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Review Article

Systemic Sclerosis and Atherosclerosis: Potential Relations in the Cardiovascular Field

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Abstract

Atherosclerosis, a chronic inflammatory condition of medium and large blood vessels, poses a significant risk for cardiovascular morbidity and mortality globally. This review examines the interplay between atherosclerosis and autoimmune diseases, particularly focusing on Systemic Sclerosis (SSc) due to its unique pathophysiological features. The involvement of inflammatory mediators-such as cytokines and immune cells-in accelerating atherosclerosis is highlighted, with particular emphasis on how traditional cardiovascular risk factors interact with disease-specific mechanisms. Patients with SSc face an increased cardiovascular risk, largely driven by immune dysregulation and endothelial dysfunction, which contribute to both microvascular and macrovascular complications. While research suggests a potential link between SSc and accelerated atherosclerosis, findings remain inconsistent, warranting further investigation into the underlying mechanisms and implications for patient care. We also explore the roles of various immune cell types, including macrophages, B and T cells, and dendritic cells, in shaping the atherosclerotic process within the context of SSc. Importantly, pharmacological strategies are being considered to mitigate this risk. Aspirin, due to its combined anti-inflammatory and antiplatelet properties, has the potential to reduce atherosclerotic progression in SSc. Other agents, such as statins and hydroxychloroquine, are also emerging as promising therapies aimed at targeting inflammation and vascular damage. Given the rising cardiovascular-related mortality rates in SSc patients, there is a pressing need for targeted pharmacological interventions, alongside comprehensive disease management, to improve cardiovascular outcomes in this patient.

Keywords: Atherosclerosis; Cardiovascular Field; Blood vessels; Immune cells

Introduction

Atherosclerosis is a long-term, complex condition that occurs in medium and large blood vessels. It is the major reason for vascular disease all over the world. Atherosclerosis is increasingly recognized as a complex inflammatory disorder characterized by the involvement of various immune cells, including monocytes, macrophages, and T-cells, as well as autoantibodies, autoantigens, and a range of cytokines [1,2]. This understanding shifts the perspective on atherosclerosis from being merely a lipid storage disease to one where inflammatory processes play a pivotal role. Literature suggests a significant correlation between certain autoimmune diseases, such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE), and the accelerated progression of atherosclerosis. These conditions are often accompanied by increased cardiovascular morbidity and mortality, highlighting a critical intersection between autoimmune pathology and cardiovascular health [3-5].

The underlying mechanisms for this association are multifaceted. Traditional cardiovascular risk factors, combined with the chronic inflammatory state present in autoimmune diseases, contribute to this increased risk. Notably, some therapeutic interventions, particularly the use of corticosteroids at high doses, have been highlighted for their atherogenic potential, further complicating the cardiovascular risk landscape for these patients [6,7].

Focusing on SSc, this chronic disorder, characterized by skin fibrosis, microvascular changes, and multi-organ dysfunction, presents a unique challenge in understanding cardiovascular implications. SSc has been shown to exhibit endothelial dysfunction, particularly in capillaries and

arterioles. This dysfunction is closely linked to an impaired vasomotor response, suggesting that the pathophysiology of SSc may predispose patients to cardiovascular events [8,9]. Despite advances in treating Pulmonary Arterial Hypertension (PAH) and scleroderma renal crisis, cardiovascular complications-particularly those related to atherosclerosis-remain poorly managed in SSc. Current challenges include the lack of standardized cardiovascular screening, limited biomarkers to predict risk, and insufficient data on effective preventive therapies.

Over the past four decades, the patterns of mortality associated with SSc have evolved significantly. While the incidence of death due to complications directly related to the disease has decreased, there is a concerning upward trend in mortality from atherosclerotic cardiovascular and cerebrovascular diseases. Presently, cardiovascular-related deaths now account for approximately 20%-30% of the total mortality observed in SSc patients, signifying an urgent need for targeted cardiovascular risk assessment and management in this population [10].

In recent years, research focusing on subclinical atherosclerosis in individuals with SSc has yielded inconsistent and sometimes conflicting results. It remains to be fully elucidated whether accelerated atherosclerotic changes are indeed present in SSc patients and, if so, whether the prevalence is significantly higher when compared to individuals without the disease [11,12].

This uncertainty highlights the importance of evaluating not only the natural history of vascular disease in SSc but also the potential benefits of pharmacological interventions. Drugs such as aspirin, with its dual anti-inflammatory and antiplatelet properties, as well as statins and immunomodulatory agents like hydroxychloroquine, may provide cardiovascular protection by directly influencing immune pathways and vascular integrity.

Understanding how these drugs modulate immune cells and endothelial function is crucial, as both immune dysregulation and endothelial injury are central to the pathogenesis of SSc-associated atherosclerosis. By integrating insights from immunology, vascular biology, and pharmacology, this review aims to explore immune-mediated mechanisms in SSc-related atherosclerosis and assess how emerging therapies may alter disease progression.

Atherosclerosis in rheumatic diseases

The relationship between early Atherosclerosis (ATS) and autoimmune diseases remains only partially understood when it comes to the conventional risk factors, including obesity, smoking, and hyperlipidemia. While these classical Cardiovascular (CV) risk factors undoubtedly contribute to the progression of ATS, emerging evidence suggests that the acceleration of this condition is also significantly influenced by systemic inflammation and the use of medications known for their pro-atherogenic properties [13].

Additionally, a diverse array of cellular mechanisms and cytokine signaling pathways has been implicated in the pathophysiology of ATS, reinforcing its classification as an immune-inflammatory disease. This highlights the need to consider not just traditional risk factors, but also the intricate interplay of immune responses and inflammatory processes in understanding and managing early ATS in individuals with autoimmune conditions. When the immune system is hyperactivated, it may cause premature ATS and contribute to the atherosclerotic plaque formation and ATS clinical manifestations emerging earlier [14,15].

The risk factors associated with autoimmune-inflammatory conditions exhibit considerable heterogeneity. Various cytokines, particularly Tumor Necrosis Factor alpha (TNF-α), play a pivotal role in the inflammatory processes associated with autoimmune diseases. This includes conditions such as Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and systemic lupus erythematosus (SLE) [16,17]. In contrast, certain autoantibodies, including those targeting oxidized low-density lipoproteins (anti-oxLDL), cardiolipin (anti-CL), and beta-2-glycoprotein I (anti-β2GPI), are prominently involved in vascular complications linked to SLE and antiphospholipid syndrome (APS) [18,19].

Autoimmune rheumatic diseases, which are characterized by systemic inflammation and an accelerated rate of ATS, are associated with various types of vasculopathies. The manifestations of these vasculopathies can differ significantly, reflecting the underlying autoimmune condition affecting the patient. While the link between traditional accelerated ATS and diseases like RA and SLE is well-documented, obliterative vasculopathy is often associated with SSc. These conditions exhibit marked differences in both vascular morphology and function, underscoring the complexity of vascular involvement in autoimmune rheumatic diseases [20,21].

Atherosclerosis in SSc

SSc is a complex autoimmune disorder that affects multiple organ systems and is characterized by immune dysregulation, vascular abnormalities, and fibrosis. The pathogenesis of SSc is closely associated with three principal features: the presence of vasculopathy, which includes distinctive microvascular alterations; the development of fibrosis affecting both the skin and internal organs; and a systemic inflammatory response characterized by the presence of circulating autoantibodies and elevated pro-inflammatory cytokines [22-24].

The precise causes of accelerated ATS in SSc remain unclear. It is likely that a variety of contributing factors interact in this process, including traditional cardiovascular risk factors, increasing endothelial damage, and disease-specific immunological and autoimmune elements. These factors may collectively initiate and exacerbate the progression of ATS in individuals with SSc [25,26].

In terms of inflammatory mediators linked to ATS, several studies have indicated that levels of cytokines such as TNF-α, Interleukin-6 (IL-6), and high-sensitivity C-Reactive Protein (hsCRP) are elevated in SSc patients compared to healthy controls. However, the precise relationship between these mediators and Cardiovascular Disease (CVD) in the context of SSc has yet to be fully elucidated [27,28]. Despite this, it is plausible that chronic systemic inflammation could promote the development of accelerated ATS. It should be noted that the level of inflammation observed in SSc is generally lower than in conditions like RA and Systemic Lupus Erythematosus (SLE), suggesting that the atherosclerotic process in SSc may be less aggressive and is often identified only in limited studies [29].

Microvascular involvement is one of the earliest manifestations of SSc, potentially leading to tissue ischemia, which contributes significantly to the widespread fibrosis characteristic of the disease. Pathological changes in SSc include the disruption of the endothelial lining, infiltration by mononuclear cells within the vascular walls, formation of obstructive lesions, and a progressive loss of capillary networks [30,31].

Endothelial dysfunction is frequently observed in both capillaries and arterioles in patients with SSc, which can impede normal vasomotor function and regulatory mechanisms [32,33].

Although macrovascular disease was not initially considered a hallmark of SSc, recent studies have highlighted an increasing prevalence of large-vessel conditions in both the upper and lower extremities of affected individuals. The significance of coronary artery disease and cerebrovascular incidents in the context of SSc is an area that warrants further investigation to fully understand its implications [34,35].

Prevalence of atherosclerosis in SSc

The mortality rate associated with SSc is reported to be approximately three times higher than that of the general population, primarily due to cardiopulmonary complications such as Pulmonary Arterial Hypertension (PAH) and Interstitial Lung Disease (ILD). Notably, the ten-year survival rate for patients with SSc has shown considerable improvement, climbing from 54% between 1972 and 1981 to between 66% and 82% in the period from 1982 to 1991. This enhancement is largely attributed to advancements in early diagnosis and the introduction of targeted treatments for conditions like PAH and Scleroderma Renal Crisis (SRC) [36-38].

As a result of these developments, the focus of clinical attention has shifted towards the management of comorbidities associated with SSc, particularly accelerated ATS, which can adversely affect the long-term prognosis of the disease. The risk of mortality from atherosclerotic CVD and cerebrovascular incidents has become a significant concern, with cardiovascular-related deaths now accounting for approximately 20%-30% of all deaths in SSc patients [39,40].

A notable investigation conducted in 2010 using data from the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) database revealed that 26% of deaths directly attributable to SSc were related to cardiac issues, primarily heart failure and arrhythmias. Additionally, 29% of deaths not specifically linked to SSc were due to ATS and cardiovascular causes [41-43].

The evidence concerning the prevalence of ATS among individuals with SSc presents a mixed picture. Some studies suggest that the involvement of large epicardial coronary arteries in SSc resembles the rates observed in the general population. However, the extent of primary cardiac symptoms in SSc can vary widely, complicating efforts to pinpoint the prevalence of these manifestations. Factors such as the diversity of cardiac symptoms, the presence of asymptomatic phases, variations in diagnostic techniques, and differences in patient demographics contribute to this complexity [44,45].

Key clinical manifestations arising from microvascular damage in SSc include Raynaud's phenomenon, PAH, and SRC. These conditions are characterized by both vasospastic events and structural changes, which are considered hallmark features of SSc. Collectively, these elements are thought to contribute to the progressive development of macrovascular atherosclerosis over time [46].

Risk factors for atherosclerosis in SSc

As with many autoimmune disorders, traditional cardiovascular risk factors alone do not fully explain the prevalence of atherosclerotic disease in patients with SSc. These risk factors are found to be distributed similarly among SSc patients and matched healthy individuals of comparable age and sex. Research conducted in 2012 indicated that SSc patients exhibited elevated blood pressure and fasting plasma glucose levels when compared to controls; however, this study also noted that the control group had a similar lipid profile and a lower body mass index. Conversely, other studies have suggested a notable increase in the prevalence of obesity, dyslipidemia, diabetes mellitus, and hypertension among individuals with SSc [47-49].

Recent investigations into the relationship between cardiovascular risk factors and biological markers of atherosclerosis have revealed that patients with SSc tend to have significantly higher levels of various markers compared to age- and sex-matched controls, even when traditional cardiovascular risk factors are accounted for. Specifically, research has found elevated concentrations of: a. LDL cholesterol; b. homocysteine; c. C-Reactive Protein (CRP); d. lipoprotein; and e. anti-oxidized-LDL antibodies in the SSc population [50,51]. Additionally, a reduction in HDL cholesterol levels has been observed in individuals

with SSc compared to healthy counterparts.

Moreover, emerging data suggest alterations in hemostatic balance among SSc patients, indicating an increased tendency toward coagulation along with reduced fibrinolytic activity. Some studies have pointed out an elevation in heat shock protein HSP70 levels, which is associated with various manifestations in SSc, including pulmonary fibrosis, skin sclerosis, renal vascular impairment, oxidative stress, and inflammation. Notably, there is also evidence to suggest that HSP70 may offer protective effects against coronary events [52,53].

Role of Immune Cells in the Pathogenesis of Systemic Sclerosis and Atherosclerosis

The abnormal activation of immune cells can serve as a hallmark of the autoimmune nature of SSc. The formation of microvascular lesions within SSc is attributed to endothelial injury and the subsequent migration of smooth muscle cells into the vascular intima, closely resembling the processes observed in atherosclerosis [54]. Contemporary understanding posits that the unchecked activation of both innate and adaptive immune responses contributes to the development and persistence of chronic inflammation. This chronic inflammatory state is critical across all stages of SSc and atherosclerosis, with the latter increasingly recognized as an autoimmune-related condition.

Immunological factors and inflammatory processes have been identified as central components in the pathophysiology of both SSc and atherosclerosis [55-57]. Inflammation triggers the release of various cytokines, which can disrupt nitric oxide signaling, leading to vasoconstriction. The immune dysregulation seen in SSc is marked by the activation and recruitment of immune cells, the production of autoantibodies, and the release of profibrotic cytokines. The presence of these immune cells, combined with the secretion of pro-inflammatory cytokines and chemokines, may facilitate the progression of atherosclerotic plaques and increase the risk of plaque rupture [58,59].

The role of mitochondria has emerged as a significant factor in the abnormal functioning of immune cells. Recent studies suggest that mitochondria are integral to the processes of inflammation and cellular damage. Mitochondrial dysfunction resulting from mutations in mitochondrial Deoxyribonucleic Acid (DNA) may lead to persistent activation of monocytes, thereby contributing to chronic inflammatory states [60-62] (Table 1).

Table 1: Immune Cells Involved in Atherosclerosis and Systemic Sclerosis (SSc).

Cell Type	Role in Atherosclerosis	Role in Systemic Sclerosis
Macrophages	Differentiation into M1 (pro-inflammatory) and M2 (profibrotic)	Infiltration in skin and lungs
	Contribute to plaque development	Production of profibrotic cytokines (TGF-β)
B cells	Produce autoantibodies	Regulate immune response
	Influence T cell responses and cytokine secretion (IL-6, TNF-α).	Contribute to microvasculopathy
T cells	CD4+ T cells activate B cells	Participate in fibrosis and inflammation
	Th1 and Th17 cells promote chronic inflammation and atherogenesis	Dysfunction contributes to disease progression
Dendritic Cells (DCs)	Activate T cells and promote Th2 responses	Drive autoimmune responses
	Produce pro-inflammatory cytokines (IFN-α)	Modulate T cell polarization
Neutrophils	Release NETs contributing to chronic inflammation	Impaired function and response
	Impair endothelial function	Involved in the inflammatory process

Macrophage dysfunction in systemic sclerosis and atherosclerosis

A comprehensive examination of macrophages, monocytes, and cytokines is necessary due to their significant role in autoimmune disease pathogenesis. Macrophages also play a key role in atherosclerosis. Several studies have shown that circulating monocyte levels correlate with atherosclerotic plaque progression and size. As monocytes are recruited, they differentiate into macrophages, which may then transform into foam cells as lipid accumulates [63-65].

In SSc, macrophage phenotype imbalances may contribute to the disease's development. In Systemic Lupus Erythematosus (SLE), macrophages play an important role in the pathogenesis of inflammation by producing cytokines that cause additional immune cells, including monocytes and neutrophils, and through the polarization of T cells, as well as the activation of fibroblasts to attract to the area [66,67]. Based on the inflammatory response of macrophages, they can be classified into two types: M1 and M2. Activated M1 macrophages promote inflammation, while activated M2 macrophages promote tissue repair and produce cytokines that promote fibrosis. Macrophage activation abnormalities are increasingly recognized as significant factors in SSc [68,69].

It has been established that SSc is associated with macrophage activation and monocyte activation, with an increase in macrophages detected in the skin of affected persons since the 1990s. The serum of SSc patients has also been shown to contain higher levels of cells expressing cluster of differentiation 163 (CD163), a marker commonly associated with M2 macrophages [70,71]. Interleukin-34 (IL-34) levels are elevated in individuals with SSc, a cytokine that promotes the survival, proliferation, and differentiation of monocytes into profibrotic macrophages.

Further investigations have reported an increased expression of genes associated with monocyte and macrophage activity, such as IL-8, Vascular Endothelial Growth Factor (VEGF), and epiregulin, in mononuclear cells from SSc patients [72-74]. Macrophages also represent a significant source of Transforming Growth Factor-beta (TGF-β), a potent fibrogenic cytokine. The activation of macrophages and the upregulation of genes regulated by TGF-β and Interferon (IFN) are critical in the development of pulmonary fibrosis associated with SSc. Transcriptomic analyses of skin tissue have illustrated that M2 macrophages participate in various molecular processes affecting SSc skin, including IFN activation, the modulation of adaptive immune responses, extracellular matrix remodeling, and promoting cellular proliferation [75,76].

Cytokines such as IL-4 and IL-13 play crucial roles in fibrotic disorders. In normal fibroblasts, IL-4 enhances proliferation, chemotaxis, and collagen synthesis while also increasing the production of TGF-β and connective tissue growth factor. TGF-β serves as a robust stimulator of fibrogenesis in mesenchymal cells, facilitating collagen synthesis, as well as the proliferation, migration, adhesion, and differentiation of these cells into myofibroblasts. Earlier studies have documented the presence of profibrotic M2 phenotype macrophages in both the skin and peripheral circulation of SSc patients, contributing to the development of Interstitial Lung Disease (ILD). Notably, the gene expression profile of these macrophages differs between skin and lung tissues, suggesting distinct mechanisms of immunopathogenesis related to fibrosis in these two sites, despite their similar roles [77-79].

Innumerable studies employing a mouse model have revealed that IFN-8 deficiency enhances mRNA levels in myeloid cells. Extracellular matrix components and increase bleomycin-induced skin fibrosis. Moreover, ILD is characterized by elevated pulmonary artery systolic pressure, positive antibodies against topoisomerase I, and increased numbers of M1/M2 macrophages [80–82]. Scientists have discovered that SSc-positive (FCGR3A+) cutaneous macrophages, as well as SSc-positive (SPP1+) pulmonary macrophages exist in SSc-associated diseases.

New pathogenesis theories of SSc focus on the role of macrophages and propose that greater expression of fibrosis mediators such as TGF-β and IL-6 occurs upon activation of the signaling pathways, including Wnt, JAK/STAT, and Sonic Hedgehog (SH), following genetic and environmental stimuli. Upon monocyte migration into injured tissues, profibrotic macrophages become activated and secrete profibrotic cytokines and other inflammatory mediators. TGF-β-induced activation of platelet-derived growth factor in SSc, production of (PDGF) aggravates the fibrotic process [85-88]. They all have the potential to aggravate atherosclerotic damage in individuals with SSc; they finally lead to chronic fibrosis, collagen accumulation, and increased extracellular matrix formation.

Numerous recent studies have explored the putative coagulation pathway activation within SSc and the implications for fibrotic and inflammatory responses, focusing on the role of PDGF and Protease-Activated Receptor 1 (PAR-1). Much studied, PDGF is a fibrogenic mediator; certain autoantibody-regulated epitopes in SSc can initiate intracellular signaling cascades and lead to an upregulation of the collagen gene. The IgG concentration in SSc patients has been shown to modify PAR-1 signaling and negatively influence human endothelial cells' synthesis of IL-6 [89-91].

The role of B- and T cells in systemic sclerosis and atherosclerosis

Autoimmune diseases are significantly affected by interactions between B-cells and T-cells, which are necessary for coordinating adaptive immune responses. Adaptive immune responses are coordinated by B-cells and T-cells, and their interactions determine the pathophysiology

of autoimmune diseases. SSc immunopathogenesis is dependent on the differentiation of B cells into certain subtypes with particular functions under the influence of various cytokines and mediators [92,93].

Activated B-cells produce autoantibodies that are often detectable even before the onset of fibrosis. Some of these antibodies exert a direct profibrotic effect, while others contribute to microvasculopathy. In SSc patients, diverse immune cells-including B cells and plasma cells-have been found infiltrating the skin, lungs, and gastrointestinal tract. These B-cells partake in various regulatory immune functions within SSc, including antigen presentation, the production of cytokines, T-cell development and differentiation, as well as the structural reorganization of lymphoid organs. The upregulation of costimulatory molecules such as CD80/86 and CD28 further enhances the activation of autoreactive T-cells and increases the secretion of profibrotic cytokines [94,95]. Concurrently, the capacity of B-cells to produce interleukin-10 (IL-10), a cytokine involved in the suppression of regulatory B cells (Bregs), is altered. B-cells express multiple surface molecules involved in activation and survival pathways while concurrently downregulating co-receptor inhibitors. They also express co-receptors crucial for modulating T-cell activities. Interaction with other immune cells-such as macrophages, fibroblasts, and endothelial cells-occurs through direct and indirect mechanisms [96-98]. Collectively, these interactions contribute to profibrotic and pro-inflammatory activities, vascular remodeling, and compromised immune regulation.

B-effector cells are known to stimulate macrophages through the production of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), which fosters the development of inflammatory and fibrotic lesions. These cells belong to the memory B cell subgroup and are active producers of IL-6 and TNF-α. TNF-α promotes acute inflammatory responses, while IL-6 is another significant cytokine in inflammatory settings [99,100].

In SSc-involved organs, there is a buildup of hyperactive B-cells that engage with other immune cells locally, performing an important function in the secretion of pro-inflammatory and profibrotic cytokines like IL-6 and Transforming Growth Factor-Beta (TGF-β). Topoisomerase I antibody-high B-cells secrete IL-6, inducing fibrosis, while topoisomerase I antibody-low B-cells secrete anti-inflammatory IL-10, which suppresses fibrosis [101-103]. T-cells are also essential in regulating the autoimmune response by being involved in the co-stimulatory processes of B-cells in the interaction of B-T cells. The participation of CD4+ T-cells in the immunopathogenesis of SSc has been well established, particularly with respect to their role in antigen presentation and co-stimulation of B-cells upon sensitization with minute quantities of antigen-this process is important for the pathogenesis of autoimmune rheumatic diseases (ARDs). Several subsets of T-cells, such as CD8+ effector T-cells, T helper (Th) 17 cells, and regulatory T-cells (Tregs), are involved in the secretion of profibrotic and pro-inflammatory cytokines (IL-4, IL-5, IL-9, IL-13, IL-17, TGF-β, and TNF-α) in SSc [104,105].

Recent research shows that CD4+ T-cell activation results in enhanced production of interferon-gamma, IL-2, IL-12, TNF-α, retinoic acid-Related Orphan Receptor gamma (ROR-γ), and IL-17, while inhibiting the regulatory T-cell cytokines (IL-4, IL-6, IL-13) and Forkhead box p3 (Foxp3) products (IL-10 and TGF-β) in both in vivo and in vitro models, indicating their dual catalytic and inhibitory role on immune responses [106,107]. A significant pathophysiologic feature of IL-34-induced macrophages is their function in converting memory T-cells into Th17 cells. Their increased levels have been noted in the peripheral blood and skin of active SSc patients. The concentrations of Th17 cytokines IL-17 and IL-23 in the peripheral circulation and exhaled condensate are also associated with the severity of interstitial lung disease in SSc patients. At the same time, Th1 and Th17 cells are involved in the development of atherosclerosis [108,109]. However, Tregs contribute to protection in the process of atherosclerosis.

Lipid accumulation within arterial walls instigates the onset of atherosclerosis. Under the influence of oxidative enzymes produced by vascular wall cells, lipids transform into Oxidation-Specific Epitopes (OSEs), which can activate vascular cells and generate adhesion molecules, cytokines, and chemokines. This cascade subsequently attracts circulating monocytes and T-cells to the vessel wall [110,111]. Recent studies have shown that antibodies against OSEs can inhibit the uptake of Oxidized Low-Density Lipoproteins (OxLDL), supporting the idea that B-cells play a functional role in the development of atherosclerosis [112-114].

Neoantigens like OSEs are capable of interacting with Toll-Like Receptors (TLRs), further amplifying the inflammatory response in macrophages and T-cells. The role of B-cell responses in atherogenesis is underscored by genome-wide association studies and transcriptomic analyses, which indicate that B-cell activation and proliferation are significant risk factors for cardiovascular disease [115-117]. Antigen-presenting B-cells facilitate specific interactions with T-cells through signaling mediated by co-stimulatory molecules such as CD40, CD80, and CD86, which recognize peptides presented by Major Histocompatibility Complex (MHC) molecules. This process triggers T-cell activation as the antigen-presenting cell displays MHC class II molecules along with the relevant antigen [118].

In recent studies, B-cells have been shown to play a vital role in atherosclerosis. The individual roles of subsets such as B1 cells, follicular B cells, marginal zone B cells, regulatory B cells (Breg), and innate response activator B cells have been accentuated. Chronic inflammatory processes drive the recruitment of B-cells to atherosclerotic plaques and induce the development of tertiary lymphoid tissues within arterial walls. CD19+-CD11b+ B-cells have

been reported to interfere with T-Cell Receptor (TCR) signaling and inhibit TCR-mediated responses [119,120]. Different chemokines and their respective receptors, including C-X-C motif ligand (CXCL) 13/C-X-C motif receptor (CXCR)5 and C-C motif ligand (CCL)19/CCL21/CC motif receptor (CCR)7, mediate the migration of B-cells into both lymphoid and non-lymphoid tissues and assist in their homing back to lymphoid structures. CXCL13 and CCL21 have been recognized as essential chemokines for B-cell retention within adventitial tertiary lymphoid structures, and the function of CCR6 in B-cell recruitment into the atherosclerotic-prone areas of the aorta has more recently been described, notably under differentiation inhibitor-3 [121-123].

The role of dendritic cells in systemic sclerosis and atherosclerosis

Dendritic Cells (DCs) are important for the activation of T cells and are heavily implicated in the chronic low-grade inflammation seen in both SSc and atherosclerosis. The cells are key participants in the disease processes of SSc. The activation of DCs is controlled by mature activated B cells and is characterized by the upregulation of surface molecules including CD83, CD80, CD86, CD40, and HLA-DR, which are all driven through the B cell receptor and BAFF receptor. Maturation B cell-derived DCs also exhibit an interesting secondary effect on polarization and activation of naive CD4+ T cells that drive their differentiation towards Th2 cells. This polarization also enhances the secretion of interleukins IL-4, IL-5, and IL-13, playing a role in the autoimmune processes involved in SSc [124,125].

DCs can be divided into two major categories: conventional dendritic cells and plasmacytoid Dendritic Cells (pDCs). Plasmacytoid DCs are unique cells that produce large amounts of Interferon (IFN) upon activation. Recent research has indicated that pDCs infiltrate SSc skin, resulting in increased production of IFN-α and CXC ligand 4 (CXCL4. The concentration of CXCL4 is particularly higher in pDCs derived from SSc patients and can be found in elevated amounts in the plasma of such patients [126,127]. In addition, the presence of CXCL4 is also predictive of the severity of the disease, making it a possible biomarker for SSc.

In experiments utilizing mouse models, it was observed that depleting pDCs can prevent the onset of SSc and result in diminished fibrosis in mice prone to developing this condition. Conversely, in TLR8 transgenic mice, SSc severity was exacerbated, with pDCs accumulating in fibrotic skin, suggesting that TLR8, an RNA-sensitive toll-like receptor, plays a significant role in the fibrotic process. Similar findings were reported in a biotic ligand model, where a higher prevalence of pDCs was noted in the affected skin and lung tissues of these models compared to their wild-type counterparts [128,129].

Moreover, pDCs express the BAFF ligand, which may enhance interactions between B cells and pDCs in the context of SSc. This interaction not only promotes autoantibody production but also perpetuates chronic inflammation. Therapeutically, BAFF inhibitors represent a promising targeted approach, as they can disrupt this B cell–DC crosstalk, thereby dampening autoimmunity and potentially reducing vascular complications.

The involvement of pDCs has also been explored in the context of atherosclerotic vascular lesions, where their functionality is known to be compromised. Notably, increased expression of CD83, an activation marker for DCs, has been observed in plaque tissues from patients with ischemic complications. In humans, the secretion of IFN-α mediated by pDCs has been linked to the activation of pro-inflammatory pathways, resulting in the apoptosis of effector T cells, consequent death of Vascular Smooth Muscle Cells (VSMCs), plaque destabilization, and an elevated risk of acute coronary syndromes [130,131].

From a therapeutic perspective, several agents have the potential to modulate DC activity. Aspirin, through its Cyclooxygenase (COX) inhibitory effects, may attenuate DC-mediated inflammation, thereby reducing T-cell activation and the pro-atherogenic cytokine milieu. Hydroxychloroquine has been shown to interfere with toll-like receptor signaling and may dampen plasmacytoid DC activation, leading to reduced interferon-α production-a central pathogenic factor in both SSc and atherosclerosis. Together with BAFF inhibitors, these pharmacological strategies highlight emerging opportunities to target dendritic cell-driven immune dysregulation in order to mitigate vascular damage in SSc.

The role of neutrophils in systemic sclerosis and atherosclerosis

Recent research has highlighted the significant role of neutrophils in both the progression of atherosclerosis and the broader context of inflammation and cardiovascular repair. In cardiometabolic diseases, the dysregulation of cholesterol and glucose metabolism contributes to a persistent state of inflammation, which is further amplified by neutrophils activating various inflammatory pathways [132,133].

The accumulation of lipoproteins and immune cells in the artery intima causes atherosclerotic plaques to erode and become unstable. Further neutrophil infiltration and the release of Neutrophil Extracellular Traps (NETs) into atherosclerotic tissues can be promoted by reducing the outflow of cholesterol to neutrophils, which can also increase their inflammatory activation. Atherosclerotic lesions may develop more quickly as a result of this procedure [134–136]. NETs are intricate structures made up of proteins, including enzymes and other antimicrobial agents, and DNA–histone complexes that are produced by active neutrophils. Activated neutrophils have a well-established function in innate immunity, but they also release granular proteins like cathepsin G and cathelicidin

that aid in myeloid cell recruitment. Additionally, the pathophysiology of certain autoimmune disorders has been linked to NET formation [137,138].

It is becoming more widely acknowledged that oxidative stress has a role in the pathophysiology of SSc. Reactive Oxygen Species (ROS) are produced in large quantities by Polymorphonuclear Neutrophils (PMNs) throughout the course of the illness. However, a number of effector molecules and functions, including the ability to form NETs, phagocytose bacterial particles, and key chemokine receptors, are lacking in neutrophils from people with SSc. Inadequate antimicrobial defense, increased inflammation, and impaired tissue remodeling can result from this functional deficit [139–141].

Significant morphological and functional alterations are seen in neutrophils from SSc patients. For example, these neutrophils frequently exhibit decreased surface expression of CD16 and CD62L, increased phosphorylation of signal transducer and activator of transcription proteins (STAT3 and STAT6), and a number of functional deficiencies, such as the lack of common chemokine receptors like CXCR1 and CXCR2, which are essential for migration to the powerful neutrophil attractant CXCL8 [142–144].

Markers indicating neutrophil activation, such as elevated calprotectin levels in bronchoalveolar lavage fluid and serum, are associated with increased pulmonary fibrosis and a positive antitopoisomerase I test in SSc patients. Elevated calprotectin levels have also been observed in patients with vascular complications, such as cutaneous pitting scars. However, there has been no established correlation between autoantibodies, intracellular antigens, and circulating NET levels [145,146]. Furthermore, neutrophil activation in response to blood plasma from SSc patients was found to be inhibited when the binding sites for immune complexes on Fcγ receptors were blocked. Notably, researchers have first reported elevated levels of mitochondrial N-formylmethionine (fMet) in the circulation of SSc patients, suggesting that this mitochondrial component is vital for stimulating neutrophil activation within the context of SSc.

During the development of atherosclerosis, neutrophil granular proteins-like cathelicidin and α-defensin-enhance macrophage activation towards a pro-inflammatory phenotype [147,148]. Neutrophils also secrete myeloperoxidase, which facilitates the interaction with Oxidized Low-Density Lipoprotein (OxLDL), thereby promoting foam cell formation. Additionally, NETs encourage plasmacytoid Dendritic Cells (pDCs) to produce pro-atherogenic Interferon-Alpha (IFN-α) and stimulate macrophages to secrete cytokines such as IL-1β and IL-18. The release of ROS and proteolytic enzymes from neutrophils along the luminal and intimal sides of atherosclerotic plaques contributes to endothelial cell activation and matrix dysregulation, leading to increased leukocyte infiltration and Low-Density Lipoprotein (LDL) extravasation. The action of neutrophil-derived metalloproteinases can also cause Vascular Smooth Muscle Cell (VSMC) death by degrading the extracellular matrix. This degradation process, along with VSMC death, leads to the thinning of the fibrous cap and fosters the development of plaques that are prone to rupture [149,150].

The role of endothelial cells in systemic sclerosis and atherosclerosis

In the early stages of SSc, damage to Endothelial Cells (ECs) and subsequent apoptosis can trigger a cascade of inflammatory responses, oxidative stress, and tissue hypoxia. Various clinical manifestations associated with SSc, such as Raynaud's phenomenon, edema of the hands, digital ulcers, pulmonary hypertension, erectile dysfunction, scleroderma renal crisis, and cardiac involvement, are primarily linked to dysfunction within the endothelial cells. The activation of ECs occurs as a result of specific cell adhesion molecules, including E-selectin, Vascular Cell Adhesion Molecule 1 (VCAM-1), and Intercellular Adhesion Molecule 1 (ICAM-1) [151,152]. Increased expression of these molecules on the endothelium can lead to their release into the bloodstream. Furthermore, elevated levels of circulating soluble adhesion molecules have been related to peripheral microvascular dysfunction in SSc and are implicated in the progression of atherosclerotic plaques, transitioning from neovascularization to fibrotic lesions in the general population. The angiopoietin (Ang)-Tie signaling system plays a critical role in both embryonic cardiovascular and lymphatic system development, as well as in regulating postnatal angiogenesis, vascular remodeling, and permeability [153].

Disruptions in the function of this system are involved in the pathophysiology of vascular network anomalies seen in SSc and atherosclerosis. Research indicates that damage to endothelial cells can lead to a reduction in Angiotensin-Converting Enzyme (ACE)-2 activity, along with decreased levels of Angiotensin (AT) 1–7 and anti-inflammatory cytokines, while simultaneously increasing the activity of angiotensin II (AT II) and pro-inflammatory cytokines. A decline in ACE-2 coupled with a rise in AT II could precipitate endothelial dysfunction, arterial intima injury, and enhanced vascular permeability [154]. Components of the Renin Angiotensin Aldosterone System (RAAS) may be produced by inflammatory cells; for example, neutrophils secrete cathepsin G, while macrophages generate AT II and ACE. The Angiotensin II Type 1 Receptor (AT1R) is present on a variety of cell types, including immune cells, vascular smooth muscle cells, endothelial cells, and fibroblasts. The presence of antibodies targeting AT1R (anti-AT1R) and endothelin-1 type A receptors may contribute to the pathophysiology of SSc through their vasoconstrictive, pro-inflammatory, and profibrotic effects. Anti-AT1R may also serve as a potential marker for high-risk atherosclerotic plaques and the progression of atherosclerosis [155,156].

There have been mixed findings regarding the role of Anti-

Endothelial Cell Antibodies (AECA) in the development of atherosclerosis. Recent studies indicate that elevated AECA levels might correlate with a lower incidence of coronary atherosclerosis, reduced calcified lesions, and decreased cardiovascular mortality. Chronic damage to the endothelium can occur due to ischemia and reperfusion, leading to cellular dysfunction, compromised integrity, and tissue injury [157,158]. In SSc, tissue hypoxia and prolonged reduced blood flow are associated with microvascular abnormalities that serve as stimuli for atherosclerosis development. Increased levels of serum endostatin have been linked to carotid atherosclerosis among healthy individuals. Thrombospondin-1 (TSP-1), an extracellular matrix glycoprotein, can influence cellular adhesion, motility, proliferation, and survival in various cell types, including immune cells, and is recognized as a potent inhibitor of angiogenesis [159]. Both endostatin and Vascular Endothelial Growth Factor (VEGF) contribute to fibrosis formation and the associated inflammatory processes, such as TSP-1-related brachiocervical inflammatory myopathy. Endothelin-1, produced by endothelial cells, exhibits strong vasoconstrictor and mitogenic properties. Endothelin Receptor Antagonists (ERAs), already used in the treatment of pulmonary arterial hypertension in SSc, have demonstrated benefits in improving vascular tone, reducing vasospasm, and attenuating fibrosis, making them a relevant therapeutic strategy in vascular complications of SSc.

Additionally, an activated endothelium releases numerous factors, including von Willebrand factor, soluble Thrombomodulin (TM), and tissue plasminogen activator, which may act as indicators of procoagulant activity [160,161]. Studies have shown that levels of serum TM are elevated in patients with SSc and are associated with an increased risk of atherosclerotic disease in the carotid arteries. Pharmacological interventions such as aspirin and statins improve endothelial function by reducing inflammation, oxidative stress, and platelet activation, thereby restoring nitric oxide bioavailability and vascular homeostasis. Similarly, ACE inhibitors and Angiotensin Receptor Blockers (ARBs) counteract RAAS dysregulation, improve endothelial health, and reduce vascular stiffness, reinforcing their therapeutic relevance in both SSc and atherosclerosis. Endothelial dysfunction can lead to heightened levels of pro-inflammatory, pro-atherosclerotic, and pro-thrombotic factors, which collectively elevate the risk of cardiovascular disease in these patients [162-164].

Conclusion

Atherosclerosis represents a significant and multifaceted challenge in SSc, profoundly impacting morbidity and mortality. The accelerated vascular damage seen in these patients is largely driven by chronic inflammation and endothelial dysfunction, which together amplify the effects of traditional cardiovascular risk factors. This pathogenic synergy underscores the unique vulnerability of SSc patients to cardiovascular disease. Aspirin emerges as a particularly attractive therapeutic candidate in this setting, given its dual anti-inflammatory and antithrombotic properties that may help reduce immune-mediated vascular injury. Other pharmacological agents including statins, hydroxychloroquine, ACE Inhibitors/Angiotensin receptor blockers (ACEi/ARBs), and BAFF inhibitors hold promise by targeting immune dysregulation, improving endothelial health, and modulating fibro-inflammatory pathways. Collectively, these strategies highlight the growing importance of immune- and endothelium-focused interventions in mitigating cardiovascular risk in SSc.

However, despite advances in our mechanistic understanding, robust clinical trial data remain limited. There is an urgent need for translational studies and prospective trials to clarify the efficacy and safety of these agents in SSc. Personalized medicine approaches, incorporating biomarkers of inflammation, immune activation, and endothelial dysfunction, may ultimately enable more precise risk stratification and individualized treatment strategies.

In conclusion, addressing the immune-inflammatory drivers of atherosclerosis in SSc offers an important opportunity to reduce cardiovascular burden. Future progress will depend on integrating immunology, vascular biology, and pharmacology into carefully designed clinical studies, with the ultimate goal of improving cardiovascular outcomes and survival in this high-risk patient population.

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