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Atherosclerosis and Cardiovascular Risk in Systemic Sclerosis

Sabina Oreska and Michal Tomcik

Abstract

Atherosclerosis (ATS) has been considered to be a degenerative disease affecting large and medium-sized arteries, resulting in a passive build-up of cholesterol in the artery wall. In the last decade, immune system was proved to play the key role in the pathogenesis of ATS, suggesting ATS to be more progressive and accelerated in chronic inflammatory conditions. Studies in patients with autoimmune diseases, particularly in the most prevalent ones such as rheumatoid arthritis and systemic lupus erythematosus, confirmed the significantly more serious atherosclerotic disease and increased cardiovascular (CV) risk compared to the general population, suggesting these diseases as an independent risk factor for CV diseases. There are only few studies evaluating ATS and CV risk in systemic sclerosis (SSc). Moreover, these studies present contradictory results. Furthermore, it is complicated to differentiate primary vascular affection related to the pathogenesis of SSc from the secondary vascular infliction due to ATS. Nevertheless, most of the studies to date suggest ATS and its clinical manifestations to be more prevalent in SSc. Future studies evaluating larger cohorts of patients are required to determine the relevance of ATS and CV disease and management of these comorbidities in SSc.

Keywords: atherosclerosis, cardiovascular risk, systemic sclerosis

1. Introduction

Accelerated atherosclerosis (ATS) with increased cardiovascular (CV) morbidity and mortality is a well-known complication of many systemic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [1], resulting in higher rates of CV morbidity and mortality compared to general population [2, 3]. Therefore, ischemic heart disease secondary to coronary ATS is the leading cause of CV mortality in
RA patients and in late stages of SLE (while intercurrent infections are the leading cause in early disease) [4].

There is emerging data that the same process of early accelerated ATS occurs in systemic sclerosis (SSc). Epidemiological studies suggest that a cardiac cause contributes to approximately one-third of the non-SSc-related deaths. Moreover, deaths from CV causes occur in SSc more than a decade earlier than in the general population [5, 6].

In the 1960s and 1970s, the main cause of death in SSc was scleroderma renal crisis (SRC), whereas clinically manifested ATS was rare in SSc patients, and CV involvement was most likely the result of vasospasm of coronary arteries. Thanks to recent advances in the treatment of SRC and pulmonary arterial hypertension (PAH), causes of mortality in SSc have changed. The prevalence of ATS has increased according to recent studies in SSc patients [7–9].

Novel laboratory markers of ATS and non-invasive tools to evaluate subclinical coronary ATS and peripheral artery disease (PAD) have been described. Most of these are used mainly in experimental settings, because of their cost and only partially clear significance of some biomarkers [10].

2. Atherosclerosis

Atherosclerosis (ATS) is a chronic multifactorial process evolving in the medium and large arteries. It figures as a leading cause of cardiac and non-cardiac-related morbidity and mortality worldwide [1]. According to the World Health Organization (WHO) definition, it is a variable combination of changes of the innermost layer of the artery—the intima and is associated with deposits of lipids (mainly cholesterol particles), polysaccharide molecules, and blood elements. The traditional view suggests that ATS results from a passive build-up of cholesterol in the artery wall [11]. In fact, it is a multifactorial disease that can be considered an immune/inflammatory response of intima to tissue damage [4].

Inflammation is a key component of ATS [12]. Even a relatively minor elevation of inflammatory markers (such as C-reactive protein, CRP) is predictive of CV events in the general population [13]. In ATS, endothelial cell dysfunction is the common pathway by which factors (such as elevated low-density lipoprotein (LDL), hypertension, diabetes mellitus, elevated plasma homocysteine, various infectious agents, and exposure to free radicals from smoking) are proposed to contribute to pathogenesis [12]. Endothelial dysfunction leads to upregulation of adhesion molecules on the endothelium and increased vessel wall permeability, which enables the accumulation of the foam cells, that is, lipid-laden monocytes and macrophages. Migration and proliferation of vascular smooth-muscle cells lead to remodeling of the vessel wall and atherosclerotic plaque formation [12].

Cardiovascular diseases (CVDs) have become the most frequent cause of death globally [14]. Myocardial infarction (MI) and ischemic stroke caused by ATS dominate the mortality and disability statistics in all regions of the world [15].
3. Atherosclerosis in rheumatic diseases

Early ATS associated with autoimmune diseases is not fully explained by traditional risk factors such as obesity, smoking, or hyperlipidaemia [16–19]. The acceleration of ATS may be attributed (beside the traditional CV risk factors) also to systemic inflammation and use of pro-atherogenic drugs (Table 1) [2]. In addition, various cellular and cytokine pathways have been implicated in the pathogenesis of ATS, as an immuno-inflammatory disease [2, 12, 20–25]. The hyperactivation of the immune system leads to premature ATS, contributes to the formation of atherosclerotic plaque [3], and earlier occurrence of ATS clinical manifestations [4].

There is heterogeneity with respect to autoimmune-inflammatory risk factors. Cytokines, such as tumor necrosis factor alpha (TNF-α), and immune complexes are primarily involved in arthritis, such as RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA), as well as in SLE. On the other hand, autoantibodies including anti-oxidized low-density lipoproteins (anti-oxLDL), anti-cardiolipin (anti-CL), and anti-beta-2-glycoprotein I (anti-β2GPI) are rather involved in SLE and antiphospholipid syndrome (APS)-associated vascular conditions [26].

Autoimmune rheumatic diseases characterized by systemic inflammation and accelerated ATS are associated with various types of vasculopathies [12, 20, 27]. The characteristics of vasculopathies may significantly differ depending on the underlying disease. While classical accelerated ATS has

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<th>Traditional risk factors</th>
<th>Disease (inflammation) related risk factors</th>
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<td>Smoking</td>
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<td>Sedentary life style</td>
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<td></td>
<td>Endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin)</td>
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<th>Therapy-related risk factors</th>
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<td>Adipokines (resistin, adiponectin, leptin)</td>
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Acronyms: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; CRP, C-reactive protein; APL, antiphospholipid antibodies; anti-oxLDL, anti-oxidized low-density lipoprotein antibodies; anti-Hsp, anti-heat shock protein antibodies; TNF-α, tumour necrosis factor α; IL-1, interleukin-1; IL-6, interleukin-6; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Adapted from: Soltész et al. [26].

Table 1. Risk factors for atherosclerosis and cardiovascular diseases.
been associated with RA and SLE, obliterative vasculopathy may be characteristic for SSc. All of these diseases greatly differ in vascular pathomorphology and function (Table 2) [24, 28–56].

<table>
<thead>
<tr>
<th>Leading mechanisms</th>
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<td>Accelerated atherosclerosis</td>
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<td>Proliferative obliteration</td>
<td>SSc, MCTD</td>
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*Acronyms: RA, rheumatoid arthritis; SpA, spondyloarthritis; SLE, systemic lupus erythematosus; APS, anti-phospholipid syndrome; SSc, systemic sclerosis; MCTD, mixed connective tissue disease*

Adapted from: Soltész et al. [26].

Table 2. Different vascular pathogenesis in autoimmune rheumatic diseases.

**4. Atherosclerosis in SSc**

Systemic sclerosis (SSc) is a multi-system autoimmune disease characterized by immune dysregulation, vasculopathy, and fibrosis. In the pathogenesis, three hallmarks have been proposed to play the key role: (1) vasculopathy with the pathognomonic microvascular involvement; (2) fibrosis of skin and visceral organs; (3) systemic inflammation characterized by the presence of circulating autoantibodies and pro-inflammatory cytokines [57, 58].

The etiology of ATS in SSc is unknown. It may be secondary to concomitant multiple factors, including traditional CV risk factors, increased endothelial damage, and disease-specific immunologic and autoimmune factors, which may contribute to both induction and progression of ATS [2, 8, 53, 59–61].

Numerous inflammatory mediators implicated in the pathogenesis of ATS, including TNF-α, interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hsCRP), have been demonstrated to be increased in patients with SSc compared with controls [62]. The relationship between these mediators and CVD in SSc is unclear. However, chronic systemic inflammation probably promotes accelerated ATS. Nevertheless, the level of inflammation in SSc is lower than in RA and SLE, thus the atherosclerotic process may not be so aggressive and easily detectable in small-number studies [63].

Involvement of the microvasculature is one of the earliest features of SSc, preceding and potentially contributing via tissue ischemia to the widespread fibrosis characteristic of this condition. Pathological changes include disruption of the endothelium, mononuclear cell infiltration of the vessel wall, frank obliterative lesions, and progressive loss of capillaries.

Endothelial dysfunction in the capillaries and arterioles, common in SSc, results in disturbed vasomotor regulation [64].

Although macrovascular disease was not originally considered as a feature of SSc, multiple studies have revealed an increased prevalence of large-vessel disease of the upper and lower
limbs in patients with SSc [65, 66]. The prevalence of coronary artery and cerebrovascular disease in SSc, however, remains to be elucidated.

4.1. Prevalence of atherosclerosis in SSc

Mortality in SSc was described to be approximately three times increased as compared to the general population, in particular due to cardiopulmonary complications, including pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) [67]. The 10-year survival of SSc has improved significantly from 54% (1972–1981) to 66–82% (1982–1991), largely due to the early diagnosis and treatments available for PAH and scleroderma renal crisis (SRC) [68]. Emphasis has thus shifted to comorbidities in SSc, such as ATS, that may affect the long-term outcomes of SSc [68] with the substantially increased death rates due to atherosclerotic CVD or cerebrovascular disease [63]. Currently, CV-related deaths are responsible for a 20–30% mortality rate in SSc patients [63].

In particular, the 2010 survey from the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) database estimated that 26% of SSc-related causes of death were due to cardiac causes (mainly heart failure and arrhythmias) and 29% of non-SSc-related causes of death were due to ATS and CV causes [69].

There are contradictory reports regarding the prevalence of ATS in SSc [70]. According to some authors, the prevalence of ATS of the large epicardial coronary arteries is similar to that of general population [71].

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 [10].

Raynaud’s phenomenon, PAH, and SRC represent the main clinical manifestations of microvascular damage (involvement) in SSc, characterized by both vasospasm and structural alterations, pathognomonic features of SSc. All these components are thought to predict macrovascular ATS over time [70, 72].

4.2. Risk factors for atherosclerosis in SSc

There is limited data regarding the prevalence of traditional CV risk factors in SSc. Their prevalence has been found to be either similar [73, 74] or reduced [75–77] when compared with general population. The majority of these studies showed a similar distribution of CV risk factors between SSc patients and controls, thereby suggesting that other factors may contribute to the increased prevalence of CV disease in SSc [77].

In addition to age [75, 77], hypercholesterolaemia [75–77], male gender [77], hypertension [78], and diabetes [78], SSc appears to be an independent risk factor for coronary artery disease (CAD) after adjustment for traditional risk factors [73, 78], including the SSc-related factors: PAH [75, 77], renal involvement [76], and disease duration [75]. Moreover, particularly the disease duration, in addition to age and LDL levels, can act as an independent determinant for more severe coronary calcification [75]. Renal involvement in SSc relates to ischemic heart disease (after exclusion of the impact of age) [76].
Studies mostly failed to show an increased frequency of obesity, hyperlipidaemia, hypertension (there was no difference in blood pressure on 24-hour ambulatory blood pressure monitoring [79]), and diabetes in SSc [7, 73, 75, 79]. These findings were confirmed also in the Australian Scleroderma Cohort Study [77]. Moreover, significantly lower cholesterol levels and diastolic blood pressure were described in SSc compared to controls [75]. On the other hand, one study revealed a slight increase in blood pressure and fasting glucose and a lower BMI in SSc population [80].

Factors contributing to ATS in SSc, beside the traditional risk factors, include chronic inflammation, increased levels of CRP and homocysteine, autoantibodies, deranged lipid function and profile, corticosteroid treatment, increasing age and disease duration [40, 65, 66, 81]. Beside these factors, there is also association with the dysfunction of the coagulation and fibrinolytic system and increased production of adhesion molecules [82–86]. Specifically, corticosteroids and immunosuppression seem not to be associated with the risk of CAD [76].

Results from studies on lipids are contradictory. Lipid metabolism seems to be altered and accompanied by lower levels of high-density lipoprotein (HDL) [87] or significantly elevated lipoprotein(a) (LpA) without any significant difference in other cholesterol parameters [88]. High levels of LpA in SSc are usually associated with increased CV risk [88]. In addition, high levels of LpA adversely affect the effect of thrombosis, due to reduced fibrinolysis [88, 89]. Of interest, the presence of anti-centromere antibodies (ACA) is associated with decreased levels of HDL [87]. SSc patients may have some higher detected pro-inflammatory-HDL levels (representing an increased risk for ATS) [74]. Of note, increased IgG autoantibody against the lipoprotein lipase (anti-LPL) in SSc (detected in 24% of SSc patients) may cause elevation of triglyceride (TG) levels [90]. On the other hand, some studies have not described any alteration of the components of the lipid profile in SSc patients [88].

Some novel CV risk factors have been reported to be elevated in SSc, such as oxidized low-density lipoprotein (oxLDL) and endothelin [7]. In terms of pro-thrombotic state in SSc, the coagulation system can be activated, and fibrinolysis can be impaired [89].

4.3. Pathogenesis and risk factors specific for SSc

Pathogenesis of SSc is characterized by inflammatory, vascular, and fibrotic events. It primarily affects the microvessels (e.g. Raynaud’s phenomenon); however, macrovascular obliterative disease has also been described in SSc [40, 42, 70, 82, 83, 91].

Endothelial dysfunction, one of the earliest events in the pathogenesis of SSc and vasculopathy, is critical in the development of ATS, and represents a loss in vasodilatory function, together with increased platelet aggregation and leukocyte adhesion due to decreased nitric oxide (NO) as a key vasodilator [92]. Endothelial injury results in lumen occlusion and tissue hypoxia. The histopathological picture of scleroderma includes intima proliferation, the proliferation of endothelial and smooth muscle cells, destruction of internal elastic lamina and transmural lympho-plasmocytic infiltration of the vessel wall. Thus, vasculopathy in SSc does not represent the classical ATS but rather an obliterative vasculopathy [40, 82]. This has been documented by reports of very severe clinical cases of obliterative peripheral artery disease (PAD)
despite the lack of traditional risk factors for ATS. About 15–20% of scleroderma patients exert multiple vascular abnormalities including the combination of CVD, stroke and PAD [2, 70, 82]. In addition, ischemia, oxidative stress, and oxLDL may trigger inflammation in the vessel wall. Homocysteine levels correlate with the development of macrovascular disease and PAH, and decreased vitamin B12 release in SSc [83].

Regarding vascular pathogenesis, the possible role of methylene-tetrahydrofolate reductase (MTHFR) gene C677T polymorphism was described in the development of macrovascular manifestations of SSc [83].

4.4. Mechanisms of endothelial damage

Vascular endothelium as a functionally remarkable organ regulates coagulation, fibrinolysis, permeability, vasomotion, and inflammation. Clinical and pathological features of vascular damage and endothelial cell activation represent an important hallmark of SSc vasculopathy, even in the absence of other concomitant risk factors [10]. Endothelial dysfunction is a component of the pathophysiology of both SSc and ATS. In SSc, the initiating injury is unknown [72].

Endothelial cell damage leads to enhanced expression of adhesion molecules and elevated levels of circulating soluble adhesion molecules, such as soluble E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), which are all significantly increased in SSc, reflecting endothelial activation [93]. This results into adhesion of inflammatory cells, trans-migration across the vessel wall, and infiltration of the extracellular matrix.

Different mechanisms may induce and perpetuate endothelial dysfunction, which contributes to the pathogenesis of atherosclerotic risk, and progressive vasculopathy in SSc. The main pathogenic mechanisms underlying endothelial damage have been proposed: (1) dysregulation of vascular tone, as a consequence of an imbalance between vasoconstrictor and vasodilator mediators; (2) defective angiogenesis; (3) injury/activation elicited by the activation of innate and adaptive immune response; and (4) functional defects of endothelial progenitor cells (EPCs) [94, 95].

1) The important component of endothelial dysfunction in SSc is derangement of vasoactive mediators, with an increase in vasoconstrictive endothelin and a decrease in the vasodilator nitric oxide (NO) [93]. In addition, increased levels of endothelin, the most potent vasoconstrictive peptide released from the endothelial layer, play a pivotal role in endothelial dysfunction in both SSc and ATS [96]. An impairment of endothelium-dependent vasodilation occurs before the onset of clinical ATS in SSc [40].

2) Although there is an increased circulation of angiogenic factors, such as vascular endothelial growth factor (VEGF) [97], a reduction in the density of blood vessels is one of the hallmarks of vascular disease in SSc [97]. Abnormal angiogenesis results from increased VEGF, which is stimulated particularly by severe tissue hypoxia associated with chronic blood flow reduction in SSc. This leads to a condition of defective vascularization. There is also a reduction in circulating EPCs [98–100]. Moreover, the up-regulation of VEGF also
contributes to the development of fibrosis in both inflammatory and non-inflammatory stages of the disease [101].

3) In the early stage of scleroderma, the endothelial cell layer of microcirculation is activated and/or injured by unknown and various mechanisms, including infection-induced apoptosis, immune mediated cytotoxicity, anti-endothelial antibodies, or ischemia-reperfusion injury [96].

4) In particular, new blood vessels may form as a consequence of endothelial sprouting from pre-existing endothelial cells (angiogenesis) or as peripheral recruitment of bone marrow-derived circulating EPCs. EPCs contribute, at least in the early stage of the disease, to vascular healing by homing in the damaged endothelium [102].

5. Components involved in the atherogenesis in SSc

5.1. Endothelial progenitor cells

The elevation of endothelial progenitor cells (EPCs) in early disease is followed by its decrease during the disease duration [103], suggesting a probable exhaustion of the precursor endothelial pool during disease course. A decreased number of EPCs in the peripheral circulation has been shown to be predictive of recurrent acute coronary artery events [104]. Moreover, a low number of circulating EPCs seems to characterize a more active disease phenotype, identified by a higher risk of digital vascular lesions and higher severity score. Scleroderma circulating EPCs are characterized by a defective functional phenotype with consequent defective migratory activity and impaired recruitment to ischemic damaged tissue [100, 105–107].

The true significance of EPCs as a potential biomarker of both CV risk and SSc disease activity is not determined. It is not clear whether the cells are true progenitor cells [99] that incorporate into new blood vessels or rather cells of hematopoietic lineage, which have a paracrine effect on blood vessel formation [108]. Assessment of EPCs levels in SSc may be conflicting mainly because of the different methods of detection [109, 110].

5.2. Circulating endothelial cells

Circulating endothelial cells (CECs) are released into the systemic circulation after detachment of cells from basement membrane in response to endothelial injury. Increased number of CECs, a novel marker of endothelial damage, has been demonstrated not only in patients with myocardial infarction (MI), unstable angina, peripheral vascular disease (PAD), but also in SSc, suggesting their role as a marker of chronic endothelial damage [111, 112].

5.3. Antibodies against the anti-oxidized low-density lipoproteins (anti-oxLDL)

Patients with diffuse cutaneous SSc (dcSSc) were found to have higher levels of anti-oxidized LDL (oxLDL) antibodies [113], the titer of which correlates with the severity of ATS as well as
with CV complications [114]. In addition, higher levels of circulating complexes of anti-beta-2-glycoprotein I (anti-oxLDL/β2GPI), considered as pro-atherogenic, were demonstrated in SSc as well [115, 116].

5.4. Antiphospholipid antibodies

Anti-β2-glycoprotein I (anti-β2GPI) in the presence of anticardiolipin (aCL) antibodies could be independently predictive of incident ischemic stroke and MI over 20 years of follow-up [117]. The prevalence of aCL and anti-β2GPI antibodies occurring in the absence of typical clinical manifestations of antiphospholipid syndrome (APS) has been demonstrated to be increased in patients with SSc compared to controls [118]. Anti-β2GPI is associated with both higher mortality and vascular disease, including digital ischemia and PAH, in SSc [119].

5.5. Anti-endothelial cell antibodies

Elevated anti-endothelial cell antibodies (AECA) correlate with increased subclinical ATS in non-rheumatic patients [120], SLE patients [121], and may contribute to an increased risk of early ATS in SSc, similarly as elevated levels of ICAM-1 [122]. However, in general the levels of AECA do not always have to be increased in all cases of chest pain and atherosclerotic involvement of the coronary arteries (compared with patients with chest pain and normal coronary angiography) [123]. The presence of circulating antibodies with anti-endothelial activity in scleroderma patients may be considered as an adjunctive mechanism associated with chronic endothelial damage [109, 110].

5.6. Angiotensin converting enzyme gene polymorphism

Polymorphism (insertion or deletion, I/D) of the angiotensin converting enzyme (ACE) gene can be another factor possibly influencing ATS. The highest levels of plasma ACE are associated with the DD genotype and the lowest levels are associated with the II genotype [124]. The D allele of the ACE gene, associated with ATS severity [125], has an increased frequency in SSc [2]. The risk of MI in patients with the DD genotype is higher compared with those with either the II or ID genotype [126, 127]. The presence of a D allele in SSc correlates with increased carotid intima-media thickness (CIMT) [128].

5.7. Microparticles

Microparticles (MPs), small circulating membrane-coated vesicles, are important mediators of intercellular signaling arising from a variety of cell types. MPs contribute to the immunopathogenesis of various thrombotic and rheumatic diseases via their role in the regulation of inflammation, thrombosis, and angiogenesis. MPs have been suggested as a biomarker of CAD. High levels result in severe endothelial dysfunction by selectively impairing the production of NO and are found in patients with acute MI [129].

MPs levels are also elevated in patients with SSc and correlate with the presence of ILD [130].
6. Types of damage

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 particular in late disease [131]. SSc is associated with about a twofold increased risk of developing MI and stroke, and a fourfold increased risk for peripheral vascular disease, even after adjustment for CV risk factors (BMI, smoking, hypertension, diabetes, and hyperlipidaemia). This fact suggests that the increased risk of CV events in SSc may depend on both ATS and non-atherosclerotic factors, such as vasospasm, SSc specific vasculopathy, vasculitis, and thrombosis [73]. Presence of plaques and ischemic arterial events positively correlates with the positivity of ACA, while anti-topoisomerase I antibodies (ATA) positivity in SSc is rather associated with fewer ischemic events. The antibody profile and different disease subsets are supposed to contribute to macrovascular involvement [76].

6.1. Coronary arteries

Even though cardiac disease is a major cause of death in SSc patients, clinical signs of cardiac disease are apparent in only 10% [71], mostly appearing late in the course of disease [132], and predicting an adverse prognosis [133]. Up to 80% of postmortem evaluation of SSc patients’ hearts may reveal a form of cardiac involvement [134]. The prevalence of ATS involving coronary vessels and its clinical manifestation, including angina, MI, and sudden death, is difficult to evaluate in SSc, because of the primary cardiac involvement possibly depending on myocardial damage secondary to microvascular alterations, myocardial fibrosis, arrhythmias resulting from the conduction system involvement, and last but not least, pericardial and valvular disease [135]. Myocardial fibrosis in SSc patients is considered a hallmark cardiac manifestation [133]. Foci of fibrosis not corresponding to coronary artery distribution were reported in 50% of autopsies conducted on SSc patients [136].

Moreover, secondary heart disease due to renal vasculopathy, ILD, and PAH could adversely influence cardiac function. Thus, symptoms of cardiac complications could be nonspecific, and could overlap with those of other comorbidities. Furthermore, hypertension, obesity, diabetes, and other comorbidities may contribute to adverse influence on cardiac function, mainly in older SSc patients [135].

The risk of acute MI may be 2.45x greater in SSc than in population of the same age, sex, and comorbidities [78]. In addition, the impact of SSc on acute MI risk may be even greater than that of hypertension (increasing the risk 2.08x), and diabetes (2.14x), while immunosuppressant drugs probably do not reduce this risk of MI [78].

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 [136]. 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 [137].

On the other hand, while the frequency of epicardial coronary vessel ATS appeared to be similar in SSc and general population (48% vs. 43%), the atherosclerotic lesions of the small coronary arteries or arterioles occurred significantly more often in SSc patients, compared with controls [138].

The coronary vessel involvement was ascertained invasively by coronarography with the conclusion, that the prevalence of CAD in SSc patients with suspected CAD was similar to that detected in controls [71]. Angiographic abnormalities may be higher than previously thought in asymptomatic patients with SSc, including significant coronary artery stenosis, coronary artery ectasia, slow flow, tortuosity, calcification, and spasm, and must not be related to traditional CV risk factors [132]. These abnormalities (demonstrated in asymptomatic female SSc patients free from CV risk factors) suggest that coronary artery vasculopathy is common even in the absence of classic CV risk factors, supporting the role of SSc as a relevant risk factor for CAD [132].

The presence of coronary calcified plaques in SSc patients asymptomatic for angina evaluated by computed tomography (CT) coronary angiography confirms the subclinical ATS as a common one in SSc [139]. In addition, SSc seems to be an independent risk factor for increased coronary artery calcium deposition [75].

6.2. Peripheral macrovascular abnormalities in SSc

Macrovascular complications (involving the arms and legs) may be detected even in SSc patients with minimal underlying CV risk factors [140]. Peripheral vascular disease (PAD) in patients with SSc has been reported to be significantly increased, with use of techniques such as the ankle brachial pressure index (ABPI), lower-limb Doppler ultrasound, and angiography [140–143]. Similarly, evaluation of the PAD using the WHO questionnaire for intermittent claudication may reveal more frequent impairment in SSc (almost 22%) than in general population (4.5%) [65]. PAD diagnosed by the ABPI may reach 17% of patients with SSc (in contrast to no healthy control), while there is no difference in the traditional CV risk factor profile [66].

Studies have showed a six times increased prevalence of PAD, detected by angiography, Doppler ultrasound, or physical examination in patients with limited cutaneous SSc (lcSSc) compared to healthy controls [141], and almost five times greater presence of intermittent lower limb claudication in SSc, detected by Edinburgh Claudication questionnaire, than the prevalence of symptomatic PAD in the general population, as reported by a similar WHO claudication questionnaire [65]. According to one study, approximately 4.2% of SSc patients (including the ones treated with vasodilators) suffer from clinical intermittent claudication, and even may develop ischemic stroke [143]. However, other studies failed to prove the increased prevalence of stroke in SSc [7].
The traditional CV risk factors seem to contribute to proximal, but not distal, vascular disease in the lower limb, as demonstrated in angiograms performed in a single SSc cohort [142]. In at least some cases, peripheral vascular disease in SSc is not atherosclerotic but related to the vasculopathy of SSc itself, which is supported by finding of chronic obliterative thromboangiitis on histological examination of an amputated limb [141]. Involvement of the vasa vasorum has been suggested as a potential cause of macrovascular disease in SSc [144].

Macrovascular disease, defined as an involvement of blood vessels with an internal diameter >100 microns, is probably associated with the more distal small vessel pathology [96]. Morphology and blood flow of the proper palmar digital arteries correlate with nailfold capillary morphology, and progression of microvascular disease (detected by capillaroscopy—from early capillaroscopy pattern to an active and late capillaroscopy pattern) is linked to macrovascular disease. ATA may represent an independent predictive factor for macrovascular damage [145].

6.3. Cerebrovascular disease

Literature data aimed to estimate the prevalence of cerebrovascular disease in SSc and the relationship between disease and risk of ischemic stroke is inconclusive [146]. Several studies suggested that cerebral disease may be underestimated [147–149]. The prevalence 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 was found to be 1.3-times higher compared to controls [141]. The increased ischemic stroke risk in SSc may be due to different pathogenic mechanisms such as vascular injury, chronic inflammation, and vasospasm [146]. SSc may be independently associated with a 43% increase in ischemic stroke risk compared to healthy controls [73]. This risk is not even modified by commonly employed medications (such as calcium channel blockers, angiotensin converting enzyme inhibitors, oral corticosteroids, or immunosuppressant drugs) [146].

Cerebral vascular involvement may be caused by endothelial dysfunction, as well as by ATS [150]. The role of inflammatory or immune mechanisms can be declared by the apparent efficacy of immunosuppressive drugs in stroke treatment [151]. Finally, cerebral vasospasm (“Raynaud’s phenomenon-like”) may be associated with transient ischemic attacks or focal neurological defects and it is evidenced by reversibility of arterial lesions and absence of specific histologic findings [152].

Stenosis of carotid arteries, a predictive factor of stroke, is more often found in SSc patients with respect to general population with no difference in the traditional CV risk factor profile, supporting the increased risk of stroke in SSc [66]. Moreover, intracerebral vascular calcifications, an independent risk factor of ischemic stroke in the general population [153], are significantly more prevalent in asymptomatic SSc patients compared to the controls investigated by non-contrast CT scan [154]. Similarly, white matter hyperintensities on brain magnetic resonance imaging (MRI), a known risk factor for future symptomatic stroke [155], are more common in asymptomatic SSc patients than in population without autoimmune diseases [156, 157].
Another tool for examining cerebral artery involvement, a single photon emission computed tomography (SPECT), showed focal or diffuse hypoperfusion in mainly neurologically asymptomatic SSc patients, probably caused by the microangiopathic damage of brain vessels [158].

Of note, central nervous system may be affected by microvascular damage as a complication of systemic involvement [159]. A higher risk for developing neurological complications is associated with circulating anti-U1 RNP (ribonucleoprotein) and ATA [160].

6.4. Carotid arteries

Regarding vascular morphology and function, carotid ATS has been detected in more than 60% of scleroderma patients [40, 64, 161–163]. In line with this finding, the prevalence of carotid plaque, carotid wall thickening, and carotid artery stenosis has been showed to be significantly higher in SSc compared to the general population of the same age and gender [66].

Some studies found no difference in CIMT values between scleroderma patients and controls [161, 164, 165], while others depicted increased CIMT in SSc patients [64, 166]. Nevertheless, significantly higher CIMT values in SSc demonstrating increased risk of ATS were found in less than half of the studies [8, 167]. The data interpretation may be hampered by small size of the cohorts enrolled and by variability of CIMT ultrasonographic measurement among studies [7].

CIMT values seem to directly correlate with disease duration, similarly to the observations in patients with RA, diabetes mellitus, or familial hypercholesterolemia [8]. High CIMT was variably associated with age, oxLDL [166], corticosteroid treatment [168], ACE gene polymorphism, and antibodies against human heat shock protein (HSP)-60, and mycobacterial HSP-65 [166]. Increase in CIMT (≥0.10 mm) correlates with age- and sex-adjusted relative risk of 1.15 for MI, and 1.18 for stroke [131].

SSc patients with plaques are characterized by increased concentration of serum proteins implicated in both vasculopathy, and fibrosis in comparison to patients without plaques [169].

7. Methods of detection

To elucidate the prevalence of PAD in SSc, several techniques, beside the physical examination (history of claudication or absence of pulses), have been employed. In particular, surrogate markers of atherosclerotic damage have been demonstrated to be useful indicators of atherosclerotic wall damage. These include ankle brachial pressure index (ABPI) for arterial involvement of the lower extremities, blood pressure interarm difference (systolic/diastolic interarm difference) for proximal arterial disease of the upper extremities, and pulse wave velocity (PWV) and pulse wave analysis (PWA) to evaluate arterial stiffness. A novel non-invasive tool to evaluate subclinical coronary ATS, a multidetector CT, generates a coronary calcium score, a surrogate marker for coronary ATS [170, 171].
7.1. Intima-media thickness in SSc

Vessel intima-media thickness (IMT) is calculated by measuring the average thickness of the intima-media complex, the distance between the first and the second echogenic lines from the lumen [40, 64]. Carotid intima-media thickness (CIMT) as measured by high-resolution ultrasound is a well-validated marker of subclinical ATS. Increased CIMT has been shown to correlate with traditional CV risk factors, and to independently predict future vascular events in general population [64, 131].

A meta-analysis of CIMT in rheumatic diseases, including RA, SLE, and SSc, found significantly increased values of CIMT in this population compared with healthy, age- and sex-matched controls [167]. The pooled result of the SSc studies demonstrated a greater CIMT in SSc than in controls, suggesting an increased prevalence of subclinical ATS in both dcSSc and lcSSc [166, 172, 173]. The effect size seen in SSc was also greater than those in RA and SLE. Higher CIMT values are associated with increased age, but probably not with disease type, duration, or clinical characteristics [166].

In contrast to these findings, a number of individual studies have found no increase in CIMT in patients with SSc [40, 79, 161, 164, 165, 174]. Interestingly, there is also an anecdotal report of significantly lower CIMT in 10 SSc patients than in an age- and sex-matched control group without coronary risk factors [175].

7.2. Ultrasonographic evaluation and duplex scanning

SSc patients may have more severe, as well as more frequent, carotid disease (evaluating common carotid and its branches as well as the vertebral arteries) than the general population with similar rates of CV risk factors [66]. Carotid plaques are present in SSc, but probably not significantly more when compared to controls [161]. Evaluating other arteries using the ultrasonographic examination, the most impaired arteries in SSc are ulnar arteries, which are significantly narrower than those of the healthy controls. Other arteries are not significantly altered [176].

7.3. Flow-mediated dilation

Flow-mediated vasodilation (FMD) is usually evaluated by ultrasonographic measurement of artery diameter at baseline and maximal vasodilation following periodic ischemia, achieved by external cuff inflation [64]. FMD is calculated as a change in percentage following cuff release divided by baseline diameter [64]. The dilation is dependent on the endothelium function following the release of endogenous substance from endothelial cells, such as NO [70, 163, 177]. Endothelial dysfunction (as reflected by abnormally lower FMD values) is a key mechanism in predicting ATS involvement [63, 74].

Impaired FMD is associated with the presence of traditional CV risk factors [178], and is independently predictive of incident CV events [179].

Many, but not all, studies have found FMD to be decreased in SSc compared with controls [8, 40, 64, 162, 163, 165, 172, 177, 180–182]. The results were independent of SSc type, disease
duration, clinical findings, and traditional CV risk factors [64]. On the other hand, unchanged FMD in SSc patients was reported as well [163].

It was suggested that increased levels of LpA in SSc patients cause impaired FMD, since LpA is capable of inhibiting inducible NO synthase [88].

7.4. Nitroglycerin-mediated dilation in SSc

Nitroglycerin-mediated dilation (NMD) is measured by evaluating the percentage of change of the arterial diameter from baseline following administration of 25–400 μg of sublingual nitroglycerin [40, 162]. Unlike FMD, the NMD value is independent of endothelium function [163].

Several studies have reported abnormally low NMD values in SSc patients. However, an impaired FMD was also demonstrated in SSc, while NMD was preserved [40, 70].

NMD values appear to be reduced in dSSc with Raynaud’s phenomenon compared to controls [172, 180]. However, some studies did not find abnormal NMD in SSc patients [40, 163, 165, 183].

Impaired NMD was found to correlate with increased age in SSc patients [40]. Reduced nitrate-mediated dilation [172, 180, 184] could suggest a coexisting functional or structural abnormality of arterial smooth muscle, adventitia, or both.

7.5. Ankle Brachial Pressure Index in SSc

Ankle Brachial Pressure Index (ABPI) is a validated diagnostic tool for PAD of the lower extremity. It is calculated by dividing the posterior tibial artery systolic pressure by the brachial systolic pressure (both in mmHg) [66]. Normally ABPI equals 1.0, whereas abnormal ABPI is defined as a continuous variable less than 0.90 (American College of Cardiologist/American Heart Association Practice Guidelines for Management of Patients with PAD). Increasingly lower values reflect an increased rate of arterial disease [66, 80]. According to the American Diabetes Association consensus paper, values lower than 0.9 are only mildly abnormal, and a ratio lower than 0.4 reflects a severe disease [185].

Several studies found that ABPI was more commonly abnormal in SSc patients.

Values of ABPI of 0.9–1.0 are described in about 60% of SSc patients, compared to 0–10% of general population with the same rate of CV risk factors [66]. When comparing the subsets of SSc, dSSc may rather tend to have altered ABPI than lcSSc [143]. ABPI values remain stable in most SSc patients over time [186].

7.6. Arterial stiffness

Arterial stiffness is increased in the presence of CV risk factors [187], and is an independent predictor of CV events and CV and all-cause mortality across a wide range of patient populations [188]. This parameter performs as a well-validated surrogate marker of subclinical ATS, and an independent predictor of CV events and mortality [188].
Arterial stiffness has been examined in SSc but with varying results [122, 162–165, 177, 189]. This parameter is measured by the techniques of pulse wave analysis (PWA), and pulse wave velocity (PWV). Carotid-femoral PWV is considered the current “gold-standard” measurement of arterial stiffness [190]. PWA, expressed as the augmentation index (AI), reflects the stiffness of the aorta, whereas carotid-femoral PWV reflects the velocity of the pulse wave along the aortic and aortoiliac pathways. Increased arterial stiffness results in premature return of reflected waves in late systole, causing increased load on the left ventricle and increased myocardial oxygen demand [72].

Elevated values of PWA and PWV have been described in patients with dcSSc [162] and even more increased in patients with lcSSc. Moreover, PWV correlates positively with disease duration. Thus, it could be postulated that PWV may be a better measure of arterial stiffness than AI in SSc [122].

Arterial stiffness elevated in patients with SSc may correlate with elevated levels of soluble markers of endothelial activation, including plasma nitrate, soluble E-selectin, and soluble VCAM-1 [163]. However, microvascular disease or myocardial dysfunction may also contribute to the observed abnormality in AI [191]. SSc patients free from CVD were demonstrated to have higher AI, with respect to healthy controls. PWV, however, was not significantly increased. Interestingly, there was a paradoxical association between calcium channel blocker therapy and higher AI. This correlation may reflect generalized vasculopathy rather than atherosclerotic disease [192].

Significantly increased stiffness parameters (evaluating the macrovascular disease and subclinical ATS) may correlate positively with ATA serum levels and inversely with ACA [193].

7.7. Angiography examination

Angiographic findings of the lower and upper extremity in SSc patients showed a correlation between CV risk factors and proximal, but not distal, PAD. The microvasculopathy related to disease pathogenesis may be considered the leading mechanism of peripheral vascular abnormalities in SSc according to a retrospective study of angiograms, when compared to atherosclerotic damage [142].

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

8. Cardiac evaluation in SSc

8.1. Coronary artery evaluation

Angiographic evaluating of SSc patients with suspected coronary artery disease can reveal coronary artery disease, which seems to affect 22% of SSc patients. However, comparing the findings with the calculated standardized prevalence ratios according to Diamond and
Forrester’s probability analysis, the prevalence of coronary artery disease in SSc patients seems not to be larger than expected in patients without SSc [71].

A novel method of assessing coronary artery disease is the coronary calcium score, as determined by multidetector computed tomography. This technique measures coronary artery calcification that occurs in atherosclerotic plaque and has a good negative predictive value for CAD in the general population [194]. There is an evidence of higher presence of coronary calcification and higher coronary calcium score in patients with SSc compared to the healthy controls. Nevertheless, the correlation of coronary calcification with the angiographic findings in SSc is unknown [74].

Coronary artery calcifications may represent the same process as the process of subcutaneous calcinosis in SSc. However, in SSc patients, who did not have any subcutaneous calcinosis, coronary artery calcifications can be often detected as well [74]. Hence, subcutaneous calcinosis in SSc does not necessarily need to be associated with increased risk of coronary artery calcification.

8.2. Coronary flow reserve in SSc

Coronary flow reserve (CFR) is calculated by dividing the peak diastolic velocity during adenosine infusion, with the peak diastolic velocity at rest, and with a resting velocity time integral [195]. Abnormal CFR may reflect coronary artery disease or the incapability of microcirculation to supply the heart in cases of increased demand [134].

Several reports have found abnormal CFR in SSc patients. Reduced CFR alone cannot differentiate vasospasm from anatomic arterial stenosis. Therefore, abnormal CFR in SSc does not necessarily imply the presence of atherosclerotic plaque [134]. Examination by myocardial multidetector CT may elucidate the relationship between CFR and coronary anatomy [196].

Assessing CFR in the left anterior descending coronary artery using contrast enhanced trans-thoracic Doppler during adenosine infusion, even severe reduction can be detected in 50% of SSc patients, who have no heart disease symptoms [134, 195, 197].

Patients with dcSSc seem to have more severe reduction of CFR than lcSSc. Even younger dcSSc than lsSSc may suffer from worse damage of coronary arteries [195, 197].

8.3. Assessment of myocardial perfusion in SSc patients

Using 99m-Tc sestamibi gated myocardial perfusion SPECT with a stress-rest protocol reveals perfusion defects reported in 38% of SSc patients, which are probably not associated with age, sex, SSc subset or duration of Raynaud’s phenomenon [198]. On the other hand, this perfusion defects may be associated with severe skin thickness, digital ulcers, and esophageal involvement [198].

Stress perfusion defects in cardiac MRI are common in asymptomatic SSc patients. There can be a non-segmental perfusion defect too, not corresponding to epicardial coronary artery distribution, which suggests microvascular impairment [199]. Most of SSc patients have at least one segmental MRI perfusion defect (e.g. reduced signal intensity or delayed wash-in) at
Nifedipine can cause a significant increase in myocardial perfusion, according to an increased MRI perfusion index [200].

9. Prevention, management, and treatment of ATS in SSc

In general, early CV screening is mandatory in order to prevent and early treat vascular disease. A European League Against Rheumatism (EULAR) task force has published recommendations for screening, prevention and treatment of CVD in arthritis [47]. Similar recommendations regarding SLE and scleroderma are to follow soon [26]. According to the EULAR recommendations for inflammatory arthritis, CV risk assessment should follow the national guidelines, or in case of absence of such guidelines, Systemic Coronary Risk Evaluation (SCORE) function mode should be used [47]. Detection of CV risk includes laboratory screening, physical examination (blood pressure, body composition, and body mass index), and non-invasive imaging methods [171].

9.1. Laboratory markers

Laboratory markers include: (1) the parameters of lipid metabolism: total cholesterol (TC), LDL, HDL, TC/HDL ratio, TG or LpA and oxLDL, both associated with ATS in autoimmune diseases [171]; (2) glucose metabolism alteration and insulin resistance: fasting glucose or oral glucose tolerance test [171, 201]; (3) acute phase reactants, hsCRP, and erythrocyte sedimentation rate (ESR), which are associated with the presence of subclinical ATS, CV events, and CV mortality [202–204].

The association of specific biomarkers of endothelial activation, markers of inflammatory pathways, and specific genes with ATS and increased CV risk have been described, for example: cytokines (TNF superfamily and receptors for TNF, interferon gamma (IFNγ), interleukin 6 (IL-6), IL-1, transforming growth factor beta 1 (TGF-β1)), chemokines, and adipokines [205].

Biologic markers of possible cardiac dysfunction such as brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) are often elevated in patients with SSc [133]. Troponin has not been found to be elevated in SSc, so its elevated levels are suspected from non-scleroderma CVD or myopericarditis [206].

9.2. Non-invasive imaging methods

Screening non-invasive and imaging techniques include a broad spectrum of methods for detection of ATS: US of peripheral arteries, and especially of common carotid arteries to provide CIMT measurement and plaque detection, assessment of subclinical ATS (using ABPI, FMD, NMD, PWA, PVW, AI), assessment of cardiac disease (using coronary calcium score detected by CT, SPECT or PET, MRI, etc.), all of which were mentioned above [170].

9.3. Therapy

Beside the administration of vasculoprotective pharmacological agents, such as aspirin, statins, ACE inhibitors, and angiotensin II receptor blockers [47, 207–209], tight control over
the disease activity and inflammatory activity is needed, using low-dose corticosteroids, immunosuppressive agents, or biologics [43, 207, 208, 210, 211].

There are no specific recommendations for management of traditional risk factors, such as dyslipidemia, diabetes mellitus, or smoking in SSc patients. Their treatment mostly follows the national guidelines. According to the EULAR recommendations, statins, ACE inhibitors, and angiotensin II (AT-II) blockers are considered as preferred treatment options [47, 212].

Statins significantly reduce the risk of CV disease by lipid lowering effect and modulation of inflammatory pathways [213, 214]. Aspirin is used in general population to prevent the risk of CVD. Glitazones (peroxisome proliferator-activated receptor gamma, PPARγ agonists) are preferred in treatment of insulin resistance because of their potential vasculoprotective and anti-inflammatory effects [215].

The most severe complications (e.g. PAH and SRC) are treated according to the EULAR recommendations for SSc, with use of calcium channel blockers in case of PAH, and ACE inhibitors in case of SRC [216]. Both of them, similarly as endothelin receptor antagonist (ERA) bosentan [217], have been demonstrated to have beneficial effects on myocardial perfusion, and on limiting further progression of life-threatening complications [200, 218, 219].

Nonsteroidal anti-inflammatory drugs (NSAIDs), administrated in pericarditis in SSc [216], are not recommended for long-term use with respect to the CV perspective [220].

To control the disease activity and inflammation, proper anti-inflammatory therapy should be administered. Corticosteroids and disease modifying antirheumatic drugs (DMARDs), used in some SSc manifestations according to the EULAR recommendation [216], may influence the CV risk.

Corticosteroids (used e.g. for treatment of myocarditis) may reduce vascular risk by effectively suppressing systemic inflammation [47]. On the other hand, they are pro-atherogenic and lead to dyslipidaemia, diabetes and hypertension [220, 221]. A daily threshold dose of 8 mg of prednisone was established, above which the number of deaths increases in a dose-dependent manner [222]. Corticosteroids should be used at the lowest doses possible for the shortest period of time possible [47].

Methotrexate (MTX), recommended particularly to treat the skin manifestations, exerts bimodal effects on the vasculature. It increases the production of pro-atherogenic homocysteine, which can promote endothelial injury, and increases LDL oxidation [223, 224]. On the other hand, hyperhomocysteinemia can be reversed by folate supplementation [225]. However, MTX may also be atheroprotective by inhibiting foam cell formation and modifying reverse cholesterol transport [226]. In the EULAR cardiovascular recommendations for inflammatory arthritis, administration of MTX to the adequate control of disease activity is preferred to the possible negative CV effects of treatment [47].

Cyclophosphamide (CPA), used in treatment of ILD, induces cardiac damage and heart failure by its influence on the myocardial cells metabolism and induction of apoptosis [227]. According to experimental studies, CPA may influence the lipid metabolism [228], for example, via the cholesterol transfer activity enhancement [229].
Regarding the biologics, studies in CV effects are almost exclusively in RA, and these drugs are not commonly used in patients with SSc. Numerous recent studies concluded, that infliximab, etanercept, adalimumab and rituximab may improve endothelial function and decrease CIMT and arterial stiffness in arthritis patients [208, 210, 211].

There may be differences among anti-TNF agents in terms of their effects on CV risk. There are controversial results on the effects of TNF blockers on lipid profiles, while infliximab may worsen the atherogenic index [211, 230]. On the other hand, biologics may also improve insulin sensitivity, decrease resistin, and increase adiponectin production [211, 231]. Rituximab may also exert vasculoprotective effects [232–234].

10. Conclusion

Systemic sclerosis is a chronic, progressive, potentially lethal rheumatic disease. The management and treatment of life-threatening disease manifestations, such as pulmonary arterial hypertension or scleroderma renal crisis, have improved over the last decades. Other causes, which increase the morbidity and mortality, have arisen, including the cardiovascular diseases in the first place. Similar to other rheumatic diseases, and based on many above-mentioned studies on pathogenesis of atherosclerosis in autoimmune conditions, cardiovascular risk in scleroderma is believed to be increased compared to the general population. The rate of this risk is not clear to date. Angiographic, sonographic, and computed tomography studies have provided conflicting data regarding the presence of macrovascular coronary lesions and accelerated atherosclerosis in scleroderma. Screening for subclinical cardiac involvement provides an opportunity for early diagnosis and treatment, which is crucial for positive outcome and prognosis. Thus, patients with systemic sclerosis should be closely observed, followed, and modifiable risk factors should be treated in the early stage. Moreover, future studies assessing larger cohorts of patients using standardized tools are needed to elucidate the cardiovascular risk in scleroderma patients.

Acknowledgements

This chapter was supported by grant projects AZV 16-33542A, AZV 16-33574A, SVV 260263, PRVOUK, and the Ministry of Health of the Czech Republic [Research Project No. 00023728].

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