SYSTEMIC SCLEROSIS: PATHOGENESIS OF VASCULAR AND FIBROTIC PROCESSES

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Abstract: Systemic sclerosis (SSc, scleroderma) is a chronic autoimmune connective tissue disease characterized by the triad of vasculopathy, immune dysregulation, and progressive fibrosis affecting the skin and internal organs. This narrative review synthesizes current evidence on the pathogenesis of the vascular and fibrotic processes underlying SSc, drawing on the 2013 ACR/EULAR classification criteria and the 2023 EULAR recommendations for the treatment of systemic sclerosis. Vascular injury is now recognized as the earliest event in SSc pathogenesis: endothelial cell damage from autoantibodies, ischemia-reperfusion injury, and oxidative stress leads to endothelial dysfunction, intimal proliferation, platelet activation, and progressive vascular remodeling, clinically manifesting as Raynaud phenomenon, digital ulcers, pulmonary arterial hypertension, and scleroderma renal crisis. In parallel, dysregulated innate and adaptive immunity — including autoantibody production and a dominant Th2/Th17 cytokine profile driven by transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6) — activates dermal and visceral fibroblasts, promoting their differentiation into myofibroblasts and excessive deposition of collagen and other extracellular matrix proteins, compounded by impaired matrix degradation. The 2023 EULAR recommendations introduced, for the first time, synthetic and biologic disease-modifying agents — including mycophenolate mofetil, nintedanib, rituximab, and tocilizumab — for key fibrotic manifestations, alongside first-line combination therapy for newly diagnosed pulmonary arterial hypertension, reflecting a therapeutic shift toward mechanism-targeted intervention across both vascular and fibrotic domains. A mechanism-based understanding of SSc pathogenesis, combined with early classification and individualized, organ-specific

management, is central to limiting irreversible organ damage and improving long-term outcomes, including within the healthcare system of Uzbekistan.

Keywords: Systemic sclerosis, scleroderma, vasculopathy, fibrosis, Raynaud phenomenon, myofibroblast, transforming growth factor-beta, pulmonary arterial hypertension.

Methods

This work was prepared as a narrative literature review. A literature search was conducted in August 2026 using PubMed, the ACR and EULAR publication databases, and the websites of major rheumatology societies, with the search terms "systemic sclerosis," "scleroderma," "vasculopathy," "fibrosis," "myofibroblast," and "EULAR recommendations," combined with filters for publication in English between 2016 and 2026. Priority was given to the 2023 EULAR recommendations for the treatment of systemic sclerosis, the 2013 ACR/EULAR classification criteria, systematic reviews, and peer-reviewed original research; narrative summaries from established clinical reference sources were included for foundational background. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

Introduction

Systemic sclerosis is a rare but severe autoimmune connective tissue disease characterized by the interplay of three core pathogenic processes: microvascular injury, immune activation with autoantibody production, and progressive fibrosis of the skin and internal organs. The disease follows a heterogeneous course, ranging from limited cutaneous involvement with a relatively indolent trajectory to diffuse cutaneous disease with rapid skin thickening and early, severe internal organ involvement.

Contemporary understanding positions vascular injury as the initiating event in SSc, occurring years before clinically apparent fibrosis, with endothelial dysfunction and immune dysregulation acting in a mutually reinforcing manner to ultimately drive fibroblast activation and excessive extracellular matrix deposition. This mechanistic framework — often described as a "vascular-to-fibrotic continuum" — has directly informed the development of the first mechanism-targeted therapies for SSc, reflected in the substantially revised 2023 EULAR treatment recommendations.

The aim of this review is to summarize current evidence on the vascular and fibrotic pathogenic mechanisms, classification, and organ-specific manifestations of systemic sclerosis, with particular emphasis on recently updated international recommendations and their relevance to clinical practice.

Understanding the modern approach to SSc is relevant across several areas of clinical practice, including:

- Rheumatology (diagnosis, classification, disease activity assessment, long-term management)
- Pulmonology (screening and treatment of interstitial lung disease and pulmonary arterial hypertension)
- Nephrology (recognition and emergency management of scleroderma renal crisis)
- Cardiology (evaluation of myocardial fibrosis and conduction abnormalities)
- Gastroenterology (management of esophageal dysmotility and gastric antral vascular ectasia)
- Dermatology (assessment of skin thickening and digital ulcer care)

Pathogenesis of Vascular Injury

Vascular injury is considered the earliest detectable abnormality in systemic sclerosis, frequently preceding clinically evident fibrosis by years and underlying the near-universal presence of Raynaud phenomenon at disease onset. The initiating event is endothelial cell injury, triggered by anti-endothelial cell autoantibodies, ischemia-reperfusion cycles associated with recurrent vasospasm, viral or other environmental insults, and oxidative stress from reactive oxygen species.

Injured endothelium develops a pro-vasoconstrictive, pro-thrombotic phenotype: nitric oxide-mediated vasodilation is impaired while endothelin-1, a potent vasoconstrictor and pro-fibrotic mediator, is markedly upregulated, and expression of adhesion molecules promotes leukocyte recruitment. Over time, this dysfunction progresses to intimal proliferation, in which smooth muscle-like myointimal cells accumulate within the vessel wall and progressively narrow the luminal diameter — a process of vascular remodeling that is largely irreversible once established.

Concurrent platelet activation and impaired fibrinolysis create a pro-coagulant microenvironment, promoting microthrombosis and progressive capillary rarefaction (loss of capillary density), which is directly visualized on nailfold capillaroscopy as a hallmark diagnostic finding in SSc. The cumulative result of this vascular cascade is chronic tissue ischemia, manifesting clinically along a continuum from reversible digital vasospasm (Raynaud phenomenon) to irreversible ischemic complications, including digital ulcers, pulmonary arterial hypertension, and the life-threatening scleroderma renal crisis. This stepwise vascular cascade is illustrated in Figure 1.

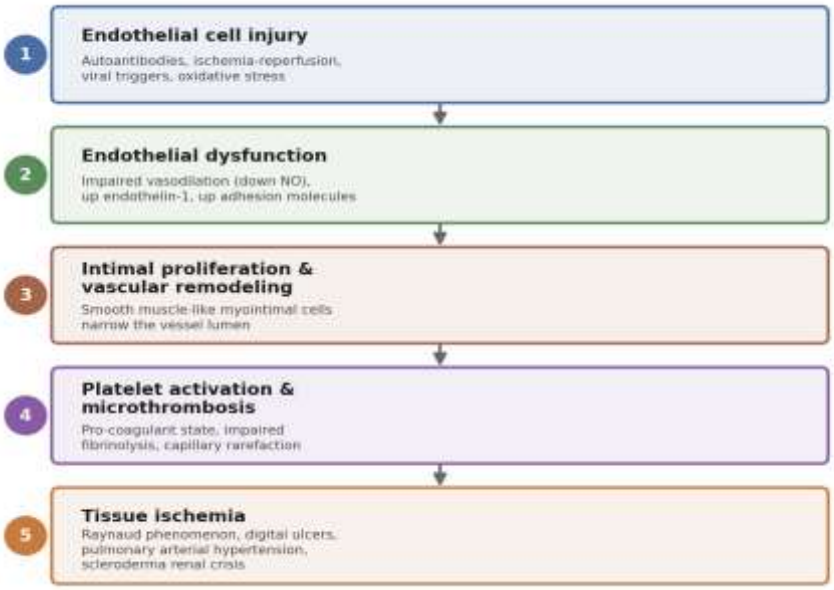

Figure 1. The stepwise vascular cascade in systemic sclerosis: endothelial cell injury progresses through endothelial dysfunction, intimal proliferation and vascular remodeling, and platelet activation with microthrombosis, culminating in chronic tissue ischemia.

Pathogenesis of Fibrotic Processes

Fibrosis in SSc arises from a self-amplifying cycle in which immune dysregulation drives fibroblast activation and excessive extracellular matrix accumulation. Autoantibody production — most notably anti-topoisomerase I (anti-Scl-70) and anti-centromere antibodies, which carry distinct prognostic implications — reflects an underlying loss of immune tolerance, accompanied by activation of both innate and adaptive immune pathways.

A dominant Th2/Th17 cytokine profile, characterized by elevated interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-13 (IL-13), and transforming growth factor-beta (TGF-β), drives the central pathogenic event of SSc fibrosis: activation of resident fibroblasts and their differentiation into myofibroblasts, a contractile, matrix-secreting cell phenotype that is normally confined to transient wound healing but becomes persistently activated in SSc. TGF-β signaling, acting through canonical SMAD pathways, is considered the master regulator of this fibrotic program and a principal target of emerging therapies.

Activated myofibroblasts secrete excessive quantities of type I and type III collagen and other extracellular matrix (ECM) components, while simultaneously the balance of matrix turnover shifts toward accumulation: matrix metalloproteinase (MMP) activity is suppressed and tissue inhibitors of metalloproteinases (TIMPs) are upregulated, impairing normal ECM degradation. The combination of excess synthesis and deficient clearance results in progressive, often irreversible fibrosis of the skin, lungs, gastrointestinal tract,

and heart, which in turn perpetuates local tissue hypoxia and further immune activation, closing a self-reinforcing fibrotic loop, as depicted in Figure 2.

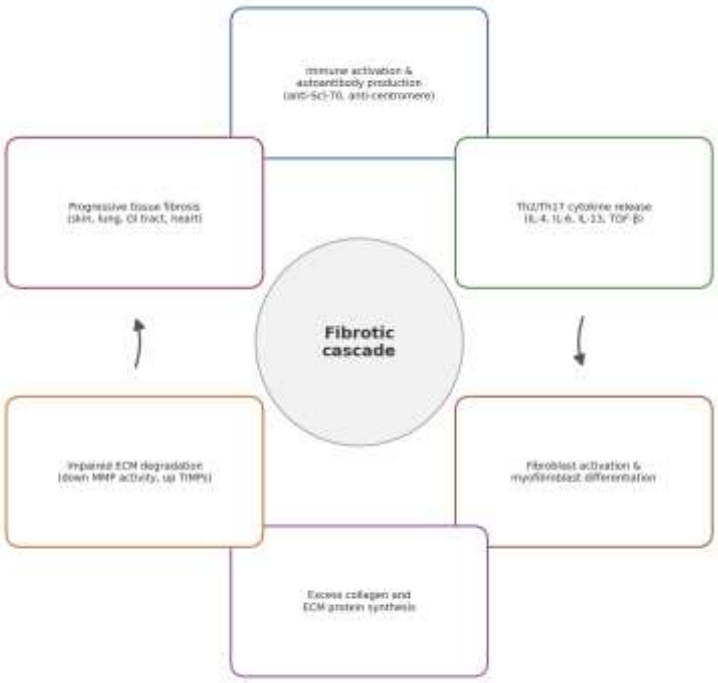

Figure 2. The self-amplifying fibrotic cascade in systemic sclerosis: immune activation and autoantibody production drive Th2/Th17 cytokine release, fibroblast activation and myofibroblast differentiation, excess collagen synthesis, and impaired matrix degradation, culminating in progressive tissue fibrosis that perpetuates further immune activation.

Vascular and fibrotic pathways are not independent processes but are mechanistically interconnected: chronic tissue hypoxia resulting from vascular injury directly stimulates fibroblast activation and collagen synthesis, while fibrotic tissue remodeling further compromises microvascular perfusion, reinforcing a shared "vascular-to-fibrotic continuum" that explains the co-occurrence of vasculopathy and fibrosis across nearly all affected organs in SSc.

Organ-Specific Clinical Manifestations

Because vascular and fibrotic processes affect nearly every organ system, SSc produces a wide and heterogeneous range of clinical manifestations, with the relative severity of vascular versus fibrotic involvement varying considerably between patients and between organs within the same patient. The principal organ systems and their vascular and fibrotic manifestations are summarized in Table 1.

Table 1. Vascular and Fibrotic Manifestations of Systemic Sclerosis by Organ System

Organ System	Vascular Manifestations	Fibrotic Manifestations
● **Peripheral / Digital**	Raynaud phenomenon, digital ulcers, digital pitting scars, critical digital ischemia	Sclerodactyly, joint contractures, calcinosis cutis
● **Cutaneous**	Telangiectasia, nailfold capillary dropout and dilation	Diffuse or limited skin thickening (modified Rodnan skin score); loss of skin appendages
● **Pulmonary**	Pulmonary arterial hypertension (isolated vasculopathy)	Interstitial lung disease / pulmonary fibrosis, leading cause of SSc-related mortality
● **Renal**	Scleroderma renal crisis: malignant hypertension, thrombotic microangiopathy	Interlobular arterial intimal fibrosis on biopsy
● **Gastrointestinal**	Gastric antral vascular ectasia ("watermelon stomach")	Esophageal dysmotility, GERD, small bowel bacterial overgrowth, fibrotic strictures
● **Cardiac**	Myocardial ischemia from small-vessel coronary vasculopathy	Myocardial fibrosis, conduction abnormalities, pericardial fibrosis

Classification and Modern Treatment Approaches

The 2013 ACR/EULAR classification criteria assign weighted points across clinical and serologic domains, with skin thickening of the fingers extending proximal to the metacarpophalangeal joints as a sufficient criterion on its own; additional points are contributed by skin thickening of the fingers (puffy fingers or sclerodactyly), fingertip lesions (digital ulcers or pitting scars), telangiectasia, abnormal nailfold capillaries, pulmonary arterial hypertension or interstitial lung disease, Raynaud phenomenon, and

SSc-related autoantibodies (anti-centromere, anti-topoisomerase I, or anti-RNA polymerase III). A cumulative score of 9 or more classifies a patient as having definite systemic sclerosis.

Reflecting the dual vascular-fibrotic pathogenesis, the 2023 EULAR recommendations introduced a coordinated "vascular therapeutic continuum," applying comparable classes of vasodilator and antiplatelet agents across Raynaud phenomenon, digital ulcer disease, and pulmonary arterial hypertension. For pulmonary arterial hypertension specifically, first-line combination therapy with two or more disease-targeted agents is now recommended for newly diagnosed patients, reflecting evidence that combination therapy improves outcomes over sequential monotherapy.

For fibrotic manifestations, the 2023 update introduced the first synthetic and biologic disease-modifying agents formally recommended by EULAR: mycophenolate mofetil and nintedanib for SSc-associated interstitial lung disease, and rituximab and tocilizumab as additional options for skin and lung fibrosis, marking a decisive shift from purely symptomatic management toward mechanism-targeted, disease-modifying therapy. Scleroderma renal crisis, a vascular emergency, is managed with angiotensin-converting enzyme inhibitors, which remain the standard of care and have transformed what was once a near-uniformly fatal complication into a manageable, though still serious, event. Hematopoietic stem cell transplantation may be considered in carefully selected patients with early diffuse cutaneous disease and poor prognostic features, based on observational and randomized evidence of sustained benefit.

Conclusion

Systemic sclerosis pathogenesis reflects the convergence of two mechanistically interconnected processes: a progressive vascular cascade beginning with endothelial cell injury and culminating in chronic tissue ischemia, and a self-amplifying fibrotic cascade in which immune-driven cytokine release activates myofibroblasts and drives excessive, poorly degraded extracellular matrix deposition.

Accurate classification using validated criteria and systematic, organ-by-organ assessment of both vascular and fibrotic involvement are essential to guide individualized management. The 2023 EULAR recommendations mark a significant therapeutic shift, introducing the first disease-modifying agents for fibrotic manifestations alongside a coordinated vascular treatment continuum spanning Raynaud phenomenon, digital ulcers, and pulmonary arterial hypertension.

Continued application of mechanism-based classification and guideline-directed, individualized treatment holds the potential to limit irreversible organ damage, reduce SSc-related mortality, and improve long-term quality of life for patients with systemic sclerosis.

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