Systemic sclerosis: one year in review 2025

M. Di Battista[1], G. Lepri[2], V. Codullo[3], L. Bianchessi[3], G. Ghezzi[1], A. Della Rossa[1], S. Guiducci[2], F. Del Galdo[4,5]

[1]*Rheumatology Unit, University of Pisa, Italy;* [2]*Department of Experimental and Clinical Medicine, University of Florence, Section of Rheumatology, AOU Careggi, Florence, Italy;* [3]*Rheumatology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;* [4]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK;* [5]*NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, Leeds, UK.*

Marco Di Battista, MD, PhD
Gemma Lepri, MD, PhD
Veronica Codullo, MD, PhD
Lorenzo Bianchessi, MD
Giulio Ghezzi, MD
Alessandra Della Rossa, MD, PhD
Serena Guiducci, MD, PhD
Francesco Del Galdo, MD, PhD

Please address correspondence to:
Alessandra Della Rossa
U.O. di Reumatologia,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: a.dellarossa@ao-pisa.toscana.it

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ABSTRACT

Systemic sclerosis is a rare and chronic connective tissue disease with a complex pathogenesis and highly heterogeneous clinical manifestations. Although significant progress has been made in understanding its underlying mechanisms, early diagnosis and therapeutic strategies, SSc remains a clinical challenge. Each year, several studies explore new insights into its pathogenesis, organ involvement, and treatment. This review provides an overview of the most relevant studies published in the literature in 2024.

Introduction

Systemic sclerosis (SSc) represents one of the most challenging pathologies for the rheumatologist due to its heterogeneous clinical presentation and different degrees of severity, and for the patient it is a chronic condition with a very high impact on the quality of life. Continuing *Clinical and Experimental Rheumatology*'s editorial effort to offer valuable recent perspectives on rheumatic diseases through the "One Year in Review" format (1, 2), we present here a narrative critical summary of the most impactful studies on SSc published in 2024. A MedLine search was conducted using the keyword 'systemic sclerosis' (MeSH terms and semantic search), with a focus on pathogenesis, clinical manifestations, treatment, and patient-reported outcomes. We included the most relevant articles in English on adult SSc patients published between 1st January 2024 and 31st December 2024.

Pathogenesis

To define and describe SSc pathogenesis represents a challenge for researchers and clinicians and many points still need to be understood. Extremely summarised, three pathogenetic processes are recognised represented by immune system alterations leading to inflammation and specific-autoantibodies production, vasculopathic phenomena and finally a fibrotic process.

Immune system

Dysregulation in T and B cells seems to play a crucial role in SSc pathogenesis and in this context, the correlation between peripheral T and B cell and SSc progression has been investigated by Wu *et al*. The authors enrolled 47 SSc patients and 45 healthy controls (HC) reporting levels in CD4+ T cells, CD8+ T cells and in total T cells not significantly different between SSc and controls, while a reduction in B cells (marginal zone B cells, Breg cells, memory B cells and non-switched B cells) was observed in SSc. In addition, specific T and B cells subsets significantly differed in the two groups: SSc patients presented a decrease in Th1 cells and an increase in Th2 cells. In addition, Th1/Th2 ratio, (Th1+Th17)/Th2 ratio, Treg levels and Treg/Th17 ratio decreased in SSc. Follicular helper T1 (Tfh1) cells were reduced in SSc population that conversely presented an increase in Tfh2 levels. The authors reported a correlation between the modified Rodnan skin score (mRSS) and Th17, Tph (peripheral helper T cells), Tfh1 and plasma cells, suggesting the possible role of some T and B cells subset not only in SSc pathogenesis but also in the disease progression and prognosis (3).

A recent study assessed the frequency of monocyte subpopulations and their correlation with SSc features. Patients with SSc (n=26) had lower levels of classical (CD14+ CD16-) and intermediate (CD14+ CD16+) monocytes, while they presented an increased expression of non-classical (CD4- CD16+) monocytes compared to controls (n=20). In addition, the ratio CD14+CD16-/CD4-

CD16+ was significantly reduced in SSc suggesting the potential role of some monocyte subpopulations in the disease pathogenesis. In this study no significant correlations were found between monocyte subtypes (classical, intermediate or non-classic) and SSc clinical or laboratory features (4).

CXCL4 seems to play an important role in SSc pathogenesis, probably influencing monocyte apoptosis and macrophages phagocytic functions. This hypothesis has been strengthened by Le Tallec *et al*. reporting significantly increased serum levels of CXCL4 in SSc than in controls. Monocytes-derived macrophages (MDMs) when exposed to SSc plasma presented a reduction in efferocytosis compared with MDMs exposed to HC plasma. The *in vitro* analysis also confirmed pro-inflammatory properties of M4-MDMs with a higher ability to produce interleukine-6 (IL)-6 and tumour necrosis factor (TNF)-α than M0-MDMs. M4-MDMs had a lower phagocytic and efferocytosis function and this datum was partially explained by the lower expression of CD36 receptor despite the enhancement of LC3-associated phagocytosis (5).

Evaluation of pro-inflammatory cytokine levels in cultured monocytes from SSc patients (n=35) and controls (n=25) revealed a significant increase in TNF-α, IL-1β, and IL-6 in SSc, both at baseline secretion and following lipopolysaccharide (LPS) stimulation. Moreover, the SSc cohort exhibited significantly higher levels of IL-1β, monocyte chemoattractant protein (MCP)-1, IL-6, and IL-8 after LPS re-stimulation. Notably, 11 out of 35 SSc patients demonstrated the same or even higher MCP-1 secretion after LPS re-stimulation compared to the initial LPS stimulation, suggesting impaired immune tolerance in macrophages. These patients, in comparison to those with preserved immune tolerance, were younger and had a higher prevalence of anti-topoisomerase I antibodies (ATA). Collectively, these findings indicate a pro-inflammatory activation of monocytes/macrophages in SSc, along with a defective immune tolerance. In this context, MCP-1 may represent a potential therapeutic target (6).

The association between Tfh cells and SSc was also investigated in the study by Sahinoglu *et al*., highlighting the potential role of these cells in the pathogenesis of SSc-related lung involvement. The authors enrolled 50 SSc patients, including 19 with the limited cutaneous subtype (lcSSc) and 31 with the diffuse subtype (dcSSc). Their findings revealed that Tfh cells (CD4+ CXCR5+) were elevated in SSc patients exhibiting specific disease manifestations, such as Raynaud's phenomenon, digital ulcers (DUs), and cardiopulmonary involvement, as well as in those with severe lung disease, as assessed by the Medsger disease severity index (7).

Vasculopathy

Vasculopathy is a key pathogenic process in SSc, leading to increased vascular permeability, extravasation, and endothelial dysfunction. Endothelial cells (ECs) are believed to play a crucial role in SSc-related vasculopathy, and phenotypic alterations in EC subpopulations within SSc-affected skin have been reported. A recent study analysing skin biopsies from 27 SSc patients and 10 HCs revealed an upregulation of extracellular matrix gene expression in capillary ECs. Additionally, a comparison of venous ECs between SSc patients and controls demonstrated increased expression of MT-ND3 and PFN1, genes associated with hypoxia, in the SSc group. Arterial ECs were found to be less abundant in SSc skin biopsies compared to controls and exhibited increased expression of apoptosis-related genes, such as IGFBP3. Furthermore, two distinct EC subpopulations – tip ECs and proliferating ECs – were identified in SSc patients. Tip ECs expressed genes associated with angiogenesis, contributing to SSc vasculopathy, while proliferating ECs were characterised by enhanced proliferative activity. Notably, an increase in tip ECs and a decrease in arterial and lymphatic ECs were positively correlated with skin fibrosis, whereas DUs were associated with an upregulation of BIRC5, PCLAF, and UBE2T in proliferating ECs (8).

Pulmonary arterial hypertension (PAH) is a crucial feature in SSc vasculopathy. Analysis of lung tissue from 16 SSc patients with pulmonary hypertension (PH), 3 individuals with idiopathic PAH, and 15 healthy controls (HCs) identified specific EC subpopulations potentially associated with SSc-PH. Arterial EC levels were reduced in all PH patients, who also exhibited an increased presence of tip and phalanx ECs. These two subpopulations, rarely observed in HC lungs, were linked to vascular development, endothelial barrier integrity, and Notch signalling. Additionally, the study highlighted PPAR-γ and Smad1 as potential key regulators of angiogenesis, suggesting their involvement in the function of tip and phalanx ECs (9).

Evaluating skin biopsies form 27 active dcSSc and 10 HC, Tirelli *et al*. investigated the role of H19 X-linked (H19X) co-expressed long non-coding RNA (lncRNA) in SSc vasculopathy. The authors reported an increased expression of H19X after stimulation with interferon (IFN)-I and -II, particularly with IFN-α after 48 and 72 h. Interestingly, evaluating human dermal microvascular endothelial cells (HDMECs), the mRNA levels of different adhesion molecules reduced after H19X knockdown, in particular levels of VCAM1 with a significant decrease of its signalling pathway. Therefore, H19X seems to contribute to SSc vasculopathy as the authors also reported a reduction in contractility of H19X knockdown HDMECs (10).

The role of Th17-related cytokines in SSc patients with PAH was also investigated in a study that enrolled 72 SSc patients and 51 HC evaluating heparinised peripheral blood. In these samples the authors measured the levels of Th-17 related cytokines: IL-17A, IL-17A/F, IL-17B, IL-17C, IL-17D, IL-1β, IL-6, IL-21, IL-22, and IL-23. SSc patients presented a greater level of Th1 and Th17 cells compared with controls and the mRSS positively correlated with Th17 cells levels suggesting their role in skin profibrotic process in SSc. In addition, mRSS also correlated with activated Th17 and Th2 cells, while lung function, particularly the diffusing capacity for carbon monoxide (DLCO), was negatively correlated with Th1 cells. Regarding

cytokines expression, the authors reported greater levels of serum IL-17A, IL-17D, IL-1β and IL-6 and lower levels of IL-17A/F in SSc patients than in HC. As observed for Th1 cells, DLCO negatively correlated with IL-17A, IL-6 and IL-22. Interestingly, comparing SSc patients with PAH and those without, serum levels of IL-17A were increased in the first patients suggesting this cytokine as a potential predictor of PAH in SSc population. In addition, SSc patients with increased levels of IL-17A and IL-6 had a higher prevalence of PAH compared to the SSc population characterised by undetected IL-17A and low levels of IL-6 (11).

Fibrosis

The study of Zhu *et al*. confirmed the role of some fibroblast subpopulations in the pathogenesis of SSc, suggesting the possibility to try to stop or slow down the skin pro-fibrotic and/or pro-inflammatory process targeting specific fibroblast population signatures. Evaluating the PRESS (Prospective Registry of Early Systemic Sclerosis) and the GENISOS (Genetics versus Environment in Scleroderma Outcome Study) cohorts through an analytic tool based on machine learning named CIBERSORTx, altered proportions of fibroblast subpopulations have been reported in SSc skin compared with HC. In the first cohort, composed of 48 dcSSc patients and 33 HC, the subpopulation COMP+, COL11A1+, MYOC+ and CCL19+ were increased in SSc than in HC, and similar results were observed in the GENISOS cohort (composed by 18 lcSSc patients, 43 dcSSc subjects and 36 HC). In addition, an increase in SFRP4/SFRP2+ and PRSS23/SFRP2+ fibroblasts was reported in SSc compared with HC in both populations. Among SSc patients, an increase in COMP+, COL11 and CCL19+ fibroblasts and a reduction in PI16+ fibroblasts were observed in clinically affected skins than in non-affected ones. To note that CCL19 fibroblasts have a proinflammatory phenotype promoting immune cell recruitment and activation, while COMP+, COL11A1+, SFRP4/SFRP2+ and PRSS23/SFRP2+ fibroblasts have a more profibrotic phenotype. In this context, the authors reported a positive correlation between the proinflammatory and the profibrotic subpopulations and the clinical and histopathological parameters of skin fibrosis as mRSS and the alpha-smooth muscle actin (α-SMA)-positive myofibroblasts and collagen thickness. Interestingly, the composition in fibroblast subpopulations seemed to predict the course of skin fibrosis: GENISOS patients could be classified in skin fibrosis progressors or non-progressors with the application of machine learning models using fibroblast signatures together with demographic and clinical features. Results suggested that the evaluation of SFRP4/SFRP2+, PRSS23/SFRP2+, COL11A1+, and COMP+ fibroblast signatures at the time of biopsy may improve the classification of SSc patients in those who will progress in skin fibrosis *versus* those with a stable skin involvement (12).

Although the exact mechanism of fibrosis in SSc has not been yet explained, epidermis and dermis cells seem to play a crucial role in SSc fibrotic processes. Chitinase 3-like 1 protein (Chi3L1) is part of the chitinase-like proteins, and it is involved in several inflammatory diseases. The study of Wang et al. detected a subset of basal cells expressing Chi3L1 suggesting this protein as a promising target for the treatment of SSc. The authors investigated possible interactions between keratinocytes and fibroblasts reporting Chi3L1 basal cells, enriched in SSc, as those with the strongest interaction with fibroblasts. In addition, skin and serum levels of Chi3L1 were greater in SSc patients compared to controls, particularly in dcSSc, and serum levels of this protein correlated with skin involvement. The *in vitro* evaluation confirmed the interaction between Chi3L1 and dermal fibroblasts: these cells, stimulated with recombinant Chi3L1 (rChi3L1), increased their ability to differentiate into myofibroblasts. Furthermore, after the stimulation of fibroblast with rChi3L1, the authors described an increase in IL-11 secretion, a cytokine with profibrotic activities and secreted by SSc fibroblasts, again remarking the ability of Chi3L1 to activate SSc dermal fibroblasts. In addition, Chi3L1 may directly interact with IL-17 receptor on fibroblasts (13).

Toll-like receptor 8 (TLR8), a pattern recognition receptor, works as an innate immune mediator. To investigate its role in promoting skin inflammation and fibrosis in SSc, a recent study analysed TLR8 expression in skin tissue and skin fibroblasts from 48 SSc patients and 31 HC. Their findings revealed a significant increase in TLR8 expression in SSc skin tissue compared to controls, particularly in patients positive for anti-RNA polymerase III antibodies, with TLR8 levels correlating with skin fibrosis. Moreover, isolated skin fibroblasts from SSc patients exhibited higher TLR8 protein expression than those from HC. The study further demonstrated that transforming growth factor (TGF)-β upregulated TLR8 expression in SSc and that TLR8 inhibition attenuated the fibrotic response in skin fibroblasts. Collectively, these findings highlight a key role of TLR8 in skin fibrosis and inflammation, suggesting it as a potential therapeutic target in SSc (14).

Ayub *et al*. investigated the role of TGF-β1 in the pathogenesis of SSc by analysing its expression in both serum and peripheral blood mononuclear cells (PBMCs) from 50 SSc patients and 30 HC. Their findings demonstrated a correlation between TGF-β1 levels and fibrotic as well as vascular disease manifestations. Specifically, TGF-β1 mRNA expression was elevated in SSc patients, particularly in those with dcSSc. Serum TGF-β1 levels were significantly higher in both dcSSc and lcSSc patients compared to HC. Further analysis revealed a positive association between serum TGF-β1 levels and key clinical features of SSc, including interstitial lung disease (ILD), DUs, and ATA. Additionally, TGF-β1 mRNA expression in PBMCs correlated positively with its serum levels (15).

Integrins are cell adhesion and signalling proteins that are activated by talins and kindlins. The role of integrins in SSc was investigated by Xu *et al*., who reported elevated talin 1 mRNA levels in SSc skin compared to HC, with a more pronounced increase in dcSSc. In contrast, kindlin 1 expression was

found to be reduced in SSc. The study also identified a positive correlation between talin 1 expression and the mRSS. Furthermore, levels of serum talin 1 were significantly higher in SSc patients than in controls, particularly in those with dcSSc. Notably, knockdown of talin 1 in SSc fibroblasts led to decreased expression of Collagen type I alpha 1 and α-SMA, along with impaired fibroblast migratory capacity. Additionally, integrin subunits beta 1 and 5 mRNA levels were reduced in SSc fibroblasts following talin 1 knockdown treatment. These findings indicate an upregulation of talin 1 in SSc and suggest that its inhibition reduces fibroblast activation and collagen production, highlighting talin 1 as a potential therapeutic target for SSc (16).

BAG3 (Bcl-2-associated athanogene 3) is a member of the BAG family of proteins, and increased BAG3 gene expression has been reported in various malignancies. Given its association with fibrotic processes in tumours, its role in systemic sclerosis (SSc) pathogenesis has also been investigated. De Marco *et al*. analysed 106 SSc patients (47 lcSSc and 59 dcSSc) and 106 HC, reporting significantly elevated serum BAG3 levels in dcSSc. Similarly, BAG3 expression was increased in skin biopsies from dcSSc patients compared to controls. While BAG3 expression did not correlate with the extent of skin involvement, a positive association was observed with the severity of lung disease and the late capillaroscopic pattern. These findings suggest that BAG3 is linked to SSc features indicative of advanced fibrosis, consistent with its role in tumour-associated fibrotic processes, further supporting its pathological relevance in SSc (17).

A study comparing 28 SSc patients with ILD and 46 without reported elevated serum levels of Krebs von den Lungen-6 (KL-6) and IL-18 in SSc-ILD subjects. KL-6 and IL-18 levels were negatively correlated with pulmonary function, particularly forced vital capacity (FVC) and DLCO. Additionally, a positive correlation between KL-6 levels and extensive lung involvement was observed. No association was found between KL-6 levels and mRSS, whereas IL-18 levels were significantly higher in patients with dcSSc. Collectively, these findings suggest that KL-6 and IL-18 may serve as potential biomarkers for screening SSc-ILD (18). Similarly, also Takei *et al*. evaluated dcSSc patients with ILD measuring KL-6 levels and reported a negative correlation between annual change in KL-6 levels and the annual variation of FVC at one year from baseline. This datum strengthens KL-6 as a possible marker in the evaluation of SSc-ILD (19).

IL-41 is reported to have immunoregulatory activities particularly in inflammatory disease. Few data are available regarding the possible role of IL-41 in SSc. Enrolling 18 SSc patients with an early diffuse subset and 18 HC, the retrospective study of Freedman *et al*. would suggest IL-41 as a probable antifibrotic cytokine. The authors reported a decrease in serum levels of IL-41 in SSc patients, and the mRNA expression in skin biopsies from SSc patients was reduced compared to samples from HC. Interestingly, IL-41 may activate the AMP-kinase that negatively regulates mTOR (mammalian target of rapamycin), and in this study the analysis of mTOR expression in skin biopsies revealed higher levels in SSc than in HC (20).

Microbiome

In recent years, scientific interest has increasingly focused on the potential role of the microbiome in the pathogenesis of rheumatic diseases, including SSc, where the gastrointestinal system is one of the earliest affected organs. Bellando-Randone *et al*. analysed gut microbiome (GM) composition and its metabolites in 26 SSc patients, 18 individuals with very early diagnosis of SSc (VEDOSS), and 20 HCs. Findings from this study suggest an early GM imbalance that may contribute to dysbiosis, impaired intestinal barrier integrity, and inflammation from the initial phases of the disease. Notably, the faecal microbiota composition of VEDOSS subjects resembled that of SSc patients more than that of controls, with the presence of two bacterial genera (Megasphaera and Rikenellaceae) that were absent in the control group. Additionally, both SSc patients and individuals in the early disease phase exhibited lower levels of butyrate and higher levels of acetic and nonanoic acids compared to controls (21). Another study investigated intestinal permeability abnormalities in SSc assessing markers of microbial translocation, inflammation, and intestinal damage comparing 60 SSc patients with 20 HC. Lipopolysaccharide-binding protein (LBP) and EndoCab IgM were analysed as markers of microbial translocation, IL-6 as an inflammatory marker, and intestinal fatty acid-binding protein and zonulin as indicators of intestinal damage. SSc patients exhibited significantly higher mean levels of all markers compared to controls. Moreover, LBP and zonulin levels positively correlated with UCLA gastrointestinal scores, and logistic regression analysis identified LBP as the only marker associated with moderate-to-severe UCLA diarrhoea scores. These findings confirm increased microbial translocation, inflammation, and intestinal damage in SSc, reinforcing the hypothesis that gut dysbiosis may contribute to disease progression and manifestations, particularly gastrointestinal symptoms, which appear to be strongly linked to microbial translocation (22).

Take-home messages

- Specific T and B cell subsets seem to be involved in SSc pathogenesis also representing potential markers of SSc progression and prognosis (3, 4, 7).
- ECs play a crucial role in SSc vasculopathic phenomena and correlate with vascular disease manifestation. Proliferating ECs upregulating BIRC5, PCLAF and UBE2T are associated with DUs. Tip and phalanx ECs (associated with vascular development and integrity) are discovered higher in PH patients (8, 9).
- Recent data confirm the possible role of epidermis and dermis cells in SSc pathogenesis and basal cells expressing Chi3L1 seem to activate SSc dermal fibroblasts (13).
- Biomarkers to predict PAH and ILD course are largely investigated: KL-6 and IL-18 may be useful as potential

biomarkers in ILD screening and progression (18, 19).
- New insights in microbiome seem to suggest that the potential early dysbiosis in SSc patients may promote inflammatory processes already from the first phases of the disease (21).

Clinical manifestations

Skin involvement

Skin fibrosis is a hallmark of SSc and its extent, measured by the mRSS, correlates with visceral organ involvement and disease severity. According to a recent analysis from the EUSTAR registry, regression of skin thickening, defined as decrease in mRSS >5 and ≥25% in 12 months, is associated with a lower probability of ILD progression and with a lower probability of all-cause death. Furthermore, the rate of intestinal, cardiac involvement progression and new-onset scleroderma renal crisis were similar among patients with skin regression, skin stability, and skin progression (23). The mRSS remains the most widely used tool for the assessment of skin involvement in SSc patients, but it has some limitations, such as low sensitivity to subtle changes and skin tethering, and inter-observer variability. High frequency ultrasound (HFU) and shear wave elastography (SWE) seemed to offer good reproducibility and high sensitivity in assessing skin thickness and stiffness. Yu *et al*. showed that HFU/SWE is able to discriminate between SSc patients and HC and that the measured skin thickness of the forehead, dorsum of middle fingers, dorsum of hands, forearms, forehead and legs positively correlates with mRSS, although with different performance depending on the site evaluated (24).

Gastrointestinal involvement

In patients with SSc, the entire length of the gastrointestinal tract can be involved, often affecting patients' quality of life. A study conducted on a French cohort of 90 SSc patients found that gastro-oesophageal involvement was very common, with a prevalence of 93.3%, while anorectal and intestinal involvement were less common but more impactful on quality of life. Notably, pulmonary function test parameters were significantly worse in patients with gastro-oesophageal involvement. A cluster analysis showed 3 distinct phenotypes: cluster 1, characterised by lcSSc involvement, anti-centromere (ACA) positivity, less frequent intestinal or anorectal involvement; cluster 2 with more frequent intestinal, anorectal cardiac involvement; and cluster 3 with dcSSc, a higher mRSS, more frequent gastro-oesophageal involvement and ILD (25). In terms of the impact of gastrointestinal involvement on quality of life, Cano-García *et al*. showed that in a cohort of 75 SSc patients, more than half had moderate, severe or very severe reflux, dysphagia, constipation and just less than half of them had abdominal distension. Severe malnutrition was not common, but 5.3% of patients were malnourished and required intervention. In particular, patients with dysphagia were more likely to have a higher mRSS, a higher frequency of osteoporosis, microstomia and DUs. After multivariate analysis, mRSS was positively correlated with the severity of gastrointestinal symptoms, while the presence of dysphagia was associated with malnutrition (26). These data were in line with another analysis from the Australian Scleroderma Cohort Study, where UCLA GIT questionnaire was administered to 907 SSc patients. Reflux, distension, diarrhoea and constipation were the most common symptoms; higher total UCLA GIT scores, reflux scores and distension scores were associated with worse quality of life and depression, and higher diarrhoea scores were found to be associated with unemployment, while the presence of GI symptoms was not associated with death (27).

Alterations in the autonomic nervous system and enteric nervous system are known to contribute to gastrointestinal dysmotility. Alvarez-Hernandez *et al*. found that dysautonomia was a common feature of SSc patients with gastrointestinal involvement and, in particular, a higher autonomic burden as measured by the Composite Autonomic Symptom Score (COMPASS) questionnaire-31 was found in patients who experienced reflux, bloating and constipation. The authors also demonstrated an association between autonomic dysfunction and upper gastrointestinal transit dysfunction using scintigraphy (28).

Musculoskeletal involvement

Musculoskeletal involvement in SSc is heterogeneous and can result in arthralgias, synovitis, tenosynovitis, tendon friction rubs and joint contractures, which can lead to significant functional impairment, particularly of the hand. Inflammatory arthritis (IA) is common and may be present in up to one third of SSc patients. IA is more frequent in dcSSc and is often associated with tendon friction rubs (50.1% of IA patients), joint contractures (12.3%), myositis (11.2%). Unsurprisingly, the presence of IA is associated with higher inflammatory markers, ATA, anti-RNA polymerase III, anti-U1RNP and anti-CCP antibodies, but is not differently distributed between rheumatoid factor positive and negative patients. Patients with IA are more likely to be treated with prednisolone, methotrexate and hydroxychloroquine (29).

Functional hand impairment can occur early in the course of SSc and is strongly correlated with disability; the main tool used to assess it is the Cochin Hand Function Scale (CHFS). In a large cohort of 201 SSc patients, repeated CHFS assessment over a 24-months period showed that hand function worsened in the entire cohort, with median CHFS increasing from 12.9 at baseline to 17.0 at 24 months, and CHFS rarely improved in these patients, suggesting that functional hand impairment is progressive and often irreversible despite treatment. After multivariate analysis, the absence of DUs at baseline, treatment with immunosuppressants or second-line analgesics and a baseline CHFS patient acceptable symptom state were associated with greater functional hand deterioration over time (30). In addition, Fourmond *et al*. compared functional hand disability in both dominant and contralateral hand using CHFS, scleroderma Health Assessment Questionnaire and Kapandji functional score, showing that joint flexion or extension limitations and mRSS were significantly greater in the dominant hand (31).

Heart involvement

Cardiac involvement in SSc is common and can range from mild manifestations such as pericardial disease and subclinical diastolic dysfunction to potentially life-threatening complications, such as arrhythmias, myocardial ischaemia and heart failure (HF). A large study showed that patients with SSc who were hospitalised for HF had a higher mortality rate than patients without SSc; in addition, SSc patients were also younger, more likely to be female, and had lower rates of traditional cardiovascular risk factors (coronary artery disease, dyslipidaemia, diabetes and obesity), but higher rates of PH and ILD (32).

Left ventricular (LV) dysfunction is one of the most prevalent complications of SSc heart involvement. In an analysis of 1141 Australian SSc patients with no history of secondary cause of LV dysfunction, 2.4% had LV ejection fraction (LVEF) <50% and 0.6% had LVEF <40%. Male sex, dcSSc, presence of peripheral oedema and pulmonary crepitations, tendon friction rubs and biopsy-proven myositis were all risk factors for LVEF < 50%. A subsequent analysis of the subgroup of patients with LVEF >50% and available LV global longitudinal strain (LV GLS) measurements (211 patients) showed that the prevalence of subclinical LV dysfunction, defined as LV GLS > -16%, was 20.9% (33).

Cardiac conduction abnormalities are common in patients with SSc. In a Swedish national patient register study of 1565 SSc patients and 16009 matched controls, SSc patients had a significantly higher cumulative probability of developing arrhythmias. In particular, the main risk factors for arrhythmia incidence were male sex (HR 1.8), age at index (HR 1.05) and PAH (HR 2.8). In addition, the risk of death was higher in SSc patients with incident arrhythmia (HR 2.2) (34). Moreover, Delliaux *et al*. explored the role of heart rate variability (HRV), a marker of sinus node autonomic dysfunction, in the distinction between dcSSc and lcSSc: dcSSc patients had a higher median HR both in decubitus and in orthostatic position and lower HRV (35).

Pulmonary arterial hypertension

According to the 2022 ESC/ERS guidelines, PH is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg, and the threshold for pulmonary vascular resistance (PVR) has been lowered to 2 WU. In an analysis of the ASPIRE registry of 839 patients who underwent right heart catheterisation (RHC) between 2000 and 2020, 61 out of 839 were classified as having left heart disease-related PH (LHD-PH), 385 out of 839 as having PAH, and 231 as having chronic lung disease-related PH (CLD-PH). PAH and CLD-PH patients had similar hemodynamic features, while LHD-PH patients had higher pulmonary arterial wedge pressure (PAWP) and cardiac index and lower PVR compared to PAH patients. PAH patients had a significantly higher median survival compared to CLD-PH patients (3.98 *vs*. 2.69 years), and the worst prognosis was seen in patients with combined fibrosis and emphysema syndrome. On multivariate analysis, male sex, age, and lower DLCO and 6-minute walking distance were associated with worse survival. Using the 2022 ESC/ERS guidelines definition, 616 out of 839 patients were classified as having precapillary PH, compared to 503 out of 839 patients classified as having precapillary PH using the 2015 ESC/ERS guidelines definition (mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 WU). In addition, patients with PVR ≤2 WU had a significantly better survival compared to patients with PVR between 2 and 3 WU (median 9.5 *vs*. 6.1 years), while no differences were seen in patients with PVR between 2 and 3 WU compared to patients with PVR between 3 and 4 WU. Among LHD-PH patients, 40 out of 61 were classified as combined pre- and postcapillary PH. In the entire cohort, patients with a PAWP ≤12 mmHg had higher PVR and lower DLCO compared to patients with a PAWP between 13 and 15 mmHg (36).

PAH is the most common form of PH in SSc and early diagnosis has a major impact on prognosis: DETECT and ASIG algorithms are the main tools for PAH screening. Erdogan *et al*. compared the RHC referral performance of DETECT, ASIG and ESC/ERS screening algorithms in a cohort of 81 SSc patients. Using the 2022 ERS/ESC definition of PAH, the authors found a sensitivity of 62.5% for ESC/ERS, 75% for DETECT, and 87.5% for ASIG, and a specificity of 95% for ESC/ERS, 82% for DETECT, and 87% for ASIG. Instead, using the 2015 ERS/ESC definition of PAH, sensitivity was 100% for all three algorithms, while specificity was 85% for ESC/ERS, 73% for DETECT, and 76% for ASIG algorithm (37). In an observational, cross-sectional study of the EUSTAR registry, Colalillo *et al*. analysed the diagnostic performance of DLCO and echocardiographic parameters in identifying patients with mPAP of 21 to 24 mmHg at RHC, who were defined borderline according to the previous 2015 ESC/ERS guidelines. The authors found that tricuspid annular plane systolic excursion/systolic PAP ratio (TAPSE/sPAP) <0.55 mm/mmHg was the parameter with the highest specificity (78.9%) and positive predictive value (50%), while DLCO < 80% was the parameter with the highest sensitivity (88.9%) and negative predictive value (80%), but specificity and positive predictive value were very low (18.2% and 30.8%, respectively). After ROC curve analysis, the TAPSE/sPAP ratio had the higher AUC (0.653, 0.562–0.745) (38).

Cardiovascular magnetic resonance (CMR) is a valuable imaging modality for SSc-PAH and primary cardiac involvement. In patients with SSc-PAH classified as intermediate risk according to ESC/ERS guidelines, exercise CMR (Ex-CMR) may provide improved prognostic stratification. In a single-centre observational study involving 50 SSc patients with intermediate-risk PAH, resting CMR parameters, including indexed right ventricular end-systolic volume (RVESVi), myocardial T2, and indexed right atrial (RA) area, as well as peak Ex-CMR RVESVi and right ventricular ejection fraction, were associated with all-cause mortality in univariable Cox regression analysis. However, in stepwise Cox regression analysis, only peak Ex-CMR RVESVi emerged as an independent prognostic predictor, with an optimal threshold of <39 mL/m^2. Patients with a peak RVESVi <39

mL/m² demonstrated significantly better survival compared to those with a peak RVESVi >39 mL/m² (39).

Interstitial lung disease

SSc-ILD is nowadays the leading cause of death among SSc patients. Throughout 2024, much effort has been put into the early identification of patients with a high likelihood of developing progressive ILD. In particular, Kuwana *et al*. tried to develop a prediction model for progressive SSc-ILD based on the SENCSIS placebo cohort. Progressive SSc-ILD was observed in 86 out of 288 patients (29.9%) over a 52-week period. In univariable regression analysis, DLCO was the only variable associated with ILD progression. In the early/inflammatory subgroup of 155 patients, multivariable analysis identified lower DLCO, shorter disease duration, higher mRSS, ATA positivity, and absence of mycophenolate mofetil (MMF) use at baseline as independent predictors of progressive ILD. In this subgroup, the authors developed a predictive model for progressive SSc-ILD, achieving an apparent AUC of 0.75 (40). Similarly, Hui *et al*. tried to develop a prediction model for progressive SSc-ILD based on Chinese Rheumatism Data Center database. The authors selected a subgroup of 154 SSc patients with progressive ILD and identified 9 variables as predictors: age ≥50 years (HR 1.82), hyperlipidaemia (HR 4.05), dcSSc (HR 1.97), arthritis (HR 2.00), dyspnoea (HR 2.04), decreased serum IgA level (HR 2.39), ATA positivity (HR 1.95), and treatment with cyclophosphamide or MMF (HR 0.42) (41).

In a real-life study of the Zurich and Oslo cohorts of 386 patients with SSc-ILD, only 99 out of 386 were treated at baseline, while 74.3% were untreated. After multivariable analysis, patients with ACA (OR 6.75), corticosteroids treatment (OR 0.45), limited extent of ILD (OR 2.39), higher DLCO (OR 1.02) and longer disease duration (OR 1.04) were less likely to receive treatment at baseline. In untreated patients, dcSSc (HR 2.99) and extensive ILD (HR 2.65) were found to be predictors of ILD progression (42). When interpreting lung function tests, it is important to consider that patients with SSc often have unique involvement, such as microstomia, which can affect the quality of the FVC assessment. A study performed on 98 SSc patients showed that dcSSC, higher mRSS, ILD, ATA positivity, immunosuppressive treatment, flexion contractures of hands, microstomia and decreased chest expansion were associated with low quality FVC measurement and this limitation should be taken into account when evaluating single-patient spirometry curves (43).

Take-home messages

- Regression of skin fibrosis, measured by mRSS, correlates with reduced ILD progression and mortality in SSc. Tools like HFU and SWE offer increased sensitivity compared to mRSS (23, 24).
- Gastrointestinal involvement in SSc is frequent and significantly impacts quality of life, with symptoms like reflux, dysphagia, and abdominal distension. Gastrointestinal symptom severity is linked to mRSS and autonomic dysfunction (27, 28).
- Inflammatory arthritis and hand dysfunction are common in SSc, with progressive functional decline observed. Functional hand assessment is crucial, with tools like the CHFS (30).
- Cardiac involvement in SSc ranges from diastolic dysfunction to heart failure, with an elevated risk of arrhythmias. LV dysfunction and conduction abnormalities are common complications (33, 34).
- PAH in SSc demands early detection for improved outcomes. Screening algorithms like DETECT and ASIG aid in timely diagnosis. CMR enhances risk stratification in intermediate-risk patients (37, 39).

Treatment

Immunosuppressants

Immunosuppressive therapies have been used for decades as the mainstay to control the most severe organ complications in SSc such as ILD and skin involvement. In 2024, a wide range of studies on immunosuppressants in SSc were published, from multicentric real-life data on conventional synthetic DMARDs to announced trials on new biological ones. De Lorenzis *et al*. investigated the retention rate of MMF reporting real-world data from 554 SSc patients followed at nine academic centres. The 5-year MMF retention rate was 70.7%, with a discontinuation rate that stood at 6.5 per 100 patient-years, and a 5-year cumulative incidence of MMF-related adverse events of 19.6% (44). Rituximab (RTX) is another immunosuppressant widely used in SSc, and among its various indications there is also joint involvement. A recent case series reported that RTX and T-cell-targeted therapies appear to be a promising therapeutic option to control joint activity in patients with SSc overlapping with rheumatoid arthritis refractory to conventional synthetic DMARDs (45). However, a unanimous consensus on RTX dosage and frequency of administration has not yet been reached. In fact, a regimen derived from rheumatoid arthritis is often used with 1000 mg (2 weeks apart) every 6 months, while others prefer a haematological scheme of 375 mg/m² once per week for 4 weeks. In this context, an Austrian study recently proposed a new scheme of quarterly RTX infusions (500 mg at days 0 and 14 every 3 months), reporting data on 40 SSc patients treated for a median of 3.9 years. The authors observed improvement in skin involvement as assessed by mRSS and stabilisation of FVC, with no new or unexpected safety concerns (46). A randomised controlled trial (RCT= evaluating the optimal B-cell depletion regimen in SSc is needed. Finally, the DAISY study, which will evaluate the efficacy of anifrolumab in SSc, is arousing much interest. This drug is already approved for systemic lupus erythematosus, but many evidences clearly indicate that increased interferon signalling is also present in SSc. Anifrolumab is a fully-human IgG monoclonal antibody that targets the type I interferon receptor α, thus blocking downstream type I interferon signalling so to suppress the interferon gene signature. DAISY trial will be conducted on over 150 SSc patients and will last 2 years: the first year will be double-blind, placebo-controlled, while the second one will be open-label for all patients. A composite

score (Revised-CRISS-25) will be used as the primary endpoint, and changes in FVC and mRSS will be considered for secondary endpoints (47).

Antifibrotics

Since the publication of the SENSCIS study, the use of nintedanib (NIN) as an antifibrotic drug in SSc-related progressive pulmonary fibrosis has helped fill a therapeutic gap and has seen steady growth, to the point of being introduced in the recent EULAR guidelines (48). A recent *post-hoc* analysis of the SENSCIS trial and its open-label extension demonstrated that NIN is able to slow down the FVC decline also in the subset of progressive patients with limited cutaneous involvement (49). Post-marketing safety data collected over 9 years on more than 2800 SSc patients showed that NIN has a real-world safety profile comparable to that outlined in clinical trials (50). The importance of antifibrotic therapy is such that, in addition to new imaging methods to monitor its effect over time (51), the scientific community is starting to evaluate possible combination strategies with immunosuppressive drugs. In fact, in addition to the already known safe combination with MMF, a study reported positive efficacy and safety data regarding the combination of NIN and tocilizumab in 20 SSc patients with ILD (52). Finally, great expectations are arousing around nerandomilast, a novel phosphodiesterase-4 inhibitor whose efficacy on progressive pulmonary fibrosis associated with autoimmune diseases will be assessed in a phase III (FIBRONEER-ILD) trial (53).

Vasoactive therapies

Several papers were published in 2024 on the treatment of both macro- and microvascular involvement in SSc. Among the most remarkable ones on microcirculation, a large multicentric French study assessed the effect of vasodilators on cardiovascular outcomes on more than 1000 SSc patients over a 3-year period. The authors reported that sildenafil use was associated with a reduced incidence of diastolic dysfunction and impaired ejection fraction <50%, with no clear effect of sildenafil on the incidence of PAH. In contrast, no significant effects on diastolic dysfunction, impaired ejection fraction and incidence of PAH were observed for bosentan, iloprost or ACE inhibitors (54). Further research is needed on the utility of sildenafil as a therapeutic option in SSc cardiac involvement. When considering papers on SSc microangiopathy, a large Australian study on over 1200 SSc patients treated with calcium channel blockers (CCB) had the merit of reiterating on a very large cohort that CCBs have no efficacy in the healing or prevention of DUs (55). In contrast, selexipag, an oral prostacyclin agonist approved for PAH, has been reported to have beneficial effects on SSc microvascular involvement. Selexipag was administered to a small cohort of SSc patients with severe, refractory digital vasculopathy, and after twelve months of follow-up a sustained improvement in Raynaud's phenomenon and DUs healing rate was observed, paralleled by an increased peripheral blood perfusion as assessed by laser speckle contrast analysis (56). These promising results encourage the design of a new RCT to evaluate the effect of selexipag on SSc digital vasculopathy.

Other therapies

Autologous hematopoietic stem cell transplantation (AHSCT) is a therapy reserved for a subgroup of eligible SSc patients with rapidly progressive disease, especially in the event of failure of other first-line therapies. Compared to RTX and conventional immunosuppressive therapies, AHSCT has shown greater effectiveness in prolonging survival and inducing sustained remission in patients with rapidly progressive dcSSc. Specifically, AHSCT-treated patients exhibited a significantly lower probability of lung function decline and a significantly higher likelihood of achieving a revised EUSTAR Activity Index (REAI) score below 2.5 compared to those receiving RTX or conventional immunosuppressive therapies (57). However, the risk-benefit ratio must be carefully evaluated. A retrospective study comparing SSc patients who underwent AHSCT with those who met the eligibility criteria for AHSCT but received upfront combination therapy with MMF and RTX showed that, in rapidly progressive forms of SSc, immunosuppressive therapy demonstrated a better safety profile at 24 months (58). Infusion of CD19 chimeric antigen receptor (CAR) T cells after lymphodepleting preconditioning treatment is a promising new therapy that ideally could represent a paradigm shift in all connective tissue diseases, including SSc. To date, the treatment of approximately 10 cases of patients with severe diffuse SSc has been described. CAR T-cell therapy led to a depletion of antinuclear antibodies and a reduction of SSc-specific autoantibodies. More importantly, an improvement in lung involvement due to a reduction in the extent of ground-glass opacities on CT scans, as well as an improvement in skin involvement and global disease activity, as assessed by mRSS and REAI, was described. Of note, relatively low rates of cytokine release syndrome were observed and no immune effector cell-associated neurotoxicity syndrome events were identified (59, 60).

Finally, in 2024 interesting studies on the therapy of gastrointestinal involvement and malnutrition were also published. Based on some evidence suggesting a role for gastroesophageal reflux in the development of ILD, an Australian study on over 1600 SSc patients evaluated the impact of reflux therapies, specifically proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA), on ILD features and survival. Despite no associations were noted between reflux therapies and time to ILD development or ILD severity, treatment with PPI or H2RA was associated with improved survival in patients with ILD. Moreover, combination therapy with both a PPI and a H2RA was associated with a greater survival benefit than single agent therapy with PPI alone (61). Given the frequent coexistence of malnutrition as a comorbidity, correction of nutritional status is becoming one of the therapeutic goals in SSc. It has been demonstrated that in malnourished patients with SSc, a high-protein oral nutritional supplement significantly improved the nutritional status on the subjective global

assessment scale and on the body composition parameters assessed by bioelectrical impedance analysis (62).

Take-home messages

- MMF and RTX remain key treatments for SSc, with intriguing real-world retention rates for MMF and ongoing efforts to define optimal RTX dosing (44, 46). The DAISY trial is expected to clarify the role of anifrolumab in SSc therapy (47).
- NIN continues to demonstrate efficacy in slowing pulmonary function decline in SSc-ILD, with growing interest in combination therapies, including NIN with MMF or tocilizumab (49, 52).
- Sildenafil may reduce diastolic dysfunction in SSc (54), while selexipag shows potential for severe digital vasculopathy, warranting further randomised trials (56).
- AHSCT improves survival in aggressive SSc but carries risks (57, 58), while CD19 CAR T-cell therapy emerges as a promising novel approach with potential disease-modifying effects (59, 60).

Patient-reported outcomes

Most RCTs in SSc patients have dcSSc as the main entry criterion, therefore the development of patient-reported outcome measures (PROMs) specific to dcSSc patients is fundamental for constructing valid and effective RCTs. The majority of PROMs in SSc are designed to address specific disease manifestations, such as RP or hand disability, while PROMs focusing on patients' perceptions of global disease activity are less common. The EULAR Systemic sclerosis Impact of Disease (ScleroID) questionnaire is a PROM designed for the assessment of dcSSc patients. In a cohort of 152 dcSSc patients, ScleroID demonstrated good construct validity, with Spearman's correlation coefficients between ScleroID and SSc-HAQ, Health Assessment Questionnaire-Disability Index (HAQ-DI) and SF-36 physical score of 0.79, 0.72 and -0.69, respectively. ScleroID also showed good internal consistency (Cronbach's alpha 0.87), test-retest reliability (intraclass correlation coefficient 0.89) and sensitivity to change (SRM -0.63 in the improved subgroup and 0.48 in the worsened subgroup) (63).

Several PROMs have been developed to assess RP, the hallmark manifestation of SSc. In a recent multicentre study involving 420 SSc patients, the 27-item Assessment of Systemic Sclerosis-Associated Raynaud's Phenomenon (ASRAP) and its 10-item short form (ASRAP-SF) were validated. Both ASRAP and ASRAP-SF demonstrated strong internal consistency, with Cronbach's alpha values of 0.918 and 0.899, respectively, and high mutual correlation (rho=0.976). They also correlated well with the Scleroderma Health Assessment Questionnaire RP visual analogue scale (SHAQ RP VAS) (rho=0.719 and 0.727 for ASRAP and ASRAP-SF, respectively). However, both showed weaker correlations with RP attack duration (rho= 0.272 and 0.258), RP attack frequency (rho=0.504 and 0.421), pain intensity VAS (rho=0.555 and 0.575), and the HAQ-DI (rho=0.438–0.490). ASRAP scores were significantly higher in patients with discrete short-lived SSc-RP attacks, persistent digital ischaemic symptoms, a history of DUs or active DUs, and a history of calcinosis (64). Regarding DUs, Davison *et al*. developed a smartphone app for SSc patients to capture images of digital lesions and PROMs (such as Daily Pain Score, RP and DUs VAS, Disease Severity VAS, etc.), which is capable of extracting data from the photos and analysing size and colour to determine lesion healing status. All the patients were able to use the app despite the severity of hand disability, and there was a strong correlation between average gradients of manual and automated measurements over 30 days (65).

In a large analysis of the Scleroderma Patient-centred Intervention Network (SPIN) registry conducted in 2571 SSc patients, minimal detectable changes (MDCs) were evaluated on the HAQ-DI, the seven domains of the Patient-Reported Outcomes Measurement Information System-29 Profile version 2.0 (PROMIS 29v2.0), and the Patient Health Questionnaire (PHQ)-8. The smallest detectable change with 95% confidence was 0.41 points for the HAQ-DI, between 4.88 points and 9.02 points for the seven PROMIS-29v2.0 domains, and 5.16 points for the PHQ-8 (66). In the same SPIN cohort, Dal Santo *et al*. administered the Short Form of the PROMIS-29v2.0 physical function domain to 2385 SSc patients to assess physical function and identify risk factors associated with its impairment. Compared to the general population, the mean PROMIS-29v2.0 physical function score was significantly lower (43.7 ±8.9 *vs*. 50 ±10). In addition, physical function was mildly impaired in 21% of patients, moderately impaired in 33% and severely impaired in 4%. After multivariate analysis, the main risk factors associated with poor physical function were dcSSc, gastrointestinal involvement, DUs, severe small and large joint contractures, large joint contractures, ILD, PAH and smoking (67).

Take-home messages

- Validated PROMs, such as ScleroID and ASRAP, are crucial for assessing disease impact in dcSSc and RP. Smartphone apps also offer innovative ways to track DUs (63-65).
- SSc significantly impairs physical function, with dcSSc, gastrointestinal involvement, DUs, joint contractures, ILD, PAH, and smoking as key risk factors. Reliable PROMs, like PROMIS-29, help quantify these impacts and establish minimal detectable changes for clinical research (66, 67).

Conclusions

This narrative review highlights some of the most innovative studies published in 2024, reflecting the continuous efforts of researchers to better understand and manage the complexity of SSc. Significant advances have been made in elucidating disease pathogenesis, characterising organ involvement, and refining therapeutic strategies. The ultimate objective is to move towards precision medicine, enabling earlier diagnosis and personalised treatment tailored to each patient's trajectory. Achieving this goal is essential to improve prognosis, enhance survival, and ultimately optimise the quality of life of individuals with SSc.

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