrovascular disease and systemic sclerosis. Ann Rheum Dis 2000;59:39-43.

44. Wan MC, Moore T, Hollis S, et al. Ankle brachial pressure index in systemic sclerosis: influence of disease subtype and anticentromere antibody. Rheumatology (Oxford) 2001;40:1102-5.

45. Wig S, Wilkinson J, Moore T, et al. A longitudinal study of ankle brachial pressure indices in a cohort of patients with systemic sclerosis. Rheumatology (Oxford) 2014;53:2009-13.

46. Bartoli F, Angotti C, Fatini C, et al. Angiotensin-converting enzyme I/D polymorphism and macrovascular disease in systemic sclerosis. Rheumatology (Oxford) 2007;46:772-5.

47. Kaloudi O, Basta G, Perfetto F, et al. Circulating levels of Nepsilon-(carboxymethyl)lysine are increased in systemic sclerosis. Rheumatology (Oxford) 2007;46:412-6.

48. Domsic RT, Dezfulian C, Shoushtari A, et al. Endothelial

dysfunction is present only in the microvasculature and microcirculation of early diffuse systemic sclerosis patients. Clin Exp Rheumatol 2014;32:S-154-60.

49. Colaci M, Giuggioli D, Manfredi A, et al. Aortic pulse wave velocity measurement in systemic sclerosis patients. Reumatismo 2012;64:360-7.

50. Timár O, Soltész P, Szamosi S, et al. Increased arterial stiffness as the marker of vascular involvement in systemic sclerosis. J Rheumatol 2008;35:1329-33.

51. Gosse P, Taillard J, Constans J, et al. Evolution of ambulatory measurement of blood pressure and parameters of arterial stiffness over a 1-year period in patients with systemic sclerosis: ERAMS study. J Hum Hypertens 2002;16:627-30.

52. Dick EA, Aviv R, Francis I, et al. Catheter angiography and angioplasty in patients with scleroderma. Br J Radiol 2001;74:1091-6.

53. Emad Y, Al-Sherbeni H, Ragab Y, et al. Arterial vasculopathy in systemic sclerosis: Computerized tomography (CT) angiographic features of macrovascular and microvascular upper limbs arteries. Joint Bone Spine 2014;81:433-7.

54. Lekakis J, Mavrikakis M, Papamichael C, et al. Short-term estrogen administration improves abnormal endothelial function in women with systemic sclerosis and Raynaud's phenomenon. Am Heart J 1998;136:905-12.

55. Bartoli F, Blagojevic J, Bacci M, et al. Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. Ann N Y Acad Sci 2007;1108:283-90.

56. Rollando D, Bezante GP, Sulli A, et al. Brachial artery endothelial-dependent flow-mediated dilation identifies early-stage endothelial dysfunction in systemic sclerosis and correlates with nailfold microvascular impairment. J Rheumatol 2010;37:1168-73.

57. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318-27.

58. Ngian GS, Sahhar J, Wicks IP, et al. Arterial stiffness is increased in systemic sclerosis: a cross-sectional comparison with matched controls. Clin Exp Rheumatol 2014;32:S-161-6.

59. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. Hypertension 2005;46:1118-22.

60. Cypiene A, Laucevicius A, Venalis A, et al. The impact of systemic sclerosis on arterial wall stiffness parameters and endothelial function. Clin Rheumatol 2008;27:1517-22.

61. Turiel M, Gianturco L, Ricci C, et al. Silent cardiovascular involvement in patients with diffuse systemic sclerosis: a controlled cross-sectional study. Arthritis Care Res (Hoboken) 2013;65:274-80.

62. Piccione MC, Bagnato G, Zito C, et al. Early identification of vascular damage in patients with systemic sclerosis. Angiology 2011;62:338-43.

63. Liu J, Zhang Y, Cao TS, et al. Preferential macrovasculopathy in systemic sclerosis detected by regional pulse wave velocity from wave intensity analysis: comparisons of local and regional arterial stiffness parameters in cases and controls. Arthritis Care Res (Hoboken) 2011;63:579-87.

64. Sfikakis PP, Papamichael C, Stamatelopoulos KS, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis Rheum 2007;56:1985-93.

65. Peled N, Shitrit D, Fox BD, et al. Peripheral arterial stiffness and endothelial dysfunction in idiopathic and scleroderma associated pulmonary arterial hypertension. J Rheumatol 2009;36:970-5.

66. Roustit M, Simmons GH, Baguet JP, et al. Discrepancy between simultaneous digital skin microvascular and brachial artery macrovascular post-occlusive hyperemia in systemic sclerosis. J Rheumatol 2008;35:1576-83.

67. Chiang CH, Liu CJ, Huang CC, et al. Systemic sclerosis and risk of ischaemic stroke: a nationwide cohort study. Rheumatology (Oxford) 2013;52:161-5.

68. Lee JE, Haynes JM. Carotid arteritis and cerebral infarction due to scleroderma. Neurology 1967;17:18-22.

69. Schedel J, Kuchenbuch S, Schoelmerich J, et al. Cerebral lesions in patients with connective tissue diseases and systemic vasculitides: are there specific patterns? Ann N Y Acad Sci 2010;1193:167-75.

70. Terrier B, Charbonneau F, Touzé E, et al. Cerebral vasculopathy is associated with severe vascular manifestations in systemic sclerosis. J Rheumatol 2009;36:1486-94.

71. Bertinotti L, Mortilla M, Conforti ML, et al. Proton magnetic resonance spectroscopy reveals central neuroaxonal impairment in systemic sclerosis. J Rheumatol 2006;33:546-51.

72. Pathak R, Gabor AJ. Scleroderma and central nervous system vasculitis. Stroke 1991;22:410-3.

73. Hietarinta M, Lassila O, Hietaharju A. Association of anti-U1RNP- and anti-Scl-70-antibodies with neurological manifestations in systemic sclerosis (scleroderma). Scand J Rheumatol 1994;23:64-7.

74. Chen XY, Lam WW, Ng HK, et al. Intracranial artery calcification: a newly identified risk factor of ischemic stroke. J Neuroimaging 2007;17:300-3.

75. Heron E, Hernigou A, Chatellier G, et al. Intracerebral calcification in systemic sclerosis. Stroke 1999;30:2183-5.

76. Tanabe J. White matter hyperintensities are associated with an increased risk of stroke, dementia and mortality. Evid Based Ment Health 2011;14:1.

77. Sardanelli F, Iozzelli A, Cotticelli B, et al. White matter hyperintensities on brain magnetic resonance in systemic sclerosis. Ann Rheum Dis 2005;64:777-9.

78. Mohamed RH, Nassef AA. Brain magnetic resonance imaging findings in patients with systemic sclerosis. Int J Rheum Dis 2010;13:61-7.

79. Nobili F, Cutolo M, Sulli A, et al. Brain functional involvement by perfusion SPECT in systemic sclerosis and Behçet's disease. Ann N Y Acad Sci 2002;966:409-14.

80. Roquer J, Segura T, Serena J, et al. Endothelial dysfunction, vascular disease and stroke: the ARTICO study. Cerebrovasc Dis 2009;27:25-37.

81. Faucher B, Granel B, Nicoli F. Acute cerebral vasculopathy in systemic sclerosis. Rheumatol Int 2013;33:3073-7.

82. Héron E, Fornes P, Rance A, et al. Brain involvement in scleroderma: two autopsy cases. Stroke 1998;29:719-21.

83. Hettema ME, Zhang D, de Leeuw K, et al. Early atherosclerosis in systemic sclerosis and its relation to disease or traditional risk factors. Arthritis Res Ther 2008;10:R49.

84. Sherer Y, Cerinic MM, Bartoli F, et al. Early atherosclerosis and autoantibodies to heat-shock proteins and oxidized LDL in systemic sclerosis. Ann N Y Acad Sci 2007;1108:259-67.

85. Tyrrell PN, Beyene J, Feldman BM, et al. Rheumatic disease and carotid intima-media thickness: a systematic review and meta-analysis. Arterioscler Thromb Vasc Biol 2010;30:1014-26.

86. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459-67.

87. Vettori S, Maresca L, Cuomo G, et al. Clinical and subclinical atherosclerosis in systemic sclerosis: consequences of previous corticosteroid treatment. Scand J Rheumatol 2010;39:485-9.

88. Schiopu E, Au KM, McMahon MA, et al. Prevalence of subclinical atherosclerosis is increased in systemic sclerosis and is associated with serum proteins: a cross-sectional, controlled study of carotid ultrasound. Rheumatology (Oxford) 2014;53:704-13.

89. Ferri C, Giuggioli D, Sebastiani M, et al. Heart involvement and systemic sclerosis. Lupus 2005;14:702-7.

90. Chu SY, Chen YJ, Liu CJ, et al. Increased risk of acute myocardial infarction in systemic sclerosis: a nationwide population-based study. Am J Med 2013;126:982-8.

91. Nordin A, Jensen-Urstad K, Björnådal L, et al. Ischemic arterial events and atherosclerosis in patients with systemic sclerosis: a population-based case-control study. Arthritis Res Ther 2013;15:R87.

92. Derk CT, Jimenez SA. Acute myocardial infarction in systemic sclerosis patients: a case series. Clin Rheumatol 2007;26:965-8.

93. Akram MR, Handler CE, Williams M, et al. Angiographically proven coronary artery disease in scleroderma. Rheumatology (Oxford) 2006;45:1395-8.

94. Tarek el-G, Yasser AE, Gheita T. Coronary angiographic findings in asymptomatic systemic sclerosis. Clin Rheumatol 2006;25:487-90.

95. Khurma V, Meyer C, Park GS, et al. A pilot study of subclinical coronary atherosclerosis in systemic sclerosis: coronary artery calcification in cases and controls. Arthritis Rheum 2008;59:591-7.

96. Mok MY, Chiu SS, Lo Y, et al. Coronary atherosclerosis using computed tomography coronary angiography in patients with systemic sclerosis. Scand J Rheumatol 2009;38:381-5.

97. Ungprasert P, Charoenpong P, Ratanasrimetha P, et al. Risk of coronary artery disease in patients with systemic sclerosis: a systematic review and meta-analysis. Clin Rheumatol 2014;33:1099-104.