Chapter 2

Atherosclerosis and Cardiovascular Risk in Systemic Sclerosis

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Additional information is available at the end of the chapter

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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].

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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

Traditional risk factors	**Disease (inflammation) related risk factors**
Age	Disease duration
Smoking	Smoking (RA, SLE)
Hyperlipidaemia	Acute phase reactants (CRP, fibrinogen)
Diabetes mellitus	Autoantibodies (APL, anti-oxLDL, anti-Hsp, etc.)
Obesity	Pro-atherogenic cytokines (e.g. TNF-α, IL-1, IL-6)
Sedentary life style	Chemokines
	Endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin)
Therapy-related risk factors	Proteases
Methotrexate (bimodal)	Hyperhomocysteinemia, low vitamin B12, and folate
Corticosteroids (bimodal)	Hyperprolactinemia
	Adipokines (resistin, adiponectin, leptin)

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].

Leading mechanisms	Disease
Accelerated atherosclerosis	RA, SpA, SLE, APS (SSc)
Autoantibody-mediated mechanisms	SLE, APS, RA
Proliferative obliteration	SSc, MCTD

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. Atherosclersis 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

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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].

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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 noninvasive 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 dsSSc 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, dcSSc 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 transthoracic 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

baseline [200]. 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-threating 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.

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References

[1] Krause I, Shoenfeld Y. Intravenous immunoglobulin treatment for fibrosis, atherosclerosis, and malignant conditions. Methods in Molecular Medicine. 2005;109:403-8.

[2] Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation. 2005;112(21):3337-47.

[3] Zinger H, Sherer Y, Shoenfeld Y. Atherosclerosis in autoimmune rheumatic diseases-mechanisms and clinical findings. Clinical Reviews in Allergy & Immunology. 2009;37(1):20-8.

[4] Gargiulo P, Marsico F, Parente A, Paolillo S, Cecere M, Casaretti L, et al. Ischemic heart disease in systemic inflammatory diseases. An appraisal. International Journal of Cardiology. 2014;170(3):286-90.

[5] Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Annals of the Rheumatic Diseases. 1998;57(11):682-6.

[6] Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). British Journal of Rheumatology. 1998;37(7):750-5.

[7] Hettema ME, Bootsma H, Kallenberg CG. Macrovascular disease and atherosclerosis in SSc. Rheumatology. 2008;47(5):578-83.

[8] Au K, Singh MK, Bodukam V, Bae S, Maranian P, Ogawa R, et al. Atherosclerosis in systemic sclerosis: A systematic review and meta-analysis. Arthritis and Rheumatism. 2011;63(7):2078-90.

[9] Soriano A, Afeltra A, Shoenfeld Y. Is atherosclerosis accelerated in systemic sclerosis? Novel insights. Current Opinion in Rheumatology. 2014;26(6):653-7.

[10] Cannarile F, Valentini V, Mirabelli G, Alunno A, Terenzi R, Luccioli F, et al. Cardiovascular disease in systemic sclerosis. Annals of Translational Medicine. 2015;3(1):8.

[11] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.

[12] Ross R. Atherosclerosis: An inflammatory disease. The New England Journal of Medicine. 1999;340(2):115-26.

[13] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. The New England Journal of Medicine. 2004;350(14):1387-97.

[14] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.

[15] Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. The New England Journal of Medicine. 2013;368(21):2004-13.

[16] Alkaabi JK, Ho M, Levison R, Pullar T, Belch JJ. Rheumatoid arthritis and macrovascular disease. Rheumatology. 2003;42(2):292-7.

[17] de Leeuw K, Freire B, Smit AJ, Bootsma H, Kallenberg CG, Bijl M. Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. Lupus. 2006;15(10):675-82.

[18] Hak AE, Karlson EW, Feskanich D, Stampfer MJ, Costenbader KH. Systemic lupus erythematosus and the risk of cardiovascular disease: Results from the nurses' health study. Arthritis and Rheumatism. 2009;61(10):1396-402.

[19] Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. The New England Journal of Medicine. 2003;349(25):2399-406.

[20] Sherer Y, Shoenfeld Y. Mechanisms of disease: Atherosclerosis in autoimmune diseases. Nature Clinical Practice Rheumatology. 2006;2(2):99-106.

[21] Hansson GK. Immune mechanisms in atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001;21(12):1876-90.

[22] Hansson GK. Inflammatory mechanisms in atherosclerosis. Journal of Thrombosis and Haemostasis. 2009;7(Suppl 1):328-31.

[23] Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: From pathophysiology to practice. Journal of the American College of Cardiology. 2009;54(23):2129-38.

[24] Soltesz P, Prohaszka Z, Fust G, Der H, Kerekes G, Szodoray P, et al. Vasculopathiak autoimmun vonatkozasai [The autoimmune features of vasculopathies]. Orvosi Hetilap. 2007;148(Suppl 1):53-7.

[25] Szekanecz Z. Pro-inflammatory cytokines in atherosclerosis. The Israel Medical Association Journal. 2008;10(7):529-30.

[26] Soltesz P, Kerekes G, Der H, Szucs G, Szanto S, Kiss E, et al. Comparative assessment of vascular function in autoimmune rheumatic diseases: Considerations of prevention and treatment. Autoimmunity Reviews. 2011;10(7):416-25.

[27] Hansson GK, Jonasson L, Seifert PS, Stemme S. Immune mechanisms in atherosclerosis. Arteriosclerosis. 1989;9(5):567-78.

[28] Tervaert JW. Translational mini-review series on immunology of vascular disease: Accelerated atherosclerosis in vasculitis. Clinical and Experimental Immunology. 2009;156(3):377-85.

[29] Abusamieh M, Ash J. Atherosclerosis and systemic lupus erythematosus. Cardiology in Review. 2004;12(5):267-75.

[30] Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: Atherosclerosis as a systemic manifestation of psoriasis. The British Journal of Dermatology. 2009;161(1):1-7.

[31] Ames PR. Antiphospholipid antibodies, thrombosis and atherosclerosis in systemic lupus erythematosus: A unifying 'membrane stress syndrome' hypothesis. Lupus. 1994;3(5):371-7.

[32] Belizna CC, Richard V, Thuillez C, Levesque H, Shoenfeld Y. Insights into atherosclerosis therapy in antiphospholipid syndrome. Autoimmunity Reviews. 2007;7(1):46-51.

[33] Bruce IN, Gladman DD, Urowitz MB. Premature atherosclerosis in systemic lupus erythematosus. Rheumatic Diseases Clinics of North America. 2000;26(2):257-78.

[34] Gerli R, Sherer Y, Bocci EB, Vaudo G, Moscatelli S, Shoenfeld Y. Precocious atherosclerosis in rheumatoid arthritis: Role of traditional and disease-related cardiovascular risk factors. Annals of the New York Academy of Sciences. 2007;1108:372-81.

[35] Jara LJ, Medina G, Vera-Lastra O, Shoenfeld Y. Atherosclerosis and antiphospholipid syndrome. Clinical Reviews in Allergy & Immunology. 2003;25(1):79-88.

[36] Matsuura E, Kobayashi K, Yasuda T, Koike T. Antiphospholipid antibodies and atherosclerosis. Lupus. 1998;7(Suppl 2):S135-9.

[37] Merrill JT. The antiphospholipid syndrome and atherosclerosis: Clue to pathogenesis. Current Rheumatology Reports. 2003;5(5):401-6.

[38] Sherer Y, Shoenfeld Y. Antiphospholipid syndrome, antiphospholipid antibodies, and atherosclerosis. Current Atherosclerosis Reports. 2001;3(4):328-33.

[39] Shoenfeld Y, Harats D, George J. Atherosclerosis and the antiphospholipid syndrome: A link unravelled? Lupus. 1998;7(Suppl 2):S140-3.

[40] Szucs G, Timar O, Szekanecz Z, Der H, Kerekes G, Szamosi S, et al. Endothelial dysfunction precedes atherosclerosis in systemic sclerosis: Relevance for prevention of vascular complications. Rheumatology. 2007;46(5):759-62.

[41] Kerekes G, Szekanecz Z, Der H, Sandor Z, Lakos G, Muszbek L, et al. Endothelial dysfunction and atherosclerosis in rheumatoid arthritis: A multiparametric analysis using imaging techniques and laboratory markers of inflammation and autoimmunity. The Journal of Rheumatology. 2008;35(3):398-406.

[42] Soltesz P, Der H, Kerekes G, Szodoray P, Szucs G, Danko K, et al. A comparative study of arterial stiffness, flow-mediated vasodilation of the brachial artery, and the thickness of the carotid artery intima-media in patients with systemic autoimmune diseases. Clinical Rheumatology. 2009;28(6):655-62.

[43] Szekanecz Z, Kerekes G, Der H, Sandor Z, Szabo Z, Vegvari A, et al. Accelerated atherosclerosis in rheumatoid arthritis. Annals of the New York Academy of Sciences. 2007;1108:349-58.

[44] Szekanecz Z, Koch AE. Vascular involvement in rheumatic diseases: 'Vascular rheumatology'. Arthritis Research & Therapy. 2008;10(5):224.

[45] Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Dierssen T, Vaqueiro I, Blanco R, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. Medicine. 2009;88(6):358-65.

[46] Heeneman S, Daemen MJ. Cardiovascular risks in spondyloarthritides. Current Opinion in Rheumatology. 2007;19(4):358-62.

[47] Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;69(2):325-31.

[48] Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. Annals of the Rheumatic Diseases. 2009;68(7):1131-5.

[49] Gonzalez-Juanatey C, Llorca J, Miranda-Filloy JA, Amigo-Diaz E, Testa A, Garcia-Porrua C, et al. Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis and Rheumatism. 2007;57(2):287-93.

[50] Vegh J, Soos G, Csipo I, Demeter N, Ben T, Dezso B, et al. Pulmonary arterial hypertension in mixed connective tissue disease: Successful treatment with Iloprost. Rheumatology International. 2006;26(3):264-9.

[51] Numano F. Vasa vasoritis, vasculitis and atherosclerosis. International Journal of Cardiology. 2000;75(Suppl 1):S1-8; discussion S17-9.

[52] Gerli R, Vaudo G, Bocci EB, Schillaci G, Alunno A, Luccioli F, et al. Functional impairment of the arterial wall in primary Sjogren's syndrome: Combined action of immunologic and inflammatory factors. Arthritis Care & Research. 2010;62(5):712-8.

[53] Sarzi-Puttini P, Atzeni F, Gerli R, Bartoloni E, Doria A, Barskova T, et al. Cardiac involvement in systemic rheumatic diseases: An update. Autoimmunity Reviews. 2010;9(12):849-52.

[54] Sitia S, Atzeni F, Sarzi-Puttini P, Di Bello V, Tomasoni L, Delfino L, et al. Cardiovascular involvement in systemic autoimmune diseases. Autoimmunity Reviews. 2009;8(4):281-6.

[55] Zardi EM, Afeltra A. Endothelial dysfunction and vascular stiffness in systemic lupus erythematosus: Are they early markers of subclinical atherosclerosis? Autoimmunity Reviews. 2010;9(10):684-6.

[56] Turiel M, Sitia S, Atzeni F, Tomasoni L, Gianturco L, Giuffrida M, et al. The heart in rheumatoid arthritis. Autoimmunity Reviews. 2010;9(6):414-8.

[57] Dumoitier N, Lofek S, Mouthon L. Pathophysiology of systemic sclerosis: State of the art in 2014. Presse Medicale. 2014;43(10 Pt 2):e267-78.

[58] Papagoras C, Achenbach K, Tsifetaki N, Tsiouris S, Fotopoulos A, Drosos AA. Heart involvement in systemic sclerosis: A combined echocardiographic and scintigraphic study. Clinical Rheumatology. 2014;33(8):1105-11.

[59] Bartoloni Bocci E, Luccioli F, Angrisani C, Moscatelli S, Alunno A, Gerli R. Accelerated atherosclerosis in systemic lupus erythematosus and other connective tissue diseases. Expert Review of Clinical Immunology. 2007;3(4):531-41.

[60] Bartoloni E, Alunno A, Bistoni O, Gerli R. How early is the atherosclerotic risk in rheumatoid arthritis? Autoimmunity Reviews. 2010;9(10):701-7.

[61] 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 & Research. 2011;63(2):178-83.

[62] Baraut J, Michel L, Verrecchia F, Farge D. Relationship between cytokine profiles and clinical outcomes in patients with systemic sclerosis. Autoimmunity Reviews. 2010;10(2):65-73.

[63] Belch JJ, McSwiggan S, Lau C. Macrovascular disease in systemic sclerosis: The tip of an iceberg? Rheumatology. 2008;47(Suppl 5):v16-7.

[64] Bartoli F, Blagojevic J, Bacci M, Fiori G, Tempestini A, Conforti ML, et al. Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. Annals of the New York Academy of Sciences. 2007;1108:283-90.

[65] Veale DJ, Collidge TA, Belch JJ. Increased prevalence of symptomatic macrovascular disease in systemic sclerosis. Annals of the Rheumatic Diseases. 1995;54(10):853-5.

[66] Ho M, Veale D, Eastmond C, Nuki G, Belch J. Macrovascular disease and systemic sclerosis. Annals of the Rheumatic Diseases. 2000;59(1):39-43.

[67] Rubio-Rivas M, Royo C, Simeon CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2014;44(2):208-19.

[68] Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Annals of the Rheumatic Diseases. 2007;66(7):940-4.

[69] Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: A study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Annals of the Rheumatic Diseases. 2010;69(10):1809-15.

[70] Nussinovitch U, Shoenfeld Y. Atherosclerosis and macrovascular involvement in systemic sclerosis: Myth or reality. Autoimmunity Reviews. 2011;10(5):259-66.

[71] Akram MR, Handler CE, Williams M, Carulli MT, Andron M, Black CM, et al. Angiographically proven coronary artery disease in scleroderma. Rheumatology. 2006;45(11):1395-8.

[72] Ngian GS, Sahhar J, Wicks IP, Van Doornum S. Cardiovascular disease in systemic sclerosis: An emerging association? Arthritis Research & Therapy. 2011;13(4):237.

[73] Man A, Zhu Y, Zhang Y, Dubreuil M, Rho YH, Peloquin C, et al. The risk of cardiovascular disease in systemic sclerosis: A population-based cohort study. Annals of the Rheumatic Diseases. 2013;72(7):1188-93.

[74] Khurma V, Meyer C, Park GS, McMahon M, Lin J, Singh RR, et al. A pilot study of subclinical coronary atherosclerosis in systemic sclerosis: Coronary artery calcification in cases and controls. Arthritis and Rheumatism. 2008;59(4):591-7.

[75] Mok MY, Lau CS, Chiu SS, Tso AW, Lo Y, Law LS, et al. Systemic sclerosis is an independent risk factor for increased coronary artery calcium deposition. Arthritis and Rheumatism. 2011;63(5):1387-95.

[76] Nordin A, Jensen-Urstad K, Bjornadal L, Pettersson S, Larsson A, Svenungsson E. Ischemic arterial events and atherosclerosis in patients with systemic sclerosis: A population-based case-control study. Arthritis Research & Therapy. 2013;15(4):R87.

[77] Ngian GS, Sahhar J, Proudman SM, Stevens W, Wicks IP, Van Doornum S. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Annals of the Rheumatic Diseases. 2012;71(12):1980-3.

[78] Chu SY, Chen YJ, Liu CJ, Tseng WC, Lin MW, Hwang CY, et al. Increased risk of acute myocardial infarction in systemic sclerosis: A nationwide population-based study. The American Journal of Medicine. 2013;126(11):982-8.

[79] Zakopoulos NA, Kotsis VT, Gialafos EJ, Papamichael CM, Pitiriga V, Mitsibounas DN, et al. Systemic sclerosis is not associated with clinical or ambulatory blood pressure. Clinical and Experimental Rheumatology. 2003;21(2):199-204.

[80] Zeng Y, Li M, Xu D, Hou Y, Wang Q, Fang Q, et al. Macrovascular involvement in systemic sclerosis: Evidence of correlation with disease activity. Clinical and Experimental Rheumatology. 2012;30(2 Suppl 71):S76-80.

[81] Blagojevic J, Matucci Cerinic M. Macrovascular involvement in systemic sclerosis: Comorbidity or accelerated atherosclerosis? Current Rheumatology Reports. 2007;9(3):–2.

[82] Muller-Ladner U, Distler O, Ibba-Manneschi L, Neumann E, Gay S. Mechanisms of vascular damage in systemic sclerosis. Autoimmunity. 2009;42(7):587-95.

[83] Szamosi S, Csiki Z, Szomjak E, Szolnoki E, Szoke G, Szekanecz Z, et al. Plasma homocysteine levels, the prevalence of methylenetetrahydrofolate reductase gene C677T polymorphism and macrovascular disorders in systemic sclerosis: Risk factors for accelerated macrovascular damage? Clinical Reviews in Allergy & Immunology. 2009;36(2-3):145-9.

[84] Pignone A, Scaletti C, Matucci-Cerinic M, Vazquez-Abad D, Meroni PL, Del Papa N, et al. Anti-endothelial cell antibodies in systemic sclerosis: Significant association with vascular involvement and alveolo-capillary impairment. Clinical and Experimental Rheumatology. 1998;16(5):527-32.

[85] Koch AE, Kronfeld-Harrington LB, Szekanecz Z, Cho MM, Haines GK, Harlow LA, et al. In situ expression of cytokines and cellular adhesion molecules in the skin of patients with systemic sclerosis. Their role in early and late disease. Pathobiology: Journal of Immunopathology, Molecular and Cellular Biology. 1993;61(5-6):239-46.

[86] Gruschwitz M, von den Driesch P, Kellner I, Hornstein OP, Sterry W. Expression of adhesion proteins involved in cell-cell and cell-matrix interactions in the skin of patients with progressive systemic sclerosis. Journal of the American Academy of Dermatology. 1992;27(2 Pt 1):169-77.

[87] Borba EF, Borges CT, Bonfa E. Lipoprotein profile in limited systemic sclerosis. Rheumatology International. 2005;25(5):379-83.

[88] Lippi G, Caramaschi P, Montagnana M, Salvagno GL, Volpe A, Guidi G. Lipoprotein[a] and the lipid profile in patients with systemic sclerosis. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2006;364(1-2):345-8.

[89] Cerinic MM, Valentini G, Sorano GG, D'Angelo S, Cuomo G, Fenu L, et al. Blood coagulation, fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. Seminars in Arthritis and Rheumatism. 2003;32(5):285-95.

[90] Kodera M, Hayakawa I, Komura K, Yanaba K, Hasegawa M, Takehara K, et al. Anti-lipoprotein lipase antibody in systemic sclerosis: Association with elevated serum triglyceride concentrations. The Journal of Rheumatology. 2005;32(4):629-36.

[91] Czirjak L, Kumanovics G, Varju C, Nagy Z, Pakozdi A, Szekanecz Z, et al. Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Annals of the Rheumatic Diseases. 2008;67(1):59-63.

[92] Munzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. Annals of Medicine. 2008;40(3):180-96.

[93] Andersen GN, Caidahl K, Kazzam E, Petersson AS, Waldenstrom A, Mincheva-Nilsson L, et al. Correlation between increased nitric oxide production and markers of endothelial activation in systemic sclerosis: Findings with the soluble adhesion molecules E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1. Arthritis and Rheumatism. 2000;43(5):1085-93.

[94] Altorok N, Wang Y, Kahaleh B. Endothelial dysfunction in systemic sclerosis. Current Opinion in Rheumatology. 2014;26(6):615-20.

[95] Fleming JN, Nash RA, Mahoney WM, Jr., Schwartz SM. Is scleroderma a vasculopathy? Current Rheumatology Reports. 2009;11(2):103-10.

[96] Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: Evidence that systemic sclerosis is a vascular disease. Arthritis and Rheumatism. 2013;65(8):1953-62.

[97] Distler O, Distler JH, Scheid A, Acker T, Hirth A, Rethage J, et al. Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. Circulation Research. 2004;95(1):109-16.

[98] Farouk HM, Hamza SH, El Bakry SA, Youssef SS, Aly IM, Moustafa AA, et al. Dysregulation of angiogenic homeostasis in systemic sclerosis. International Journal of Rheumatic Diseases. 2013;16(4):448-54.

[99] Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997;275(5302):964-7.

[100] Kuwana M, Okazaki Y, Yasuoka H, Kawakami Y, Ikeda Y. Defective vasculogenesis in systemic sclerosis. Lancet. 2004;364(9434):603-10.

[101] Maurer B, Distler A, Suliman YA, Gay RE, Michel BA, Gay S, et al. Vascular endothelial growth factor aggravates fibrosis and vasculopathy in experimental models of systemic sclerosis. Annals of the Rheumatic Diseases. 2014;73(10):1880-7.

[102] Bartoloni E, Alunno A, Bistoni O, Caterbi S, Luccioli F, Santoboni G, et al. Characterization of circulating endothelial microparticles and endothelial progenitor cells in primary Sjogren's syndrome: New markers of chronic endothelial damage? Rheumatology. 2015;54(3):536-44.

[103] Del Papa N, Cortiana M, Comina DP, Maglione W, Silvestri I, Maronetti Mazzeo L, et al. Progenitori delle cellule endoteliali di origine midollare in corso di sclerosi sistemica: possibile ruolo nell'angiogenesi [Endothelial progenitor cells in systemic sclerosis: Their possible role in angiogenesis]. Reumatismo. 2005;57(3):174-9.

[104] Werner N, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, et al. Circulating endothelial progenitor cells and cardiovascular outcomes. The New England Journal of Medicine. 2005;353(10):999-1007.

[105] Del Papa N, Quirici N, Soligo D, Scavullo C, Cortiana M, Borsotti C, et al. Bone marrow endothelial progenitors are defective in systemic sclerosis. Arthritis and Rheumatism. 2006;54(8):2605-15.

[106] Avouac J, Juin F, Wipff J, Couraud PO, Chiocchia G, Kahan A, et al. Circulating endothelial progenitor cells in systemic sclerosis: Association with disease severity. Annals of the Rheumatic Diseases. 2008;67(10):1455-60.

[107] Allanore Y, Batteux F, Avouac J, Assous N, Weill B, Kahan A. Levels of circulating endothelial progenitor cells in systemic sclerosis. Clinical and Experimental Rheumatology. 2007;25(1):60-6.

[108] Yoder MC, Mead LE, Prater D, Krier TR, Mroueh KN, Li F, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. Blood. 2007;109(5):1801-9.

[109] Kuwana M, Okazaki Y. Brief report: Impaired in vivo neovascularization capacity of endothelial progenitor cells in patients with systemic sclerosis. Arthritis & Rheumatology. 2014;66(5):1300-5.

[110] Del Papa N, Quirici N, Scavullo C, Gianelli U, Corti L, Vitali C, et al. Antiendothelial cell antibodies induce apoptosis of bone marrow endothelial progenitors in systemic sclerosis. The Journal of Rheumatology. 2010;37(10):2053-63.

[111] Erdbruegger U, Haubitz M, Woywodt A. Circulating endothelial cells: A novel marker of endothelial damage. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2006;373(1-2):17-26.

[112] Del Papa N, Colombo G, Fracchiolla N, Moronetti LM, Ingegnoli F, Maglione W, et al. Circulating endothelial cells as a marker of ongoing vascular disease in systemic sclerosis. Arthritis and Rheumatism. 2004;50(4):1296-304.

[113] Herrick AL, Illingworth KJ, Hollis S, Gomez-Zumaquero JM, Tinahones FJ. Antibodies against oxidized low-density lipoproteins in systemic sclerosis. Rheumatology. 2001;40(4):401-5.

[114] Nussinovitch U, Shoenfeld Y. Autoimmunity and heart diseases: Pathogenesis and diagnostic criteria. Archivum Immunologiae et Therapiae Experimentalis. 2009;57(2):95-104.

[115] Lopez LR, Simpson DF, Hurley BL, Matsuura E. OxLDL/beta2GPI complexes and autoantibodies in patients with systemic lupus erythematosus, systemic sclerosis, and antiphospholipid syndrome: Pathogenic implications for vascular involvement. Annals of the New York Academy of Sciences. 2005;1051:313-22.

[116] Matsuura E, Kobayashi K, Inoue K, Lopez LR, Shoenfeld Y. Oxidized LDL/beta2-glycoprotein I complexes: New aspects in atherosclerosis. Lupus. 2005;14(9):736-41.

[117] Brey RL, Abbott RD, Curb JD, Sharp DS, Ross GW, Stallworth CL, et al. Beta(2)-glycoprotein 1-dependent anticardiolipin antibodies and risk of ischemic stroke and myocardial infarction: The Honolulu heart program. Stroke; A Journal of Cerebral Circulation. 2001;32(8):1701-6.

[118] Sanna G, Bertolaccini ML, Mameli A, Hughes GR, Khamashta MA, Mathieu A. Antiphospholipid antibodies in patients with scleroderma: Prevalence and clinical significance. Annals of the Rheumatic Diseases. 2005;64(12):1795-6.

[119] Boin F, Franchini S, Colantuoni E, Rosen A, Wigley FM, Casciola-Rosen L. Independent association of anti-beta(2)-glycoprotein I antibodies with macrovascular disease and mortality in scleroderma patients. Arthritis and Rheumatism. 2009;60(8):2480-9.

[120] van Haelst PL, Kobold AC, van Doormaal JJ, Tervaert JW. AECA and ANCA in patients with premature atherosclerosis. International Reviews of Immunology. 2002;21(1):19-26.

[121] Fischer K, Brzosko M, Walecka A, Ostanek L, Sawicki M. Przeciwciala przeciw komorkom endotelialnym--czynnik ryzyka miazdzycy u chorych na toczen rumieniowaty ukladowy [Antiendothelial cell antibodies as a risk factor of atherosclerosis in systemic lupus erythematosus]. Annales Academiae Medicae Stetinensis. 2006;52(Suppl 2):95-9.

[122] Timar O, Soltesz P, Szamosi S, Der H, Szanto S, Szekanecz Z, et al. Increased arterial stiffness as the marker of vascular involvement in systemic sclerosis. The Journal of Rheumatology. 2008;35(7):1329-33.

[123] George J, Meroni PL, Gilburd B, Raschi E, Harats D, Shoenfeld Y. Anti-endothelial cell antibodies in patients with coronary atherosclerosis. Immunology Letters. 2000;73(1):23-7.

[124] Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. The Journal of Clinical Investigation. 1990;86(4):1343-6.

[125] Niemiec P, Zak I, Wita K. The D allele of angiotensin I-converting enzyme gene insertion/deletion polymorphism is associated with the severity of atherosclerosis. Clinical Chemistry and Laboratory Medicine. 2008;46(4):446-52.

[126] Cambien F, Poirier O, Lecerf L, Evans A, Cambou JP, Arveiler D, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. Nature. 1992;359(6396):641-4.

[127] Keavney B, McKenzie C, Parish S, Palmer A, Clark S, Youngman L, et al. Large-scale test of hypothesised associations between the angiotensin-converting-enzyme insertion/deletion polymorphism and myocardial infarction in about 5000 cases and 6000 controls. International Studies of Infarct Survival (ISIS) Collaborators. Lancet. 2000;355(9202):434-42.

[128] Bartoli F, Angotti C, Fatini C, Conforti ML, Guiducci S, Blagojevic J, et al. Angiotensin-converting enzyme I/D polymorphism and macrovascular disease in systemic sclerosis. Rheumatology. 2007;46(5):772-5.

[129] Boulanger CM, Scoazec A, Ebrahimian T, Henry P, Mathieu E, Tedgui A, et al. Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. Circulation. 2001;104(22):2649-52.

[130] Nomura S, Inami N, Ozaki Y, Kagawa H, Fukuhara S. Significance of microparticles in progressive systemic sclerosis with interstitial pneumonia. Platelets. 2008;19(3):192-8.

[131] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation. 2007;115(4):459-67.

[132] Tarek el G, Yasser AE, Gheita T. Coronary angiographic findings in asymptomatic systemic sclerosis. Clinical Rheumatology. 2006;25(4):487-90.

[133] Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology. 2009;48(Suppl 3):iii45-8.

[134] Montisci R, Vacca A, Garau P, Colonna P, Ruscazio M, Passiu G, et al. Detection of early impairment of coronary flow reserve in patients with systemic sclerosis. Annals of the Rheumatic Diseases. 2003;62(9):890-3.

[135] Ferri C, Giuggioli D, Sebastiani M, Colaci M, Emdin M. Heart involvement and systemic sclerosis. Lupus. 2005;14(9):702-7.

[136] Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation. 1976;53(3):483-90.

[137] Derk CT, Jimenez SA. Acute myocardial infarction in systemic sclerosis patients: A case series. Clinical Rheumatology. 2007;26(6):965-8.

[138] D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. The American Journal of Medicine. 1969;46(3):428-40.

[139] Mok MY, Chiu SS, Lo Y, Mak HK, Wong WS, Khong PL, et al. Coronary atherosclerosis using computed tomography coronary angiography in patients with systemic sclerosis. Scandinavian Journal of Rheumatology. 2009;38(5):381-5.

[140] Youssef P, Englert H, Bertouch J. Large vessel occlusive disease associated with CREST syndrome and scleroderma. Annals of the Rheumatic Diseases. 1993;52(6):464-6.

[141] Youssef P, Brama T, Englert H, Bertouch J. Limited scleroderma is associated with increased prevalence of macrovascular disease. The Journal of Rheumatology. 1995;22(3):469-72.

[142] Dick EA, Aviv R, Francis I, Hamilton G, Baker D, Black C, et al. Catheter angiography and angioplasty in patients with scleroderma. The British Journal of Radiology. 2001;74(888):1091-6.

[143] Wan MC, Moore T, Hollis S, Herrick AL. Ankle brachial pressure index in systemic sclerosis: Influence of disease subtype and anticentromere antibody. Rheumatology. 2001;40(10):1102-5.

[144] Kahaleh MB, LeRoy EC. Autoimmunity and vascular involvement in systemic sclerosis (SSc). Autoimmunity. 1999;31(3):195-214.

[145] Rosato E, Gigante A, Barbano B, Cianci R, Molinaro I, Pisarri S, et al. In systemic sclerosis macrovascular damage of hands digital arteries correlates with microvascular damage. Microvascular Research. 2011;82(3):410-5.

[146] Chiang CH, Liu CJ, Huang CC, Chan WL, Huang PH, Chen TJ, et al. Systemic sclerosis and risk of ischaemic stroke: A nationwide cohort study. Rheumatology. 2013;52(1):161-5.

[147] Schedel J, Kuchenbuch S, Schoelmerich J, Feuerbach S, Geissler A, Mueller-Ladner U. Cerebral lesions in patients with connective tissue diseases and systemic vasculitides: Are there specific patterns? Annals of the New York Academy of Sciences. 2010;1193:167-75.

[148] Terrier B, Charbonneau F, Touze E, Berezne A, Pagnoux C, Silvera S, et al. Cerebral vasculopathy is associated with severe vascular manifestations in systemic sclerosis. The Journal of Rheumatology. 2009;36(7):1486-94.

[149] Bertinotti L, Mortilla M, Conforti ML, Colangelo N, Nacci F, Del Rosso A, et al. Proton magnetic resonance spectroscopy reveals central neuroaxonal impairment in systemic sclerosis. The Journal of Rheumatology. 2006;33(3):546-51.

[150] Roquer J, Segura T, Serena J, Castillo J. Endothelial dysfunction, vascular disease and stroke: The ARTICO study. Cerebrovascular Diseases. 2009;27(Suppl 1):25-37.

[151] Faucher B, Granel B, Nicoli F. Acute cerebral vasculopathy in systemic sclerosis. Rheumatology International. 2013;33(12):3073-7.

[152] Heron E, Fornes P, Rance A, Emmerich J, Bayle O, Fiessinger JN. Brain involvement in scleroderma: Two autopsy cases. Stroke; A Journal of Cerebral Circulation. 1998;29(3):719-21.

[153] Chen XY, Lam WW, Ng HK, Fan YH, Wong KS. Intracranial artery calcification: A newly identified risk factor of ischemic stroke. Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging. 2007;17(4):300-3.

[154] Heron E, Hernigou A, Chatellier G, Fornes P, Emmerich J, Fiessinger JN. Intracerebral calcification in systemic sclerosis. Stroke; A Journal of Cerebral Circulation. 1999;30(10):2183-5.

[155] Tanabe J. White matter hyperintensities are associated with an increased risk of stroke, dementia and mortality. Evidence-Based Mental Health. 2011;14(1):1.

[156] Sardanelli F, Iozzelli A, Cotticelli B, Losacco C, Cutolo M, Sulli A, et al. White matter hyperintensities on brain magnetic resonance in systemic sclerosis. Annals of the Rheumatic Diseases. 2005;64(5):777-9.

[157] Mohamed RH, Nassef AA. Brain magnetic resonance imaging findings in patients with systemic sclerosis. International Journal of Rheumatic Diseases. 2010;13(1):61-7.

[158] Nobili F, Cutolo M, Sulli A, Vitali P, Vignola S, Rodriguez G. Brain functional involvement by perfusion SPECT in systemic sclerosis and Behcet's disease. Annals of the New York Academy of Sciences. 2002;966:409-14.

[159] Pathak R, Gabor AJ. Scleroderma and central nervous system vasculitis. Stroke; A Journal of Cerebral Circulation. 1991;22(3):410-3.

[160] Hietarinta M, Lassila O, Hietaharju A. Association of anti-U1RNP- and anti-Scl-70-antibodies with neurological manifestations in systemic sclerosis (scleroderma). Scandinavian Journal of Rheumatology. 1994;23(2):64-7.

[161] Hettema ME, Zhang D, de Leeuw K, Stienstra Y, Smit AJ, Kallenberg CG, et al. Early atherosclerosis in systemic sclerosis and its relation to disease or traditional risk factors. Arthritis Research & Therapy. 2008;10(2):R49.

[162] Cypiene A, Laucevicius A, Venalis A, Dadoniene J, Ryliskyte L, Petrulioniene Z, et al. The impact of systemic sclerosis on arterial wall stiffness parameters and endothelial function. Clinical Rheumatology. 2008;27(12):1517-22.

[163] Andersen GN, Mincheva-Nilsson L, Kazzam E, Nyberg G, Klintland N, Petersson AS, et al. Assessment of vascular function in systemic sclerosis: Indications of the development of nitrate tolerance as a result of enhanced endothelial nitric oxide production. Arthritis and Rheumatism. 2002;46(5):1324-32.

[164] Liu J, Zhang Y, Cao TS, Duan YY, Yuan LJ, Yang YL, 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 & Research. 2011;63(4):579-87.

[165] Roustit M, Simmons GH, Baguet JP, Carpentier P, Cracowski JL. Discrepancy between simultaneous digital skin microvascular and brachial artery macrovascular post-occlusive hyperemia in systemic sclerosis. The Journal of Rheumatology. 2008;35(8):1576-83.

[166] Sherer Y, Cerinic MM, Bartoli F, Blagojevic J, Conforti ML, Gilburd B, et al. Early atherosclerosis and autoantibodies to heat-shock proteins and oxidized LDL in systemic sclerosis. Annals of the New York Academy of Sciences. 2007;1108:259-67.

[167] Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. Rheumatic disease and carotid intima-media thickness: A systematic review and meta-analysis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;30(5):1014-26.

[168] Vettori S, Maresca L, Cuomo G, Abbadessa S, Leonardo G, Valentini G. Clinical and subclinical atherosclerosis in systemic sclerosis: Consequences of previous corticosteroid treatment. Scandinavian Journal of Rheumatology. 2010;39(6):485-9.

[169] Schiopu E, Au KM, McMahon MA, Kaplan MJ, Divekar A, Singh RR, 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. 2014;53(4):704-13.

[170] Kerekes G, Soltesz P, Nurmohamed MT, Gonzalez-Gay MA, Turiel M, Vegh E, et al. Validated methods for assessment of subclinical atherosclerosis in rheumatology. Nature Reviews Rheumatology. 2012;8(4):224-34.

[171] Szekanecz Z, Kerekes G, Vegh E, Kardos Z, Barath Z, Tamasi L, et al. Autoimmune atherosclerosis in 3D: How it develops, how to diagnose and what to do. Autoimmunity Reviews. 2016;15(7):756-69.

[172] Lekakis J, Mavrikakis M, Papamichael C, Papazoglou S, Economou O, Scotiniotis I, et al. Short-term estrogen administration improves abnormal endothelial function in women with systemic sclerosis and Raynaud's phenomenon. American Heart Journal. 1998;136(5):905-12.

[173] Kaloudi O, Basta G, Perfetto F, Bartoli F, Del Rosso A, Miniati I, et al. Circulating levels of Nepsilon-(carboxymethyl)lysine are increased in systemic sclerosis. Rheumatology. 2007;46(3):412-6.

[174] Cheng KS, Tiwari A, Boutin A, Denton CP, Black CM, Morris R, et al. Carotid and femoral arterial wall mechanics in scleroderma. Rheumatology. 2003;42(11):1299-305.

[175] Kawasaki M, Ito Y, Yokoyama H, Arai M, Takemura G, Hara A, et al. Assessment of arterial medial characteristics in human carotid arteries using integrated backscatter ultrasound and its histological implications. Atherosclerosis. 2005;180(1):145-54.

[176] Stafford L, Englert H, Gover J, Bertouch J. Distribution of macrovascular disease in scleroderma. Annals of the Rheumatic Diseases. 1998;57(8):476-9.

[177] Sfikakis PP, Papamichael C, Stamatelopoulos KS, Tousoulis D, Fragiadaki KG, Katsichti P, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis and Rheumatism. 2007;56(6):1985-93.

[178] Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. Journal of the American College of Cardiology. 1994;24(6):1468-74.

[179] Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: The Cardiovascular Health Study. Circulation. 2007;115(18):2390-7.

[180] Lekakis J, Papamichael C, Mavrikakis M, Voutsas A, Stamatelopoulos S. Effect of long-term estrogen therapy on brachial arterial endothelium-dependent vasodilation in women with Raynaud's phenomenon secondary to systemic sclerosis. The American Journal of Cardiology. 1998;82(12):1555-7, A8.

[181] D'Andrea A, Stisi S, Caso P, Uccio FS, Bellissimo S, Salerno G, et al. Associations between left ventricular myocardial involvement and endothelial dysfunction in systemic sclerosis: Noninvasive assessment in asymptomatic patients. Echocardiography. 2007;24(6):587-97.

[182] Rollando D, Bezante GP, Sulli A, Balbi M, Panico N, Pizzorni C, et al. Brachial artery endothelial-dependent flow-mediated dilation identifies early-stage endothelial dysfunction in systemic sclerosis and correlates with nailfold microvascular impairment. The Journal of Rheumatology. 2010;37(6):1168-73.

[183] D'Andrea A, Caso P, Cuomo S, Scotto di Uccio F, Scarafile R, Salerno G, et al. Myocardial and vascular dysfunction in systemic sclerosis: The potential role of non-invasive assessment in asymptomatic patients. International Journal of Cardiology. 2007;121(3):298-301.

[184] Rossi P, Granel B, Marziale D, Le Mee F, Frances Y. Endothelial function and hemodynamics in systemic sclerosis. Clinical Physiology and Functional Imaging. 2010;30(6):453-9.

[185] Al-Qaisi M, Nott DM, King DH, Kaddoura S. Ankle brachial pressure index (ABPI): An update for practitioners. Vascular Health and Risk Management. 2009;5:833-41.

[186] Wig S, Wilkinson J, Moore T, Manning J, Chevance A, Vail A, et al. A longitudinal study of ankle brachial pressure indices in a cohort of patients with systemic sclerosis. Rheumatology. 2014;53(11):2009-13.

[187] Oliver JJ, Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;23(4):554-66.

[188] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. Journal of the American College of Cardiology. 2010;55(13):1318-27.

[189] Peled N, Shitrit D, Fox BD, Shlomi D, Amital A, Bendayan D, et al. Peripheral arterial stiffness and endothelial dysfunction in idiopathic and scleroderma associated pulmonary arterial hypertension. The Journal of Rheumatology. 2009;36(5):970-5.

[190] Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. European Heart Journal. 2006;27(21):2588-605.

[191] Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. Hypertension. 2005;46(5):1118-22.

[192] Ngian GS, Sahhar J, Wicks IP, Van Doornum S. Arterial stiffness is increased in systemic sclerosis: A cross-sectional comparison with matched controls. Clinical and Experimental Rheumatology. 2014;32(6 Suppl 86):S-161-6.

[193] Piccione MC, Bagnato G, Zito C, Di Bella G, Caliri A, Catalano M, et al. Early identification of vascular damage in patients with systemic sclerosis. Angiology. 2011;62(4):338-43.

[194] Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovascular Imaging. 2009;2(6):675-88.

[195] Sulli A, Ghio M, Bezante GP, Deferrari L, Craviotto C, Sebastiani V, et al. Blunted coronary flow reserve in systemic sclerosis. Rheumatology. 2004;43(4):505-9.

[196] Vacca A, Siotto P, Cauli A, Montisci R, Garau P, Ibba V, et al. Absence of epicardial coronary stenosis in patients with systemic sclerosis with severe impairment of coronary flow reserve. Annals of the Rheumatic Diseases. 2006;65(2):274-5.

[197] Sulli A, Ghio M, Bezante GP, Deferrari L, Craviotto C, Sebastiani V, et al. Blunted coronary flow reserve in systemic sclerosis: A sign of cardiac involvement in asymptomatic patients. Annals of the Rheumatic Diseases. 2004;63(2):210-1.

[198] Belloli L, Carlo-Stella N, Ciocia G, Chiti A, Massarotti M, Marasini B. Myocardial involvement in systemic sclerosis. Rheumatology. 2008;47(7):1070-2.

[199] Kobayashi H, Yokoe I, Hirano M, Nakamura T, Nakajima Y, Fontaine KR, et al. Cardiac magnetic resonance imaging with pharmacological stress perfusion and delayed enhancement in asymptomatic patients with systemic sclerosis. The Journal of Rheumatology. 2009;36(1):106-12.

[200] Vignaux O, Allanore Y, Meune C, Pascal O, Duboc D, Weber S, et al. Evaluation of the effect of nifedipine upon myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue Doppler echocardiography in systemic sclerosis. Annals of the Rheumatic Diseases. 2005;64(9):1268-73.

[201] Montecucco F, Mach F. Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. Rheumatology. 2009;48(1):11-22.

[202] Gonzalez-Gay MA, Gonzalez-Juanatey C, Pineiro A, Garcia-Porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. The Journal of Rheumatology. 2005;32(7):1219-23.

[203] Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Pineiro A, Garcia-Porrua C, Miranda-Filloy JA, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis and Rheumatism. 2007;57(1):125-32.

[204] Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. The Journal of Rheumatology. 2005;32(3):430-4.

[205] Lopez-Mejias R, Castaneda S, Gonzalez-Juanatey C, Corrales A, Ferraz-Amaro I, Genre F, et al. Cardiovascular risk assessment in patients with rheumatoid arthritis: The relevance of clinical, genetic and serological markers. Autoimmun Rev. 2016 Nov;15(11):1013-1030

[206] Montagnana M, Lippi G, Volpe A, Salvagno GL, Biasi D, Caramaschi P, et al. Evaluation of cardiac laboratory markers in patients with systemic sclerosis. Clinical Biochemistry. 2006;39(9):913-7.

[207] Tomasoni L, Sitia S, Borghi C, Cicero AF, Ceconi C, Cecaro F, et al. Effects of treatment strategy on endothelial function. Autoimmunity Reviews. 2010;9(12):840-4.

[208] Atzeni F, Turiel M, Caporali R, Cavagna L, Tomasoni L, Sitia S, et al. The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases. Autoimmunity Reviews. 2010;9(12):835-9.

[209] Bruce IN. Cardiovascular disease in lupus patients: Should all patients be treated with statins and aspirin? Best Practice & Research Clinical Rheumatology. 2005;19(5):823-38.

[210] Kerekes G, Soltesz P, Der H, Veres K, Szabo Z, Vegvari A, et al. Effects of biologics on vascular function and atherosclerosis associated with rheumatoid arthritis. Annals of the New York Academy of Sciences. 2009;1173:814-21.

[211] Szekanecz Z, Kerekes G, Soltesz P. Vascular effects of biologic agents in RA and spondyloarthropathies. Nature Reviews Rheumatology. 2009;5(12):677-84.

[212] Giles JT, Post W, Blumenthal RS, Bathon JM. Therapy insight: Managing cardiovascular risk in patients with rheumatoid arthritis. Nature Clinical Practice Rheumatology. 2006;2(6):320-9.

[213] Costenbader KH, Coblyn JS. Statin therapy in rheumatoid arthritis. Southern Medical Journal. 2005;98(5):534-40; quiz 41, 72.

[214] Timar O, Szekanecz Z, Kerekes G, Vegh J, Olah AV, Nagy G, et al. Rosuvastatin improves impaired endothelial function, lowers high sensitivity CRP, complement and immuncomplex production in patients with systemic sclerosis: A prospective case-series study. Arthritis Research & Therapy. 2013;15(5):R105.

[215] Ormseth MJ, Oeser AM, Cunningham A, Bian A, Shintani A, Solus J, et al. Reversing vascular dysfunction in rheumatoid arthritis: Improved augmentation index but not endothelial function with peroxisome proliferator-activated receptor gamma agonist therapy. Arthritis & Rheumatology. 2014;66(9):2331-8.

[216] Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirjak L, et al. EULAR recommendations for the treatment of systemic sclerosis: A report from the EULAR Scleroderma Trials and Research group (EUSTAR). Annals of the Rheumatic Diseases. 2009;68(5):620-8.

[217] Allanore Y, Meune C, Vignaux O, Weber S, Legmann P, Kahan A. Bosentan increases myocardial perfusion and function in systemic sclerosis: A magnetic resonance imaging and tissue-Doppler echography study. The Journal of Rheumatology. 2006;33(12):2464-9.

[218] Kahan A, Devaux JY, Amor B, Menkes CJ, Weber S, Guerin F, et al. Pharmacodynamic effect of nicardipine on left ventricular function in systemic sclerosis. Journal of Cardiovascular Pharmacology. 1990;15(2):249-53.

[219] Allanore Y, Avouac J, Kahan A. Systemic sclerosis: An update in 2008. Joint, Bone, Spine: Revue du Rhumatisme. 2008;75(6):650-5.

[220] Nurmohamed MT, van Halm VP, Dijkmans BA. Cardiovascular risk profile of anti-rheumatic agents in patients with osteoarthritis and rheumatoid arthritis. Drugs. 2002;62(11):1599-609.

[221] Kerekes G, Nurmohamed MT, Gonzalez-Gay MA, Seres I, Paragh G, Kardos Z, et al. Rheumatoid arthritis and metabolic syndrome. Nature Reviews Rheumatology. 2014;10(11):691-6.

[222] del Rincon I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis & Rheumatology. 2014;66(2):264-72.

[223] Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis and Rheumatism. 2006;55(4):531-6.

[224] van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: A case control study. Arthritis Research & Therapy. 2006;8(5):R151.

[225] van Ede AE, Laan RF, Blom HJ, Boers GH, Haagsma CJ, Thomas CM, et al. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. Rheumatology. 2002;41(6):658-65.

[226] Reiss AB, Carsons SE, Anwar K, Rao S, Edelman SD, Zhang H, et al. Atheroprotective effects of methotrexate on reverse cholesterol transport proteins and foam cell transformation in human THP-1 monocyte/macrophages. Arthritis and Rheumatism. 2008;58(12):3675-83.

[227] Finsterer J, Ohnsorge P. Influence of mitochondrion-toxic agents on the cardiovascular system. Regulatory Toxicology and Pharmacology: RTP. 2013;67(3):434-45.

[228] Loudet AM, Dousset N, Carton M, Douste-Blazy L. Effects of an antimitotic agent (cyclophosphamide) on plasma lipoproteins. Biochemical Pharmacology. 1984;33(19):2961-5.

[229] Loudet AM, Dousset N, Perret B, Ierides M, Carton M, Douste-Blazy L. Triacylglycerol increase in plasma very low density lipoproteins in cyclophosphamide-treated rabbit: Relationship with cholesteryl ester transfer activity. Biochimica et Biophysica Acta. 1985;836(3):376-84.

[230] Garces SP, Parreira Santos MJ, Vinagre FM, Roque RM, da Silva JA. Anti-tumour necrosis factor agents and lipid profile: A class effect? Annals of the Rheumatic Diseases. 2008;67(6):895-6.

[231] Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, et al. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology. 2006;24(1):83-6.

[232] Kerekes G, Soltesz P, Der H, Veres K, Szabo Z, Vegvari A, et al. Effects of rituximab treatment on endothelial dysfunction, carotid atherosclerosis, and lipid profile in rheumatoid arthritis. Clinical Rheumatology. 2009;28(6):705-10.

[233] Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, Diaz-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis and Rheumatism. 2008;59(12):1821-4.

[234] van Leeuwen M, Damoiseaux J, Duijvestijn A, Tervaert JW. The therapeutic potential of targeting B cells and anti-oxLDL antibodies in atherosclerosis. Autoimmunity Reviews. 2009;9(1):53-7.