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Systemic Sclerosis: Pathogenesis, Diagnosis, and Management

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Background

Systemic sclerosis (SSc) is an autoimmune fibrosing disease with internal organ involvement leading to significant morbidity and mortality. The average age of diagnosis ranges from 33.5–59.8 years with a strong female predominance (3.8–15 times more common).[1]

Epidemiology

Previous studies in Canada have demonstrated a prevalence of 74.4 cases per 100,000 females and 13.3 cases per 100,000 males (Canadian SSc prevalence data, 2003), which accounts for approximately 2,500 males and 14,000 females who are affected by this debilitating condition in Canada.[2] The highest point prevalence reported in the world, 47/100,000 persons, was observed among Canadian First Nation residents. Globally, the prevalence of SSc is estimated to be between 7–489 cases per million individuals, with large variability, at least in part, due to differences in diagnosis and in the heterogeneity of the disease.[3] Consistently higher case numbers are reported in North America and Australia compared to continental Europe, the United Kingdom, and Japan.[3] In the United States, the estimated period prevalence is 50/100,000 persons, and the age-sex adjusted annual incidence was 5.6/100,000 person-years for the years 2003-2008.[4,5] Globally, the annual incidence has been estimated to be 0.6–5.6/100,000 adults. A recent updated study in Quebec, Canada, showed an overall age-standardized incidence rate of 4.14 cases per 100,000 person-years, with a 4:1 female predominance.[6] The age-standardized incidence rate increased steadily over time, with an average increase of approximately 4% each year.

Variable geographic distribution has been observed, suggesting that extrinsic/environmental factors may play a role in disease development. For example, in Europe, a north–south gradient was observed with an increased prevalence of SSc in

southern countries.[3] Small studies also reported clusters of SSc cases in boroughs near international airports in London, United Kingdom,[7] a rural community near Rome, Italy,[8] and in Libby, Montana, where mining activities are predominant.[9] Other reported clusters include Woodstock, Canada,[10] and the Kahnawake First Nations Community in Quebec, Canada.[11] These studies suggest a non-random distribution of SSc cases and highlight the need to further investigate the epidemiology and environmental risk factors for this disease.

Pathogenesis

The pathogenesis of SSc is not fully understood, but it is hypothesized to be due to an environmental trigger in a genetically susceptible host.[12] A three-step hypothesis has been proposed, which includes endothelial cell dysfunction/vasculopathy, inflammation due to immune system dysregulation, and fibrosis **(Figure 1)**.[1] The low concordance rate in monozygotic twins and the evidence of geographic clustering suggests the importance of an extrinsic factor leading to disease development.[13] The nature of such triggers and other factors accounting for the variability in SSc clinical severity and prognosis remains unknown.

Possible external factors that have been studied in SSc include infectious agents, chemicals, occupational or environmental pollutants, and medications/supplements, all of which could affect the immune response and trigger microvascular damage and inflammation, subsequently leading to fibrosis.[15] Air pollution, a frequently studied environmental factor, is known to negatively contribute to many diseases, and was designated by the World Health Organization (WHO) as the primary environmental threat to humanity. It accounts for at least 7 million deaths globally every year.[16] Currently, the highest level of evidence for extrinsic triggers for SSc points to occupational or environmental exposures to silica (18-fold increased risk) and organic solvents (2–4-fold increased risk).[14,17] Silica exposure was associated with lower survival rates and a more severe disease phenotype, including diffuse cutaneous systemic sclerosis (dcSSc), digital ulcers, interstitial lung disease (ILD), myocardial dysfunction, and positive anti-topoisomerase (ATA) antibodies.[14] Other occupational exposures proposed to increase SSc risk include epoxy resins, asbestos, and particulate air pollution.[14]

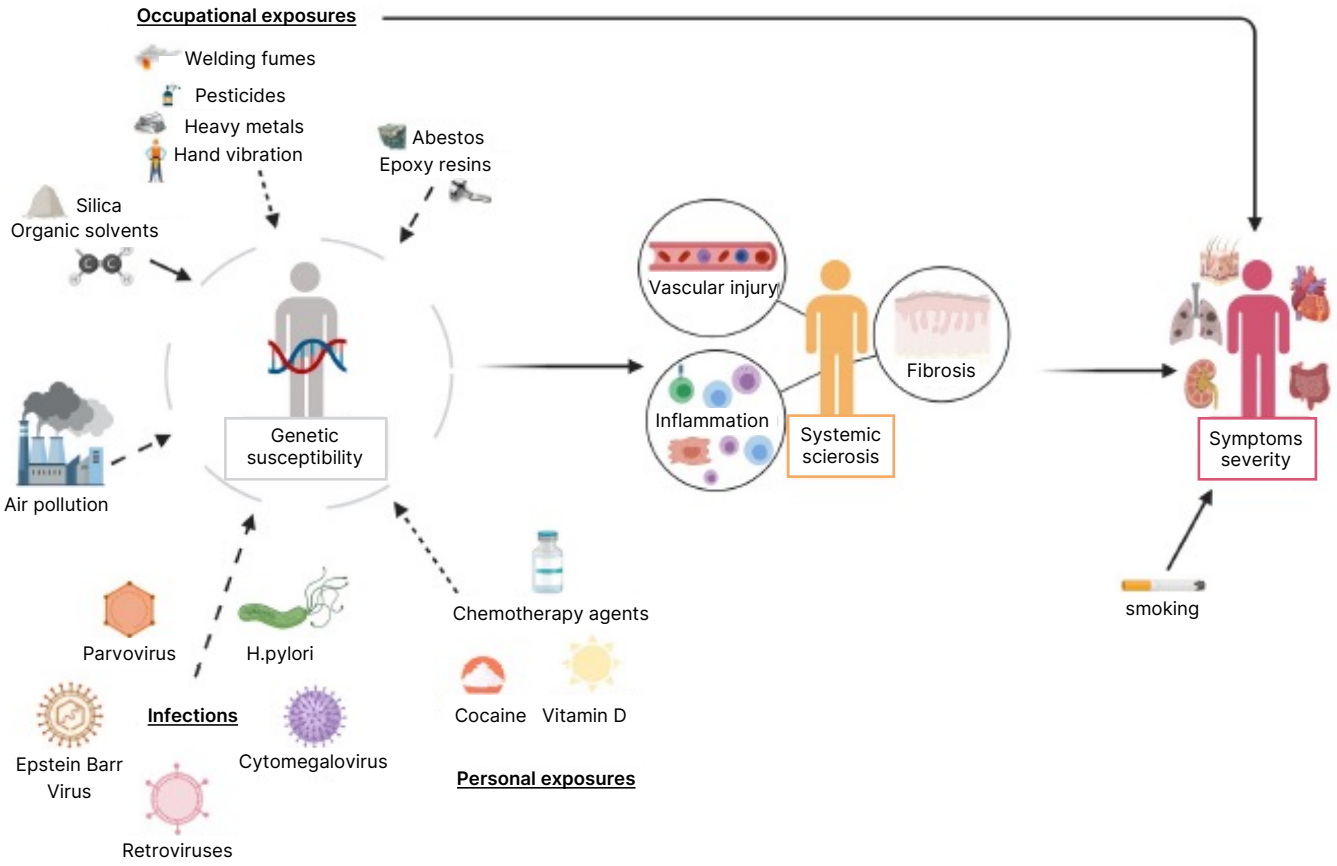

Figure 1. Pathogenesis of SSc and the role of occupational, environmental, and personal exposures to disease development. *H. pylori* - *Helicobacter pylori*. Thick lines—exposures increasing the incidence and/or severity of SSc risk based on observational studies. Dashed lines—exposures with probable increased incidence and/or severity of SSc (limited data). Dotted lines—exposures with anecdotal/unproven data only. Adapted from Ouchene et al.[14]

Clinical Presentation

Given that many manifestations of SSc are cutaneous, dermatologists play an important role in diagnosis, especially for early onset disease. The disease is classified into the following based on the extent of the skin fibrosis and the pattern of internal organ involvement: limited cutaneous (lcSSc) (the most common form) involving the distal limbs and face; dcSSc, involving the distal and proximal extremities, trunk and face; sine scleroderma, presenting without skin thickening but with internal organ involvement and serologic abnormalities; and overlap disease (e.g systemic lupus erythematosus, rheumatoid arthritis, polymyositis, or Sjögren's disease).[18] The most commonly affected organs are those with direct exposure to the environment such as the skin, gastrointestinal tract, and lungs.[19] In all forms, and especially in dcSSc, there is significant internal organ involvement leading to increased morbidity and mortality. The 10-year likelihood of survival is less than 65%,[19] and has remained unchanged for the last forty years.[20] In fact, SSc has one of the highest mortality rates of any rheumatic disease.[1]

Compared to females, SSc in males is more likely to present with a more severe phenotype including dcSSc, cardiomyopathy, ILD, and scleroderma renal crisis.[21] Whether these differences are related to sex-hormones or acquired risk factors (e.g. occupational/environmental) requires further investigation. On the other hand, females are more likely to have a younger age of disease onset and an increased rate of peripheral vascular disease and pulmonary arterial hypertension (PAH).[22]

Regarding ethnic differences, African American patients are more likely to develop the disease at a younger age and have more severe phenotypes including increased ILD and scleroderma renal crisis.[23]

Diagnostic Criteria

The diagnosis of SSc is based on the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria, which includes clinical disease manifestations, such as bilateral, symmetric skin thickening proximal to the metacarpophalangeal joints (sufficient criterion), presence of SSc-related abnormalities (e.g. Raynaud's phenomenon, fingertip lesions, telangiectasias, SSc-specific antibodies, abnormal nailfold capillaroscopy) and internal organ involvement (e.g. ILD, PAH) **(Table 1)**.[24] Patients achieving a score of ≥9 are classified as having definite SSc.

Item	Sub Item	Weight/ Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the highest score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	4
Fingertip lesions (only count the highest score)	Digital tip ulcers	2
	Fingertip pitted scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung Involvement (Maximum score is 2)	PAH	2
	ILD	2
Raynaud's phenomenon		3
Scleroderma related antibodies (Maximum score is 3)	ACA	3
	ATA	3
	RNAP3	3

Table 1. ACR/EULAR classification criteria for SSc. Patients with a total score of ≥9 are classified as having definite SSc. Adapted from van de Hoogen et al.[24]
Abbreviations: ACA: anti-centromere antibodies; **ATA:** anti-topoisomerasel/Scl-70 antibodies; **ILD:** interstitial lung disease; **MCP:** metacarpophalangeal joint; **PAH:** pulmonary arterial hypertension; **PIP:** proximal interphalangeal joint; **RNAP3:** anti-RNA polymerase III

Since internal organ involvement commonly occurs within the first 3 years, early diagnosis is important. In the last few decades, the availability of nailfold capillaroscopy, which reveals dilated capillary loops and drop out sign, as well as SSc-specific autoantibodies, have allowed an earlier diagnosis of SSc to be made. Very early diagnosis of SSc (VEDOSS) criteria were established in 2011.[25] These criteria include the presence of Raynaud's phenomenon, puffy fingers, and positive ANA as early disease features that predict progression to established SSc.[26] Hence, these early features could be helpful in establishing the diagnosis earlier, initiating treatment, minimizing end organ damage, and subsequently improving patient outcomes.

There are several specific autoantibodies that help with the diagnosis, clinical presentation, prognosis, and the exclusion of other conditions that present with skin thickening. ANA is positive in ~95% of patients.[1,27,28] SSc-specific-autoantibodies include anti-centromere

Antibody	Estimated Prevalence	Subtype of SSc	Main Systemic Associations
ACA	20–25%	lcSSc	• PAH (15–20%) • Esophageal dysmotility and gastrointestinal dysfunction • Low risk of ILD, cardiac and renal disease
ATA	20–30%	dcSSc >lcSSc	• High risk of ILD (early) • PAH • Scleroderma renal crisis • Cardiac • Myositis
PM/Scl	2–4%	Overlap Polymyositis/ lcSSc	• Myositis • ILD (50% by 15 years) • PAH (approximately 36% by 15 years) • Cardiac • Renal
To/Th ribonucleoprotein	<5%	lcSSc	• ILD (45%) • PAH (25%)
RNAP-III	1–22%	dcSSc (rapidly progressive)	• Scleroderma renal crisis (early) • Increased risk of malignancy within 3 years of diagnosis • Moderate risk of ILD • PAH (later) • Gastric antral vascular ectasia • Myositis • Less cardiac involvement
U1-RNP	5–10%	lcSSc, overlap syndromes (mixed connective tissue disease)	• Myositis • PAH • ILD
U3-RNP/ Fibrillarin	4–10%	dcSSc	• Early severe organ involvement: • PAH (highest risk) • ILD • Scleroderma renal crisis • Cardiac • Small bowel dysmotility • Myositis

Table 2. Summary of autoantibody profiles in SSc and corresponding key systemic associations. Adapted from Jerjen et al.[1]
Abbreviations: ACA: anti-centromere antibodies; **ATA:** anti-topoisomerase I/Scl-70 antibodies; **dcSSc:** diffuse cutaneous systemic sclerosis; **ILD:** interstitial lung disease; **lcSSc:** limited cutaneous systemic sclerosis; **PAH:** pulmonary arterial hypertension; **PM/Scl:** polymyositis/ scleroderma; **RNAP-III:** RNA polymerase III; **U1-RNP:** U1- ribonucleoprotein; **U3-RNP:** U3-ribonucleoprotein

System	Investigation	Explanation	Treatment
General	CBC with differential	Assess for anemia due to malabsorption, iron deficiency, or gastrointestinal blood loss	• Iron supplementation • Nutrition consultation
Lung Involvement	• HRCT of the chest • PFT with DLCO • Bronchoalveolar lavage and lung biopsy can be considered	To be completed at baseline and if clinical symptoms are present or worsening PFTs are identified	• Immunosuppression (mycophenolate mofetil, cyclophosphamide, rituximab) • Nintedanib, tocilizumab – FDA approved • Lung transplant • Autologous HSCT in rapidly progressive ILD
Pulmonary Arterial Hypertension	• Doppler echocardiography • Serum N-Tpro-BNP level • Right heart catheterization	This is recommended for initial screening for PAH	• O_2 • Anticoagulation • Endothelin receptor antagonist • Phosphodiesterase 5 inhibitor • Prostacyclin analogues • Prostacyclin receptor agonist • Soluble guanylate cyclase stimulant • Lung transplant
Cardiac Fibrosis	Echocardiography	Restrictive cardiomyopathy can occur secondary to PAH	•ACE inhibitors
• GI involvement • Esophageal dysmotility • Small bowel involvement	• Barium swallow with small bowel follow through • Manometry • Endoscopy	Evaluation should be guided by symptoms	• PPI • Promotility agent (ondansetron)
Renal crisis Hypertension	• Blood pressure measurement • Serum creatinine level • Urinalysis with urine sediment		• ACE inhibitors instituted for early treatment but not helpful for prevention
Overlap disease	• CK • Rheumatoid factor • Antibodies to CCP • Anti-double-stranded DNA and/or anti-Smith RNP antibodies	• May be elevated in patients with myopathy or myositis • These antibodies are relatively uncommon in patients with SSc and their presence points toward overlap syndromes with other systemic diseases • Usually in overlap cases there is more significant arthritis compared to SSc	

Table 3. Summary of screening recommendations and treatment approaches based on systemic involvement; *courtesy of Anastasiya Muntyanu, MD*
Abbreviations: ACE: angiotensin-converting enzyme; **CBC:** complete blood count; **CCP:** citrullinated peptides; **CK:** creatine kinase; **DLCO:** diffusing capacity for carbon monoxide; **GI:** gastrointestinal; **HRCT:** high-resolution computed tomography; **HSCT:** hematopoietic stem cell transplantation; **ILD:** interstitial lung disease; **PAH:** pulmonary artery hypertension; **PFT:** pulmonary function test; **PPI:** proton pump inhibitor; **RNP:** ribonucleoprotein; **Serum N-Tpro-BNP:** N-terminal pro-B-type natriuretic peptide; **SSc:** systemic sclerosis

antibodies (ACA), which is associated with lcSSc and PAH, ATA, associated with dcSSc and ILD, and anti-RNApolymerase (RNAP)-III antibodies, associated with malignancy and renal crisis **(Table 2)**.[1] The autoantibodies are typically mutually exclusive. Other autoantibody profiles include Polymyositis/Scl, To/Th ribonucleoprotein, U1-ribonucleoprotein (U1-RNP), and U3-RNP/fibrillarin.[1] A combination of autoantibodies can also help predict survival, timing, risk, and incidence of systemic complications.[1,29]

Systemic Involvement

Systemic manifestations include pulmonary (ILD or PAH), renal (i.e. scleroderma renal crisis or renal vasculopathy), cardiac (i.e. heart failure, arrythmias, pericardial effusion, and valve sclerosis), gastrointestinal (i.e. gastroesophageal reflux disease, impaired motility, gastric antral vascular ectasia), and urogenital (i.e. sexual dysfunction) involvement as well as an increased malignancy risk (i.e. cutaneous, breast, bladder, lung, liver, and hematological) **(Table 3)**.[1] Regular screening for lung involvement is mandatory and consists of pulmonary function tests as well as a high resolution CT scan (HRCT).[30] Cardiac involvement is more common in older patients and in those with ATA antibodies.[1,31] Scleroderma renal crisis is a severe manifestation that is less common now, given the knowledge that high dose prednisone can precipitate it, as well as the available preventative options such as angiotensin-converting enzyme (ACE) inhibitors.[32,33] Scleroderma renal crisis typically manifests within the first 5 years of the SSc diagnosis. The most commonly involved internal organ system is the gastrointestinal tract, and most patients with SSc are affected to some degree.[34]

Management

No curative treatments exist for SSc, and the available therapies may only have a limited effect on slowing disease progression, often with significant side effects.[35] Treatment is focused on the disease manifestations that are present. For skin fibrosis, immunosuppressive agents such as mycophenolate mofetil and methotrexate are typically used, with newer agents such as tocilizumab, rituximab, and brodalumab showing early promise in clinical trials.[30,36] Regarding brodalumab, a clinical trial of 100 patients randomized to brodalumab vs placebo reported that the treatment group showed a rapid, sustained, and significant reduction in skin sclerosis as measured by the modified Rodnan skin score (mRSS) up to 52 weeks.[37] Additionally, brodalumab exhibited therapeutic effects on lung/respiratory functions, formation of digital ulcers, the symptoms of gastroesophageal reflux disease, and quality of life indicators. No additional safety concerns were identified compared to treatment in other disease categories such as psoriasis.[37]

In recent years, autologous hematopoietic stem cell transplantation has provided tremendous hope.[38] This procedure reduces the number of aberrant immune cells and allows re-population with a self-tolerant immune system. This intervention continues to have the largest effect on skin fibrosis to date (e.g., a 10-point greater decrease in mRSS compared to 12 monthly infusions of cyclophosphamide).[39] While several studies have shown a decrease in skin involvement, improvements in organ function, quality of life measures, and overall survival,[40] this procedure is associated with significant risks, which limits its use to certain subsets of patients.

Conclusion

In conclusion, SSc is a complex, autoimmune fibrosing disease that significantly impacts morbidity and mortality due to its multi-organ involvement. The pathogenesis likely involves environmental triggers in genetically predisposed individuals, leading to immune dysregulation, endothelial damage, and progressive fibrosis. The variability in incidence/prevalence rates across regions and globally suggests that geographic/environmental factors could play a role.

Early diagnosis is essential for optimizing treatment, particularly as severe manifestations often develop within the first few years after disease onset. Recent advancements in diagnostic tools, such as nailfold capillaroscopy, SSc-specific autoantibodies, and VEDOSS classification facilitate earlier detection, which may improve outcomes. Management is tailored to specific organ systems, but little is known with regards to disease modification. Continued research is needed to better understand the underlying mechanisms of SSc and to develop targeted therapies that could help reduce the significant disease burden.

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Financial Disclosures

None declared.

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