Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITORS

Monique Hinchcliff

Dr. Monique Hinchcliff is Director of Clinical and Translational Research for Rheumatology, Allergy & Immunology at the Yale School of Medicine and the Director of the Yale Scleroderma Program. She received her medical degree from the Rosalind Franklin University Chicago Medical School and completed her medicine residency at Norwalk Hospital in Connecticut. She completed rheumatology fellowship training at Northwestern University Feinberg School of Medicine in Chicago, IL while earning a Master of Science degree in Clinical Investigation.

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Patient-reported outcomes in systemic sclerosis: insights into quality of life and disease burden

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Purpose of review
Assessing the impact of active therapy on how patients 'feel and function' is considered a necessary requirement by regulatory agencies for the approval of future treatments for SSc. In this context, patient-reported outcome measures (PROMs) have become a cornerstone of therapeutic assessment in randomized controlled trials (RCTs).

Recent findings
This narrative review will discuss a selection of main available PROMs used in SSc RCTs, with a specific focus on recently developed PROMs, highlight ongoing initiatives related to SSc-PROMs, and provide points to consider for future use of SSc-PROMs.

Summary
Several recent initiatives include a patient-centered approach [such as the Systemic Sclerosis-Associated Raynaud's Phenomenon (ASRAP), the MCQ (Mawdsley Calcinosis Questionnaire], the COAST (Clinical Outcome Assessments for Systemic Sclerosis Clinical Trials), and the CRISTAL (Combined Response index for scleroderma trials assessing limited systemic sclerosis) initiatives] to develop new PROMs and actively involve patient partners in each step of the process. Using a combined response index incorporating PROMs as the primary outcome measure in future SSc trials, such as the CRISS index for diffuse cutaneous SSc, could ensure that the perspectives of both physicians and patients would be incorporated to assess the efficacy of future interventions.

Keywords
patient partners, patient-reported outcome measures, randomized controlled trials, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by a triad of immune-mediated manifestations including widespread microangiopathy, inflammatory features, and fibrosis of the skin and internal organs such as lung [1]. SSc is the rheumatic disease with the highest individual mortality rate, mainly due to cardiopulmonary manifestations such as lung fibrosis [or SSc-related fibrotic interstitial lung disease (ILD)] and primary cardiac involvement [2]. Beyond this impact on survival, SSc also has a significant detrimental impact on health-related quality of life (HRQOL). All the domains of SSc can impact daily living, including general domains, such as fatigue or pain, and SSc-related specific domains such as gastro-intestinal manifestations or pulmonary symptoms [3]. SSc can notably impact hand function through several key manifestations from the SSc-pathogenic triad, including vasculopathy-related symptoms (Raynaud's phenomenon, digital ulcers, calcinosis), fibrosis (skin fibrosis/sclerodactyly, fibrotic tenosynovitis) and inflammatory features (inflammatory synovitis and tenosynovitis) [4–6].

Although the primary objectives of recent randomized controlled trials (RCTs) have mainly focused on physician-reported outcomes [such as modified Rodnan Skin Score (mRSS) for skin fibrosis [7]] or performance outcomes [such as forced vital capacity (FVC) for ILD [8]], assessing the impact of active therapy on how patients 'feel and function' is now considered a necessary requirement by

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KEY POINTS

- PROMs have become a cornerstone of treatment evaluation in SSc trials, and impact of medication on PROMs is a requisite from regulatory agencies for drug approval.
- Several recent initiatives include a patient-centered approach (such as the ASRAP, the MCQ, the COAST, and the CRISTAL initiatives) to develop new PROMs and actively involve patient partners in each step of the process.
- Using a combined response index incorporating PROMs as the primary outcome measure in future SSc trials could ensure that the perspectives of both physicians and patients would be incorporated to assess the efficacy of future interventions.

regulatory agencies for the approval of future treatments for SSc. In this context, patient-reported outcome measures (PROMs) have become a cornerstone of therapeutic assessment in RCTs. PROMs allow the evaluation of the impact of an intervention (both pharmacological and nonpharmacological interventions) on disease burden directly by the patients, either through the assessment of symptoms experience (i.e. severity or frequency of symptoms) or through the assessment of symptoms impact on daily living (i.e. ability of performing tasks in the everyday life).

For SSc trials, several PROMs are available including PROMs specifically developed for SSc patients (such as the SSPRO for skin manifestations [9]), existing generic PROMs modified to assess SSc manifestations in addition to manifestations already included in the initial PROMs (such as the scleroderma HAQ-DI or sHAQ-DI [10]), generic PROMs unchanged but validated in SSc populations (such as the PROMIS-29 [11] and the Connor–Davidson Resilience Scale [12]), specific PROMs developed for other diseases but validated in SSc patients (such as the St George questionnaire for ILD [13]). Despite this effort of developing and including PROMs for SSc patients in RTCs, some important neglected domains such as calcinosis [14▪], still lack validated PROMs. Ongoing initiatives intend to fill this gap [15].

This narrative review will discuss a selection of main available PROMs used in SSc RCTs, with a specific focus on recently developed PROMs, highlight ongoing initiatives related to SSc-PROMs, and provide points to consider for future use of SSc-PROMs. The literature search was conducted using PubMed/MEDLINE with the keywords 'systemic sclerosis' AND 'patient-reported outcome'. This is a narrative review and not a systematic review. Article selection was based on the authors' expertise and subjective judgment of the most recent and relevant publications, and it does not aim to provide a comprehensive overview of all existing SSc-PROMs. Priority was given to RCTs and articles published in the past 18 months as per editorial guidelines.

MAIN AVAILABLE PROMS USED IN RECENT SYSTEMIC SCLEROSIS-RANDOMIZED CONTROLLED TRIALS

Seven RTCs with published results (main analyses or post hoc analyses) in the past 18 months used patient-reported outcome as primary or secondary outcomes (Table 1) [16,17▪,18▪,19,20▪▪,21–23].

Assessment of overall disease and disease impact in using patient-reported outcome measures in recent published randomized controlled trials

Health Assessment Questionnaire – Disability Index (HAQ-DI) and scleroderma-HAQ (SHAQ) were the most frequently used questionnaire in these trials (in five out of seven trials). HAQ-DI is a self-administered questionnaire focusing on functional impact of a rheumatic diseases in daily living. HAQ-DI includes 20 questions assessing the level of functional ability, including questions on fine movements of the upper extremities, locomotor activities of the lower extremities, and activities that involve both the upper and lower extremities. The SHAQ adds six visual analog scales (from 0 to 100) assessing scleroderma-related domains: gastrointestinal involvement, respiratory symptoms, Raynaud's phenomenon, digital ulcers, and overall impact of pain and discomfort on daily function. Although it was developed almost 30 years ago, SHAQ is still the most utilized PROMs to assess overall disease impact on HRQOL [24]. SF-36 was also frequently used to evaluate HRQOL [25]. It is a self-administrated questionnaire based on eight scales exploring physical functioning, role physical, general health, vitality, social functioning, role of emotional and mental health. Patient-global assessment and global impression of change is also largely used, despite marked heterogeneity in the wording and measurement scales of these global assessment methods and their lack of validation in SSc [26].

Patient-reported outcome measures assessing specific systemic sclerosis-related domains

Beyond these PROMs assessing overall disease impact, SSc-specific domains were also explored in

Table 1. Patient-reported outcome measures used in recent randomized controlled trials

RCTs with related articles published in the past 18 months	Patient-reported outcome measures	Domains
Fretheim *et al. The Lancet Rheumatology*, 7(5), e323–e332. https://doi.org/10.1016/S2665-9913(24)00334-5 Reference [16]	UCLA-SCTC GIT 2.0 Score. Available at: https://www.rws.com/industries/life-sciences/instruments/ucla-sctc-git-2-0/	Overall GI assessment
	Faecal incontinence quality of life scale	Fecal incontinence
	Patient global assessment	Overall disease
	HAQ DI	Health-related quality of life in rheumatic diseases
	EuroQol Five Dimensional (EQ-5D)	Health-related quality of life
	Fatigue visual analogue scale	Fatigue
Kersten *et al. Rheumatology (Oxf)*, 64(3), 1261–1269. https://doi.org/10.1093/rheumatology/keae156 Reference [17▪]	sHAQ DI	Health-related quality of life in rheumatic diseases including six scleroderma-related VAS
	Medical Outcomes Study 36-item Short Form	Health-related quality of life
	UCLA-SCTC GIT 2.0 Score	Overall GI assessment
	Fatigue visual analogue scale	Fatigue
Tornling *et al. Rheumatology (Oxf)*, 64(2), 704–713. https://doi.org/10.1093/rheumatology/keae049 Reference [18▪]	Number of Raynaud's attacks, length (minutes), pain using Numerical Rating scales (NRS 0-10)	Raynaud's phenomenon
	Raynaud's condition score	Raynaud's phenomenon
	Patient global impression of Change	Overall assessment
	ASRAP 39-item beta version and 27-item version	Raynaud's phenomenon
Distler *et al. The Lancet Rheumatology*, 5(11), e660–e669. https://doi.org/10.1016/S2665-9913(23)00238-2 Reference [19]	HAQ DI	Health-related quality of life in rheumatic diseases
	sHAQ DI	Health-related quality of life in rheumatic diseases including six scleroderma-related VAS
	Medical Outcomes Study 36-item Short Form	Health-related quality of life
	Patient global assessment	Overall disease
	UCLA-SCTC GIT 2.0 Score	Overall GI assessment
	Patient-Reported Outcomes Measurement Information System-29	Health-related quality of life
	Patient assessment of Raynaud's phenomenon including pain, numbness and tingling during attacks	Raynaud's phenomenon
	Raynaud's condition score	Raynaud's phenomenon

Table 1 (*Continued*)

RCTs with related articles published in the past 18 months	Patient-reported outcome measures	Domains
Murphy *et al. Arthritis Care & Research*, 76(3), 318–327. https://doi.org/10.1002/acr.25253 References [20■■,21]	Functional Assessment of Chronic Illness Therapy-Fatigue short form (FACIT-F)	Fatigue
	PROMIS-Pain Interference short form	Pain
	PROMIS-Depression short form	Depression
	10-item Connor-Davidson Resilience Scale	Resilience
	Patient global impression of Change	Overall assessment
	PROMIS-Anxiety short form	Anxiety
	PROMIS-Sleep Disturbance short form	Sleep
	PROMIS-Social Isolation	Social insertion
	Positive and Negative Affect Schedule	Multimodal emotional impact
	Fatigue Severity Scale	Fatigue
Allanore *et al. Rheumatology (Oxf)*, 63(3), 639–647. https://doi.org/10.1093/rheumatology/kead280 References [8,22]	St. George's Respiratory Questionnaire (SGRQ)	Cardiopulmonary involvement
	Functional Assessment of Chronic Illness Therapy (FACIT)–Dyspnea questionnaire	Cardiopulmonary involvement
	HAQ DI	Health-related quality of life in rheumatic diseases
Kuwana *et al. Modern Rheumatology*, 34(3), 530–540. https://doi.org/10.1093/mr/road068 References [7,23]	HAQ DI	Health-related quality of life in rheumatic diseases
	sHAQ DI	Health-related quality of life in rheumatic diseases including six scleroderma-related VAS
	St. George's Respiratory Questionnaire (SGRQ)	Cardiopulmonary involvement
	Functional Assessment of Chronic Illness Therapy-Fatigue short form (FACIT-F)	Fatigue
	Patient global assessment	Overall disease

HAQ-DI, Health Assessment Questionnaire – Disability Index; SHAQ, scleroderma-HAQ; UCLA SCTC GIT 2.0, University of California Scleroderma Clinical Trial Consortium Gastrointestinal Instrument.

recent trials, such as gastrointestinal involvement, assessed in the recent trials with the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Instrument (UCLA SCTC GIT 2.0). The UCLA SCTC GIT 2.0 is a validated PROM assessing gastrointestinal tract symptoms and HRQOL in SSc [27]. This 34-item instrument has seven scales – reflux, distention or bloating, diarrhea, fecal soilage, constipation, emotional well being, and social functioning – and a total gastrointestinal tract score. It takes 5–6 min to complete. To date, it is the most commonly used PROM in RTCs to assess SSc-related gastrointestinal involvement. It has been translated in 76 different languages and is available for use at https://www.rws.com/industries/life-sciences/instruments/ucla-sctc-git-2-0/. Raynaud's phenomenon is the hallmark feature of SSc with a significant detrimental impact on HRQOL. One of the VAS from the SHAQ assesses interference in

daily activities as a result of Raynaud's phenomenon and is considered feasible, reliable, and valid [28]. The Raynaud's condition score (RCS) is another tool used in recent trials to assess Raynaud's phenomenon. RCS assesses the level of difficulty experienced because of Raynaud's phenomenon each day (from 'no difficulty' to 'extreme difficulty') on a 0–100 mm Visual Analog Scale (VAS) or an 11-point numeric rating scale, the score being calculated by averaging the daily score on the considered time period (generally 1–2 weeks). There are ongoing initiatives to develop new tools for the assessment of Raynaud's phenomenon, including the Systemic Sclerosis-Associated Raynaud's Phenomenon (ASRAP), a 27 item-long questionnaire based on the results from focus groups of patients with SSc. ASRAP and the 10-item-long Short form of ASRAP are valid and reliable novel PROMs showing good correlation with reference instruments for assessing disability, hand function, pain, and global health assessment in SSc [29▪▪].

NEW PATIENT-REPORTED OUTCOME MEASURES RECENTLY DEVELOPED

Considering the importance of 'feel and function' in the approval of future therapies, several new PROMs have been developed using patient-centered approaches, including focus groups and cognitive debriefing to ensure content and face validity of these instruments.

Overall assessment

A PROM evaluating overall disease impact was developed through an international multicenter initiative under the aegis of EULAR (European League Against Rheumatisms). Relevant domains were chosen and prioritized by patient partners with SSc. The resulting Systemic Sclerosis Impact of Disease (ScleroID) questionnaire was subsequently weighted and validated using the OMERACT filter [which includes major psychometric properties such as truth (encompassing content, face, and construct validity), discrimination and feasibility] in an observational cohort study. This ScleroID questionnaire includes 10 health dimensions and has excellent reliability and good sensitivity to change, superior to all comparators assessed in the validation study [SSc-Health Assessment Questionnaire (HAQ), EuroQol Five Dimensional (EQ-5D), Short Form-36 (SF-36)] [30▪▪]. The psychometric properties of the ScleroID were also recently assessed in patients with dcSSc, using the same comparators as anchors. In this study, ScleroID showed good construct validity, good consistency, and excellent test–retest reliability [31]. The ScleroID only had moderate sensitivity to change in dcSSc, but it was superior to the comparators (HAQ, EQ-5D, and SF-36) [31].

Composite measures incorporating patient-reported outcome measures

Several recent combined response indices or activity indices assess overall disease also include PROMs in their scoring strategy. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis (ACR-CRISS) is a two-step process for use in a clinical trial that assesses overall disease improvement in patient with early dcSSc. In step 1, patients who develop new onset of renal crisis, new onset or worsening of lung fibrosis, new onset of pulmonary arterial hypertension, or new onset of left ventricular failure are considered as not improved. For those who do not meet step 1, a probability score is calculated that incorporates changes in two clinician-reported outcomes (mRSS, physician global assessment), one performance outcome (FVC% predicted on pulmonary function tests), and two PROMs directly assessing how patients feel and function (HAQ-DI and patient global assessment) [32]. This index was secondly revised to limit some ceiling effect, particularly encounter in RCTs with background immunosuppressive therapy, and to change the probability score from step 2 into the proportion of participants who improved by a predefined percentage (25%, 50%, or more) in at least three out of five core measures (in the initial revision from 2021 [33]), providing an equal weight to each step 2 component and making the results less difficult to interpret [33]. The revised CRISS-25% has been incorporated as the primary outcome in an ongoing phase III trial evaluating the efficacy of anifrolumab, an interferon-type I receptor antagonist, in patients with diffuse or limited cutaneous SSc [34]. In this trial, to be considered a responder, a patient must show improvement in at least two core step-2 measures, without worsening in more than one core step-2 measure, and without experiencing any step-1 event. This strategy ensures that no single outcome can drive the overall result of the combined index, requiring a general improvement to qualify as a responder, while accounting for potential heterogeneity in patient responses.

The Scleroderma Clinical Trials Consortium (SCTC) recently developed a disease activity index (SCTC AI) including 24 items in its preliminary version. The SCTC AI explores nine domains and showed a predictive value on overall disease trajectory in an Australian cohort [35▪▪]. In this activity index, in case of unavailable clinician-reported outcomes or performance outcomes, PROMs are proposed as an alternative, to assess worsening of skin

and pulmonary involvement. Raynaud's phenomenon and gastrointestinal involvement are also assessed using PROMs, directly evaluating feeling and function.

Domain-specific patient-reported outcome measures

Skin involvement, ranging from oedema, skin thickening, and skin inflammation with pruritus, is a hallmark feature of the SSc, and many trials use the mRSS, a clinician-reported outcome, to assess skin involvement in SSc. The patients' perspective on SSc-related skin disease may have been neglected in trials in the past and the Scleroderma skin PRO (SSPRO) was developed based on patient input to fill this gap [9]. SSPRO consists of 18 items within four domains, that is, physical effects, physical limitations, emotional effects, and social effects, assessing patient's experience in the past 4 weeks. SSPRO includes important aspect of SSc-related skin involvement, which are not covered by mRSS assessment, such as itchiness or discoloration. The psychometric properties of the SSPRO were assessed in an observational cohort [9]. SSPRO has face, content, and construct validity, it is complementary to mRSS and is now included in several SSc-RCTs.

Calcinosis refers to calcium hydroxyapatite depositions in soft tissues, not only in skin but also in other structures such as joint or the synovial membrane. Calcinosis may partly result from SSc-related vasculopathy [36]. Calcinosis is reported in one-third of patients with SSc and can induce flares characterized by skin inflammation, digital ulcers, or calcinosis-related synovitis or tenosynovitis [37]. The Mawdsley Calcinosis Questionnaire (MCQ) is the first SSc-specific PROM assessing calcinosis experience [14▪]. The MCQ was constructed in accordance with the Food and Drug Administration (FDA) guidance, engaging patient partners to form question-item options from relevant concepts derived from focus groups and then field-tested with SSc patients from several nationalities. The latest published version of the MCQ consists of a two-part questionnaire [14▪]. The first part (part A) assesses the number of calcinosis and calcinosis-related complications as reported by the patient, and the second part (part B) assesses calcinosis impact and interference on HRQOL, as well as the severity of calcinosis-related symptoms using 17 numerical scales ranging from 0 to 10. The psychometric properties of the MCQ are still to be evaluated, but this new PRO may help foster research and clinical trials assessing new treatments for SSc-related calcinosis, which is still a neglected area of research despite the major impact of this manifestation on HRQOL [38,39].

Hand involvement is a major aspect of SSc experience, as major symptoms of the disease mostly express in the hands in a majority of patients, including manifestations such as Raynaud's phenomenon, digital ulcers, calcinosis, sclerodactyly, or synovitis/tenosynovitis. Regarding digital ulcers, the Hand Disability in Systemic Sclerosis–Digital Ulcers (HDISS-DU) patient-reported measure has been developed to evaluate the impact of digital ulcers on hand function [6]. Digital ulcer's impact on function was favored over symptoms experience or severity. The HDISS-DU was developed using qualitative concept-elicitation interviews and blinded data from two randomized, controlled, phase 3 trials in patients with SSc-DUs [40]. The HDISS-DU demonstrated excellent internal consistency and test–retest reliability, with satisfactory construct validity. The HDISS-DU was also highly responsive to change in digital ulcer severity. Beyond digital ulcers, although the Cochin Hand function scale has been validated in patients with SSc [41], a new scale called the Hand scleroderma lived Experience (HAnDE) scale has been recently developed, to assess the overall impact of SSc on hand function [42]. This new PROM includes 16 scales (2 scales out of 18 were removed after psychometric analyses) ranging from 0 to 4 and assessing both symptom severity (dryness, skin thickening, and pain) and symptom impact (functional, aesthetic, relational, existential, and emotional impact). Internal consistency of the 16-item version was excellent (Cronbach's alpha = 0.946). Construct validity was also considered very good [42].

ONGOING INITIATIVES FOR FUTURE SYSTEMIC SCLEROSIS-RELATED PATIENT-REPORTED OUTCOME MEASURES

Beyond the already discussed ASRAP and MCQ, there are other ongoing initiatives for the construction of PROMs in SSc. Two initiatives following a similar methodology are currently in development, the COAST (Clinical Outcome Assessments for Systemic Sclerosis Clinical Trials) and CRISTAL (Combined Response index for scleroderma trials assessing limited systemic sclerosis) PROM initiatives [15]. Both projects utilize a patient-centered approach using the following steps: qualitative concept elicitation interviews or focus groups [3], concept mapping analysis to identify bothersome domains from the patients' perspectives, concept prioritization through mixed methods analysis and using disease expert input, developed the item pool by utilizing existing resources, item pool reduction through clinical and research expert review, and candidate PROM production.

The COAST project aims to create a robust SSc-specific PROM for early SSc clinical trials, that could be used for patients with dcSSc or with lc/ssSSc [43]. Two candidate measures were produced in the COAST initiative: COAST Symptoms and Side Effects Questionnaire (COAST SSEQ), a 33-item candidate measure covering 11 domains and 27 concepts for clinical trials, and COAST Function and Life Quality Questionnaire is a 20-item candidate measure covering 8 domains and 17 concepts as a complementary measure, more focused on symptoms impact and interference. The COAST SSEQ is being incorporated in the CONQUEST trial for psychometric validation (NCT06195072 on clinicaltrials.gov).

The CRISTAL project is an international initiative, which aims to create a combined response index for lcSSc for use in clinical trials (the CRISTAL index) [44]. A key milestone of CRISTAL is the development of a novel PROM to assess the most common and/or bothersome symptoms experienced by patients with lcSSc [15]. The overall objective of this initiative is to foster research on lcSSc, a frequent but neglected subset of the disease. The final preliminary CRISTAL PROM includes 37 items assessing symptom experiences reflecting 4 general (including Fatigue and pain) and 8 lcSSc-specific domains (from Raynaud's phenomenon to digital ulcer and ILD), with a recall period of 7 days. The psychometric properties of this CRISTAL PROM are currently being investigating in a multicenter prospective study under the aegis of the SCTC.

CONCLUSION: POINTS TO CONSIDER FOR THE USE OF PATIENT-REPORTED OUTCOME MEASURES IN SYSTEMIC SCLEROSIS

PROMs have become a cornerstone of treatment evaluation in SSc trials, and impact of medication on PROMs is a requisite from regulatory agencies for drug approval. Several recent initiatives include a patient-centered approach (such as the ASRAP, the MCQ, the COAST, and the CRISTAL initiatives) to develop new PROMs and actively involve patient partners in each step of the process. Innovative initiatives also propose the use of digital application to foster home-based measurements, including completion of PROMs in combination with objective measures such as photographs of digital ulcers (SALVE project: Scleroderma App for Lesion Verification) [45]. The use of such electronic devices may be limited due to difficulties related to hand function but the first results from the SALVE project and other studies suggest that even patients with severe hand involvement and digital ulcers are able to properly complete the PROM using their device [46].

The use of PROMs in clinical trials may also face the challenge of a potential high placebo effect, which may especially be a concern for manifestations that are closely linked to emotional well being, such as Raynaud's phenomenon, which can be triggered by stress and emotions. To address this limitation, combined responses indices, such as the revised CRISS for dcSSc [33], have been developed. These indices integrate clinician-reported outcomes, performance outcomes, and PROMs, thereby combining subjective and objective measures to provide a more comprehensive assessment and overcome such a problem. Using a combined response index as the primary outcome measure in future SSc trials could ensure that the perspectives of both physicians and patients would be incorporated to assess the efficacy of future interventions.

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Conflicts of interest

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Unraveling the relationship between disordered sleep and systemic sclerosis outcomes

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Purpose of review
This review aimed to synthesize the current knowledge regarding the prevalence, underlying mechanisms, and clinical implications of sleep disturbances in patients with systemic sclerosis (SSc). Furthermore, it highlights the potential for targeted interventions to address sleep dysfunction and improve overall disease management and patient quality of life.

Recent findings
Sleep disturbances, including poor sleep quality, insomnia, sleep apnea, and restless leg syndrome, are common in patients with SSc, with multiple contributing factors such as immune activation, fibrosis, pain, and gastrointestinal symptoms. However, comprehensive assessment methods and targeted treatments for sleep disorders in this population remain limited. Evidence suggests a close association between sleep disruption and disease severity or progression, with inflammatory cytokines (e.g., IL-6 and TNFα) implicated in sleep and SSc pathophysiology.

Summary
Sleep disorders are an under-recognized but significant burden in SSc, driven by complex interactions among disease manifestations and psychological and physiological factors. Early comprehensive assessment and integrated management of sleep disturbances and underlying SSc symptoms may improve patient outcomes.

Keywords
scleroderma and related disorders, sleep disorders, sleep disturbance, sleep quality, systemic sclerosis

INTRODUCTION

Research has focused on physical manifestations and internal complications, but sleep disturbances are a significant, overlooked burden [1,2]. This study examines sleep abnormalities in systemic sclerosis (SSc), their causes, their effects on clinical outcomes, and management options.

While sleep is an essential process, its exact functions are unknown but likely include energy conservation, cellular repair from damage, memory consolidation, facilitating cognition, enhancing immunity, and maintaining normal metabolism [3]. Sleep consists of two stages: nonrapid eye movement (NREM) and rapid eye movement (REM). NREM is subdivided into NREM1, NREM2, and NREM3, whereas REM is subdivided into phasic and tonic. NREM1 is light sleep. Typically, NREM1 accounts for 5% of total sleep time. NREM2 is a deeper sleep that continues from NREM1 sleep and accounts for 50% of total sleep time. NREM 3 is known as slow-wave sleep, the deepest sleep. Slow wave sleep usually refers to the slow, high-amplitude brain waves seen in electroencephalography (EEG) recordings—especially during deep sleep—and is a marker of synchronization in neuronal activity, indicating restorative sleep. Among adult humans, NREM1, NREM2, NREM3, and REM sleep account for 5%, 45–50%, 20–25%, and 20–25% of total sleep time, respectively. When sleep occurs, the sleep cycle starts with NREM1 and progresses to deeper sleep, that is, NREM2, NREM3, and REM sleep. Each sleep cycle lasts 90–110 min. Hence, sleep comprises 4–5 cycles. The first REM sleep is short but lengthens later in the night [4].

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KEY POINTS

- Sleep disorders are highly prevalent and frequently underdiagnosed in patients with systemic sclerosis (SSc).
- The causes of sleep disturbances in SSc are multifactorial, involving immune dysregulation, organ fibrosis, inflammation, and related symptoms, i.e., pain and gastrointestinal issues.
- Comprehensive assessment and management of sleep disorders are important for improving the quality of life in patients with SSc; however, disease-specific guidelines remain elusive.

EPIDEMIOLOGY OF SLEEP DISORDERS IN SYSTEMIC SCLEROSIS

Sleep disorders categorization

Sleep disorders are categorized using the International Classification of Sleep Disorders, third edition (ICSD-3) [5▪▪], including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders (Table 1).

Prevalence of sleep disorders in systemic sclerosis

Sleep disorders are prevalent among individuals with SSc, although their rates depend on the population studied, assessment methods, and definitions of sleep disorders. Insomnia, obstructive sleep apnea (OSA), excessive daytime sleepiness, restless legs syndrome (RLS), and poor overall sleep quality have all been frequently documented in patients with SSc. Most studies evaluated sleep quality using subjective tools (questionnaires), while some used objective tools, such as polysomnography (PSG), for sleep disorder detection and diagnosis. However, no study has investigated the epidemiology of parasomnia and sleep-related breathing disorders other than OSA. The prevalence of poor sleep quality in SSc ranged from 55–90%, depending on the study method, study population, and number of participants [1,2,6,7–10,11▪▪,12▪13▪]. While the prevalence of insomnia was ~4% [11▪▪], daytime sleepiness, sleep apnea by PSG, and RLS was 6.8–20% [11▪▪,12▪], 29–53.8% [14,15▪], and 22–40.7%, respectively [6,16]. Sleep disorders among SSc patients vary, underscoring the diversity of sleep-related issues and assessment methods (Table 2).

FACTORS ASSOCIATED WITH SLEEP DISORDERS IN SYSTEMIC SCLEROSIS

Several parameters are implicated in sleep disorders in SSc; however, the greater the degree of organ fibrosis and vasculopathy, the greater the deleterious effects on sleep. Limitations of mouth opening, esophageal dysmotility, gastroesophageal reflux (GERD) [6], interstitial lung disease (ILD), and steroid treatment [17] may increase sleep problems. A study of cardiovascular autonomic control and sleep quality revealed a significant negative correlation between sleep quality evaluated by Pittsburgh Sleep Quality Index (PSQI) and cardiovascular parameters derived from heart rate variability analysis of electrocardiogram recordings. Specifically, lower sleep quality was associated with alterations in low-frequency bands – an index of sympathetic modulation and baroreceptive activity – and high-frequency bands – an index of parasympathetic modulation that is synchronous with respiration [10]. This may indicate that autonomic control affects sleep quality. Sleep disorders (sleep apnea) have also shown a correlation with ILD, but their correlation with lung function, as assessed by spirometry, has not been proven [18,19▪]. The high prevalence of sleep apnea in ILD may be caused by increased upper airway resistance and reduced upper airway stability related to decreased lung volume in restrictive lung disease [18]. The potential factors associated with various sleep disorders in SSc are presented in Table 3.

Although several studies have explored the burden of sleep disorders in SSc, internal factors such as psychological problems (anxiety, depression), genetic factors, coexisting comorbidities, and environmental and external factors such as temperature, noise, brightness, humidity, air quality or air pollution, and medications that may affect sleep quality have not been thoroughly investigated [20▪].

PATHOPHYSIOLOGICAL LINKS BETWEEN SYSTEMIC SCLEROSIS AND SLEEP DISORDERS

Sleep disorders in SSc are complex and have multifactorial pathophysiology. The complex interplay between vascular dysfunction, inflammation, and fibrosis directly and indirectly affects sleep architecture. Vascular abnormalities, particularly pulmonary hypertension and digital ulcers, contribute to sleep-disordered breathing and chronic pain. Inflammatory processes induce fatigue and exacerbate pain perception, further compromising sleep quality. Fibrosis, including chest wall restriction, ILD, and cutaneous involvement (resulting in pruritus and body image concerns), collectively generates nocturnal

Table 1. Sleep disorders categorized according to the ICSD-3 [5▪▪]

Section	Subsection	Definition
Insomnia	Chronic insomnia disorder	Difficulty in initiating or maintaining sleep lasting at least three months
	Short-term insomnia disorder	Insomnia symptoms last less than three months
	Other insomnia disorders	Insomnia that does not meet criteria for chronic or short-term insomnia
Sleep-related breathing disorders	Obstructive sleep apnea disorders	Repeated collapse of the upper airway during sleep, causing breathing pauses
	Central sleep apnea syndrome	Breathing pauses during sleep due to lack of respiratory effort
	Sleep-related hypoventilation disorders	High carbon dioxide levels during sleep due to insufficient ventilation
	Sleep-related hypoxia disorder	Sleep-related low oxygen levels not fully explained by apnea or hypoventilation
Central disorders of hypersomnolence	Narcolepsy type 1	Excessive daytime sleepiness with cataplexy and low hypocretin levels
	Narcolepsy type 2	Excessive daytime sleepiness without cataplexy and normal hypocretin levels
	Idiopathic hypersomnia	Persistent excessive sleepiness without known cause
	Kleine-Levin syndrome	Recurrent episodes of excessive sleep, eating, and behavioral changes
	Hypersomnia due to a medical disorder	Excessive sleepiness caused by a medical condition
	Hypersomnia due to a medication or substance	Excessive sleepiness caused by drugs or substances
	Hypersomnia associated with psychiatric disorders	Excessive sleepiness related to psychiatric illness
	Insufficient sleep syndrome	Chronic insufficient sleep leading to excessive daytime sleepiness
Circadian rhythm sleep-wake disorders	Delayed sleep-wake phase disorder	Sleep schedule is delayed, leading to late sleep onset and wake times
	Advanced sleep-wake phase disorder	Early sleep onset and early morning awakening
	Irregular sleep-wake rhythm disorder	Lack of a clear sleep-wake cycle, with fragmented sleep
	Non24-h sleep-wake rhythm disorder	Daily sleep-wake rhythm lengthens, common in totally blind individuals
	Shift work disorder	Sleep disturbances associated with work schedules outside normal hours
	Jet lag disorder	Sleep disturbances due to crossing multiple time zones
	Circadian sleep-wake disorder not otherwise specified	Circadian rhythm disorder that does not fit specific categories
Parasomnias	Nonrapid eye movement-related parasomnias	Undesirable events occurring during NREM sleep, such as sleepwalking or night terrors
	Rapid eye movement-related parasomnias	Undesirable events during REM sleep, like REM sleep behavior disorder or nightmares
	Other parasomnias	Parasomnias not classified as NREM or REM-related

Table 1 (*Continued*)

Section	Subsection	Definition
Sleep-related movement disorders	Restless leg syndrome	Urge to move legs, usually accompanied by uncomfortable sensations, worse at night
	Periodic limb movement disorder	Repetitive limb movements during sleep, disrupting rest
	Sleep-related leg cramps	Sudden, intense leg pain or cramps during sleep
	Sleep-related bruxism	Teeth grinding or jaw clenching during sleep
	Sleep-related rhythmic movement disorder	Repetitive movements (e.g., head banging) typically seen in children during sleep
	Benign sleep myoclonus of infancy	Brief muscle jerks in infants during sleep, typically benign
	Propriospinal myoclonus at sleep onset	Sudden muscle jerks involving trunk at sleep onset
	Sleep-related movement disorder due to a medical disorder	Movement disorder during sleep caused by a medical condition
	Sleep-related movement disorder due to a medication or substance	Movement disorder during sleep caused by drugs or substances
	Sleep-related movement disorder, unspecified	Movement disorder during sleep that does not fit other classifications
Other sleep disorders	Fatal Familial insomnia	Rare genetic disorder causing progressive insomnia and neurodegeneration
	Sleep-related epilepsy	Seizures that predominantly occur during sleep
	Sleep-related headaches	Headache attacks that predominantly occur during sleep or on awakening
	Sleep-related laryngospasm	Sudden closure of the vocal cords during sleep, causing breathing difficulty
	Sleep-related gastroesophageal reflux	Acid reflux episodes that occur predominantly during sleep
	Sleep-related myocardial ischemia	Reduced blood flow to the heart muscle occurring during sleep

NREM, nonrapid eye movement; REM, rapid eye movement.

discomfort and psychological distress. These factors ultimately affect sleep quality. The pathophysiological mechanisms of sleep disorders in SSc are presented in Fig. 1. A study revealed that patients with SSc showed significantly elevated arousal levels and periodic limb movements compared to healthy controls [15▪]. These physiological disruptions are recognized as alterations in autonomic nervous system functioning; therefore, autonomic dysfunction might play a role in contributing to the underlying mechanisms of sleep disturbances in SSc [15▪].

Pro-inflammatory cytokines have been linked to sleep disturbances in connective tissue diseases such as SSc. Key inflammatory cytokines associated with sleep disorders include interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β), interleukin-4 (IL-4), and transforming growth factor beta (TGFβ) [21▪]. IL-6 plays multiple roles and is linked to depression, daytime sleepiness, and hormonal dysregulation, whereas TNFα and IL-1β are associated with restless leg syndrome (RLS), and IL-4 and TGFβ are inhibitors of nonrapid eye movement (NREM) sleep [21▪]. In general, pain can result in sleep deprivation and depression. Sleep deprivation is also associated with increased IL-6, TNFα, and IL-1β levels, and depression is bidirectionally associated with IL-6. Elevated IL-6 and TNF-α levels have been associated with daytime sleepiness, poor sleep quality, and OSA [22]. IL-6 is associated with increased adrenocorticotropic hormone and cortisol levels, leading to poor sleep quality [21▪]. Steroid treatment may result in insomnia [17], and smoking contributes to the risk of poor sleep quality [23] and OSA [24]. Genetic polymorphisms of proinflammatory cytokines, particularly IL-6 and IL-1β, have also been reported to be associated with sleep problems (Fig. 2).

Table 2. Prevalence of sleep disorders in patients with SSc

Study	Year	Number	Sleep disorder	Assessment method	Prevalence
Sariyildiz *et al.*[8]	2013	48 (dcSSc 54.5%)	Sleep quality	PSQI	68.8% (PSQI > 5)
Horsley-Silva *et al.* [9]	2019	287 (dcSSc 36%)	Sleep quality	PSQI	68% (PSQI > 5)
Figueiredo *et al.*[2]	2020	60 (dcSSc 36.6%)	Sleep quality	PSQI	73.3% (PSQI ≥ 7)
Carandina *et al.* [10]	2021	20 (dcSSc 20%)	Sleep quality	PSQI	90% (PSQI > 5)
Wongthawa *et al.* [1]	2021	88 (dcSSc 63.6%)	Sleep quality	PSQI	54.6% (PSQI > 5)
Bagheri *et al.* [11▪▪]	2024	103 (dcSSc 40.8%)	Sleep quality	PSQI ISI ESS STOP-Bang Questionnaire	68% poor sleep quality 3.9% severe insomnia 6.8% daytime sleepiness 31.1% at risk of sleep apnea
Santos *et al.*[12▪]	2024	50 (dcSSc 36%)	Sleep quality	PSQI ESS	84% poor sleep quality 20% daytime sleepiness
Gokcen *et al.*[13▪]	2025	70 (dcSSc 41.4%)	Sleep hygiene	Sleep Hygiene Index (SHI) PSQI	57.1% poor sleep quality (PSQI > 5)
Prado *et al.*[6]	2002	27 (dcSSc 29.6%)	Sleep-related breathing disorder (sleep apnea)	PSG[a]	70% reduced sleep insufficiency 69.2% increased slow wave sleep 22% RLS 77% reduced percentage of REM sleep 22% RLS
Pihtili *et al.*[18]	2013	18 of 62 cases of ILD	Sleep apnea	PSG	55% sleep apnea
Nokes *et al.*[38▪▪]	2019	171 (dcSSc 34.1%)	Sleep-related breathing disorder	Overnight forehead oximetry PSG	32.1% abnormal overnight forehead oximetry
Gundogdu *et al.* [19▪]	2021	38 with lung involvement (dcSSc 21%)	Sleep apnea	PSG	58% sleep apnea 59% mild sleep apnea 27% moderate sleep apnea 14% severe sleep apnea
Edis *et al.*[14]	2021	39 (dcSSc 36%)	Sleep apnea	PSG	53.8% sleep apnea (5% severe sleep apnea) 12.8% REM-dependent sleep apnea
Turk *et al.*[39▪]	2024	36 (dcSSc 75%)	Sleep apnea	PSG	25.9%
Ostojic *et al.*[16]	2013	27 (dcSSc 66.7%)	Restless leg syndrome	International RLS Study Group Criteria	40.7% RLS
Gök *et al.*[15▪]	2025	31 (dcSSc 71%)	Sleep structure (cyclic alternating pattern)	PSG PSQI ESS	29% sleep apnea 71% poor sleep quality 25.8% daytime sleepiness

[a]No pulse oximetry evaluation.
AHI, apnea-hypopnea index; dcSSc, diffuse cutaneous systemic sclerosis; ESS, Epworth Sleepiness Scale; GERD, gastroesophageal reflux disease; ISI, Insomnia Severity Index; ND, no data available; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RLS, restless leg syndrome.

Table 3. Factors associated with sleep disorders in SSc

Factors	Sleep disorders
Insomnia	Interstitial lung disease [11▪▪] Telangiectasia [11▪▪]
Sleep apnea	Interstitial lung disease [11▪▪], diffuse lung involvement [18] Obesity [14] Pulmonary hypertension [39▪] Telangiectasia [11▪▪] Witnessed apnea [19▪]
Daytime sleepiness	None
Poor sleep quality	Cardiovascular autonomic control [10] Depressive symptoms [2,7,8,10,13▪] Digital ulcer [1,40–43] Fatigue [8] Functional disability [12▪] Functional status [8] Gastrointestinal symptoms (GERD, esophageal involvement, dyspepsia) [1,2,6,7,9,13▪,44] Interstitial lung disease [11■■,18] Pain [8,10,44,45] Pruritus [44] Skin stiffness [11▪▪] Telangiectasia [11▪▪]
Restless leg syndrome	Metoclopramide [16]

GERD, gastroesophageal reflux disease; SSc, systemic sclerosis.

Therapeutic intervention points are highlighted using continuous positive airway pressure (CPAP), which has been shown to modulate IL-6 and TNFα pathways [21▪] and cannabidiol (CBD) targeting IL-1β [25] (Fig. 2). However, the relationship between pro-inflammatory cytokines and sleep quality is complex, emphasizing how various physiological and behavioral factors can initiate or perpetuate the cycle of inflammation and impaired sleep.

ASSESSMENT AND MEASUREMENT OF SLEEP DISORDERS IN SYSTEMIC SCLEROSIS

A comprehensive evaluation of sleep disturbances in SSc requires integrating both subjective and objective assessment tools. Subjective instruments are easy, cheap, noninvasive, and quickly completed, and have been validated and tested for accuracy [26]; however, they may cause recall bias. In contrast, objective techniques provide quantitative data on sleep architecture, continuity, and circadian rhythms. The features, benefits, and limitations of the commonly employed sleep assessment tools are presented in Table 4.

MANAGEMENT STRATEGIES FOR SLEEP DISTURBANCES IN SYSTEMIC SCLEROSIS

Poor sleep correlates significantly with increased functional impairment and reduced quality of life [12▪]. It may also affect disease activity and progression, impact physical function, and have mental health consequences. Early detection and treatment may reduce adverse clinical outcomes. No specific guidelines exist for treating sleep disorders in patients with SSc. Therefore, we propose three approaches based on general sleep disorder treatment principles for addressing sleep disturbances

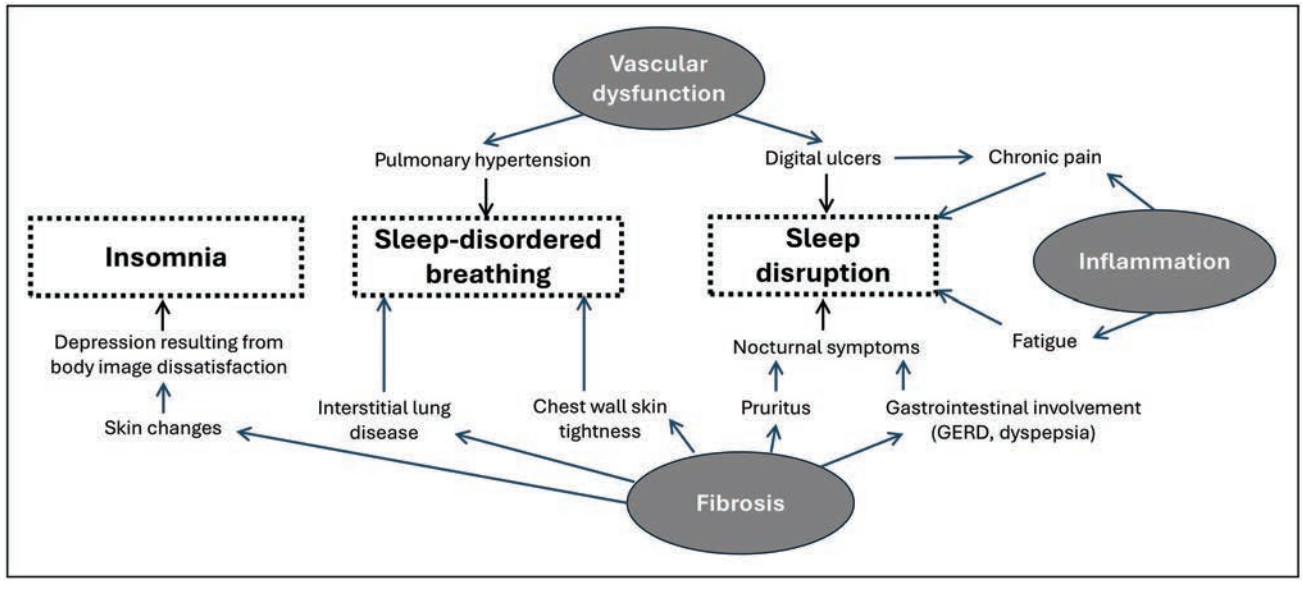

FIGURE 1. Pathophysiological mechanisms linking SSc to sleep disorders. GERD, gastroesophageal reflux disease.

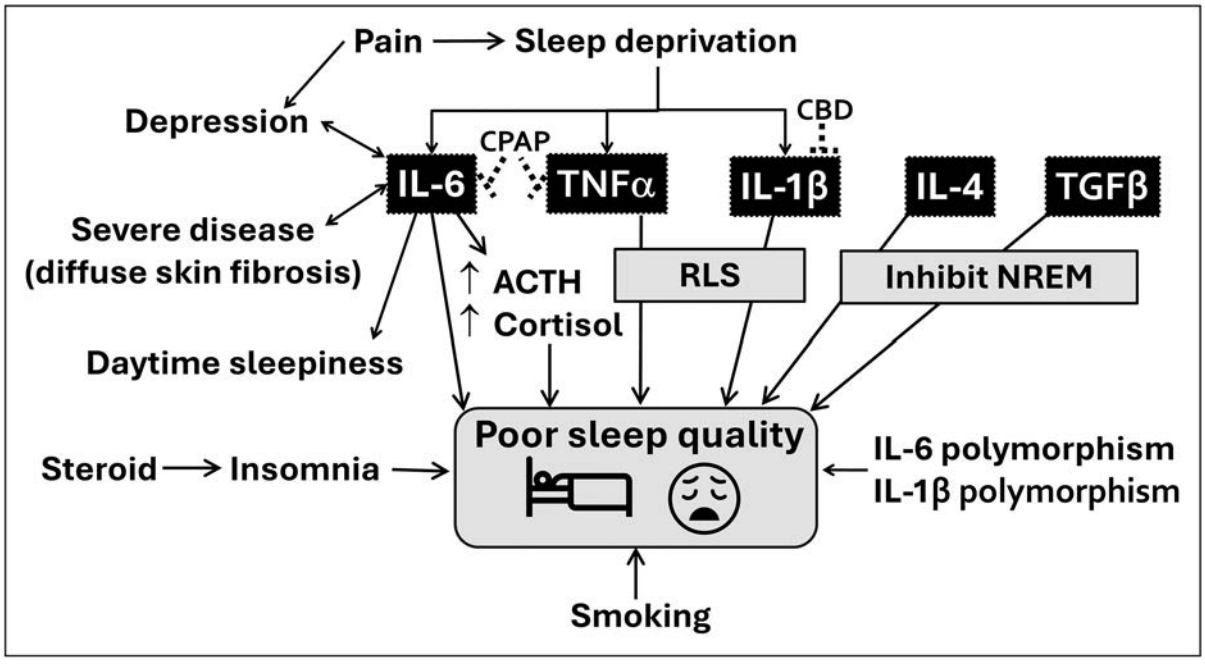

FIGURE 2. The role of inflammatory cytokines in sleep disorders among SSc patients. ACTH; adrenocorticotropic hormone; CBD, cannabidiol; CPAP, continuous positive airway pressure; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; NREM, nonrapid eye movements; RLS, restless leg syndrome; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Table 4. Sleep assessment tools used in SSc research

Tools	Purposes	Strengths	Limitations
Subjective measures			
Pittsburgh Sleep Quality Index [46]	Subjective sleep quality	Easy to use •Validated in numerous populations	Recall bias •Unable to capture short-term fluctuations or acute sleep disturbances •Unable to distinguish between different sleep disorders •Complex scoring system
Epworth Sleepiness Scale [47]	Daytime sleepiness	Quick screening •Simple scoring system •Validated in numerous populations	No nighttime sleep quality assessment •Unable to differentiate between the causes of sleepiness •Unable to capture variations in sleepiness throughout the day or across different days
Sleep hygiene index [48]	Sleep hygiene	Quick and easy-to-administer measurement •Validated in numerous populations	Recall bias •Cultural variations •No capturing of physiological or environmental factors
Medical Outcomes Study Sleep scale [7]	Sleep quality and sleep quantity	Quick screening •Covers multiple aspects of sleep •Validated in numerous populations	Recall bias •Less sensitive to change
Objective measures			
Polysomnography [49]	Sleep stages and disturbances	Gold standard	Expensive •Resource-intensive
Actigraphy [50,51]	Sleep-wake cycles	Noninvasive, long-term monitoring	Less precise than polysomnography •Requires proper compliance and data interpretation expertise

SSc, systemic sclerosis.

Table 5. Management strategies for sleep disturbances in SSc

Management approach	Management strategies	Note
Nonpharmacological approaches	*For insomnia:* Cognitive Behavioral Therapy for Insomnia (CBT-I), sleep hygiene education	Sleep restriction by limiting time in bed, relaxing training, maintaining a consistent sleep schedule, creating a comfortable sleep environment, limiting screen exposure before bedtime, avoiding caffeine close to bedtime, engaging in a relaxing presleep routine
	For sleep apnea: continuous positive airway pressure	
Pharmacological interventions	*For insomnia:* benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, melatonin agonists, low-dose antidepressants, antipsychotics, and diphenhydramine	Caution: risk of drug interactions and side effects
	For sleep quality: cannabinoids	Caution: risk of drug interactions and side effects
Management of SSc-related symptoms and coexisting conditions	Minimize steroid dosage •Pain relievers and anti-inflammatory agents •Immunosuppressants (esp. for ILD) Antipruritic medications •Proton-pump inhibitors and prokinetics for GI symptoms Antidepressants and/or antianxiety medications for psychiatric comorbidities	Addressing underlying SSc manifestations to improve sleep

GI, gastrointestinal; ILD, interstitial lung disease; SSc, systemic sclerosis.

in SSc: nonpharmacological approaches, pharmacological interventions, and management of SSc-related symptoms and coexisting conditions.

Nonpharmacological approaches for patients with SSc depend on the category of sleep disorder. For insomnia, nonpharmacological treatments commonly include cognitive behavioral therapy for insomnia and sleep hygiene education. Cognitive behavioral therapy for insomnia (CBT-I) is recommended in various clinical practice guidelines [27▪▪,28]. Multiple therapeutic components have been proven effective, including sleep restriction by limiting time in bed, stimulus control, cognitive restructuring by identifying and challenging unhelpful beliefs about sleep, and relaxation training [29]. Sleep hygiene education includes maintaining a consistent sleep schedule, creating a comfortable sleep environment, limiting exposure to screens before bedtime, avoiding stimulants like caffeine and alcohol close to bedtime, and engaging in relaxing presleep routines [30]. A report showed the efficacy of sleep hygiene education on sleep quality, pain, and depression in individuals with fibromyalgia [31▪]. The systematic review revealed some improvement in sleep quality between pre and postintervention; however, the effectiveness of sleep hygiene education has proven inferior to cognitive behavioral therapy for insomnia and mindfulness-based therapeutic techniques [32]. For sleep apnea, continuous positive airway pressure is recommended by many clinical practice guidelines, as it is highly effective in reducing apnea events and significantly improves quality of life [33,34,35▪▪].

Pharmacological interventions are not the primary approach for sleep disorders because patients require polypharmacy for disease control, including vasodilators to alleviate Raynaud's phenomenon and digital ulcers, immunosuppressants to control inflammation (particularly ILD), and proton pump inhibitors and/or prokinetics to alleviate gastrointestinal symptoms. These medications may interact with each other or increase the risk of side effects. Pharmacological treatments that have been approved for the treatment of insomnia include benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, melatonin agonists, low-dose antidepressants, antipsychotics, and diphenhydramine [36▪]. Cannabinoids may improve sleep quality among SSc patients, but can have unwanted interactions [37▪].

Management of underlying SSc-related symptoms and coexisting diseases includes minimizing steroid dosage, administering pain relievers, anti-inflammatory agents, immunosuppressants, antipruritic medications, proton-pump inhibitors, and prokinetics for pain reduction, inflammation control, pruritus relief, and alleviation of SSc-related gastrointestinal symptoms, respectively. Antidepressants and/or antianxiety medications may be necessary for depression or anxiety disorders.

The management strategies for sleep disturbances in SSc are summarized in Table 5.

CONCLUSION

Sleep disorders are common in patients with SSc; however, their prevalence and associations vary owing to differences in definitions, study methods, and populations. Sleep disorders in SSc have multifaceted clinical impacts, affecting disease progression, quality of life, and treatment outcomes. Sleep disruption and SSc manifestations (i.e., pain, respiratory problems, and GI issues) have a bidirectional relationship that can accelerate disease progression. Knowledge gaps remain regarding the links between SSc pathophysiology and sleep disruption, the predictive value of sleep parameters for disease progression, and the development of SSc-specific sleep interventions. Early intervention and modified treatment approaches could improve patient outcomes, and sleep quality could be a prognostic marker and treatment target for SSc management.

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- ■ of special interest
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Harnessing artificial intelligence to advance insights in systemic sclerosis skin and lung disease

Kimberly S. Lakin, Michael Parides and Jessica K. Gordon

Purpose of review
The purpose of this review is to summarize the uses of artificial intelligence for advancing systemic sclerosis (SSc) skin and lung disease research through 2024.

Recent findings
Applications of AI in SSc research have expanded markedly in recent years. The most common artificial intelligence method identified was supervised machine learning for predictive modeling. Supervised machine learning uses input data labeled with a known outcome to train a model to predict outcomes when encountering new data. Using machine learningassisted feature selection and posttraining feature importance techniques also highlighted key predictors within complex datasets, informing possible mechanisms underlying heterogeneous patient outcomes. Additionally, unsupervised machine learning approaches have been used to identify patient subsets with distinct clinical trajectories. Unsupervised machine learning identifies groups with similar characteristics within a dataset, without considering a specific outcome. Digital image analysis using deep learning has also been undertaken in lung imaging studies to quantify interstitial lung disease (ILD) extent and automate ILD subtype classification, as well as skin biopsy analysis to quantify histologic changes. These scalable tools could efficiently automate prognostic assessments for use across centers of varying local expertise.

Summary
Artificial intelligence represents a tool for analyzing high-dimensional, complex datasets to derive robust results, even within relatively small SSc cohorts. To date, artificial intelligence driven insights to SSc skin and lung disease have focused on identifying patient subsets, quantifying disease severity, and building predictive models to inform personalized patient care.

Keywords
artificial intelligence, biomarkers, imaging, lung fibrosis, machine learning, precision medicine, pulmonary, skin, skin fibrosis, systemic sclerosis

INTRODUCTION

Applications and accessibility of artificial intelligence have expanded in recent years with considerable enthusiasm. In scientific research, artificial intelligence offers an exciting platform for solving problems, including those in rare, poorly understood conditions such as systemic sclerosis (SSc; scleroderma).

The pathophysiology of SSc is characterized by inflammation, vasculopathy, and fibrosis. Individuals with SSc experience heterogeneous disease manifestations and trajectories. Individuals with similar disease trajectories may have different responses to treatment depending on the phase of their disease at time of treatment. Others have completely divergent trajectories of disease and may not be responsive to the same treatment approach even if given during an optimal "window of opportunity." Improved strategies for phenotyping patients and predicting outcomes are needed, and artificial intelligence presents an opportunity to address this deficiency. The purpose of this review is to summarize the literature to date using artificial intelligence for skin and lung disease research, highlighting ways in which

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KEY POINTS

- Applications of artificial intelligence in systemic sclerosis (SSc) skin and lung disease are increasing, with a notable acceleration in the number of studies published in 2024.
- Applications of artificial intelligence in SSc research to date have identified patient subsets and generated models to diagnose SSc, quantify disease severity, improve treatment approaches, better understand SSc pathogenesis, and predict organ involvement, treatment response, and disease progression.
- In multiple studies, machine learning-assisted feature selection (such as LASSO) enabled the identification of key predictors of an outcome of interest within high-dimensional, complex SSc datasets comprised of clinical as well as molecular variables.
- Several studies have applied artificial intelligence methodologies to publicly available data to derive additional insights toward understanding disease pathogenesis.
- The most common application of artificial intelligence to date in SSc skin and lung research involves predictive modeling, identifying key factors associated with disease outcomes and generating tools for individual risk assessments to improve SSc patient care approaches.

artificial intelligence can help overcome obstacles in SSc research and patient care.

MATERIALS AND METHODS

We conducted an Ovid MEDLINE and Embase literature search to identify artificial intelligence applications in skin and lung SSc research as of December 2024. The following search terms were used: "scleroderma, systemic" AND "artificial intelligence" OR "scleroderma, systemic" AND "machine learning." Only peer-reviewed, original, full text manuscripts studying SSc were included. Conference abstracts, review articles, book chapters, editorials, and nonpeer reviewed articles were excluded. Studies focused upon SSc generally or skin and/or lung manifestations specifically were reviewed, including those related to diagnosis, patient subsets, and skin or lung progression. Studies focused on gastrointestinal disease, vascular manifestations, including pulmonary hypertension and nailfold capillaroscopy, as well as renal crisis were beyond the scope of this review. Any additional manuscripts known by the authors to use artificial intelligence in SSc lung and skin research were also included. We also acknowledge that the landscape of artificial intelligence in SSc research is methodologically diverse, and some studies not indexed with the terms "artificial intelligence" or "machine learning" may not have been identified.

RESULTS

Fifty-four studies, published between 2010 and 2024, were included (Table 1, Fig. 1). The most common artificial intelligence application was supervised machine learning (Fig. 2). Machine learning is an application of artificial intelligence focused on developing algorithms from provided data to identify patterns and make predictions based on what was "learned," providing a framework for assessing new information. In supervised machine learning, groups are defined by a labeled outcome, and a model is trained on input data to predict that outcome when presented with new data. In unsupervised machine learning, the algorithm identifies structure in the data to generate groupings without using outcome labels. Deep learning has also been used for SSc research, a subset of machine learning using natural language or images as inputs to solve a specific problem. In SSc, artificial intelligence has provided tools to identify patient subsets, diagnose SSc and SSc organ involvement, quantify disease severity, predict disease trajectory and treatment response, optimize treatment, and better understand SSc pathogenesis. We describe the literature to date using these themes.

Identify patient subsets

Supervised machine learning methods have been used to classify patients with SSc into molecular subsets (e.g., inflammatory, fibroproliferative, and normal-like [1]) that have been associated with treatment response [2–4]. Studies have applied supervised machine learning [e.g., support vector machine (SVM), multifocal generalized linear model net (GLMnet)] to gene expression data from skin [5,6] and blood [3] as well as skin histology scores [7] to classify patients into these subsets (Table 1a). While supervised learning can be used to predict membership in predefined groups, unsupervised learning uses patterns identified within the data to group patients, potentially revealing novel subsets. In skin, Xu *et al.* [8] applied consensus clustering with ML-assisted feature selection to publicly available SSc microarray data and identified eight patient clusters distinguished by pathways that included potential SSc treatment targets. In blood, Wang *et al.* [9▪] analyzed gene expression from 120 patients with SSc and identified three clusters with distinct stromal and immune scores, and Makinde *et al.* [10] identified three groups, based upon classical monocytes'

Table 1. Artificial intelligence applications for systemic sclerosis skin and lung disease, through 2024

Ref.	Journal	Patients	Methods	Findings
a. Identify patient subsets				
Franks *et al.* [5]	*Arthritis Rheumatol*	58 SSc; 49 HC	Supervised ML: SVM	A classifier was developed to assign patient skin biopsy samples to molecular subsets dubbed 'intrinsic' subsets using skin tissue gene expression as input.
Xu *et al.* [8]	*PLoS One*	126 dcSSc, 15 lcSSc; 80 HC	Unsupervised clustering, ML feature selection	Eight distinct patient clusters/subsets were identified using skin microarray gene expression data from nine publicly available studies.
Franks *et al.* [3]	*Ann Rheum Dis*	63 SSc	Supervised ML: Multifocal GLMnet	'Intrinsic' gene expression subsets were assigned for participants in the SCOT trial by ML algorithm using peripheral blood gene expression as input.
Showalter *et al.* [7]	*Ann Rheum Dis*	26 dcSSc	Supervised ML: SVM	Skin histology features (e.g., collagen, infiltrate, aSMA, CD34) were used as inputs to predict skin gene expression 'intrinsic' molecular subset assignment.
Mehta *et al.* [6]	*JCI Insight*	84 dcSSc	Supervised ML: SVM	SVM classifier used to assign SSc samples to 'intrinsic' subset; subsequently, mRSS change was evaluated within each 'intrinsic' subset; inflammatory and normal-like had greatest mRSS improvement relative to placebo.
Schniering *et al.* [11]	*Eur Respir J*	156 SSc-ILD	Unsupervised clustering	Among SSc-ILD patients, two clusters were identified using 1355 radiomic features as inputs; these clusters had distinct clinical and prognostic features.
Makinde *et al.* [10]	*Arthritis Rheumatol*	14 dcSSc 15 HC	Unsupervised clustering	Three groups were identified based upon transcriptional signatures of classical monocytes in blood; there were between-group differences in pulmonary function decline, but no difference in mRSS at baseline or longitudinally.
Wang *et al.* [9▪]	*Front Immunol*	120 SSc 113 HC	Unsupervised consensus clustering; Supervised ML: multiple methods	Consensus clustering of peripheral blood gene expression data revealed three clusters with distinct microenvironment, stromal, and immune scores. ML-assisted feature selection identified 8 genes used in a classification model and correlated with B cells, monocytes, and epithelial cells.
b. Diagnose SSc				
Moinzadeh *et al.* [65]	*J Eur Acad Dermatol Venereol*	86 dc- or lc-SSc; 64 SSc overlap; 40 HC	Supervised ML: SVM	Whole blood gene expression data used as input to predict SSc vs. SSc-overlap status with accuracy of 72%.
Norimatsu *et al.* [12]	*J Invest Dermatol*	99 SSc or other CTD; 30 HC	Deep learning: CNN	Hand photographs (palms and dorsum of hands) were analyzed by CNN to classify images as SSc vs. non-SSc (AUC 0.89).
Choi *et al.* [17]	*Acta Derm Venereol*	Morphea: 150 localized,16 generalized; 15 SSc	Supervised ML: Random Forest	ML algorithm was developed to classify disease status (localized or generalized morphea or SSc) using clinical and histological features as inputs. Variables most highly weighted in the model included: Scl-70, centromere, rheumatoid factor, trunk involvement, and noncutaneous manifestations present.
Bellocchi *et al.* [16▪▪]	*Front Immunol*	33 PreSSc 16 HC	Supervised ML: multiple methods; Unsupervised clustering	541 differentially expressed pathways were identified between preSSc and HC gene expression (blood); model classified samples with AUC 0.792; 4 groups identified using unsupervised clustering. No pathway predicted progression from preSSc to SSc.
c. Diagnose SSc organ involvement				
Huang *et al.* [18]	*BMC Bioinformatics*	119 SSc	Supervised ML: multiple methods	Clinical and peripheral blood flow cytometry data were used as inputs to classify ILD status among individuals with SSc.
Andrade *et al.* [19]	*Biomed Eng Online*	52 SSc 30 HC	Supervised ML: multiple methods	Classifier was developed using respiratory oscillometry as input to diagnose SSc lung involvement as measured by abnormal spirometry.

Table 1 (*Continued*)

Ref.	Journal	Patients	Methods	Findings
Joye *et al.* [20]	*Eur J Radiol*	166 SSc	Supervised ML: LR and MSDSK models	ML used to compare radiomic data from slice-reduced chest CT (less radiation) vs. full-chest CT for diagnosing and staging (none, limited, extensive) SSc-ILD; model using slice-reduced CT yielded accuracy for diagnosing and staging of 0.85 and 0.82, respectively, similar to full CT accuracy.
Györfi *et al.* [21▪▪]	*Rheumatology (Oxford)*	225 SSc	Supervised ML: Random Forest	RF model used to evaluate the performance of multiple biomarkers (KL-6, CCL18, YKL-40, MMP-7) for identifying those with vs. without ILD; ML model yielded an accuracy of 85% for classifying patients with vs. without ILD; KL-6 and SP-D were associated with higher odds of ILD progression.
d. Quantify disease severity				
Taroni *et al.* [37]	*J Invest Dermatol*	51 SSc (5 study meta-analyses)	Unsupervised network-based ML	Gene expression pathways downregulated by treatment (MMF, rituximab, abatacept, nilotinib, fresolimumab), including those that may not have been differentially expressed, were identified using ML approach. Clinical improvement associated with downregulation of inflammatory pathways.
Johnson *et al.* [35]	*PLOS One*	82 SSc (112 biopsies)	Supervised ML: SVM, RF, NB	Skin gene expression (microarray) was used as input (with ML-assisted feature selection) to predict SSc severity status (high vs. low mRSS). The gene signatures produced by the prediction model correlated with mRSS.
Chassagnon *et al.* [26]	*Radiol Artif Intell*	208 SSc	Multicomponent deep neural network: AtlasNet	An algorithm was developed to quantify SSc-ILD extent which performed similarly to radiologists and correlated with PFT results (DLCO, FVC, TLC).
Correia *et al.* [31]	*Arthritis Res Ther*	66 SSc 16 HC	Deep learning: AlexNet, deep neural network	A deep neural network was used to generate a Biopsy Score and Diagnosis Score from trichrome-stained skin that correlated with mRSS and distinguished SSc from controls. A Fibrosis Score was generated, which correlated with skin gene expression. Change in Fibrosis Score correlated with change in mRSS.
Murdaca *et al.* [29]	*Diagnostics*	38 SSc	Supervised ML: multiple methods	A model was developed with the outcome of lung severity (Warrick score). Most important features were PFT parameters (DLCO, FEV1, FVC) and esophageal assessments (mean nocturnal basal impedance at 5 and 7 cm).
Chandrasekaran *et al.* [34]	*Arthritis Res Ther*	16 SSc	Deep learning: CNN	A CNN was used to quantify calcinosis in SSc skin and demonstrated strong correlation with expert radiologist measurements.
Berkowitz *et al.* [36]	*Arthritis Rheumatol*	24 SSc	Supervised ML: LASSO	LASSO was applied to skin single-cell RNAseq data to highlight predictors of SSc severity (mRSS); novel gene markers in keratinocytes were identified as well as genes implicated in SSc within fibroblast and myeloid cell subsets.
Zhao *et al.* [27▪]	*Rheumatol Int*	58 SSc	Deep learning: U-Net network, CNN	CNN model trained to classify radiographic ILD subtype (e.g., UIP, NSIP, etc.) using HRCT data from patients with SSc.
Singh *et al.* [25]	*Eur Radiol*	102 SSc	Deep learning: CNN	3-D CNN was used to assign chest CT severity; the output was applied to Cox regression to predict postlung transplant survival.
Jia *et al.* [28▪]	*Comput Biol Med*	316 SSc	Deep learning: CNN, PNN, GNN	Chest CT images were analyzed using deep learning to predict PFT values; model with highest performance for predicting DLCO, FEV1, FVC, and TLC had accuracy (ICC) of 0.748, 0.742, 0.836, and 0.836, respectively.
Jia *et al.* [24▪]	*Sci Rep*	230 SSc suspected	Deep learning: two neural networks	SSc-ILD severity (total extent of disease, ground glass, reticulation) quantified using deep learning framework with moderate agreement with human experts (kappa 0.66, 0.58, and 0.65, respectively).

Table 1 (*Continued*)

Ref.	Journal	Patients	Methods	Findings
e. Predict SSc prognosis				
Beretta *et al.* [40]	*Clin Exp Rheumatol*	914 SSc	Supervised ML: multiple methods	Naive Bayes Classifier developed that predicts 5-year mortality using clinical variables as inputs.
Van Leeuwen *et al.* [49]	*RMD Open*	492 SSc (25% dcSSc)	Supervised ML: Elastic Net Regularization	A prediction model was developed to identify patients with SSc who are at 'low risk' for disease progression in one or more organ systems.
Chassagnon *et al.* [47]	*Radiology*	212 SSc	Deep learning: fully connected CNN	Classifier identified functional and morphologic lung disease worsening using CT images as inputs with 83% and 80% accuracy, respectively.
Li *et al.* [50]	*J Clin Med*	433 SSc	Supervised ML: LASSO	LASSO was used to select clinical predictors in a model of SSc progression defined using SCTC-DI; Scl70 and baseline anemia were key predictors.
Foocharoen *et al.* [41]	*Sci Rep*	528 SSc	Deep learning: Adam Optimizer; Supervised ML: multiple methods	Model was developed to predict SSc mortality using clinical variables as inputs, ML approach identified mRSS and WHO-Functional Class as key predictors.
Guo *et al.* [45]	*Metabolism*	127 SSc untreated 57 SSc treated 124 HC	Supervised ML: multiple models	ML used to predict progressive SSc skin fibrosis using serum metabolomic data as input; three metabolites were identified as associated with disease progression: medicagenic acid 3-O- β-D-glucuronide, 4′-O-methyl-(–)-epicatechin-3′-O-β-glucuronide, valproic acid glucuronide.
Le Gall *et al.* [42▪]	*Rheumatology (Oxford)*	318 SSc	Deep learning	ILD extent measured using computer-aided deep learning enhanced a risk prediction model for 2 and 10-year mortality.
Huo *et al.* [51▪]	*Rheumatology (Oxford)*	361 SSc	Supervised ML: LASSO	Nomogram for irreversible organ damage developed using clinical predictors as input selected through LASSO regression: digital ulcers, mRSS, weight loss, age, C-reactive protein, myoglobin, renal or cardiac involvement, and age.
De Lorenzis *et al.* [38▪]	*RMD Open*	396 SSc	Supervised ML: LASSO	LASSO regression model identified male sex, VAS pain, SSc subset, Raynaud's Condition Score, and tenosynovitis as predictors of hand function decline.
Zheng *et al.* [39▪]	*Clin Rheumatol*	517 SSc	Supervised ML: Random Survival Forest	Age, mRSS, PAH, digital ulcers and albumin level were significantly related to poor prognosis (death) in RSF model.
Hui *et al.* [48]	*RMD Open*	304 SSc-ILD	Supervised ML: LASSO	A model was generated to predict progressive fibrosing ILD using 9 of 28 candidate variables: age ≥50, smoking, hyperlipidemia, diffuse subtype, arthritis, dyspnea, low IgA, Scl70, and cyclophosphamide or MMF use; AUC 0.882.
Zhu *et al.* [46▪▪]	*J Invest Dermatol*	PRESS (33 HC, 48 dcSSc); GENISOS (36 HC, 18 lcSSc, 43 dcSSc)	Supervised ML: multiple methods	Model trained to classify patients with vs. without progressive skin fibrosis using biological (fibroblast subpopulations) and clinical data (e.g., age, disease duration, autoantibodies) as input; fibroblast subpopulation variables were heavily weighted in the model. RF had highest accuracy score among ML methods evaluated (0.759 ± 0.058).
Singh *et al.* [66]	*Clin Transplant*	92 SSc undergoing lung transplant	Supervised ML with feature selection and hyper-parameter tuning (logistic regression); Deep learning: CNN	Six features included in model predicting delayed chest closure (DCC) among patients with SSc-ILD undergoing lung transplant: previous chest operation, atrial fibrillation, BMI > 30, ACEi use, tracheostomy, and donor age (AUC 0.82). DCC was more common in those with larger mismatches with respect to donor and recipient lung volumes measured using deep learning algorithm.
Luo *et al.* [52▪]	*Semin Arthritis Rheumatol*	171 SSc	Deep learning: CNN ("DeepCAC")	DeepCAC was used to calculate coronary artery calcium (CAC) score from noncontrast chest CT scans of SSc patients; there was a strong correlation between physician-assigned and DeepCAC scores ($r=0.71$, $P<0.01$).

Table 1 (*Continued*)

Ref.	Journal	Patients	Methods	Findings
Stock *et al.* [44▪▪]	*Rheumatology (Oxford)*	522 SSc-ILD	Deep learning: CNN (SOFIA)	Higher probability of UIP on SOFIA was associated with worse baseline ILD severity (lower FVC, DLCO, worse Goh staging of CT), greater decline in those parameters over time, and lower 15-year survival (P=0.001).
f. Predict treatment response				
Ebata *et al.* [53]	*Rheumatology (Oxford)*	54 dcSSc	Supervised ML: Causal Tree	Multiple predictors evaluated as inputs to predict *skin* response to rituximab (RTX), measured by 24-week mRSS (DESIRES trial); CD19+ cell count, mRSS, and serum surfactant protein D levels; mRSS ≥17, CD19+ cell count ≥57, were associated with most mRSS improvement on RTX vs. placebo.
Kuzumi *et al.* [54▪]	*Rheumatology (Oxford)*	48 SSc-ILD	Supervised ML: Causal Tree	Multiple predictors evaluated as inputs to predict *lung* response to RTX (DESIRES trial), measured by 24-week %-predicted FVC: Serum CRP and KL-6 identified as key biomarkers to define subpopulations; those with elevated CRP had greater FVC improvement on RTX vs. placebo while those with low CRP and low KL-6 had greater FVC improvement on placebo vs. RTX.
g. Improve treatment approaches				
Zheng *et al.* [56]	*Mod Rheumatol*	10 studies; 939 SSc	Supervised ML: Bayesian network analysis	SSc-ILD therapies were compared and ranked for efficacy (FVC, DLCO) and adverse events across 10 studies. Cyclophosphamide plus azathioprine was identified as most likely to be effective in preventing FVC decline.
Yan *et al.* [55]	*Front Genet*	97 SSc 38 HC (discovery)	Unsupervised ML: WGCNA; Supervised ML: LASSO	WGCNA identified module most associated with SSc, including 7 hub genes. LASSO was used to evaluate these genes as potential diagnostic biomarkers with THY1 and SULF1 showing high diagnostic accuracy (AUC 0.922).
h. Improve understanding of SSc pathogenesis				
Zhu *et al.* [57]	*Int J Rheumatol*	18 SSc 19 HC	Supervised ML: SVM	ML algorithm distinguished between controls and SSc with 100% accuracy using 6 genes as input: F2R, CXCR6, FYN, LTBR, CTSG, and ELANE.
Kobayashi *et al.* [58]	*J Autoimmun*	21 SSc 13 HC	Supervised ML: Random Forest; Unsupervised ML: k-NN	Peripheral blood gene expression data were used as input in RF model to classify SSc vs. controls, identifying an inflammatory gene module associated with CD16+ monocytes as most discriminatory. k-NN clustering was applied to scRNA-seq data to identify distinct monocyte subsets.
Cheikhi *et al.* [67]	*PLoS One*	27 SSc (lc- and dc-) 6 HC	Supervised ML: Naive Bayes Classification	Model was developed to predict disease status (SSc vs. controls) using a 60-gene panel as input (sensitivity 0.871, specificity 1.0) and to predict disease subtype (dcSSc vs. lcSSc), (sensitivity 0.871, specificity 0.937).
Luo *et al.* [61]	*Biomolecules*	134 SSc-ILD 45 HC	Supervised ML: Random Forest, LASSO	ML methods identified LIPN and CLEC4D as key, hub Treg-regulated genes with diagnostic power (AUC) for SSc of 0.824 and 0.826, respectively; genes are involved in immune response and metabolism of Tregs in SSc-ILD.
Xie *et al.* [64▪▪]	*J Autoimmune*	48 SSc 33 HC	Supervised ML: LASSO	Skin RNAseq data were analyzed using ML to construct the "Splicing pathway-based intro regulation network" which was distinct between SSc and controls.
Wang *et al.* [62]	*Front Genet*	(A) 49 SSc, 43 HC; (B) 69 atherosclerosis, 35 HC	Supervised ML: LASSO, RF	112 genes, including 13 mitochondria-related genes, were identified for classifying samples as SSc and atherosclerosis vs. controls; Among these, four mitochondrial-related biomarkers (IFI6, FSCN1, GAL, SGCA) were predictive of disease status in both conditions and associated with immune cell infiltration.

Table 1 (*Continued*)

Ref.	Journal	Patients	Methods	Findings
Heilmeier *et al.* [68]	*Front Med*	75 SSc	Supervised ML: Random Forest; KNN used for missing data	RF model was used to investigate the association between cardiovascular disease and inflammation in SSc. Lipid levels (HDL, LDL, total cholesterol, triglycerides) and SSc duration combined with ASCVD category accurately predicted CRP elevation (AUC 0.83 and 0.86, $P<0.001$, respectively).
Zheng *et al.* [59]	*Front Immunol*	48 dcSSc 33 HC	Supervised ML: LASSO regression, SVM-RFE	ML methods identified ENHO and NOX4 as key predictors of SSc vs. controls.

6MWD, 6-min walk distance; CTD, connective tissue disease; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GNN, Graph Neural Network; HC, healthy controls; ILD, interstitial lung disease; k-NN, k-nearest neighbor; ML, machine learning; mRSS, modified Rodnan skin score; NB, Naive Bayes; PFT, pulmonary function test; PNN, Point Neural Network; RTX, rituximab; SCTC-DI, Scleroderma Clinical Trials Consortium Damage Index; SOFIA, Systematic Objective Fibrotic Imaging Analysis Algorithm; SSc, systemic sclerosis; SVM, support vector machine; TLC, total lung capacity; VAS, visual analogue scale; WGCNA, Weighted Gene Co-Expression Network Analysis.

transcriptional signatures, which had between-group differences in pulmonary function over time. Supervised learning subsequently identified eight genes that classified patients into the identified clusters. In SSc-ILD, Schniering *et al.* [11] applied unsupervised clustering to radiomic features and identified two patient subgroups with distinct clinical trajectories. These studies highlight how machine learning approaches can reveal biologically and clinically meaningful subsets.

Diagnose systemic sclerosis

Machine learning has been applied to develop SSc diagnostic support tools (Table 1b). Norimatsu *et al.* [12] used an ensemble of deep convolutional neural networks (CNN) to accurately diagnose SSc using hand photographs [area under the curve (AUC) 0.89]. Convolutional neural networks represent a subset of deep learning capable of using 2D visual images as input data [13]. This tool could be used to expedite referral for specialized consultation. Artificial intelligence has also been applied to risk-stratify those who meet criteria for the preclinical phase of SSc (PreSSc), a group with a 5-year risk of developing SSc of 50% [14,15,16▪▪]. Bellocchi *et al.* [16▪▪] analyzed blood gene expression from 33 individuals with PreSSc and 16 healthy controls. A machine learning model incorporating differentially expressed pathways distinguished PreSSc from controls (AUC 0.792). Unsupervised clustering identified four clinical subgroups (healthy controls, healthy controls and PreSSc with healthy controls like features, PreSSc and healthy controls with PreSSc-

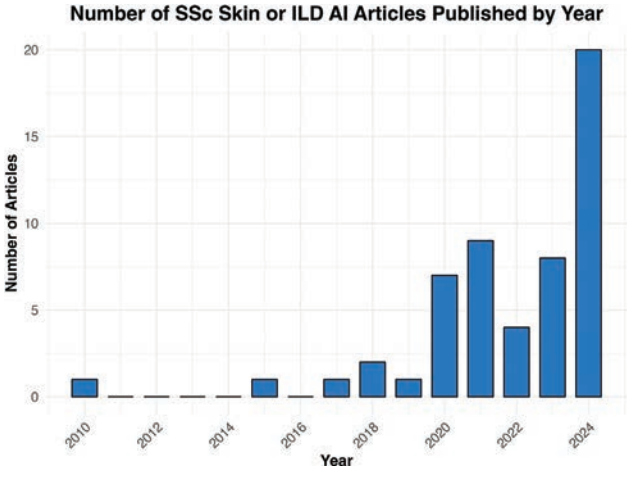

FIGURE 1. Number of systemic sclerosis skin or lung articles incorporating artificial intelligence/machine learning, by publication year.

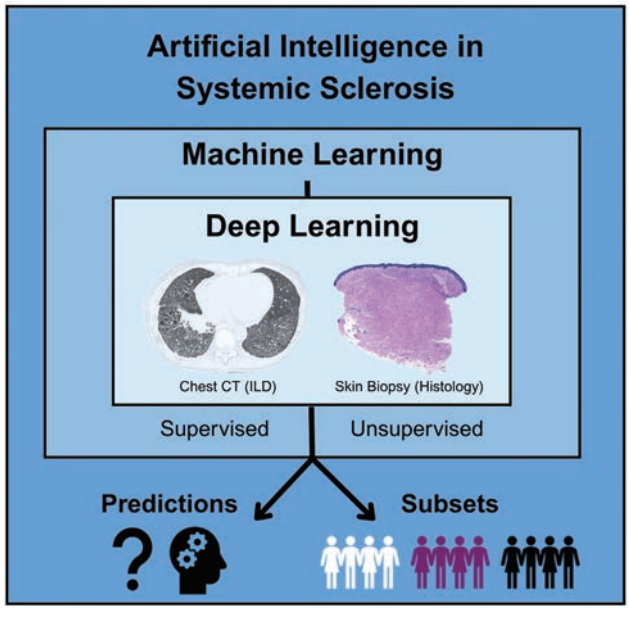

FIGURE 2. Summary of artificial intelligence applications used in systemic sclerosis skin and lung research.

like features, and PreSSc), supporting further longitudinal study.

AI-driven scleroderma subset classification has also been tested by Choi *et al.* [17] to distinguish between localized morphea, generalized morphea, and SSc using clinical and histological features. This study illustrates how artificial intelligence can be successfully applied even to heterogeneous, imbalanced datasets, as 83% of the study cohort had localized morphea. Such imbalances can lead to an algorithm that simply learns to predict the majority class to achieve a high accuracy (e.g., 83%). To address this issue, the authors used Synthetic Minority Over-sampling Technique (SMOTE) Tomek, which combines SMOTE, which adds realistic, artificial examples with the minority outcome, and Tomek links, which identifies similar majority and minority examples and removes the majority example. The random forest algorithm, a type of supervised machine learning that involves combining the predictions of multiple decision trees, was accurate for classifying morphea subtypes and SSc (AUC 0.987). Lack of pigmentation and extent of sclerosis were highly weighted, demonstrating the utility of artificial intelligence for highlighting distinguishing histologic features between groups.

Diagnose systemic sclerosis organ involvement

Several studies have applied machine learning to identify SSc-ILD (Table 1c). Huang *et al.* [18] combined conditional random forests with gene set enrichment analysis to identify flow cytometry variables that distinguished between those with and without SSc-ILD with 82.5% accuracy. Andrade *et al.* [19] evaluated the performance of several classifier methods using respiratory oscillometry for diagnosing ILD. Joye *et al.* [20] showed that radiomics from slice-reduced computed tomography, with reduced radiation exposure, enhanced predictive accuracy for diagnosing and staging ILD compared to full-chest CT. Their analytic approach included multivariate models as well as machine learning models to explore radiomic features broadly. Györfi *et al.* [21▪▪] also used traditional as well as machine learning methods in their analysis of serum biomarkers to predict SSc-ILD, demonstrating how artificial intelligence can complement traditional statistical approaches.

Quantify disease severity

Artificial intelligence offers a scalable approach to quantifying SSc lung severity for patient care and clinical trials (Table 1d). Extent of fibrosis and radiographic subtype have prognostic value in SSc-ILD [22,23] yet are not universally reported in computed tomography (CT) reads. Deep learning algorithms have been applied to chest CT images to quantify ILD extent [24▪,25,26], define radiographic subtype [27▪], and predict pulmonary function [28▪]. Supervised learning approaches have also been applied to SSc-ILD, highlighting PFT parameters (DLCO, FEV1, FVC) and esophageal assessments (mean nocturnal basal impedance at 5 and 7 cm) as predictors of radiographic severity [29].

Regarding skin, biopsies are collected in the context of clinical trials, but the approach to histology assessment is not standardized [30]. Artificial intelligence offers a scalable opportunity to quantify SSc histologically. Correia *et al.* [31] applied a deep neural network analysis to trichrome-stained skin biopsies and generated a Biopsy Score that correlated with mRSS and a Fibrosis score which correlated with longitudinal change in mRSS and gene expression, measured by the SSc skin severity score (4S) [32]. This deep learning algorithm was applied to skin samples obtained in the context of the belumosudil trial in SSc, where Fibrosis score moderately correlated with mRSS among a small sample of five participants, though this was not statistically significant [33▪]. Instead, there were stronger, significant associations between Fibrosis score and other histologic features such as hyalinized collagen, subcutaneous fat loss, intimal thickness, and eccrine entrapment. Thus, artificial intelligence may be useful for quantifying SSc-related pathologic features beyond clinical skin thickness captured by the mRSS. Deep learning (CNN) has also been used to quantify extent of calcinosis within SSc skin, demonstrating strong correlation with expert radiologist measurements [34]. If widely available, these tools could support patient management decisions. Several studies have also illustrated how applying machine learning-assisted feature selection helps to highlight specific genes and novel pathways associated with SSc severity and improvement within large datasets [35–37].

Predict systemic sclerosis prognosis

Disease outcomes in SSc are heterogeneous with some patients experiencing high mortality and functional decline, while others exhibit a more indolent course. Several studies have applied machine learning approaches to better distinguish between those groups, with predicted outcomes ranging from general disease manifestations (e.g., mortality, progression) to more specific events, such as delayed wound closure after lung transplant [25] or decline in hand function [38▪].

Five studies applied machine learning to predict mortality and/or highlight clinical variables associated with risk of death. Zheng *et al.* studied 517 patients with SSc and compared supervised ML (random survival forest model) to Cox regression and found that the machine learning approach outperformed the traditional Cox model in predicting death [39▪]. Similarly, Beretta *et al.* applied several machine learning methods to predict 5-year mortality, with the Naïve Bayes Classifier demonstrating higher accuracy than the traditional Cox regression model [40]. Machine learning has also been used to build simplified models, including a model for 5-year mortality with only two inputs: mRSS and WHO-Functional Class [41]. Le Gall *et al.* [42▪] demonstrated that an artificial intelligence assessment of ILD extent improved mortality prediction compared to Goh *et al.* ILD scoring. The authors note that using artificial intelligence is easier than the Goh *et al.* [43] approach that scores images at five levels based on total extent of disease, reticulation, ground glass, and coarseness of reticular disease. Additionally, higher UIP-pattern probability generated from a CNN algorithm, Systematic Objective Fibrotic Imaging analysis Algorithm (SOFIA), has been shown to correlate with survival [44▪▪]. While machine learning methods may be computationally complex, these results highlight how machine learning may yield more accurate, and in some cases simpler, predictions compared to traditional approaches.

Several studies have used machine learning to predict outcomes including progressive SSc skin [45,46▪▪] or lung fibrosis [29,47,48], progression in one or more organ systems [49], or damage accrual [50,51▪] (Table 1E). For example, Zhu *et al.* [46▪▪] incorporated RNAseq deconvolution results into machine learning models to predict skin progression. The random forest model performed best with an accuracy of 0.759. While mRSS was the feature with the highest importance in the model, fibroblast subtypes were next most strongly weighted, more influential than disease duration, autoantibody profile, SSc subtype, or intrinsic gene expression subset, highlighting the importance of fibroblast activation state as a biomarker for skin trajectory. Feature selection with elastic-net regularization was used in a study identifying patients with SSc with a low risk for progression, with 90 potential variables narrowed to 10 key predictors [49]. While the model demonstrated limited discrimination between progressors and nonprogressors (AUC of 0.66), the authors incorporated probability score cut-offs to identify a group at particularly low risk, for whom less intensive longitudinal monitoring may be adequate. Two studies applied machine learning to predict SSc-related damage with one demonstrating Scl-70 status and baseline anemia to be predictive of SCTC-DI [50]. Another studied "irreversible organ damage" (i.e., heart, respiratory, or renal failure, or digital gangrene) as an outcome and applied ML-feature selection, identifying digital ulcers, mRSS, weight loss, high C-reactive protein (CRP), high myoglobin, renal or cardiac involvement, and age as key predictors [51▪]. For SSc-ILD, Chassagnon *et al.* developed a deep-learning classifier using CT images as inputs to predict functional and morphologic ILD worsening [47]. Hui *et al.* [48] modeled progressive ILD using supervised machine learning (least absolute shrinkage and selection operator, LASSO) highlighting nine of 28 variables as key predictors. These studies highlight the utility of ML for identifying key predictors within high-dimensional datasets.

Deep learning methods can also enable opportunistic screening for SSc patients, particularly using chest CT imaging, commonly ordered to assess ILD. For example, a recent study analyzed chest CT images using CNN ("DeepCAC") to extract coronary artery calcium scores from chest CT images [52▪]. This study demonstrates how artificial intelligence can be deployed to assess risk factors related to poor health outcomes without requiring additional testing.

Predict treatment response

Two studies used machine learning methods to identify predictors of treatment response for skin or lung involvement (Table 1f). In a posthoc analysis of the DESIRES trial, a phase 2, double-blind, randomized, placebo-controlled trial of rituximab for dcSSc, a causal tree machine learning algorithm was used to evaluate the effect of 27 candidate predictors on change in mRSS at 24 weeks [53]. Skin response to rituximab could be predicted by higher CD-19 count and mRSS, while serum surfactant protein D levels also modified treatment effect. A subsequent DESIRES study posthoc analysis investigated pulmonary response to rituximab (26-week change in %-predicted FVC) using a similar approach [54▪]. Serum CRP and Krebs von den Lungen-6 (KL-6) were key variables that defined three subgroups with differential responses. Study results demonstrate the utility of machine learning to identify patient subsets and better understand treatment response.

Improve treatment approaches

Machine learning has been applied to skin gene-expression to identify novel treatment targets [55]. Multiple bioinformatic methods, including LASSO regression, identified seven SSc-relevant hub genes which led to the identification of several drugs with therapeutic potential, including dipyridamole and a

TGF-β receptor inhibitor. Although some of the hub genes were previously known to be key in SSc pathogenesis and some of the therapeutic agents identified are already used or are being studied, the authors approach is novel and provides rationale for future therapeutic directions. Zheng *et al.* [56] applied a Bayesian Network Analysis to compare therapies for SSc-ILD treatment across 10 studies, in the absence of head-to-head data. The authors suggest cyclophosphamide with azathioprine would be most effective for preventing FVC decline. This therapeutic combination is not likely to be adopted in clinical practice, given the current treatment landscape and potential toxicity; however, this study provides a framework for comparing newer therapies in future analyses.

Understand systemic sclerosis pathogenesis

AI is particularly useful for analyzing complex, multidimensional datasets to clarify mechanisms underlying SSc pathogenesis (Table 1h). For example, Zhu *et al.* [46▪▪] analyzed transcriptomes and DNA methylation status from peripheral blood mononuclear cells (PBMCs) of 18 SSc patients and 19 controls, mapping methylation probes to the nearest transcript starting site, with SVM as part of their integrative analysis [57]. The model highlighted a gene panel of six methylation-regulated DEGs that demonstrated 100% accuracy in differentiating SSc from controls. Kobayashi *et al.* [58] also performed an integrated analysis of bulk and single cell RNA-seq data from PBMC from 21 SSc patients and 13 controls. Using random forest model, an inflammatory gene network module and a cluster of CD16+ monocytes were identified that were highly discriminant for SSc.

Several studies applied ML to publicly available datasets expanding knowledge gained from prior studies. Zheng *et al.* [59] analyzed SSc and control skin gene expression and developed a diagnostic prediction model using LASSO regression and SVM recursive feature elimination, identifying ENHO and NOX4 as novel biomarkers. Luo *et al.* [60] performed cellular deconvolution using CIBERSORT on the GSE181228 dataset to determine the types and relative proportion of circulating immune cells in the blood of patients with SSc-ILD, with a focus on regulatory T (Treg) cells [61]. Using random forest and LASSO, two hub Treg-related genes involved in immune response and Treg metabolism were identified that had an accuracy of 0.824 and 0.826, respectively, for discriminating between SSc-ILD and controls. Wang *et al.* [62] used publicly available data to explore the connection between mitochondrial injury, endothelial dysfunction, and atherosclerosis in SSc. Xie *et al.* [63] evaluated alternative splicing and intron retention in SSc using data from the PRESS cohort and TGF-b stimulated fibroblasts in culture [64▪▪]. Using multiple machine learning methods, abnormal alternative splicing and intron retention were found in SSc and associated with fibrosis.

CONCLUSION

Given the recent, accelerated growth of artificial intelligence in SSc research, the use of artificial intelligence to analyze SSc multimodal data will likely continue to expand, providing insights into precision medicine and accelerating drug discovery. We look forward to future applications of artificial intelligence in SSc research that may focus on drug repurposing, adaptive trial designs, and automatic patient phenotyping through natural language processing.

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Conflicts of interest

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Gastrointestinal manifestations of systemic sclerosis: current approaches and emerging therapies

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Purpose of review
This review highlights recent advances in the understanding and management of gastrointestinal manifestations in systemic sclerosis (SSc). It is intended for clinicians and researchers aiming to improve diagnostic accuracy and therapeutic strategies in managing SSc-related gastrointestinal disease.

Recent findings
Gastrointestinal involvement in SSc is highly variable in terms of clinical presentation, symptom severity, progression, timing of onset, and response to treatment. Emerging research highlights early immune-mediated damage to neural and muscular gastrointestinal tissues, microbiome alterations, and vascular dysfunction – particularly in patients with late-onset gastrointestinal disease – as key factors guiding the development of personalized, precision-based approaches for well defined patient subgroups. Recent studies underscore the value of early, objective assessment of gastrointestinal motility using tools like whole-gut transit scintigraphy and abdominal vascular ultrasound. New treatment strategies are also being explored for severe manifestations, including investigating mechanisms behind acid-suppressive therapy-resistant gastroesophageal reflux disease and implementing adjunctive therapies for gastrointestinal dysmotility.

Summary
Gastrointestinal involvement in SSc poses a complex clinical challenge, particularly in patients with severe dysmotility and symptoms refractory to standard management strategies. This review offers timely, evidence-based insights to support clinicians in delivering more personalized and effective patient care and highlights critical gaps to address in future research.

Keywords
gastrointestinal, scleroderma, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by multiorgan involvement and a significant impact on both patients' quality of life (QoL) and survival [1–3]. Among internal organ manifestations, gastrointestinal involvement is the most common. Any segment of the GI tract, from the oropharynx to the colon and anorectum, can be affected, with disease progression varying widely between individuals [1,4]. Clinically, the severity of gastrointestinal involvement is highly heterogeneous, with considerable differences in symptom onset, symptom burden, disease trajectory, and outcomes [2]. This heterogeneity has long posed significant challenges in clinical practice, particularly in predicting the course of gastrointestinal disease, estimating the timing and risk of complications, and identifying patients most likely to develop severe gastrointestinal manifestations. In recent years, significant advances have been made in understanding the underlying pathophysiological mechanisms, identifying risk factors for developing severe gastrointestinal disease, and distinguishing between patients at high and low risk of progression.

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KEY POINTS

- Gastrointestinal motility dysfunction in systemic sclerosis significantly impacts patient prognosis and quality of life.
- Symptoms alone are insufficiently sensitive or specific; objective testing is essential for accurate detection and characterization of SSc-related gastrointestinal disease.
- Multidisciplinary collaboration, led by experts in systemic sclerosis, is crucial to optimize management of gastrointestinal involvement.
- Integrating clinical phenotypes with immunological biomarkers and objective gastrointestinal motility evaluation can enhance early diagnosis and targeted treatment strategies.

Additionally, advances in diagnostic modalities have improved the objective assessment of gastrointestinal dysfunction. Alongside these developments, emerging evidence now supports both therapeutic strategies aimed at improving patient outcomes and QoL. This review synthesizes and explores these recent advances in the evaluation and management of gastrointestinal involvement in SSc (Fig. 1).

Autoimmunity and neuronal dysfunction: advancing the understanding of gastrointestinal pathogenesis

Recent research has advanced our understanding of gastrointestinal involvement in SSc, supported by the hypothesis that autoimmunity and enteric neuromuscular dysfunction, including dysautonomia and muscular atrophy, are primary drivers of gastrointestinal dysfunction, rather than the historically presumed role of fibrosis [5]. Histological studies support this autoimmune-mediated pathogenesis, demonstrating early and structural damage to the autonomic nervous system in SSc, including notable reductions in interstitial cells of Cajal [6,7]. Gastrointestinal dysautonomia and muscle atrophy primarily manifest in the gut as abnormal motility, commonly known as dysmotility [8,9]. In patients with SSc, the severity of dysautonomia symptoms

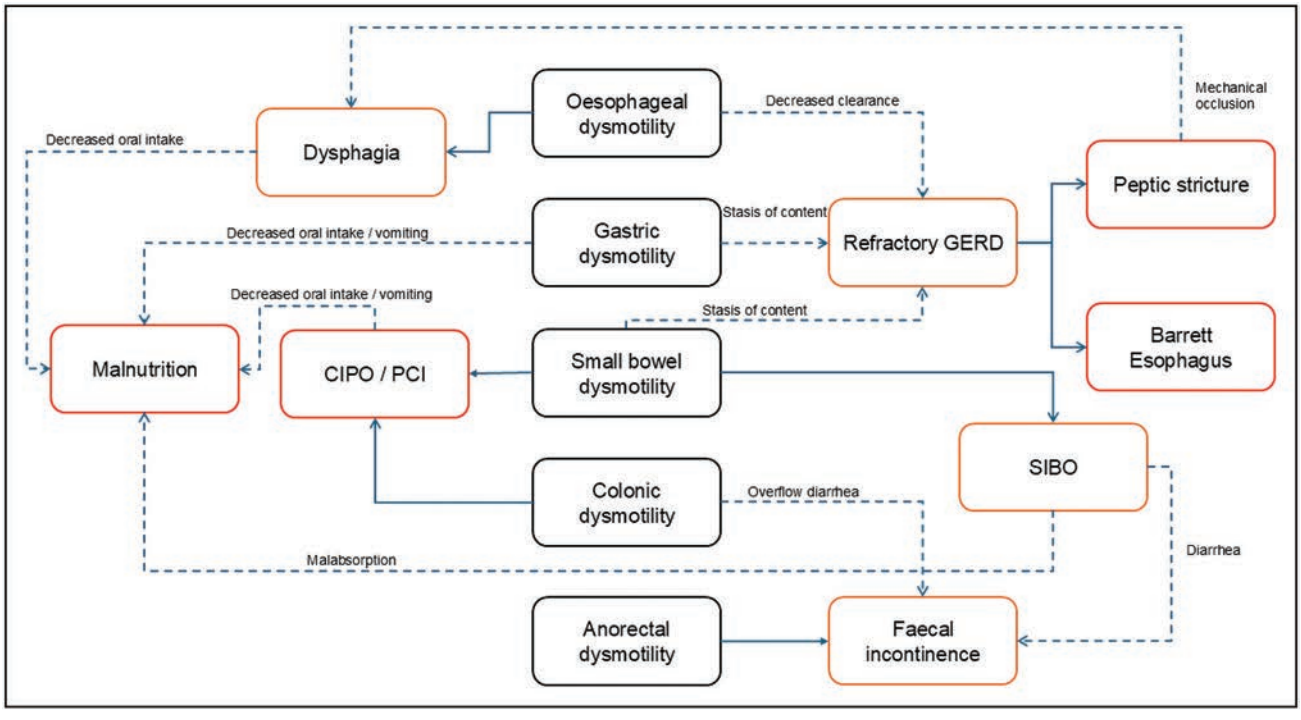

FIGURE 1. Schematic representation of gastrointestinal dysmotility across various gastrointestinal tract segments in SSc and their association with specific clinical manifestations. Solid arrows indicate direct causal relationships between gastrointestinal dysmotility and clinical complications, such as refractory gastroesophageal reflux disease (GERD), dysphagia, Barrett's esophagus, malnutrition, small intestinal bacterial overgrowth (SIBO), chronic intestinal pseudo-obstruction (CIPO), pneumatosis cystoides intestinalis (PCI), and fecal incontinence. Dotted arrows represent indirect associations mediated by secondary mechanisms, including mechanical occlusion, decrease clearance of reflux, content stasis, decreased oral intake, vomiting, overflow diarrhea, and malabsorption, emphasizing the interplay of primary dysmotility and contributing mechanisms, showing the significant clinical complexity in GI involvement in SSc.

correlates with abnormal gastrointestinal function (faster gastric and colonic transit times) [10], suggesting that a subset of patients with SSc have predominantly dysautonomia-driven gastrointestinal manifestations and delayed transit times are not the only spectrum of the disease.

Current evidence emphasizes the role of active autoantibodies targeting components of the enteric nervous system. Among these, antimuscarinic-3 antibodies have been shown to disrupt cholinergic neurotransmission, contributing to severe gastrointestinal dysmotility in early SSc [11▪]. More recently, a study identified antigephyrin antibodies in patients with SSc who have prominent lower gastrointestinal symptoms, including severe constipation and bloating [12▪]. Importantly, gephyrin is a postsynaptic scaffolding protein essential for inhibitory neurotransmission, and the presence of these antibodies supports a plausible pathogenic link between antigephyrin autoimmunity and enteric neuronal dysfunction. Furthermore, mitochondrial dysfunction has emerged as another key, likely pathogenic mechanism in SSc-related gastrointestinal disease. A recent study evaluated the associations between antimitochondrial M2 antibodies (AM2A), which are classically associated with primary biliary cholangitis and with gastrointestinal dysmotility [13]. AM2A antibodies were found to be significantly associated with slower esophageal and gastric transit times. Importantly, immunohistochemical studies revealed that AM2A target mitochondria-enriched, mesoderm-derived enteric neurons, which are critical for normal gastrointestinal motor function. The authors also demonstrated that these autoantibodies could penetrate live cells *in vitro* and localize to intracellular compartments, suggesting that AM2A may access their mitochondrial targets within enteric neurons *in vivo*. These findings highlight a novel, mitochondria-centered mechanism of enteric neuropathy in SSc and point to AM2A as a potential biomarker of gastrointestinal dysmotility and a contributor to disease pathogenesis through direct neuronal dysfunction. Additionally, a study evaluating two distinct SSc cohorts identified antibodies against the cytoskeletal protein vinculin, demonstrating that antivinculin antibodies were associated with both greater gastrointestinal symptom severity and objective measures of dysmotility, including delayed gastric emptying [14]. Taken together, these findings suggest that the presence of distinct autoantibodies, each targeting specific components of the enteric nervous system, smooth muscle cells, or other key gastrointestinal structures, may define clinically and pathogenically distinct subsets of SSc-related gastrointestinal disease. These growing serological and mechanistic insights point toward a future of precision diagnostics and more targeted, individualized therapeutic approaches.

The gut microbiome: early dysbiosis and therapeutic uncertainty

Recent research into the role of the gut microbiota in SSc has provided important new insights into its potential pathogenic and therapeutic implications. A case-control study characterized the gut microbiota and short-chain fatty acid profiles in patients with Very Early Disease of SSc (VEDOSS), patients with definite SSc, and healthy controls [15]. The authors found that both VEDOSS and patients with SSc exhibited significant gut dysbiosis, including reduced levels of beneficial butyrate-producing bacteria, accompanied by decreased fecal butyrate and increased acetate levels. These changes were already evident in the VEDOSS stage, suggesting that microbiota imbalance is an early factor in gastrointestinal involvement. Moreover, distinct microbial and lipidomic signatures differentiated VEDOSS from both SSc and healthy controls, highlighting the potential for microbiota-based biomarkers and interventions in early disease. However, a phase 2 randomized controlled trial of fecal microbiota transplantation in 67 SSc patients with moderate-to-severe lower gastrointestinal symptoms showed no significant improvement in bloating or diarrhea after 12 weeks compared to placebo [16].

Updates on the experience of gastrointestinal involvement from the patient's perspective

Gastrointestinal symptoms and manifestations exert a substantial burden from the patient's perspective. In a large international survey involving 301 patients from 14 countries, over 97% reported experiencing gastrointestinal symptoms, with heartburn, bloating, and dysphagia among the most common. Nearly three-quarters described a moderate to severe impact on QoL, particularly affecting sleep and social functioning [17]. Another study confirmed that 72% of patients report moderate-to-severe gastrointestinal symptoms by UCLA SCTC GIT 2.0, which were significantly associated with both impaired physical QoL and elevated anxiety and depression scores. Importantly, gastrointestinal symptom burden was an independent predictor of reduced physical and mental QoL, pointing to a need for holistic care models [18]. Similarly, a national study conducted in Spain with 188 patients found that gastrointestinal and vascular involvement were perceived as the organ systems with the most detrimental effect on health-related QoL. Furthermore, patients' overall

satisfaction with gastrointestinal-directed treatments apart from proton pump inhibitors (PPIs), such as prokinetics, cyclic antibiotics, and antidiarrheal agents, remained below 50%, highlighting the limited efficacy of current therapeutic options to manage the broader spectrum of SSc-related gastrointestinal symptoms [19]. Data from over 900 Australian patients show that gastrointestinal symptom burden negatively affected employment status and daily functioning, particularly in patients presenting severe reflux, distension, or diarrhea [20]. Finally, a recent scoping review represents the first comprehensive synthesis of current knowledge on fecal incontinence in SSc, a severely under-recognized yet highly impactful manifestation of gastrointestinal involvement. The presence of fecal incontinence consistently had a detrimental impact on QoL, daily functioning, and mental health across all the included studies [21▪▪]. Taken together, these data highlight the urgent need for multidisciplinary, patient-centered approaches in the management of SSc-GI disease, with an emphasis on improving symptom control, psychosocial support, and treatment satisfaction.

Trajectories of gastrointestinal involvement in patients with systemic sclerosis

One of the major challenges in clinical risk stratification and in the study of SSc-GI disease has been our inability to differentiate patients at high vs. low risk of progression in gastrointestinal severity. To address this important question, a recent study utilized a large, well characterized longitudinal cohort of 2953 patients and used gastrointestinal symptom severity (Medsger GI scale) to identify four distinct subgroups: Stable, Early Progressive, Late Progressive, and Early Severe [22▪▪]. These groups differed not only in the trajectory and severity of gastrointestinal manifestations but also in their extraintestinal and immunological characteristics. Notably, the Early Severe and Early Progressive groups exhibited the highest GI burden and mortality and were associated with distinct serological patterns, particularly increased positivity for antifibrillarin, U1RNP, and RNPC3 antibodies. However, most patients (approximately 85%) followed a stable gastrointestinal disease course. Patients in the Stable group had the mildest gastrointestinal involvement and the lowest overall mortality. These individuals were more likely to be women, younger at disease onset, and had lower cardiac and pulmonary severity scores. Limited cutaneous disease was more common in this group, with anticentromere, Ro52, and topoisomerase I antibodies (in limited cutaneous SSc) being the most frequently observed. However, it is important to note that gastroparesis, mild-moderate constipation, and faecal incontinence are not accounted for in the Medger GI severity scale. Regardless, this work is the first to highlight the temporal heterogeneity of SSc gastrointestinal disease and its association with clinically and serologically distinct subsets. Furthermore, it highlights that while most patients will experience long survival with nonlethal gastrointestinal morbidity requiring expert symptom management, particularly after failing standard therapies, a small subset will develop severe, rapidly progressive gastrointestinal disease. Targeted efforts are urgently needed to develop treatments that can halt gastrointestinal progression and improve outcomes for this high-risk population.

Rethinking the assessment of gastrointestinal involvement in systemic sclerosis: from subjective to objective

A major challenge in assessing gastrointestinal disease in SSc is the multifactorial nature of symptoms. Distinguishing between structural causes and gastrointestinal dysmotility in a cost-effective manner has become a key focus of ongoing research (Table 1). Novel research is exploring objective diagnostic techniques to improve the detection and characterization of gastrointestinal involvement in SSc, aiming to address a key clinical gap in early recognition and risk stratification. A cross-sectional study of 78 patients with SSc utilized abdominal Doppler ultrasound to evaluate blood flow in the superior and inferior mesenteric arteries. The findings revealed that elevated resistance index and pulsatility index values in the superior mesenteric artery were significantly associated with dcSSc and more severe gastrointestinal symptoms. Moreover, these vascular indices showed significant correlations with modified Rodnan skin scores and bosentan, suggesting a potential link between splanchnic macrovasculopathy and overall systemic disease activity [23]. A study evaluating 30 patients with SSc who underwent a comprehensive diagnostic workup, including esophageal manometry, gastric electrogastrography and small bowel manometry, esophageal dysmotility was present in 76% of patients, gastric dysrhythmias (mainly bradygastria) in 30%, and enteric dysmotility in 80%, with only 23% of patients showing involvement of entire gastrointestinal tract [24], revealing widespread and heterogeneous gastrointestinal dysmotility between patients. Interestingly, while the extent of gastrointestinal dysmotility correlated significantly with greater modified Rodnan skin scores, it did not correlate with patient-reported gastrointestinal symptoms (using a custom survey), reinforcing the dissociation between subjective

Table 1. Diagnostic approach to gastrointestinal involvement in systemic sclerosis based on organ involvement and clinical symptoms

Gastrointestinal organ	Clinical symptoms	First: exclude structural abnormalities	Then: evaluate objective dysmotility and severity
Oropharynx	Dysphagia (oropharyngeal), odynophagia, dry mouth	Nasoendoscopy, upper GI endoscopy, cranial CT or MRI	Endoscopic swallowing assessment, modified barium swallow study
Esophagus	Dysphagia (esophageal), noncardiac chest pain, heartburn, regurgitation, supra-gastric belching, extra-esophageal reflux (cough, dysphonia, hoarseness)	Upper GI endoscopy, thoracic CT, barium swallow esophagogram	High-resolution esophageal manometry, EndoFLIP, ambulatory reflux monitoring
Stomach	Early satiety, nausea and vomiting, epigastric discomfort, belching, bloating	Upper GI endoscopy, abdominal CT or MRI	Gastric emptying scintigraphy, whole-gut scintigraphy, antroduodenal manometry
Small bowel	Nausea and vomiting, bloating, abdominal distension, abdominal pain, altered bowel habits	Capsule endoscopy, enteroscopy, abdominal CT or MRI	Whole-gut scintigraphy, hydrogen/methane breath tests, high-resolution jejunal manometry
Colon	Abdominal distension, abdominal pain, altered bowel habits	Colonoscopy, abdominal CT or MRI	Whole-gut scintigraphy, radiopaque marker colonic transit, high-resolution colonic manometry
Anorectum	Tenesmus, fecal incontinence, obstructed defecation	Anoscopy, endoanal ultrasound, anorectal MRI	Rectal barostat, balloon expulsion test, defecography (MRI or conventional), high-resolution anorectal manometry

symptoms and objective findings. Further supporting the importance of objective motility assessment, a study of 69 SSc patients with refractory GERD undergoing endoscopy while on PPI therapy found that 33% had erosive esophagitis despite treatment [25▪]. Importantly, the presence of gastroparesis and small bowel dysmotility – but not esophageal hypomotility or hypotensive lower esophageal sphincter – was independently associated with PPI-refractory esophagitis. These findings highlight a potential role of generalized gastrointestinal dysmotility in the pathogenesis of severe GERD in SSc.

Although high-resolution manometry is considered the gold-standard technique for assessing gastrointestinal motility (esophageal [26], antroduodenal [27], jejunal [9,28], and anorectal [29]), it is cumbersome, not always tolerated by patients, and may be difficult to perform in patients with severe lung or cardiac involvement (Figs. 2 and 3). To overcome these issues, scintigraphy has emerged as a valuable diagnostic alternative. In a study conducted by Salas *et al.* [30], 131 patients with SSc underwent whole-gut scintigraphy, and the results from the esophageal transit component were systematically assessed. Delayed esophageal transit was present in 60% of participants and was significantly associated with dcSSc, severe lung involvement, and higher modified Rodnan skin scores. Importantly, the authors highlighted that this clinical phenotype mirrors that of patients with absent contractility on manometry [31], but without the need for invasive procedures. Furthermore, evaluating a subset of 24 patients in the cohort with both manometry and scintigraphy data, esophageal scintigraphy demonstrated 75% sensitivity, 38% specificity, and 71% positive predictive value for detecting absent contractility. Following this cohort study, Cheah *et al.*[32] further demonstrated the diagnostic utility of whole-gut scintigraphy by focusing on small bowel transit abnormalities. Patients with abnormal small bowel transit, defined as abnormal when less than 49% of the radiolabeled meal reached the ileocecal valve by 6 h, were more likely to be male [odds ratio (OR) = 3.70], have severe cardiac involvement (OR = 3.98), and exhibit higher mortality (hazard ratio = 4.57). Furthermore, patients with delayed small bowel transit reported worse diarrhea and impaired social functioning on the UCLA GIT 2.0 scale.

Collectively, these studies highlight the potential of Doppler ultrasound and scintigraphy as noninvasive, informative techniques that complement clinical evaluation and offer significant promise in the early diagnosis, phenotyping, and risk stratification of gastrointestinal involvement in SSc, though further validation in larger cohorts are needed

FIGURE 2. Radiological imaging findings in a patient with systemic sclerosis complicated by chronic intestinal pseudo-obstruction. Left (a) Coronal abdominal CT scan demonstrating severe dilation of multiple small bowel loops, indicative of intestinal pseudo-obstruction. There is no visible mechanical obstruction. Right (b) Barium transit study showing delayed intestinal transit and diffusely dilated small bowel loops. These findings are suggestive of advanced small bowel dysmotility.

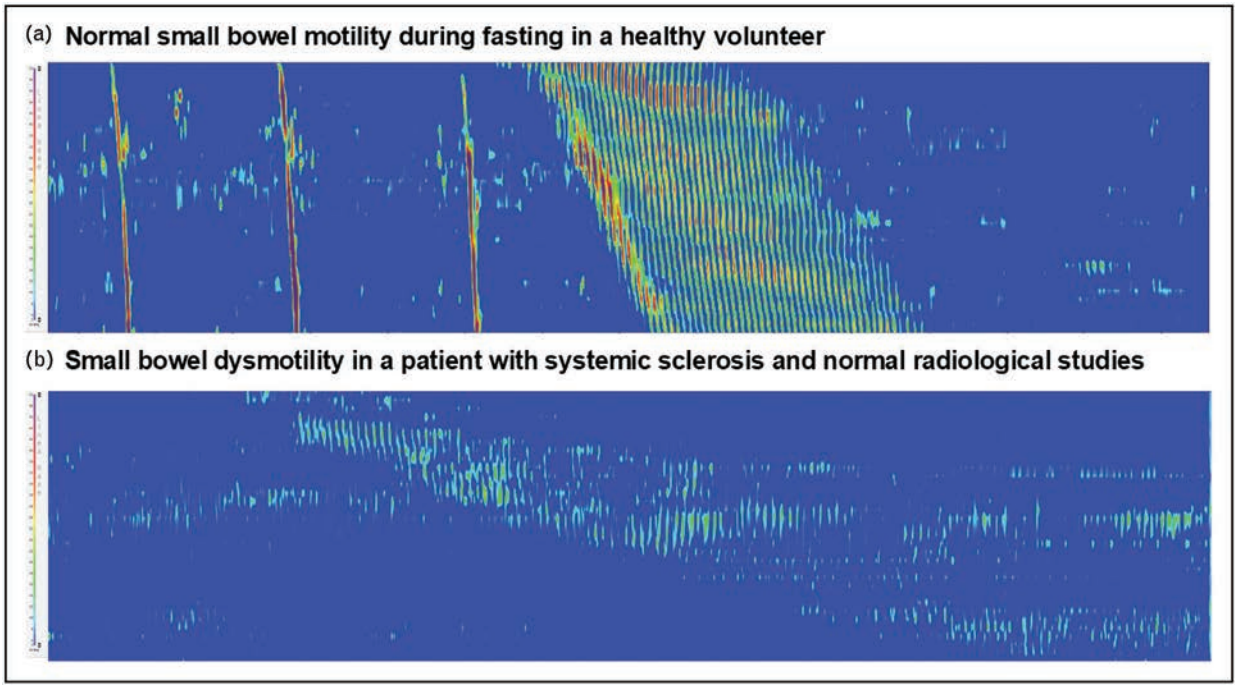

FIGURE 3. High-resolution jejunal manometry findings illustrating small bowel dysmotility in a patient with systemic sclerosis, gastrointestinal symptoms and normal radiological imaging. Upper (a) Normal migrating motor complex (MMC) recorded in a healthy individual, characterized by an initial period of irregular propagated contractions (phase II), followed by regular, high-amplitude propagated contractions (phase III), and concluding with motor quiescence (phase I). Lower (b) Abnormal migrating motor complex (MMC) recorded in our patient, demonstrating absence of propagated contractions during phase II and significantly reduced contraction amplitude during phase III, consistent with small bowel dysmotility despite normal radiology.

ADVANCES IN TREATMENT

A new approach for fundoplication

Nissen fundoplication is often avoided in patients with SSc due to the risk of inducing a lower esophageal obstruction. A case report recently described a patient with refractory dcSSc-GERD who successfully underwent a laparoscopic hiatal hernia repair and transincisoral fundoplication using the EsophyX Z device (EndoGastric Solutions, Redmond, Washington, USA). Twenty fasteners (12 and eight fasteners placed along the lesser and greater gastric curvatures, respectively) were placed to reconstruct a GE barrier. At 3 years of follow-up, GERD symptoms were controlled without any report of dysphagia for liquids or solids [33]. While larger studies are needed, this study suggests that a subset of refractory patients may benefit from novel surgical approaches.

The role of immunosuppressive and IVIG therapy

A significant caveat in the management of gastrointestinal involvement in SSc is that no disease-modifying treatments are currently approved. However, recent evidence suggests that immunomodulatory strategies may be beneficial. A retrospective cohort study analyzed 209 patients from the EUSTAR database who completed the UCLA SCTC GIT 2.0 questionnaire at two time points, approximately 12 ± 3 months apart [34]. Among them, 71 patients received immunosuppressive treatment (including methotrexate, mycophenolate mofetil, rituximab, or tocilizumab) during the observation period. Their results show that exposure to immunosuppression was independently associated with improved UCLA SCTC GIT 2.0 scores at follow-up, and these findings suggest a potential therapeutic role of immunosuppression in managing gastrointestinal manifestations. In parallel, several studies have explored the therapeutic potential of intravenous immunoglobulin (IVIG) for SSc-related gastrointestinal symptoms, particularly in refractory cases of chronic intestinal pseudo-obstruction (CIPO). A case series by Matsuda *et al.* [35] reported three patients with SSc-myositis overlap who experienced rapid and marked clinical improvement in gastrointestinal symptoms, nutritional status, and radiographic findings following IVIG (2 g/kg over 5 days), after failing standard immunomodulatory therapies. All patients showed increased bowel motility and were weaned off parenteral nutrition. Further supporting these findings, a focused case-based literature review by Neto *et al.*[36] evaluated 25 patients from four published studies and patients from their own center, all treated with IVIG for primary gastrointestinal involvement in SSc, using the UCLA SCTC GIT 2.0 as the outcome measure. Though promising, the evidence remains largely observational, underscoring the need for randomized controlled trials using both validated instruments like the UCLA SCTC GIT 2.0 and objective evidence of gastrointestinal dysmotility to rigorously assess whether immunosuppressive therapy and IVIG offer significant benefit for gastrointestinal involvement in SSc. Furthermore, the timing of therapeutic initiation, assessment of response to therapy, and subgroup(s) of patients that would benefit remain unknown.

Supporting the use of prokinetics in systemic sclerosis

A recent systematic literature review summarized the available evidence on the use of prokinetics for managing gastrointestinal dysmotility in SSc, demonstrating beneficial, organ-specific effects across various agents [37]. Metoclopramide consistently improved esophageal, gastric, and colonic motility, while cisapride and erythromycin showed selective effects on gastric and colonic transit but had limited impact on esophageal function. Octreotide enhanced small bowel motility, particularly in patients with CIPO. Symptomatic improvement with prokinetic therapy was reported in five of eight studies, although the majority employed nonvalidated assessment tools. Despite methodological heterogeneity and small sample sizes, the findings suggest that prokinetics may offer both targeted and pan-enteric benefits with minimal short-term adverse effects. However, evidence on long-term safety remains limited, highlighting the need for future well designed studies to better define patient stratification strategies and optimize treatment outcomes.

CONCLUSION

Gastrointestinal involvement represents a crucial yet frequently overlooked aspect of SSc, significantly influencing patient outcomes and QoL. Accurate assessment of gastrointestinal motility is vital, as symptoms alone lack the sensitivity and specificity needed for definitive evaluation. Objective diagnostic tools such as high-resolution manometry, scintigraphy, and advanced imaging techniques offer the potential to reliably detect early gastrointestinal involvement, guiding clinical management more effectively. Future research should continue to prioritize the establishment of clear correlations between specific clinical phenotypes, immunological biomarkers, and gastrointestinal organ dysfunction. This approach will not only enhance the precision of early diagnosis but also promote the timely initiation of targeted therapies, potentially mitigating disease

progression and improving patient prognosis. Encouraging interdisciplinary collaboration among gastroenterologists and rheumatologists remains essential to advance our understanding of SSc-related gastrointestinal disease.

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Conflicts of interest

There are no conflicts of interest.

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A comprehensive systematic literature review of the current evidence using prokinetics to manage patients with SSc.

Decoding vascular dysfunction in systemic sclerosis: from endothelial damage to clinical implications

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Purpose of review
This review explores the evolving understanding of vascular dysfunction in systemic sclerosis (SSc), from early endothelial injury to clinical manifestations and emerging therapeutic strategies.

Recent findings
Endothelial cell (EC) injury, senescence, and endothelial-to-mesenchymal transition are central to SSc vasculopathy. Single-cell and spatial omics have revealed distinct EC subtypes and dysregulated pathways, including interferon signaling and chromatin remodeling. Immune-mediated damage, viral triggers, and autoantibodies contribute to vascular pathology. Clinically, complications such as Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, and renal crisis drive morbidity and healthcare burden. Diagnostic tools such as nailfold capillaroscopy enable early detection of microvascular changes. Novel therapies including CAR-T therapy, JAK inhibitors, and complement blockade, are under investigation.

Summary
Vascular dysfunction is a hallmark of SSc and a key driver of disease progression. Advances in molecular profiling and imaging have improved our understanding of its mechanisms and opened new avenues for targeted intervention. Early diagnosis, biomarker-guided care, and multidisciplinary management are essential to improving outcomes.

Keywords
diagnosis, endothelial cells, scleroderma, treatment, vasculopathy

INTRODUCTION

Systemic sclerosis (SSc), or scleroderma, is a complex autoimmune disease marked by immune dysregulation, vascular abnormalities, and progressive fibrosis affecting multiple organs. It manifests primarily in two forms: diffuse cutaneous SSc and limited cutaneous SSc, distinguished by the extent of skin involvement. Autoantibody profiles serve as valuable biomarkers, aiding in the prediction of disease subtype and potential organ involvement. Among the most frequently used autoantibody biomarkers are anti-centromere antibody, anti-topoisomerase I, and anti-RNA polymerase III, which are associated with distinct clinical subsets of SSc. While the precise etiology remains elusive, both genetic predisposition and environmental triggers are implicated. The pathogenesis of SSc involves three interrelated mechanisms: dysregulated innate and adaptive immune responses, vascular dysfunction, and fibroblast activation, leading to excessive extracellular matrix (ECM) deposition. Current treatments are largely symptomatic, with only two FDA-approved therapies, nintedanib and tocilizumab, specifically targeting SSc-associated interstitial lung disease. This underscores the urgent need for deeper mechanistic insights and novel therapeutic strategies.

Vascular involvement is often among the earliest clinical manifestations of SSc. Complications such as Raynaud's phenomenon (RP), digital ulcers (DU), telangiectasia, gastric antral vascular ectasia, pulmonary arterial hypertension (PAH), and scleroderma renal crisis (SRC) stem from early endothelial injury. This injury initiates a cascade of functional and structural vascular changes, including increased permeability,

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KEY POINTS

- Endothelial dysfunction is a central and early event in systemic sclerosis, driving both destructive and proliferative vasculopathy.
- Immune-mediated injury, viral triggers, and endothelial senescence promote vascular rarefaction, endothelial-to-mesenchymal transition, and fibrosis.
- Single-cell and spatial omics have revealed distinct endothelial subpopulations and molecular pathways involved in SSc vasculopathy.
- Nailfold capillaroscopy is a valuable noninvasive tool for early detection and monitoring of microvascular changes in SSc.
- Novel therapies including CAR-T cells and JAK inhibitors are emerging to target vascular pathology more directly.

microvascular rarefaction, impaired nitric oxide signaling, and defective angiogenesis [1,2]. These changes are compounded by endothelial-to-mesenchymal transition (EndoMT), driven by profibrotic mediators such as TGF-β, which further promotes tissue fibrosis. Electron microscopy of nailfold capillaries in early SSc reveals hallmark features such as capillary dropout, intercellular gaps, and interstitial edema, reflecting microvascular regression [3,4]. These vascular abnormalities facilitate immune cell infiltration and fibroblast activation, linking vasculopathy directly to fibrosis.

Recent advances in molecular profiling and preclinical models have identified new therapeutic targets, particularly within inflammatory and fibrotic signaling pathways. Repurposed medications and biologics targeting these pathways are now entering clinical trials, offering hope for more effective disease-modifying treatments, ones that also improve vascular functions. In addition, diagnostic tools such as the nailfold capillaroscopy (NFC) have emerged as noninvasive tools for early detection and monitoring of microvascular changes in SSc. This review will explore the evolving landscape of SSc vasculopathy, including advances in endothelial cell (EC) biology, clinical characterization of vascular symptoms, diagnostic utility of capillaroscopy, and emerging and investigational therapies targeting vascular pathways. Understanding the vascular component of SSc is essential for developing targeted interventions that can alter disease progression and improve patient outcomes.

PATHOPHYSIOLOGY OF VASCULAR DYSFUNCTION IN SYSTEMIC SCLEROSIS

Endothelial injury and dysfunction are central to the pathogenesis of SSc, playing a critical role in both the early onset and progression of vascular complications. The endothelium, a metabolically active monolayer lining the vasculature, maintains vascular homeostasis by regulating vascular tone, coagulation, inflammation, and angiogenesis. In SSc, this regulatory balance is disrupted early in the disease course, initiating a cascade that leads to widespread vasculopathy and fibrosis (Fig. 1).

The initial insult to ECs in SSc is believed to be immune-mediated. There is growing evidence that both autoantibodies and immune cells are involved. A recent study demonstrated that immunoglobulin G (IgG) antibodies from SSc patients, particularly those with antitopoisomerase I antibodies, significantly alter the molecular signatures of ECs, affecting both gene and protein expression, and suggesting a direct pathogenic role of these antibodies in vascular injury [5]. Interestingly, antibodies against angiotensin II or endothelin-1 receptors did not appear to influence EC molecular profiles, a finding consistent with van Oostveen *et al.*, who used cell-based functional assays to assess the activity of autoantibodies against angiotensin II type 1 receptor and endothelin-1 type A receptor [6▪]. In another study, anti-IFI16 antibodies were significantly associated with the development or persistence of DU in SSc [7]. Patients positive for these antibodies exhibited more severe peripheral vasculopathy and were over eight times more likely to develop DU. Although these findings are preliminary and require further validation, they suggest that specific autoantibodies may serve as predictive biomarkers for identifying high-risk patients. These findings also underscore the role of B cells in SSc-related vasculopathy. Notably, patients treated with CD19-targeted CAR-T cells showed a reduction in DU counts, shorter ulcer duration, and decreased severity of RP [8▪▪]. In addition to B cells, T cells have also been implicated in endothelial dysfunction. Previous studies have documented the presence of cytotoxic T cells capable of inducing endothelial apoptosis in SSc [9]. More recent research has shown elevated levels of cytotoxic $CD4^+$ and $CD8^+$ T cells in SSc patients, with PAH being associated with a pro-inflammatory Th17 and T helper cell phenotype [10]. Furthermore, neutrophils and neutrophil extracellular traps (NETs) have recently been implicated in SSc vasculopathy. Elevated levels of NETs have been observed in SSc patients and were found to correlate with vascular complications [11▪], highlighting the multifaceted immune-mediated mechanisms underlying endothelial dysfunction in SSc.

Beyond immune dysregulation, external factors such as viral infections have also been implicated in the pathogenesis of vascular dysfunction in SSc. Human cytomegalovirus (hCMV) infection has been

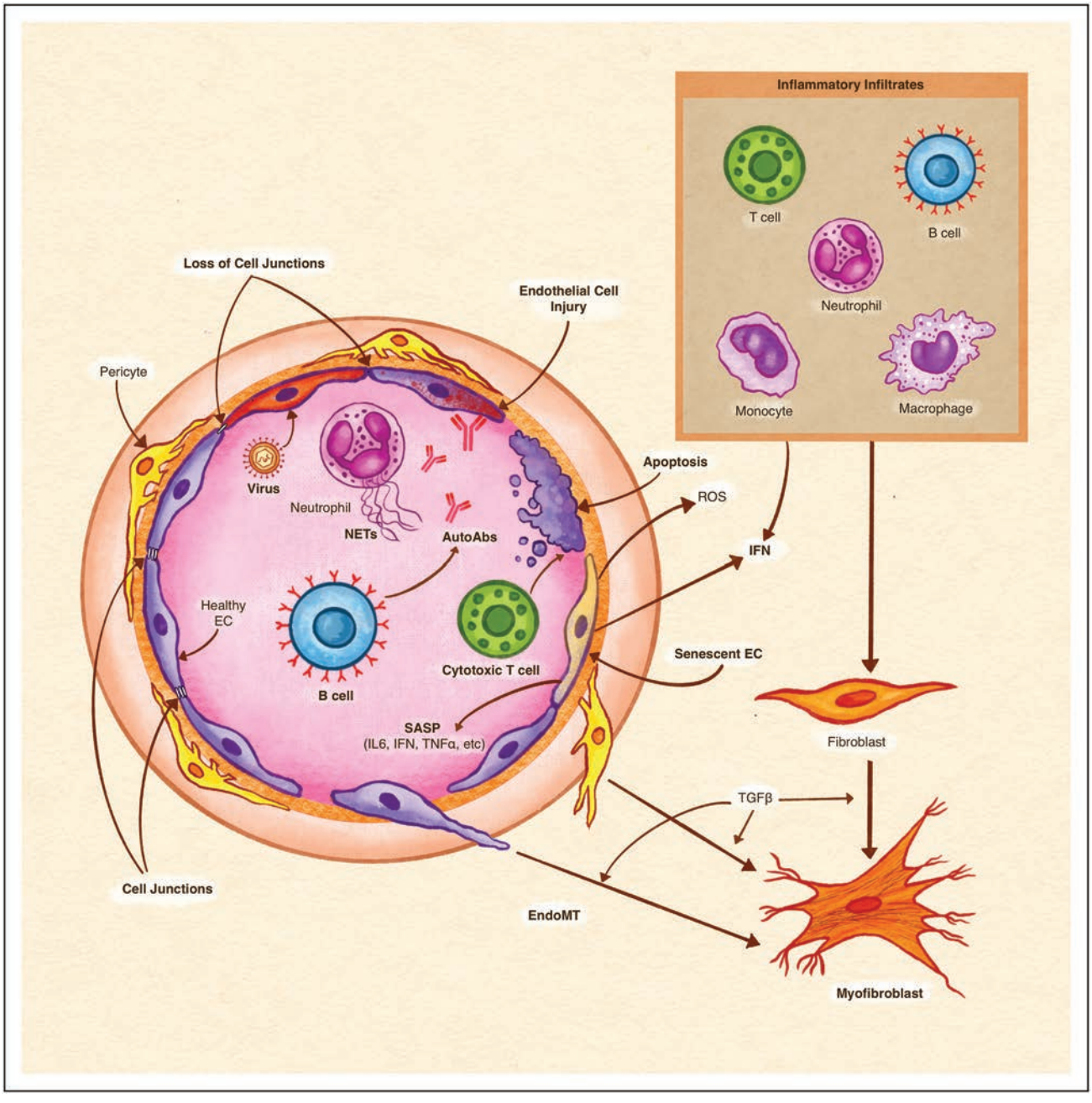

FIGURE 1. Cellular and molecular mechanisms of EC injury and inflammation in SSc, as summarized from recent studies. Endothelial cell (EC) injury is a central feature of SSc vasculopathy, leading to loss of cell junctions, apoptosis, senescence, and endothelial-to-mesenchymal transition (EndoMT). Potential triggers of EC injury include viral infections, autoantibodies (AutoAbs), neutrophil extracellular traps (NETs), and cytotoxic T cells. Injured and senescent ECs release reactive oxygen species (ROS) and pro-inflammatory mediators including interferons (IFNs). In combination with transforming growth factor β (TGFβ), these factors drive fibroblast activation and differentiation into myofibroblasts, promoting tissue fibrosis. The inset depicts the inflammatory infiltrate, comprising T cells, B cells, neutrophils, monocytes, and macrophages, which further contribute to vascular and tissue pathology. SASP: senescence-associated secretory phenotype.

shown to induce an aberrant endothelial phenotype, characterized by antiangiogenic effects, impaired EC migration, enhanced platelet adhesion, and increased expression of adhesion molecules [12,13]. Although direct causality remains to be established, indirect evidence supports a role for hCMV in SSc vasculopathy. For example, CMV-specific antibodies in the sera of SSc patients have been associated with the presence of SSc-specific autoantibodies [14]. In addition, hCMV-specific $CD8^+$ T cell responses are significantly

elevated in SSc patients compared to healthy controls, and this elevation correlates with longer disease duration and higher modified Rodnan skin scores (mRSS) [15]. Similarly, Epstein-Barr virus (EBV) has been implicated in SSc-related vascular injury. EBV DNA loads are significantly elevated in the blood, B cells, and monocytes of SSc patients [16]. EBV-infected monocytes can transfer the virus to ECs, triggering a TLR9-mediated innate immune response and upregulating markers of vascular injury. High EBV loads have also been associated with clinical signs of vascular damage, such as DU and reduced skin perfusion. These findings suggest that EBV lytic infection may directly contribute to endothelial dysfunction in SSc. Furthermore, SSc patients exhibit significantly higher levels of IgM and IgG antibodies against various EBV antigens, suggesting reactivation of latent EBV infection rather than active viral replication [17].

A hallmark of endothelial dysfunction in SSc is the imbalance between vasodilators and vasoconstrictors. Patients exhibit a marked reduction in vasodilatory mediators such as nitric oxide and prostacyclin, alongside an increase in the potent vasoconstrictor endothelin-1 [18,19]. This dysregulation contributes to vasospasm and tissue ischemia, manifesting clinically as RP and other vascular complications. Paradoxically, despite elevated circulating levels of angiogenic factors, angiogenesis is impaired in SSc. This is partly due to intrinsic dysfunction of ECs, particularly in pathways essential for angiogenesis [20]. In addition, endothelial progenitor cells, which are critical for vascular repair and regeneration, also exhibit functional impairment in SSc [21]. Beyond angiogenic dysregulation, inflammatory signaling pathways have been implicated in SSc vasculopathy. ECs from SSc patients, especially those with diffuse cutaneous involvement, display a strong type I interferon (IFN) signature [22▪]. Using single-cell RNA sequencing, animal models, and patient biopsies, IFN signaling has been shown to promote endothelial dysfunction, EndoMT, vascular rarefaction, and fibrosis. The IFN-inducible protein MX1 is elevated in SSc skin and has been identified as a potential predictor of disease progression. These findings are further supported by a recent study showing that SSc patients with higher circulating type I IFN scores had significantly worse lung function, greater functional disability, and increased mortality, although this study did not directly assess vascular endpoints [23▪▪]. Moreover, in patients with very early diagnosis of systemic sclerosis (VEDOSS), elevated levels of CXCL10 were detected in both skin and serum, further indicating activation of the IFN pathway in the earliest stages of disease [24▪▪].

The aforementioned factors collectively contribute to EC injury, resulting in a compromised vascular barrier and the initiation of inflammatory responses. Damaged ECs upregulate adhesion molecules such as VCAM-1 and ICAM-1, which facilitate leukocyte adhesion and transmigration into the vessel wall. A recent meta-analysis confirmed significantly elevated circulating levels of ICAM-1, VCAM-1, PECAM-1, E-selectin, and P-selectin in patients with SSc, supporting the role of endothelial activation in disease pathogenesis [25]. This promotes perivascular inflammation, perpetuating a cycle of endothelial damage and immune cell recruitment. A key pathological feature of SSc vasculopathy is EndoMT. This process, in which ECs acquire mesenchymal and fibrotic characteristics, has been demonstrated through immunostaining of skin biopsies, cultured ECs, and single-cell RNA sequencing and proteomics analyses [1,22▪,26,27▪,28▪▪,29]. EndoMT contributes to vascular remodeling, fibrosis, and loss of endothelial integrity. Notably, autologous stem cell transplantation has been shown to reduce EndoMT in SSc patients, suggesting a potential therapeutic avenue for reversing or mitigating vascular damage [30].

Advances in next-generation sequencing technologies have enabled detailed characterization of EC subpopulations and the molecular mechanisms underlying vasculopathy in SSc. Using single-cell RNA sequencing Gur *et al*. profiled skin biopsies from a large SSc cohort and identified diverse cell types, including immune cells, fibroblasts, pericytes, ECs, melanocytes, keratinocytes, and nerve cells [31]. Within the endothelial compartment, they identified two distinct EC subclusters: *ACKR1*$^{+}$ and *RBP7*$^{+}$ ECs. The proportion of these EC clusters was significantly increased in SSc skin, particularly in patients with high skin scores. An expansion of the pericyte population was also observed, suggesting active vascular remodeling. Furthermore, they reported disruptions in ligand-receptor signaling pathways in ECs, involving angiogenesis, vascular tone regulation, coagulation, and complement activation. In a complementary study, Huang *et al*. conducted the first multiomic analysis of ECs in SSc skin using single-cell RNA sequencing and chromatin accessibility profiling [32]. They observed a reduction in arterial ECs in SSc skin compared to healthy controls, while identifying novel EC subsets, including tip ECs and proliferating ECs, which showed varying degrees of correlation with clinical features. Chromatin accessibility analysis revealed enrichment of ETS family transcription factors in SSc ECs, suggesting epigenetic reprogramming. Ma *et al*. combined single cell RNA sequencing and spatial transcriptomics in skin biopsies from 22 patients with early diffuse SSc and 18 healthy controls to map the complex cellular landscape and intercellular communication in SSc skin [27▪]. They identified a unique EC cluster undergoing EndoMT, characterized by upregulation of ECM genes and downregulation of endothelial markers.

Bioinformatic analysis highlighted the Hippo signaling pathway as a key driver of EndoMT. Inhibition of YAP or knockdown of Hippo pathway transcriptional co-activators suppressed EndoMT in cultured ECs derived from SSc skin. In addition to transcriptomic approaches, Rigau *et al*. employed three spatial proteomics platforms to visualize the vascular niche in SSc skin [28▪▪]. They identified a population of $CD34^{+}\alpha SMA^{+}CD31^{+}$ ECs, which were increased in SSc skin and expressed EndoMT markers. These cells were surrounded by myofibroblasts and inflammatory cells, including T cells and myeloid cells. The density of these ECs correlated with skin fibrosis progression and disease activity, though not with vascular symptoms. In contrast, endothelial precursor cells were reduced in SSc skin and exhibited minimal interaction with immune cells.

Historically, research on SSc has focused on EC apoptosis, with strong evidence supporting its presence in SSc-affected skin. For instance, Huang *et al*. identified TGF-β and IFN signaling pathways in SSc EC clusters and linked them to EC apoptosis [32]. However, these same pathways are also known to induce cellular senescence. Notably, the markers validated in their study, such as IGFBP3 and PIGF, are associated with senescence [32]. Our own findings further support this, showing that dermal ECs in SSc skin exhibit the highest senescence scores, alongside fibroblasts and pericytes, when compared to healthy skin [33▪]. In fact, endothelial senescence may offer a unifying explanation for the dual forms of vasculopathy observed in SSc. Senescent ECs contribute to vascular rarefaction, leading to destructive vasculopathy, while their secretion of inflammatory and proliferative factors, collectively known as the senescence-associated secretory phenotype, can promote proliferative vasculopathy by stimulating vascular smooth muscle cell growth. Moreover, EC senescence has been mechanistically linked to EndoMT, a key process in SSc-related fibrosis [34]. Evidence of endothelial senescence has also been reported in other fibrotic diseases, further supporting its relevance as a shared pathogenic mechanism [34,35].

CLINICAL MANIFESTATIONS OF VASCULAR DYSFUNCTION

Raynaud's phenomenon, digital ulcers, and very early diagnosis of systemic sclerosis

As eluded earlier, microvascular dysfunction is an early hallmark of SSc and can manifest years before fibrosis outwardly develops [36]. VEDOSS cohort authors acknowledged that diagnosis and treatment of SSc were dependent on outward manifestations of irreversible organ damage [37]. Recognizing that microvascular dysfunction is present in early and preclinical SSc, earlier diagnosis and treatment could occur if evaluation for early microvascular changes was performed. In 2018 Bellando-Randone *et al*. published their five-year analysis of the VEDOSS cohort, identifying RP and abnormal NFC as early markers of vascular dysfunction.

RP occurs in over 90% of SSc patients and often precedes other symptoms. It is characterized by an abnormal vascular response to cold and stress, leading to excessive vasoconstriction or vasospasm of arteries and skin arterioles. This response appears as demarcated color changes in a classic biphasic or triphasic pattern: white, followed by blue, then red, or simply white to red. In SSc-related RP, nutritional capillaries may also be affected, increasing the risk of critical ischemic complications such as DU and gangrene [38]. Repeated episodes of RP and underlying microvascular dysfunction contribute to the development of DU [39].

Telangiectasias

Cutaneous telangiectasias, which are variably sized and branching dilated postcapillary vessels, commonly appear on the face, upper extremities, anterior chest, and oral mucosa. Although telangiectasias may be seen in a variety of diseases, their presence in SSc is an external indicator of vascular dysfunction. The formation of telangiectasias is believed to be linked, at least in part, to endothelial injury and its accelerated degeneration. Research shows a strong correlation between increasing telangiectasia in SSc and the progression of vasculopathy or microangiopathy [40▪]. Telangiectasias serve as visible markers of vascular dysfunction and are included in the 2013 ACR-EULAR classification criteria for SSc [41].

Pulmonary arterial hypertension

PAH is the leading cause of morbidity and mortality in SSc. It results from the involvement of small and medium-size pulmonary arteries. Vascular remodeling leads to stenosis and stiffening of the vessels, increased vascular resistance, and resultant right heart failure [42].

Scleroderma renal crisis

Chronic vasculopathy plays a critical role in various renal manifestations of SSc, although renal vasculopathy in SSc is often overlooked except in the case of SRC. SRC is a life-threatening condition characterized by severe hypertension, thrombotic microangiopathy, and acute kidney injury, evidenced by

elevated serum creatinine levels. It is driven by endothelial dysfunction, which results in the proliferation of arcuate and intralobular arteries, intimal thickening, luminal narrowing, changes in the arterial media, and fibrosis [43,44].

Gastrointestinal involvement

SSc can affect any part of the gastrointestinal (GI) tract, with symptoms arising from vascular, myopathic, and neuropathic alterations. Vascular changes, such as endothelial damage and inflammation, lead to fibrosis, impaired motility and clinical symptoms. Esophageal issues occur due to microvascular and inflammatory alterations in smooth muscle and connective tissue, resulting in fibrosis and dysfunction. Similarly, bowel involvement stems from fibrosis-induced stiffness and reduced smooth muscle contractility. Ongoing fibrosis and vascular damage can cause GI telangiectasias and gastric antral vascular ectasia, which may lead to bleeding, anemia, and further irritation of the GI tract [45,46].

DIAGNOSTIC TOOLS AND IMAGING TECHNIQUES

Nailfold capillaroscopy

Microvascular imaging with NFC is a crucial way to evaluate evolving microangiopathy in SSc. Nailfold capillaries run parallel to the skin surface near the nailfold; as such, they are a viable, noninvasive location for examination of vessel structure. As vasculopathy progresses in SSc, a clear pattern of nailfold capillary changes can be seen; dilated and hemorrhagic capillaries can progress to decreased capillary density, drop out, and eventual ramification or disorganized neoangiogenesis. These changes can be evaluated and graded based on currently accepted standardization guidelines [47].

Advancing noninvasive imaging techniques

Several additional advanced imaging techniques are being explored. Lack of standardization makes uniform application of these modalities infeasible currently, but burgeoning research and documented outcomes support further exploration of these additional imaging techniques. Optical coherence tomography (OCT), laser doppler flowmetry (LDF), infrared thermography, and finger pulp blood flow via power doppler ultrasound (PDUS) are modalities that are currently utilized in select U.S. medical facilities or in international practice. OCT detects light that is reflected from tissue, allowing noninvasive, cross-sectional, and high-contrast imaging. It can demonstrate microvascular blood flow and potential microvascular lesions [39,48,49▪].

LDF is another noninvasive imaging modality. It assesses microvascular changes by measuring blood flow via a laser beam transmitted through a single probe placed on the skin. Doppler quantifies the amount of blood perfusion to the skin region [39]. Unsurprisingly, studies have demonstrated that patients with SSc have lower hand and finger peripheral blood perfusion compared to healthy comparative subjects [50]. One downside of LDF is that it cannot assess lesion development at a capillary level without additional measures such as cold stimulation experiments, which may be painful or cause worsening damage in SSc patients who are otherwise already at risk.

Infrared thermography indirectly assesses blood flow by measuring skin surface temperature. It can be utilized to evaluate for areas of local inflammation (which appear "hot") as well as areas of ischemia ("cold" areas), providing helpful information in RP and DU evaluation. It is time-intensive but can add to baseline NFC results for additional DU and RP risk evaluation. Results are affected by the environment and instrument accuracy/performer accuracy, leading to an increased incidence of inaccuracy [39,51].

PDUS measures Doppler amplitudes, allowing for qualitative grading of nailbed and fingertip indices. This allows for evaluation of finger pulp blood flow and ulnar artery occlusion, which are closely associated with DU and disease severity in SSc [39].

Observational studies demonstrate that magnetic resonance imaging digital artery volume index (MRI DAVIX), a quantitative noninvasive image score based on time-of-flight MRI, is a promising surrogate measure of DU disease [52,53]. Time-of-flight MRI is a noninvasive, noncontrast enhanced magnetic resonance angiography that produces images between vessels and stationary tissues by inducing blood inflow effects. MRI DAVIX has differentiated patients with and without DU, and has predicted the onset of new DU in SSc patients [52,53].

CURRENT AND EMERGING THERAPEUTIC STRATEGIES

Pharmacologic approaches

Table 1 provides an overview of pharmacologic strategies for managing selected complications associated with SSc. Currently, there are no medications specifically FDA approved for RP or DU in the United States. However, the 2023 European Alliance of Associations for Rheumatology (EULAR) treatment recommendations for SSc outlines a stepwise approach to RP: dihydropyridine-type calcium antagonists (first line), phosphodiesterase 5 (PDE5) inhibitors

Table 1. Pharmacologic treatments for vascular manifestations of SSc

Manifestation	Treatment
Raynaud's phenomenon	*Dihydropyridine Calcium Channel Blockers: amlodipine nifedipine *Phosphodiesterase 5 Inhibitors: sildenafil *Prostacyclin Agonists: IV iloprost IV epoprostenol *Endothelial Receptor Agonists: bosentan *Selective Serotonin Reuptake Inhibitors: fluoxetine Others: *High-dose atorvastatin (added to standard vasodilator therapy) *Topical Nitropaste 2% *Botulinum toxin-B injections
Digital ulcerations	Same as RP with some adjunctive measures: *Local oxygen - ozone therapy Wound care
Pulmonary arterial hypertension	Phosphodiesterase 5 Inhibitors: sildenafil tadalafil Endothelial Receptor Agonists: bosentan ambrisentan Prostacyclin Receptor Agonist: selexipag Soluble Guanylate Cyclase Agonist: riociguat Prostacyclin Agonists: IV epoprostenol IV iloprost Inhaled treprostinil
Renal crisis	Complement C5 Inhibitors: eculizumab Angiogensin-Converting Enzyme Inhibitors: captopril (preferred agent)
GI vascular complications	Supportive care Proton pump inhibitors EGD surveillance and sclerotherapy Blood transfusion

EGD, esophagogastroduodenoscopy; GI, gastrointestinal; IV, intravenous; RP, Raynaud's phenomenon; SSc, systemic sclerosis.
*Off-label use.

(second line), then intravenous epoprostenol for severe disease following failure of oral therapy [54▪▪]. Atorvastatin at high doses (40–80 mg daily) could be added to vasodilator therapy for additional endothelial stabilization. PDE5 inhibitors and IV epoprostenol are considered for DU treatment along with bosentan to reduce new ulcer formation [54▪▪]. Adjunctive local oxygen-ozone treatment was proven efficacious for resistant DU in a recent small randomized placebo controlled trial [55] and could be considered where available. Angiotensin converting enzyme inhibitors remain the cornerstone of management of SRC. Morbidity and mortality, although improved, remain high with 40% of SRC patients requiring dialysis and 20-25% dying within one year of diagnosis [56]. Complement activation has been hypothesized to be involved in the pathophysiology of SRC [56], and there is a growing body of evidence supporting the adjunctive use of the complement C5 inhibitor eculizumab for refractory disease [56–58].

Role of immunosuppressive therapy

Immunosuppressive therapies are extensively utilized in managing the inflammatory and fibrotic manifestations of SSc. For the vascular complications, JAK inhibitor baricitinib may be beneficial for DU [59,60], but larger studies are needed to confirm. CAR-T therapy, which is under investigation in rheumatic diseases, involves the genetic engineering of T cells to express chimeric antigen receptors (CARs) which recognize specific antigens on cells of interest, resulting in the targeted cytotoxicity and elimination of those cells. Both autologous and allogenic CAR-T therapy have been reported in case series and reports to be effective for improvement in skin fibrosis [8▪▪,61▪,62▪,63▪▪], DU [8▪▪,64], and American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS) composite response index scores [8▪▪,62▪] in treated SSc patients. Bispecific T cell engagers (BiTEs), also presently investigated for autoimmune diseases, are engineered antibodies designed to simultaneously bind cytotoxic T lymphocytes and target cells, thereby redirecting T cell cytotoxicity to the target and inducing cell lysis independently of major histocompatibility complex recognition. Blinatumomab, a CD3/CD19 T cell engager, was successfully used in a 35-year-old male with severe diffuse SSc characterized by puffy fingers, RP with DU, rapid cutaneous fibrosis, inflammatory arthritis and myocardial fibrosis on cardiac MRI [65▪]. The fibrotic features improved after three weeks while the RP episodes improved after the fourth cycle.

IMPLICATIONS FOR CLINICAL PRACTICE

SSc has many socioeconomic and health related implications. In the United States, a retrospective study using a claims data set (Merative MarketScan; 2015–2019) demonstrated that SSc patients accrued

Table 2. Novel autoantibody biomarkers for SSc vasculopathy

Autoantibody	Target Antigen	Clinical Phenotype
Anti-eIF2B	Eukaryotic translation initiation factor 2B	Diffuse SSc, ILD, Overlap features with arthritis, myositis, possibly malignancy [71]
Anti-RuvBL1/2 complex	RuvBL1/2 double hexamer	Diffuse SSc, myositis overlap, GI dysmotility, myocardial complications [71]
Anti-RNPC-3	U11 and U12 ribonuclear proteins	Diffuse SSc/Limited SSc, Raynaud's, ILD, pulmonary fibrosis, PAH, esophageal dysmotility, myopathy, malignancy [71]
Anti-BICD2	Human protein bicaudal D homolog 2	Diffuse SSc, ILD, Inflammatory myopathy [71]
Anti-SSSCA-1	Sjogren's syndrome /scleroderma autoantigen 1	Malignancy, severe Raynaud's, cardiac involvement [72]
Anti-PRMT5	Protein arginine methyltransferase 5	Correlates with disease trajectory in SSc [73▪]
Anti-IFI16	Interferon gamma inducible protein 16	Limited SSc, PAH, persistent DU [74]
Anti-Annexin V	Annexin V	PAH and digital microangiopathy [75]
Anti-Vinculin	Vinculin	PAH, gastrointestinal manifestations [76,77]
Anti-Gephyrin	Enteric nervous system gephyrin antigen	GI disturbance - severe constipation, distention, and bloating [78]

DU, digital ulcers; ILD, Interstitial lung disease; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

greater costs and required more services than the general population cohort. Mean annual per member costs increased incrementally at intervals of two years before, one year before and one year after index diagnosis for SSc patients ($22 383 to $29 708 to $47 095) versus the general population at the same time points ($10 232 to $9656 to $9714) [66]. Among the most debilitating complications, DU significantly impair health-related quality of life, affect physical function, psychological well being, and work productivity. DU are also associated with increased healthcare utilization, hospitalization rates, and higher mortality risk [67,68]. An Australian study determined that SSc patients with DU used significantly more healthcare resources per annum than those without, including hospitalizations, emergency department (ED) presentations, and ambulatory care services. The estimated annual excess cost per patient with DU was AUD$12 474 (8574–25 677), $P<0.001$. The cost, which excluded medications, was driven by ED presentations and hospital admissions [69]. A 2024 systematic review further highlighted the mortality, humanistic, and economic burden of SSc, particularly in relation to organ-specific manifestations [70]. Pulmonary hypertension (PH), cardiac, and renal involvement were consistently associated with poorer survival outcomes. PH was a stronger predictor of mortality than interstitial lung disease in nearly all included studies ($n=24$). In addition, gastrointestinal, cutaneous, and peripheral vascular manifestations were found to impact health-related quality of life negatively. These findings underscore the importance of early diagnosis and intervention, particularly in addressing SSc vasculopathy, to reduce morbidity, mortality, and the economic burden on healthcare systems globally.

Biomarkers play a critical role in the clinical management of SSc, aiding in diagnosis, prognosis, and treatment monitoring. They can be broadly categorized into two groups: those that are diagnostic and define specific clinical phenotypes, primarily autoantibodies, and those that predict the likelihood

Table 3. Nonautoantibody serum biomarkers for SSc vasculopathy

Serum protein biomarker	Function
Chemerin	Levels elevated in patients with limited SSc-PAH and correlated significantly with peripheral vascular resistance [79]
Eotaxin (CCL24)	Higher levels found in men with Scl-70+, synovitis, ILD, calcinosis, DU, telangiectasias [80]
Pentraxin-3 (PTX3)	An endothelial protein; low PTX-3 levels associated with reduced risk of pulmonary hypertension [81]
Endostatin	An endogenous anti angiogenic glycoprotein; higher levels found in patients with DU and pulmonary hypertension [82]

DU, digital ulcers; ILD, Interstitial lung disease; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

of disease manifestations. Novel autoantibodies and circulating biomarkers associated with SSc vasculopathy have also been identified and are summarized in Tables 2 and 3. While these emerging markers show promise for improving disease stratification and monitoring, further validation is necessary before they can be routinely implemented in clinical practice.

CONCLUSION

Vascular dysfunction is a central and early feature of SSc, intricately linked to immune dysregulation, fibrosis, and clinical outcomes. EC injury, driven by autoantibodies, immune cells, viral triggers, and inflammatory signaling, initiates a cascade of events including EndoMT, vascular rarefaction, and impaired angiogenesis. These processes contribute to the dual manifestations of destructive and proliferative vasculopathy observed in SSc. Recent advances in single-cell and spatial omics have revealed distinct EC subpopulations and molecular signatures, including senescence and chromatin remodeling, offering new insights into disease mechanisms and potential therapeutic targets. Clinically, vascular complications such as RP, DU, PAH, and SRC significantly impact morbidity, mortality, and healthcare costs. Early detection through tools such as NFC and emerging imaging modalities, combined with biomarker-driven risk stratification, can facilitate timely intervention. While current therapies primarily address symptoms, novel approaches, including CAR-T cell therapy, are beginning to target the vascular pathology directly. Future research should aim to consolidate EC nomenclature across studies by performing meta-analyses of different datasets, deepen our understanding of mural cell (pericyte and vascular smooth muscle cell) contributions, and validate emerging biomarkers and therapeutic strategies. By focusing on the vascular axis of SSc, we can pave the way toward more precise, mechanism-based interventions that improve long-term outcomes for patients.

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Conflicts of interest

There are no conflicts of interest.

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OPEN

Targeting inflammation, fibrosis, and vascular dysfunction in systemic sclerosis: the role of diet and complementary and alternative medicine

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Purpose of review
Patients with systemic sclerosis (SSc) often seek advice regarding diet including functional foods, and complementary and alternative medicine (CAM) as adjunctive therapies. This review summarizes existing literature regarding these approaches.

Recent findings
Study results of low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP), Mediterranean and ketogenic diets suggest symptom reduction and beneficial microbiota modulation in SSc, though sample sizes are small. Nitrate-rich and antioxidant supplements such as omega-3 fatty acids show promise in lowering inflammation and oxidative stress in the circulation. Herbal remedies like curcumin have demonstrated antifibrotic properties in preclinical models. Topical agents (e.g., rosemary oil, vitamin E gel) and nutritional vitamins (e.g., C, D, E) are also frequently used, though robust clinical trials are lacking.

Summary
CAM, dietary interventions, and functional foods may aid in SSc management, but more rigorous research is needed to provide definitive evidence.

Keywords
complementary and alternative medicine, diet, exposome, supplements, systemic sclerosis

INTRODUCTION

The exposome – including disordered sleep, gut dysbiosis, environmental exposures, diet, and stress – has garnered interest as a factor in systemic sclerosis (SSc) pathogenesis. Complementary and alternative medicine (CAM), rooted in Eastern practices, have gained popularity among physicians and patients as a potential SSc treatment [1,2▪]. SSc typically manifests in adulthood, prompting questions about its triggers and treatment [3]. This review highlights literature on functional foods, diets, vitamins, and supplements for managing SSc (see Table 1).

We searched OVID (1/2010–4/2024) using terms [scleroderm* or systemic scleros*], [alternative medicine], [alternative or complementary], [therap* or medicine* or drug*], [diet* or food or herbal], [supplement*] and [nutraceutical* or nutriceutical* or neutraceutical*]. We prioritized evidence-based clinical trials, systematic reviews, and observational studies.

DIET

Diet refers to structured food intake tailored for therapeutic or preventive purposes [4▪]. In SSc, impaired peristalsis and dysbiosis may intensify gastrointestinal symptoms. Diet influences gut flora impacting symptoms from inflammation (e.g., fatigue, pain) and smooth muscle dysfunction (e.g., diarrhea) [5]. For instance, an observational study of 42 SSc patients found significant associations between increased dietary sodium, suboptimal caloric intake, malnutrition, and weight loss with

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KEY POINTS

- CAM, influenced by Eastern medicine, has grown in popularity, leading physicians to offer evidence-based guidance in response to rising patient interest.
- Mediterranean and low-FODMAP diets appear to improve gastrointestinal symptoms and systemic inflammation through microbiome regulation.
- Curcumin and vitamin D exhibit antifibrotic and anti-inflammatory effects in systemic sclerosis by modulating TGF-β signaling, oxidative stress, and fibroblast activity.
- Beetroot juice and L-arginine support nitric oxide pathways, showing therapeutic potential for Raynaud phenomenon and vascular dysfunction in systemic sclerosis.

pulmonary hypertension, heart failure, elevated transaminases, and skin fibrosis in SSc [6]. Specifically, Mediterranean, ketogenic, and low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) diets have been studied in SSc.

LOW FODMAP

The low-FODMAP diet restricts ingestion of short-chain carbohydrates that are poorly absorbed in the small intestine. This reduces fermentation by gut bacteria that increases osmotic load and promotes pathobiont overgrowth, bacteria with inflammatory potential. In a cross-sectional study, 66 SSc patients with moderate-to-severe gastrointestinal symptoms underwent stool microbiota 16S rRNA sequencing and completed the UCLA SCTC GIT 2.0, a questionnaire measuring reflux, bloating, and bowel-related symptom severity, and 35 completed dietary surveys. Among 19 low-FODMAP followers, abundance of *Streptococcus*, *Enterococcus*, *Klebsiella*, and *Enterobacter* (the later three correlated with bloating and reflux) were reduced compared to 16 non low-FODMAP followers. Although total GIT 2.0 scores were not different between groups ($P = 0.349$), low FODMAP diet adherence may positively influence pathobiont composition in SSc patient stool [7].

KETOGENIC

The ketogenic diet, high in unsaturated fat and low in carbohydrates, induces ketosis where β-hydroxybutyrate (BHB) becomes the primary energy source. BHB exerts anti-inflammatory effects by inhibiting the NLR family pyrin domain containing 3 (NLRP3) inflammasome, an innate immune sensor. BHB prevents potassium efflux and reduces apoptosis-associated speck-like protein with a caspase-recruitment domain (ASC) oligomerization, thereby attenuating caspase-1 activation and downstream interleukin (IL) secretion in murine and human monocytes, IL-1β and IL-18 [8].

Unlike ketone bodies or short-chain fatty acids, BHB inhibits NLRP3 activation triggered by adenosine triphosphate, palmitate, and ceramides, independent of adenosine monophosphate-activated protein kinase (AMPK), reactive oxygen species (ROS), autophagy, or G protein-coupled receptor-109a [9▪]. These mechanisms support ketogenic diet's potential as an anti-inflammatory strategy.

MEDITERRANEAN

The Mediterranean diet, rich in olive oil, whole grains, legumes, fruits, nuts, vegetables, dairy, and fish, provides antioxidants and anti-inflammatory nutrients including carotenoids, vitamins A, C, and E, flavonoids, zinc, and selenium[9]. Anti-inflammatory mechanisms include lowering lipids, reducing oxidative damage, decreasing platelet aggregation and inflammatory markers [C-reactive protein (CRP), IL-6, and tumor necrosis factor-α (TNF-α)]. Mediterranean diets support a probiotic

Table 1. Key terms definitions related to dietary and complementary interventions in systemic sclerosis

Term	Definition	Examples from this review
Diet	A structured pattern of food intake tailored for therapeutic or preventive purposes, often aimed at modulating symptoms or disease activity.	Low-FODMAP, Ketogenic, Mediterranean
Functional foods	Foods or food components providing health benefits beyond basic nutrition, frequently by modulating physiological functions or reducing disease risk.	Beetroot, Rosemary, Curcumin
Vitamins	Organic compounds essential for normal metabolism, often supplemented to support cell function, immune response, and antioxidant activity.	Vitamin C, Vitamin D, Vitamin E
Dietary supplements	Orally consumed products containing one or more dietary ingredients (e.g., minerals, amino acids, herbs) intended to supplement the diet.	L-arginine, Omega-3 Fatty Acids, Para-Aminobenzoic Acid, Zinc

gut microbiome—an ecosystem characterized by beneficial gut metabolite production and greater abundance of bacteria associated with lower inflammation and improved gut function [10▪,11].

A prospective cohort of 2,023 general population adults assessed Mediterranean diet adherence via the Mediterranean Diet Score (numeric scale: 0–9) and found that score increases of 2–6 points over twelve years significantly reduced inflammation [β= -0.372, 96% confidence interval (96% CI) -0.720 to –0.025] based on a composite score of CRP, white blood cell and platelet counts, and granulocyte:lymphocyte ratio [12]. A cross-sectional survey of 387 SSc patients using the 14-item Mediterranean Diet Adherence Screener found 15% had optimal (score > 10), 71% moderate (6–9), and 14% low (0–5) adherence. Low adherence was linked to worse quality-of-life [e.g., work absenteeism ($P = 0.05$), depression ($P = 0.048$), Raynaud phenomenon ($P = 0.03$), digital ulcers ($P = 0.001$), and reflux (inverse correlation, $P = 0.05$)] [13].

FUNCTIONAL FOODS

Functional foods, herbal substances and foods for improved health and symptom reduction, remain understudied [14]; however, beetroot, rosemary, and curcumin may be beneficial SSc treatments.

BEETROOT

Beetroot is a nitrate-rich food containing vitamins, betalains, and phytonutrients, consumed as a supplement for its vasodilatory, anti-inflammatory, and thermoregulatory properties [15]. For Raynaud phenomenon sufferers in whom nitric oxide is low, beetroot may improve vascular function by boosting nitric oxide availability.

A double-blind, randomized crossover study of 23 patients with primary and secondary Raynaud phenomenon (17% with SSc) compared beetroot juice (12.4 mmol nitrate) to nitrate-depleted beetroot juice (NDBJ; 0.1 mmol of inorganic nitrate) and found that acute (140 ml consumed on testing days) and chronic (70 ml/day for 13 days + 140 ml consumed on testing days) supplementation improved thumb blood flow postcold challenge. Regardless of treatment duration, both beetroot juice and NDBJ significantly reduced systolic BP (acute NDBJ, $P = 0.02$; acute beetroot juice, $P < 0.001$; chronic NDBJ, $P < 0.001$; chronic beetroot juice, $P < 0.001$) and diastolic BP (acute NDBJ, $P = 0.02$; acute beetroot juice, $P < 0.001$; chronic NDBJ, $P < 0.001$; chronic beetroot juice, $P < 0.001$). IL-10 levels, an anti-inflammatory cytokine, increased significantly with acute NDBJ and beetroot juice (both $P < 0.001$), chronic NDBJ ($P = 0.001$), and chronic beetroot juice ($P = 0.002$). Plasma nitrate and nitrite were significantly elevated after both acute and chronic beetroot juice compared to NDBJ ($P < 0.001$ for all comparisons), with no differences between acute and chronic supplementation ($P > 0.05$). Serum pan-endothelin, a vasoconstrictor elevated in Raynaud phenomenon, decreased significantly with beetroot juice ($P = 0.03$). Thus, direct and indirect nitric oxide supplementation may improve Raynaud phenomenon [16].

ROSEMARY

Rosemary officinalis L, a medicinal herb from the Lamiaceae family, has antioxidant, anti-inflammatory, antimicrobial, vasodilatory, and wound-healing effects. A cross-over study design case report described an SSc patient whose hands were treated with rosemary oil 10% mixed with olive oil 90% daily, followed by olive oil 100% daily, each for three days. Daily infrared thermography following oil application showed increased right index finger mean temperature for the oil mixture (28.5°C–30.6°C) but not oil olive (25.13°C–24.03°C), while the left index finger showed minimal changes that were attributed to carpal tunnel syndrome [17]. In an open-label pilot study of twelve SSc-RP patients, a one-time hand application of olive oil 100% followed by rosemary oil 10% three hours later resulted in subjective increased hand warmth, although infrared thermography failed to show significant changes [18]. Thus, rosemary oil may improve Raynaud phenomenon symptoms and index finger skin temperature though sample sizes were small.

CURCUMIN

Curcumin, the active polyphenol in turmeric (*Curcuma longa*), exhibits anti-inflammatory and antifibrotic effects. It inhibits transforming growth factor-beta (TGF-β) signaling, a central fibrosis driver in SSc. In a bleomycin-induced mouse model, the curcumin analog LG283 significantly reduced dermal thickening/collagen deposition ($P < 0.01$). These antifibrotic effects were attributed to inhibition of TGF-β–induced Smad3 phosphorylation (a key mediator of profibrotic gene expression), and SNAIL1 and SNAIL2 expression (profibrotic transcription factors) [19]. In cultured SSc, but not healthy, lung fibroblasts, 6 h of 10 μM curcumin exposure selectively induced apoptosis. This effect involved altered protein kinase C epsilon signaling and reduced detoxification enzyme expression, including glutathione S-transferase P1 and heme oxygenase-1 [20]. Furthermore, a meta-analysis of 66 randomized clinical trials (RCTs) found that turmeric/curcumin supplementation significantly reduced levels of systemic inflammatory

markers [CRP, TNF-α, and IL-6] and improved antioxidant markers [total antioxidant capacity, superoxide dismutase (SOD) activity, and malondialdehyde] in individuals with various health conditions. These findings support curcumin's potential role for modulating inflammation and oxidative stress in SSc patients [21].

VITAMINS

Vitamins – organic substances that are classified either as fat soluble (e.g., vitamin D and E) or water soluble (e.g., vitamin B and C) – support cell function and growth [22].

VITAMIN C, D, AND E

Vitamin C (ascorbic acid) is both an enzymatic and nonenzymatic antioxidant with anti-inflammatory properties. In a 6-month study of 13 diffuse cutaneous (dc) SSc patients, those receiving cyclophosphamide (500 mg/m^2 monthly) plus vitamin C (1000 mg/day) and vitamin E (400 IU/day) had significantly lower skin thickening progression rates compared to six patients only receiving cyclophosphamide ($P<0.04$) [23].

Vitamin D is a steroid hormone with immunomodulatory and antifibrotic properties. Reduced Vitamin D receptor (VDR) expression in dermal fibroblasts from SSc patients and fibrosis mouse models is partly driven by TGF-β signaling. VDR activation by the selective agonist paricalcitol blocks Smad3 phosphorylation thereby reducing collagen production and fibroblast activation. In bleomycin-induced and constitutively active TGF-β receptor I mouse models, paricalcitol significantly reduced skin fibrosis via TGF-β/Smad pathway inhibition [24]. Thus, vitamin C and D supplementation may be beneficial for SSc skin fibrosis.

A systematic review of 40 studies confirmed the high prevalence of vitamin D deficiency in SSc and its correlation with severity (e.g., pulmonary hypertension, digital ulcers). Standard supplementation (800 IU/day) is often insufficient due to malabsorption or impaired vitamin D activation in fibrotic skin [25]. Vitamin D also supports reduction/oxidation (redox) homeostasis. A prospective study of 50 female SSc patients found significantly elevated urinary oxidative DNA damage markers, especially 8-oxo-2′-deoxyguanosine (8-oxo-dG), as well as reduced serum vitamin D and lower VDR gene expression measured by RT-PCR compared to controls. After intramuscular 150 000 IU (baseline and 3 months) and oral vitamin D 800 IU (six months daily), 8-oxo-dG levels declined, and whole blood mRNA VDR expression increased, particularly among patients with lung, joint, and gastrointestinal involvement [26]. These findings advance our understanding of vitamin D's role in modulating inflammation, oxidative stress, and fibrosis.

Vitamin E, a lipid-soluble antioxidant, regulates immune and fibrotic responses. A cross-sectional study of 14 women with SSc who took vitamin E (400 mg/day) for the prior six months showed persistent abnormalities of erythrocyte oxidation-balance measures compared to 23 untreated healthy controls. Specifically, they found increased levels of lipid peroxidation products in SSc overall ($P<0.01$), and reduced catalase and SOD activity ($P<0.05$) in four dcSSc patients, and increased glutathione peroxidase activity ($P<0.01$) in ten limited cutaneous SSc patients, versus controls. Thus, SSc patients may have oxidative stress defense mechanism imbalances with reduced ability to degrade hydrogen peroxide even with vitamin E supplementation [27].

A 24-week open-label study assessed twelve SSc patients receiving pentoxifylline (800 mg/day) plus vitamin E (800 IU/day) and compared them to a group of nine dcSSc patients treated with 6 months of cyclophosphamide (0.5–1 g/m^2). The pentoxifylline/vitamin E versus cyclophosphamide group showed a significant modified Rodnan Skin Score reduction from 25.7 to 18.7 ($P=0.03$) versus 37.7 to 32.8 ($P=0.06$) at week 16, respectively [28]. An open-label study of 27 SSc patients with 86 digital ulcers among them found 15 patients treated with topical vitamin E gel twice-weekly healed significantly faster (13.22 ± 2.72 weeks) compared to 12 receiving standard ulcer care (20.94 ± 3.65 weeks); $P<0.0001$ [29]. However, a double-blind RCT of 36 SSc patients (assigned to receive vitamin E 500 mg/day or vitamin E 1000 mg/day or placebo) found no improvement in lipid peroxidation levels [urinary F(2)-isoprostanes] or microvascular perfusion (laser doppler perfusion imager) after 3 weeks of treatment [30]. These results suggest vitamin E may exert antioxidant and wound-healing effects in SSc, with greater benefits from prolonged supplementation and, possibly, higher dosage.

DIETARY SUPPLEMENTS

Dietary supplements are orally consumed products containing nutrients like trace elements or minerals to support health [31]. Supplements with some evidence in SSc include L-arginine, omega-3 fatty acids, potassium para-aminobenzoic acid, and zinc.

L-ARGININE SUPPLEMENTATION

L-arginine is an amino acid and NO precursor. Nitric oxide deficiency leads to endothelial derangements

that may contribute to vascular fibrosis in SSc (e.g., Raynaud phenomenon and pulmonary arterial hypertension) [32]. Elevated asymmetric dimethylarginine (ADMA) levels act as a competitive antagonist of nitric oxide synthesis. L-arginine supplementation may help counteract nitric oxide deficiency by promoting nitric oxide production and competing with ADMA [32].

Nitric oxide modulates the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), specificity protein-1, and activating protein-1 through multiple pathways, leading to reduced collagen gene expression [33,34]. Pathologically elevated ADMA blood levels can be seen in dcSSc patients [35]. Nitrate therapy and L-arginine supplementation to enhance the nitric oxide pathway are proposed as SSc-RP and digital ulcer treatments [36,37]. In a case series of four patients with SSc-RP, oral L-arginine supplementation depending on Raynaud phenomenon symptoms and severity (ranging from 2 to 6 g per day) reversed digital necrosis in two and improved Raynaud phenomenon symptoms in two [38]. Thus, arginine supplementation may be useful for SSc-RP patients.

OMEGA 3 FATTY ACIDS

Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid and docosahexaenoic acid, exhibit anti-inflammatory and immunomodulatory properties. Derived from cold-water fish, flaxseeds, and walnuts, PUFAs transform into resolvins and protectins, mediators which terminate inflammation by enhancing macrophage efferocytosis (apoptotic cell clearance to curb inflammation) and downregulating pro-inflammatory NF-kB and mitogen-activated protein kinase pathways [39]. They promote alternatively activated macrophages (M2) polarization, suppress IL-2, TNF-α, and interferon gamma production by $CD8^+$ T cells, and shift $CD4^+$ T cell differentiation away from T helper 1/Th1 cell and T helper 17/Th17 cell phenotypes while enhancing regulatory T cell activity, key mechanisms in SSc fibrosis and autoimmunity [40].

In preclinical models, PUFAs attenuate TGF-β–driven skin and lung fibrotic signaling [40]. Though not studied in SSc, a meta-analysis of 23 RCTs in rheumatoid arthritis patients found non-significant overall reduction in CRP (SMD: −0.11; 95%CI: −0.28–0.06; $P=0.1928$). However, meta-regression found higher doses of omega-3 fatty acids significantly reduced CRP (b-coefficient: 0.11; 95% CI: 0.02–0.20; $P=0.0243$) [41▪]. Since elevated CRP levels are a hallmark of inflammation in SSc, particularly in those with interstitial lung disease, and anti-inflammatory agents like tocilizumab have shown clinical benefits, omega-3 intake may similarly help reduce systemic inflammation [42].

POTASSIUM PARA-AMINOBENZOIC ACID

Para-aminobenzoic acid (PABA), a naturally occurring compound and intermediate in bacterial folate biosynthesis, supports nucleic acid synthesis and DNA assembly. While nonessential in humans, it is present in liver, whole grains, mushrooms, and brewer's yeast. PABA has been used as adjuvant therapy to treat fibrotic diseases such as Peyronie's disease and Dupuytren's contracture [43]. Additionally, PABAs potassium salt form, potassium para-aminobenzoate (KPAB), has been used in SSc. In a retrospective study of 390 SSc patients that assessed the effect of KPAB treatment on forced vital capacity (FVC), overall, those adequately treated (KPAB 12 or 12.5 g daily for a duration of 3 months–20.6 years) showed significantly less decline versus untreated (no KPAB) or inadequately treated patients (those with less KPAB exposure for any reason) ($P=0.003$). Specifically, lung fibrosis (on chest X-ray) patients treated ($n=15$) versus untreated ($n=10$) with KPAB demonstrated less decline in FVC (mean ± SD -0.047 ± 0.052 versus -0.191 ± 0.240) over a mean ± range follow-up 5.8 (1.1–13.0) and 2.1 (0.3–6.9) years, respectively [44]. Thus, KPAB treatment may be a useful adjunctive therapy in SSc-interstitial lung disease, but additional prospective studies need to be conducted before broad treatment is recommended.

ZINC

Zinc – an essential micronutrient and the body's second most abundant trace element – supports DNA synthesis, gene transcription, cell proliferation, collagen formation, and immune functions like antibody production and inflammatory signaling [45▪▪]. SSc patients often face malnutrition from avoidant and restrictive food intake disorder, impaired gastrointestinal function with malabsorption, anorexia, microstomia, dysmotility, SIBO, and early satiety resulting in iron, selenium, copper, and zinc deficiencies. In fact, zinc deficiencies were present in 48% of 82 patients in a retrospective cross-sectional cohort study and 15% of 176 patients in another prospective study [46,47].

Zinc serves as a cofactor for matrix metalloproteinases (MMPs), enzymes crucial for regulating collagen deposition and breakdown in the extracellular matrix. Zinc deficiency increases ROS production and dysregulated MMP activity, promoting skin fibrosis [48]. Additionally, lung fibrosis models demonstrated zinc restoration through SLC39A8 transporter facilitates

Table 2. Summary of discussed interventions including proposed mechanisms of action, pathophysiology, and supporting references

Intervention	Proposed mechanism(s)	Relevance to SSc	Reference (Author, Year), Study design
Low-FODMAP diet	↓ fermentable carbs → ↓ osmotic load ↓ pathobionts like *Klebsiella*, *Enterococcus*	Alters gut microbiota; may reduce bloating, reflux, and SIBO-related GI symptoms	Nguyen *et al.*, 2023 [7], cross-sectional SSc cohort
Ketogenic diet	↑ BHB → inhibits NLRP3 inflammasome → ↓ IL-1β, IL-18	Theoretically anti-inflammatory; no SSc trials yet	Youm *et al.*, 2015 [8], mechanistic
Mediterranean diet	↓ CRP, IL-6, TNF-α; improves microbiome & antioxidant status	Low adherence linked to worse RP, digital ulcers, depression, reflux	• Dobroslavska *et al.*, 2024 [9▪], narrative review • Abrignani *et al.*, 2024 [10▪], narrative review • Bonaccio *et al.*, 2023 [12], prospective cross-sectional cohort • Natalello *et al.*, 2023 [13], cross-sectional
Beetroot	↑ NO bioavailability, ↓ BP, ↑ IL-10, ↓ endothelin	May improve RP-related vasculopathy and digital perfusion	Shepherd *et al.*, 2019 [16], randomized crossover RP cohort (some SSc)
Rosemary oil	Antioxidant and vasodilatory properties → ↑ warmth perception	Modest improvements in self-reported RP symptoms and temperature	• Von Schoen-Angerer *et al.*, 2018 [17], case report • Vagedes et al., 2022 [18], open-label pilot
Curcumin	Inhibits TGF-β/Smad3, ↓ collagen, ↑ fibroblast apoptosis	Anti-fibrotic effects in mouse models and SSc lung fibroblasts	• Utsunomiya *et al.*, 2022 [19], preclinical • Tourkina et al., 2004 [20], cell-based
Vitamin C	Antioxidant with anti-inflammatory properties	May lower skin thickening progression rates in SSc	Ostojic *et al.*, 2011 [23], RCT SSc cohort
Vitamin D	VDR activation → ↓ Smad3 → ↓ collagen; antioxidant effects	Deficiency is common; supplementation reduces oxidative stress markers and increased VDR in SSc patients	• Schneider *et al.*, 2021 [25], systematic review • Dal-Bekar *et al.*, 2023 [26], prospective
Vitamin E	Impaired erythrocyte redox balance in SSc, patients based on SOD, glutathione peroxidase, and catalase activity. Patients may benefit from vitamin E antioxidant properties to help optimize enzyme activities. Oral formulation may reduce skin thickening rates in SSc and topical form may promote wound healing in SSc digital ulcers	Reduced MRSS scores and improved digital ulcer healing in small studies	• Dworniak K, Duchnowicz P *et al.*, 2013 [27], experimental • Souza *et al.*, 2009 [28], open-label trial • Fiori *et al.*, 2009 [29], RCT
L-Arginine	Precursor to NO; counteracts ADMA inhibition ↑ Vasodilatory properties	May improve PAH, RP, and digital ulcers via vascular NO pathway	• Dooley *et al.*, 2006 [35], observational • Rembold *et al.*, 2003 [38], case series
Omega-3 fatty acids	↑ Resolvins/protectins → ↓ NF-κB, MAPK, ↑ T_{reg}, ↓ Th17	May reduce ILD inflammation and vascular dysfunction; not yet SSc-specific trials	Gkiouras *et al.*, 2024 [41▪], meta-analysis study (rheumatoid arthritis, not SSc, patients)
PABA/KPAB	Inhibits collagen cross-linking	May slow FVC decline in patients with SSc-associated interstial lung disease	Zarafonetis *et al.*, 1989 [44], retrospective SSc cohort

Table 2 (*Continued*)

Intervention	Proposed mechanism(s)	Relevance to SSc	Reference (Author, Year), Study design
Zinc	Cofactor for matrix metalloproteinases (MMP), enzymes crucial for regulating collagen deposition and breakdown in the extracellular matrix Zinc affects collagen via specific transporters in lung tissue	High deficiency prevalence in SSc; possible anti-fibrotic and epithelial repair roles in the skin	• Dupont *et al.*, 2018 [46], retrospective cross-sectional SSc cohort • Läubli *et al.*, 2020 [47], prospective SSc cohort • Lin *et al.*, 2017 [48], mechanistic

ADMA, asymmetric dimethylarginine; BHB, β-hydroxybutyrate; BP, blood pressure; CRP, C-reactive protein; FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols; FVC, forced vital capacity; GI, gastrointestinal; IL-1β, interleukin 1 beta; IL-10, interleukin 10; IL-18, interleukin 18; IL-6, interleukin 6; ILD, interstitial lung disease; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinases; MRSS, Modified Rodnan Skin Score; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; RP, Raynaud phenomenon; SIBO, small intestinal bacterial overgrowth; Smad, Suppressor of Mothers Against Decapentaplegic; SSc, systemic sclerosis; TGF-β, transforming growth factor-beta; Th17, T helper 17 cell; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; VDR, vitamin D receptor.

alveolar cell regeneration, suggesting a protective role in pulmonary tissue [48,49]. Supporting the beneficial effects of zinc, a small pilot study with 17 SSc patients reported that high-dose zinc gluconate (83.3 mg/day) resulted in partially or completely remitted morphea based on clinical evaluation [50]. These findings support zinc supplementation as a potential adjunct therapy in SSc and morphea for its antioxidant and wound-healing properties.

CONCLUSION

Complementary and alternative medicine including functional foods, diets, vitamins, and supplements are a topic of interest among physicians and patients. Although many of these interventions, such as vitamin D, omega-3 fatty acids, and curcumin, show mechanistic plausibility and favorable safety profiles, data remain largely preclinical or observational. Likewise, while dietary patterns like the Mediterranean, low FODMAP, and ketogenic diets may support gut health, inflammation reduction, or vascular function, randomized controlled trials in SSc populations are lacking (see Table 2). Future prospective studies and RCTs of these promising therapies are needed to clarify efficacy, standardize protocols, and guide clinical recommendations.

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Conflicts of interest

There are no conflicts of interest.

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Targeted therapies in systemic sclerosis: a narrative review of novel drugs in clinical trials

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Purpose of review
Systemic sclerosis (SSc) remains a therapeutic challenge, with conventional immunosuppressive strategies showing inconsistent effects and no disease modifying activity. The lack of head-head trials comparing immunosuppressives with emerging antifibrotic agents further complicates treatment decisions in SSc. This review aims to provide an update on the recent advances in targeted therapies for SSc, with a focus on novel biologics and small molecules that specifically modulate key mechanisms.

Recent findings
Advances in molecular profiling have revealed inflammatory and fibrotic endotypes within SSc while imaging studies support a fibroinflammatory subset, highlighting potential therapeutic targets.

Summary
A literature search for clinical trials between January 2020 and April 2025 from PubMed/MEDLINE, clinicaltrials.gov, euclinicaltrials.eu databases for targeted therapies in systemic sclerosis revealed a total of 117 clinical trials, of which we described the design, methods and endpoints from 14 studies (2 conference abstracts, 11 trials and 1 case series). These study results offer hope for patients with systemic sclerosis and pave way for future studies directing the development of patient-specific guidelines.

Keywords
lung fibrosis, Raynaud phenomenon, scleroderma renal crisis, skin fibrosis, systemic sclerosis, targeted therapies, treatment

INTRODUCTION

The earliest systemic sclerosis (SSc) pathological hallmark is endothelial cell apoptosis and platelet activation [1]. Vascular injury contributes to upregulation of adhesion molecules and profibrotic factors including endothelin-1(ET-1) and platelet derived growth factor (PDGF). Damaged endothelial cells release cytokines facilitating recruitment and activation of immune cells leading to inflammation [2].

Activated immune cells release cytokines and growth factors, including interleukins (ILs) – 4, 13, transforming growth factor β (TGF β), interferon type I (IFN-1) [2–4]. IL-6 via JAK/STAT signaling plays a key role in fibroblasts differentiation into myofibroblasts causing deposition of excess extracellular matrix proteins [6]. Regulatory T cell (Treg) and T follicular helper cell (TFH) imbalance is also implicated in fibroblast activation [5]. Damaged endothelial cells can undergo endothelial-mesenchymal transformation into myofibroblasts becoming apoptosis resistant [7]. Lysophosphatidic acid (LPA), a bioactive lipid mediator produced by the enzyme autotaxin (ATX), is implicated in fibrosis [6–8]. In this context, clinical trials have targeted these pathways (Fig. 1). This review builds upon Campochiaro and Allanore's review that detailed novel SSc therapies until July 2020 [9▪].

Search strategy

Articles published in English between January 2020 and May 2025 were sourced from MEDLINE/PubMed, clinicaltrials.gov, and euclinicaltrials.eu databases using the terms “systemic sclerosis” or “scleroderma” and “phase I” or “phase II” or “phase III” trials or “observational studies” or “case series” in various combinations. Selected studies were included based on the availability of results and, as recommended, by the standards of writing a narrative review [10]. A total of 117 clinical trials were

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KEY POINTS

- Early phase I/II clinical trials investigating low dose interleukin (IL)-2, zibotentan, brentuximab vedotin, vipoglanstat, C21, FT011, and brodalumab have shown preliminary encouraging signals in systemic sclerosis (SSc) patients, though further validation is needed.
- Rituximab and brodalumab have demonstrated potential therapeutic benefit in phase III clinical trials, however larger studies are warranted to confirm efficacy and safety in diverse SSc populations.
- B cells are an increasingly recognized target in SSc as suggested by recent phase II/III trials involving rituximab and emerging observational data on CAR-T cell therapies, although these approaches remain investigational.

identified (Fig. 2). Of these, 14 published results are reviewed herein.

PHASE I/II TRIALS

This section details phase I/II trials (Table 1).

Low-dose interleukin-2

Treg cells play an important role in maintaining self-tolerance and IL-2 is required for survival and function of these cells [11]. Recent evidence shows Treg/Teffector cell imbalance in SSc [12]. Some studies report decreased levels and/or impaired functioning of Treg cells, while others report functional deficiency despite increased Treg levels in peripheral blood of SSc patients [13–15].

In TRANSREG, a prospective multicenter, uncontrolled, open-label, phase I/IIa trial (NCT01988506) of low-dose interleukin-2 (IL-2LD) in autoimmune diseases, patients on stable corticosteroid and/or hydroxychloroquine and/or immunosuppressants, the safety and biological efficacy was reported for nine SSc patients. For 2 months, participants received 1 million international units of IL-2 subcutaneously (s.c.) daily (days 1–5, induction phase), and then every 2 weeks (day 15 to month 6, maintenance phase) and were followed for 12 months [16,17]. On day 8, mean (±SD) percentage fold Treg change out of total $CD4^+$ cells was 1.8 ± 0.5 ($P=0.0015$) compared to baseline (primary outcome). Moreover, Tregs increased ≥35% for all patients, but no significant changes in Teffector or B cell occurred. At end of the maintenance phase, increase in Tregs from baseline was not statistically significant ($P=0.21$). IL-2LD was well tolerated with injection site reactions as the most common adverse drug reaction (ADR). Improvement in tenderness and joint swelling was reported in 4/5 patients while modified Rodnan Skin Scores (mRSS), Valentini activity index scores, and pulmonary function tests (PFTs) remained stable [18].

Despite these promising results, IL-2LD in SSc is controversial as Tregs also produce TGF-β (a profibrotic cytokine), and a small open-label study investigating basiliximab, a monoclonal antibody (mAb) against the IL-2 receptor alpha chain, also benefitted SSc patients [19,20].

Ziritaxestat (GLPG 1690)

Serum LPA, a product of lysophosphatidylcholine (LPC) cleavage by autotaxin, mediates lung and dermal fibrosis through the fibroblast LPA receptor 1 in patients with SSc [8,21]. Hence, ATX/LPA/LPA-receptor 1 signaling inhibition is a potential SSc therapeutic target [21].

Ziritaxestat (GLPG 1690), a selective ATX inhibitor, was evaluated in a 24-week, multicenter phase IIa, double-blind, placebo-controlled study (NOVESA – NCT 03798366). Early diffuse cutaneous SSc (dcSSc) patients with mRSS >10 and active disease were randomized to oral ziritaxestat 600 mg daily ($n=21$) or placebo ($n=12$). At 24-weeks, ziritaxestat vs. placebo group showed mean (95% CI) mRSS reductions [−8.9 (−10.6, −7.1)] vs. [−6.0 (−8.3, −3.8)], $P=0.0411$. Median ACR CRISS (Composite Response Index for SSc ≥0.6 is indicative of improvement) scores were higher in treated vs. placebo arm at week 16 [0.70 vs. 0.19, respectively] and week 24 [0.97 vs. 0.83, respectively]. In the planned 104-week open-label extension study where all patients received treatment (NCT 03976648), mRSSs assessed at 52 weeks decreased in those initially taking placebo vs. ziritaxestat (-12.2 ± 1.6 vs. -11.6 ± 3.0) but drop-out rates were high attributed to long study duration. Ziritaxestat was well tolerated with the most notable ADRs being headaches and diarrhea. Secondary endpoints including circulating LPA C 18:2 (most common type of LPA in humans) and serum collagen degradation biomarker levels collected at weeks 2, 4, 8, 16, and 24, were reduced in the ziritaxestat group at time points. Baseline and week 24 skin biopsies also showed decreased dermal myofibroblasts in the treatment vs. placebo arm. Thus, ziritaxestat may benefit early dcSSc patients when autotaxin may be most active [22].

Zibotentan

Endothelin (ET) that exerts its effects via receptors ET Receptor-1 A and B (ETRA and ETRB), is implicated in SSc vasculopathy [23,24].

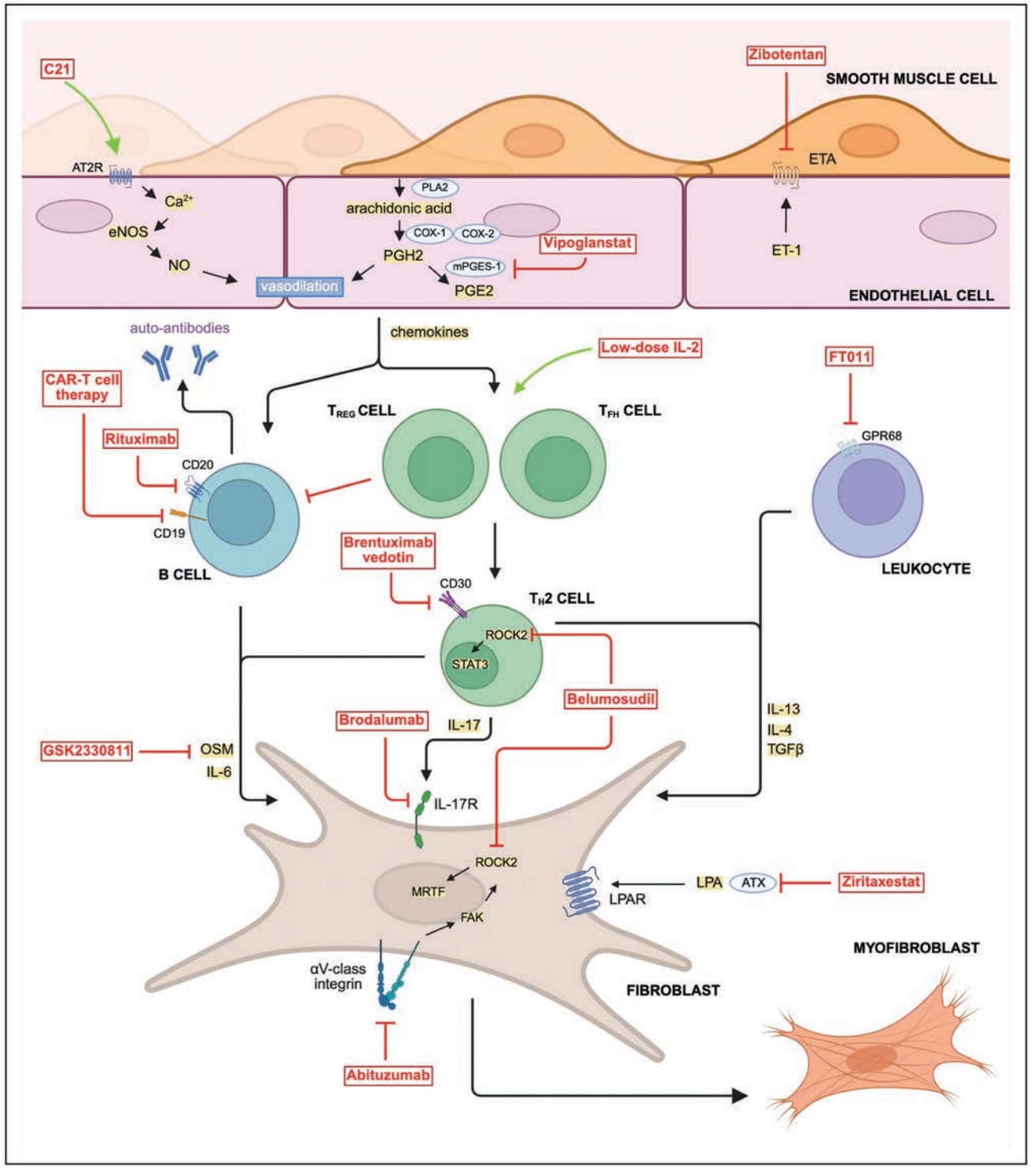

FIGURE 1. Novel therapeutic targets in systemic sclerosis. The figure highlights the three key pathological events in SSc – vascular damage, immune activation, and fibrosis. The main molecular mechanisms and targets of novel drugs in recent clinical trials are represented in this figure. AT2R, angiotensin II type 2 receptor; ATX, autotaxin; C21, compound 21; Ca^{2+}, calcium ion; CAR-T cell therapy, chimeric antigen receptor-T cell therapy; CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; CD30, cluster of differentiation 30; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; ETA, endothelin type A receptor; FAK, focal-adhesion kinase; GPR68, G protein-coupled receptor 68; IL-13, interleukin-13; IL-17, interleukin-17; IL-17R, interleukin-17 receptor; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; LPA, lysophosphatidic acid. LPAR, lysophosphatidic acid receptor; MRTF, myocardial-related transcription factor; NO, nitric oxide; OSM, oncostatin M; PGE2, prostaglandin E2; PGH2, prostaglandin H2; PLA2,

Zibotentan is a highly selective oral ETRA antagonist. A phase II randomized, placebo-controlled trial (NCT02047708) comprised of three single-center sub-studies (ZEBRA 1, 2A and 2B) compared oral zibotentan to placebo for 26 weeks in SSc renal disease patients. ZEBRA1 was a double-blind study of 10 mg Zibotentan in 13 stage 2 and 3 chronic kidney disease (CKD) patients. ZEBRA2A was a single-blind study of four patients with scleroderma renal crisis (SRC) not on dialysis starting with 2.5 mg of Zibotentan escalated to 10 mg over four weeks. ZEBRA2B was an open label pharmacokinetic study of zibotentan 2.5 mg at visit one followed by 5 mg at visit two in eight patients on hemodialysis. Safety and tolerability were primary outcomes in all studies. Additional primary outcomes included serum vascular cell adhesion molecule (VCAM-1), a candidate biomarker of SSc renal involvement, eGFR change, and maximum tolerated dose in ZEBRA 1, 2A and 2B, respectively. These studies' results demonstrated zibotentan's safety and tolerability as fluid retention and small pericardial effusion (ZEBRA 1 and 2A) and increased INR (ZEBRA 2B) were the ADRs. In ZEBRA1, VCAM-1 levels remained stable between baseline and weeks 26 and 52 in both groups; however, eGFR improved at 26 and 52 weeks in the treatment arm. Additionally, plasma ET levels remained stable without rebound hypertension (secondary outcome). Small sample size precluded definitive ZEBRA2A conclusions although eGFR improvement was noted. In ZEBRA2B, 2.5 and 5 mg doses were well tolerated [25].

Abituzumab

TGF-β is implicated in lung fibrosis [26]. In SSc, TGF-β is activated and by heterodimeric transmembrane proteins αVβ5&6 integrins on dermal and damaged pulmonary epithelial cells respectively [27].

Abituzumab is a humanized mAb that inhibits αV class integrin activity. The phase II, randomized, double-blind, placebo-controlled, multicenter STRATUS study (NCT02745145) evaluated abituzumab's ability to improve lung function in SSc-ILD patients. Twenty-four patients with SSc duration <7 years who were on stable mycophenolate with $\geq$5% lung fibrosis on high-resolution computed tomography (HRCT), diffusing lung capacity for carbon monoxide (DLCO) $\geq$ 30% predicted, forced vital capacity (FVC) 40–80% predicted and FVC:DLCO $<$ 1.8 were enrolled and randomized (2:2:1) to receive i.v. abituzumab 1500 mg or 500 mg, or placebo every 4 weeks for 104 weeks. Abituzumab was well tolerated, but the study ended early due to low enrollment with a median study duration of 25.9 weeks precluding efficacy assessment [28].

Brentuximab vedotin

Th2 lymphocyte infiltrates including $CD4^+$ $CD30^+$ (a member of the TNF-receptor superfamily)-expressing cells are seen in dcSSc skin biopsies, while free soluble CD30 levels are elevated in sera [29]. Brentuximab vedotin is an antibody drug conjugate comprising IgG1 mAb against CD30 and an antimitotic agent monomethyl auristatin-E (MMAE). Once Th2 lymphocyte's CD30 receptors bind to the mAb, endocytosis facilitates MMAE release that leads to cell cycle arrest and apoptosis [30].

The efficacy of brentuximab vedotin was explored in a phase II single center, open-label, single arm trial (NCT 03198689) in dcSSc for $\leq$5 years, mRSS $\geq$15 and/or skin worsening despite immunosuppression. Eleven participants received brentuximab vedotin 0.6 mg/kg i.v. every 3 weeks for 45 weeks alongside preexisting treatment. The primary endpoint was mRSS $\geq$ 8 decrease at 48 weeks. In the nine study completers, the mean mRSS reduction was 11.3 (95% CI 6.9, 15.8; P=0.001) while 7 out of 11 participants had mRSS $\geq$8 decrease, and the mean (SD) FVC% increase was 7.8% (12.5). The CRISS scores suggested a beneficial treatment effect (86% $\geq$ 0.6). The most common ADRs were transaminitis and leukopenia [30].

Vipoglanstat

Prostacyclin pathway augmentation improves SSc-RP symptoms [31]. Specifically, increased inducible enzyme prostaglandin E2 synthase-1 (mPGES-1) activity is associated with inflammation and pain and inhibition shunts PGH2 towards prostacyclin biosynthesis that improves RP symptoms [32,33].

Vipoglanstat (GS-248 and BI 1029539) is a selective mPGES-1 inhibitor. A phase II double-blind, placebo-controlled trial (NCT: 04744207) studied

FIGURE 1. Continued.

phospholipase A2; ROCK2, Rho-associated, coiled-coil containing protein kinase 2; STAT3, signal transducer and activator of transcription 3; Tfh cell, follicular helper T cells; TGF β, transforming growth factor β; Th2, T helper type 2 cell; Treg cell, regulatory T cells.

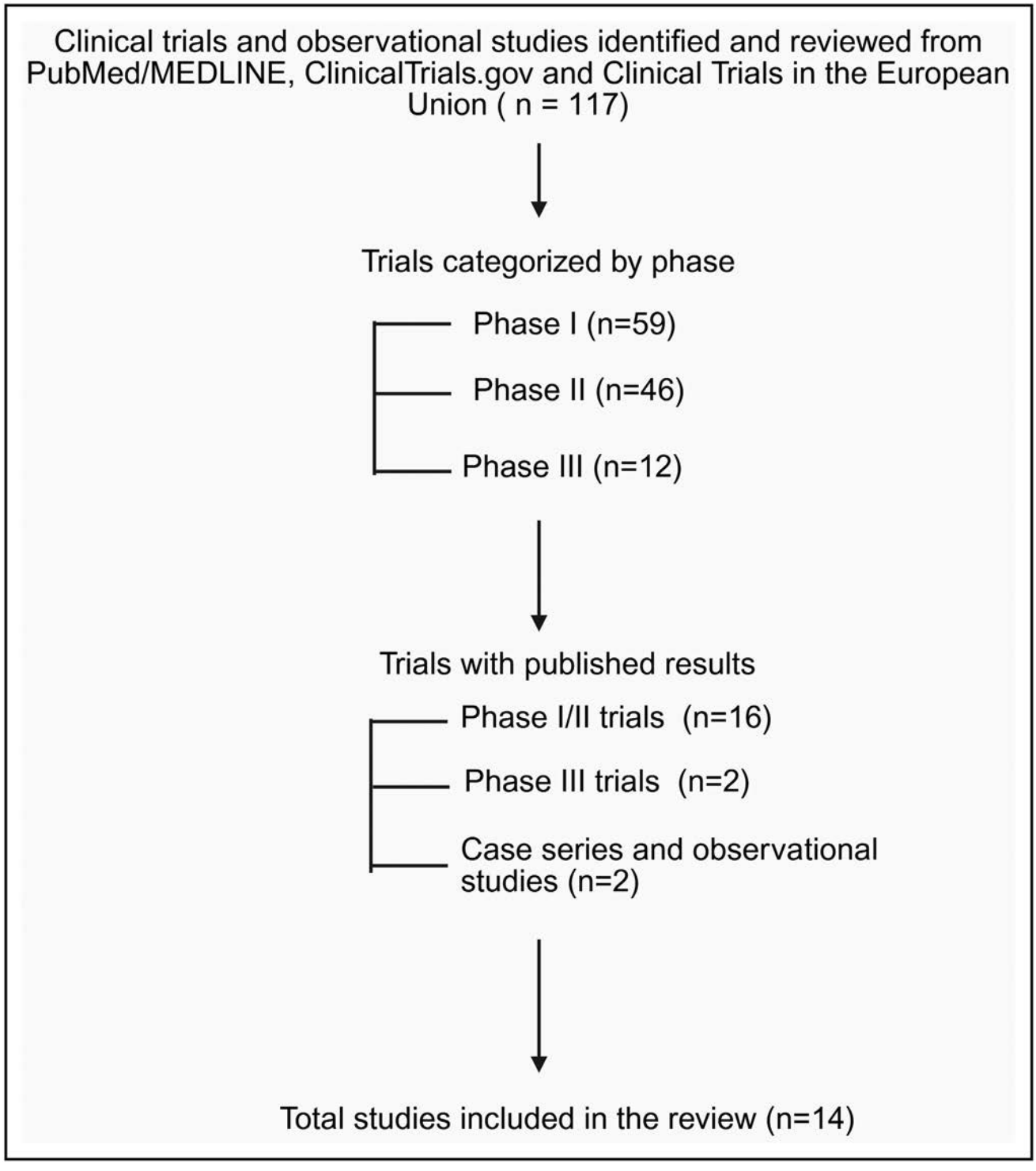

FIGURE 2. Selection of articles for review [10]. A total of 117 clinical trials were identified, of which 59 were Phase I, 46 Phase II and 12 were Phase III trials. Published results from 2 phase I, 14 phase II, and 2 phase III trials were available out of which 14 articles were included in our review.

69 SSc participants with ≥7 RP attacks/week during the four weeks preceding randomization were randomized to oral vipoglanstat 120 mg or placebo daily for 4 weeks. The primary endpoint was RP attack frequency from the last seven days of screening to end of week three of treatment. Other endpoints included the patients', and physicians' global impression of change assessment (PGA) of SSc-RP, mPGES-1 activity, urinary excretion of arachidonic acid metabolites and finger blood flow as

Table 1. Phase I/II clinical trial

Drug	Molecular target	Study design	Mean treatment duration	SSc type	Background immuno-suppression	Primary endpoints	Secondary endpoints	Clinical efficacy	Adverse drug reactions
IL-2LD s.c., 1mIU q.d. for 5 days then q2wk	Treg and TFH	Open-label, nonrandomized interventional, phase HIa study	6 months	9; early and late SSc, 8/9 lcSSc	Yes, - corticosteroids (≤15 mg/kg/day); hydroxychloroquine 200–400 mg / day; and immunosuppressants (except cyclophosphamide, rituximab, cyclosporine, rapamycin, tacrolimus, and mycophenolate)	Change in Tregs on day 8 compared to baseline	Changes in Tregs at day 15, 1st, 3rd and 5th month compared to baseline. Changes in other immunological cells from baseline, joint involvement, GI involvement, mRSS, Valenti Disease activity index, PFT, DLCO, and QOL	Stable mRSS Valenti scores, PFT, and QOLindices. Improvement in joint tenderness and GERD symptoms	Injection site reactions, influenza-like illness, fatigue, digestive troubles, and headaches
Ziritaxestat PO, 600 mg q.d.	Autotaxin	Phase II a double-blind, placebo-controlled trial	52 weeks	33, early dcSSc	Yes	Change in mRSS at week 24	Safety and tolerability, skin and blood biomarkers	Reduction in mRSS was greater with Ziritaxest than placebo (-8.9 v/s -6.0 units, P=0.0411)	Headache and diarrhea
Zibotentan PO ZEBRA 1 and 2A, escalating from 2.5 -10 mg q.d. over 4 weeks ZEBRA 2B 2.5 mg at visit 1 5.0 mg at visit 2	Endothelin receptor-1A antagonist	ZEBRA 1: Randomised, double-blind, placebo-controlled trial; ZEBRA 2A: 26-week, single blind placebo-controlled trial; ZEBRA 2B: open-label pharmacokinetic study	26 weeks	25, dcSSc or lcSSc	Yes	Serum VCAM- 1 levels	Safety and tolerability, Change in eGFR. Plasma levels of Zibotentan and endothelin concentrations	Improvement in eGFR at 26 and 52 weeks in the treatment arm in ZEBRA 1 and 2 A studies	Fluid retention, pericardial effusion, increased INR
Abituzumab i.v., 500 mg or 1500 mg QM for 104 weeks	αV integrin	Phase II, randomized, double-blind, placebo-controlled study	25.9 weeks	24, dcSSc or lcSSc	Yes, mycophenolate	Annual rate of change in FVC	Safety and tolerability	Early termination due to enrollment difficulties	Diarrhea, cough, fatigue, gastroenteritis, arthralgia, and headache . SAE reported – pneumonia and device related infection and sepsis
Brentuximab Vedotin i.v., 0.6mg/kg Q3Wk for 45 weeks	CD30 receptor on Th2 lymphocytes	Phase II, open-label, single arm trial	45 weeks	11, early dcSSc	Yes	Decrease in mRSS of ≥ 8 points	%FVC change from baseline and CRISS	Mean mRSS reduction was 11.3 (95% CI 6.9, 15.8; P=0.001)	Peripheral neuropathy
Vipoglanstat PO, 120 mg q.d.	MPGES-1 inhibitor	Phase II double-blind placebo controlled	4 weeks	69, dcSSc and lcSSc	Yes, mycophenolate	Mean change in the number of RP attacks from 7 days of screening to last 7 days of treatment	Patients' and physicians' global impression of change, assessment of scleroderma-associated RP questionnaire, mPGES-1 activity, and urinary excretion of arachidonic acid metabolites	The mean weekly number of RP attacks decreased by 3.4 (95% CI -5.8; -1.0) in the treatment group compared to 4.2 (-6.5; -2.0) attacks per week in the placebo group (P= 0.628). The mean change in recovery of peripheral blood flow after the cold challenge did not differ between groups	Headache, nausea, and upper abdominal pain

Table 1 (*Continued*)

Drug	Molecular target	Study design	Mean treatment duration	SSc type	Background immuno-suppression	Primary endpoints	Secondary endpoints	Clinical efficacy	Adverse drug reactions
C21 PO, 200 mg once per visit	AT2R agonist	Phase IIa, randomized, double-blind, cross-over study	2 treatment visits separated by 3–7 days	12, lcSSc	No	AUC for rewarming each finger over 15 min	Maximum finger temperature after rewarming	AUC for 8 fingers, rewarming was higher with C 21 than after placebo (geometric mean 20046C vs. 19558C) but was not statistically significant (P=0.380)	Dizziness and flushing
GSK2330811 s.c., 100 mg or 300 mg QWk for 12 weeks	Anti-OSM monoclonal antibody	Phase IIa, randomized, double-blind, placebo-controlled study	12 weeks	35, active dcSSc or lcSSc	Yes	Safety and tolerability	Pharmacokinetics, target engagement in blood, antidrug antibodies, biomerkers of fibrosis, inflammation, vasculopathy, and clinical endpoints (mRSS, FVC)	No meaningful differences were identified	Anemia and Thrombocytopenia in the 300 mg group
FT011 PO, 200 mg or 400 mg, q.d.	GPR68 proton sensing antagonist inhibiting TGF β and PDGF	Phase II, randomized, double-blind, placebo-controlled study	12 weeks	30, dcSSC	Details not available	Safety and tolerability	ACR-CRISS,mRSS, %FVC, SHAQ-DI, physician global assessments	60% demonstrated improvement in ACR-CRISS scores and MCID for SHAQ-DI in the 400 mg group compared to placebo. 50%in the 400 mg group exceeded % FVC MCID compared to placebo group MRSS improved in the treatment arms, however, was not statistically significant	Safe and well tolerated
Belumosudil PO, 200 mg q.d. or b.i.d.	Selective inhibitor of ROCK2	Phase II Double-blind, open-label study	52 weeks	35, dcSSC	Yes	CRISS score $\geq$ 0.60 at week 24	Continuous CRISS score at week 52, change from baseline, and improvement from week 24 in mRSS, FVC % predicted, PGA, PaGA, and SHAD-DI, PFT, biomarker signaling, safety and tolerability of the drug	Belumosudil did not exhibit an efficacy signal in the treatment vs. placebo groups	Nausea, headache, diarrhea, pruritus, hypoesthesia, infections, and fatigue
Brodalumab s.c., 210 mg for 3 weeks then b.i.d.	IL-17 receptor antagonist	Phase I single-center, open-label	50 weeks	8, dcSSC	Yes	Pharmacokinetic, Safety, and efficacy markers	mRSSs, number of digital ulcers	Decreased mRSSs and digital ulcer numbers at weeks 24 and 52. Brodalumab induced a Treg dominant response	Oral and vulvovaginal candidiasis, and arthralgias

mRSS, modified Rodnan Skin Scores; SSc, systemic sclerosis.

assessed by infrared thermography after cold challenge. In the treated vs. placebo group, mean (SD) RP attack decline was 4.2 (95% CI −6.5; −2.0) vs. 3.4 (−5.8; −1.0), $P=0.628$, respectively while mean change in recovery of peripheral blood flow after cold challenge did not differ between the study groups. Vipoglanstat fully inhibited mPGES-1 activity, resulting in 57% reduction of PGE2 and 50% increase of urinary prostacyclin metabolites. Despite its acceptable safety profile and mPGES-1 inhibition, there were no improvements in RP symptoms or finger blood flow [34].

Compound 21

Angiotensin-II mediates vasoconstriction through the angiotensin-II type I receptor [35]. Alternatively, angiotensin-II type 2 receptor (AT2R) promotes vasodilation by increasing endothelial nitric oxide (NO) synthase activity and NO release [36].

Compound 21 (C21) is a specific AT2R agonist. A phase-IIa, randomized, double-blind, cross-over study (NCT04388176) of twelve female SSc patients (median RP duration 19.0 years) randomized to oral 200 mg C21 or placebo for two visits, three to seven days apart. 40 min after treatment, patients underwent a cold challenge test. The mean area under the rewarming curve (AUC) for all eight fingers was higher with C21 than placebo (geometric mean 20046°C*s vs. 19558°C*s), but results were not statistically significant ($P=0.380$). Maximum finger temperature after rewarming was also higher in actively treated patients (geometric mean 23.5 C vs. 22.5 C; $P=0.036$) [37].

GSK2330811

Oncostatin M (OSM) is an IL-6 family member [38]. SSc patients demonstrate elevated serum OSM levels while profibrotic macrophages express increased OSM receptors that are associated with skin disease progression [38–40].

GSK2330811, an anti-OSM mAb antibody, was evaluated in a multicenter, randomized, double-blind, placebo-controlled study (NCT03041025) in 35 active dcSSc participants with mRSS $\geq$10 and $\leq$35 and background mycophenolate therapy. Active disease was defined as presence of any one criterion including CRP $\geq$6 mg/dl or disease duration $\leq$18 months at the time of screening or increase in mRSS by $\geq$3 points or involvement of new body areas over 6 months before screening. Participants were randomized to three groups GSK2330811 100 mg or 300 mg, or placebo subcutaneously weekly for 12 weeks. The primary endpoint was safety while clinical efficacy and mechanistic effects (e.g., assessed by mRSS and FVC, αSMA skin expression, etc., respectively) were exploratory endpoints. Safety was unfavorable with notable hemoglobin and platelet drops in the 300 mg group. Neither GSK2330811 dose was associated with efficacy or mechanistic effects [41].

FT011

TGFβ and PDGF induce collagen deposition and fibrosis in SSc [42,43]. FT011 (3-methoxy-4-propargyloxycinnamoyl anthranilate), a G-protein coupled receptor 68 (GPR68) proton sensing antagonist, inhibits TGFβ and PDGF pathway activation [44].

A phase II, multicenter, randomized, double-blind, placebo-controlled study evaluated the safety of oral FT011 (200 mg or 400 mg daily) in dcSSc (NCT04647890) vs. placebo (ten per group) for 12 weeks. Treatment with 400 mg but not 200 mg FT011 resulted in significant and clinically meaningful improved ACR-CRISS (including % FVC but not PGA) as well as scleroderma health assessment questionnaire-disability index (SHAQ-DI). FT011 was safe and well tolerated [45].

Belumosudil

As mentioned, circulating Th17 and Treg cell proportions are imbalanced in SSc [46]. Rho-associated coiled-containing protein kinase-2 (ROCK2) inhibition downregulates STAT3 phosphorylation and transcription of IL-21 and IL-17 that are specific to Th17 cells [47]. Belumosudil selectively inhibits ROCK2 thereby shifting the Th17/Treg balance towards Tregs through a STAT5 dependent mechanism to restore immune homeostasis [48].

A double-blind, randomized, open-label study (NCT03919799) of 1 : 1 : 1 belumosudil (200 mg daily or twice daily or placebo for 28 weeks) in 35 dcSSc patients on background immunosuppressive therapy was terminated prematurely due to low enrollment. After unblinding, patients on placebo were re-randomized to one belumosudil dose for 24 weeks. The primary end point, CRISS score $\geq$ 0.6 at week 24, did not exhibit an efficacy signal [odds ratio: 1.06 (0.19–5.82), $P=0.9472$ for once daily group and 0.39 (0.07–2.35, $P=0.3078$) for twice daily group] that was attributed to limited sample size. Belumosudil was well tolerated and targeted its intended signaling pathway [49].

Brodalumab

IL-17 is increased in SSc patient peripheral blood, skin, and lungs [50–52]. IL-17A (one of the IL-17 subtypes) increases fibroblast and endothelial cell production of inflammatory cytokines, expression

of cell adhesion molecules, and production of proteolytic enzymes like matrix metalloproteinases -1, -2, -9 that are implicated in SSc pathogenesis [53].

Brodalumab (KHK4827), an IL-17 receptor A (IL-17RA) mAb, inhibits the activity of multiple IL-17 family cytokines. A Phase-I single-center, open-label trial (NCT04368403) assessed the pharmacokinetics, safety, and efficacy of 210 mg s.c. brodalumab at weeks 0, 1, 2 and every 2 weeks for 50 weeks in eight dcSSc patients. ADRs were oral and vulvovaginal candidiasis, and arthralgias. Decreased mRSSs and digital ulcer numbers were reported at week 24 and 52. Brodalumab was noted to induce a Treg dominant response [54].

PHASE-III TRIALS

This section details phase III trials (Table 2).

Rituximab

Sustained abnormal B cell activation impacts autoimmunity and vasculopathy in SSc [55▪]. Rituximab is an anti-CD20 antibody that depletes peripheral B-cells [56].

A double-blind, placebo-controlled, phase II/III randomized trial of rituximab (DESIRES, NCT: 04274257) conducted at four Japanese hospitals included 80 SSc patients with mRSS >10 (antifibrotic and immunosuppressant discontinued 4 weeks prior). Patients were randomized using the minimization method to rituximab or placebo based on disease duration (≤ 6 years or >6 years), mRSS (≥20 or <20), and concomitant ILD (present or absent). Patients received four weekly rituximab doses 375 mg/m2 i.v. or placebo for 4 weeks and were assessed for 24 weeks. The absolute mRSS change was lower in rituximab vs. placebo group [-6.30 vs. 2.14, respectively, difference -8.44 (95% CI -11.00, -5.88; $P<0.0001$)]. ADRs were similar between groups, upper respiratory tract infections were most commonly reported (39% in rituximab and 38% in placebo). In ILD patients, FVC% decreased similarly in both groups until 12-week follow-up; however, from 12 to 24 weeks, it increased by 1.22% vs. declined in the rituximab vs. placebo group, respectively. Moreover, FVC% change from baseline to 24 weeks significantly improved in rituximab vs. placebo arm, respectively (0.09% vs. -2.87%; difference of 2.96% (95% CI 0.08–5.84, $P=0.004$)) [57].

Brodalumab

A Japanese phase-III, multicenter, randomized, placebo-controlled, double-blind, crossover study of dcSSc patients received 210 mg brodalumab s.c. ($n=46$) or placebo ($n=45$) every 2 weeks for 52 weeks. The primary endpoint was mRSS change at week 24. Brodalumab group achieved the primary endpoint (−21.2 [95% CI −23.9, 18.5, $P<0.0001$] and demonstrated a rapid, sustained reduction in mRSS at 52 weeks. Moreover, increased CRISS scores and less digital ulcers, lung fibrosis, and gastroesophageal reflux disease were reported in brodalumab treated patients [58]. No results were included in the abstract for placebo-treated patients at 52 weeks; however, authors mentioned that 37 patients initially receiving placebo who crossed over to brodalumab at or after week 24 also benefited [58]. Prior study brodalumab ADRs include infections, suicidal ideation, depression, headache, hypertension, myocardial infarction, nephrolithiasis, and oropharyngeal pain [59].

CASE SERIES

Given the novelty of chimeric antigen receptor (CAR) T-cell therapy for SSc, a case-series has been included in our review (Table 3).

Chimeric antigen receptor-T cell therapy

Dysregulated B cells influence fibrosis and vasculopathy [60▪▪,61].

Six dcSSc patients with duration <7 years, mRSS 10–35, elevated acute-phase reactants, evidence of active disease, and who failed ≥2 treatments, received lentiviral transduced chimeric antigenic T cells against human CD19 (one million cells/Kg CAR T) i.v. on day 0, following lymphodepletion with fludarabine −5 to −3, and cyclophosphamide -3, days prior to CAR T infusion. The median (IQR) follow-up time was 487 days (342, 585). The probability of ACR-CRISS improvement increased to a median (IQR) of 100% (100–100) at 6 months. Median (IQR) mRSS decreased by 31% (29–38), corresponding to a median (IQR) decrease of 8 (7–13) within 100 days. FVC improved by a median (IQR) of 195 ml (18–275) and ground glass opacities (but not reticular pattern) on HRCT decreased by a median (IQR) of 4% (3–4). ADRs reported include mild cytokine release syndrome ($n=5$) and pneumonia ($n=1$) [62]. Based upon these promising results, multiple phase-I/II anti-CD19 CAR-T clinical trials are currently enrolling SSc patients.

CONCLUSION

Recent advances in understanding the pathogenesis of SSc led to the development and testing of novel targets such as inflammatory (IL-17) and profibrotic cytokine (TGFβ, PDGF, OSM) inhibition as well as

Table 2. Phase III clinical trials

Drug	Molecular target	Study design	Mean treatment duration	SSc type	Background immunosuppression	Primary endpoints	Secondary endpoints	Clinical efficacy	Adverse drug reactions
Rituximab i.v., 375mg/m^2 QWk	CD 20 on B cells	II/III double-blind, placebo-controlled, randomized trial	4 weeks	80, dcSSc and lcSSc	No	Absolute change in mRSS 24 weeks after intervention compared to baseline	FVC% predicted, % DLCO, TLC, QOL assessment – SF36 and health assessment questionnaire disability index (HAQ-DI), changes in HRCT, biomarkers, and safety endpoints	Absolute change in mRSS 24 weeks after initiation of rituximab was lower in rituximab than placebo group (-6.30 vs. 2.14 respectively). FVC% predicted significantly improved in the treatment arm 24 weeks from baseline	Upper respiratory tract infection, decreased serum albumin levels were reported as a SAE in one participant
Brodalumab s.c., 210 mg q2wk	IL-17 receptor antagonist	III, randomized, placebo-controlled, double-blind study	52 weeks	100, dcSSc	Yes	Change in mRSS at week 24	Safety and other efficacy markers	Brodalumab achieved a sustained reduction of mRSS over 52 weeks. Increased CRISS scores, suppressed development of digital ulcers, improved lung fibrosis, and GERD symptoms were reported	Increased risk of infections, suicidal ideation, depression, headache, hypertension, myocardial infarction, nephrolithiasis, and oropharyngeal pain.

Table 3. Case series: CD19 targeting CAR-T cell therapy in SSc

Drug	Molecular target	Study design	Mean treatment duration	SSc type	Background immune suppression	Primary endpoints	Secondary endpoints	Clinical efficacy	Adverse drug reactions
CD-19 targeted CAR-T cells i.v., 1×10^6/kg single dose	CD19 on B cells	Descriptive observational study	1 dose	6, dcSSc	Yes	Event-free time (progression of ILD, onset of CHF, onset of renal failure, hypertension or initiation of new therapy)	Changes in mRSS, imaging, lab assessments, PaROs, and a modified versions of ACR-CRISS assessed at baseline, 3,6,9, and 12 months	The probability of improvement in the ACR-CRISS score increased to a median of 100% at 6 months. Median mRSS decreased by 31, corresponding to a median of 8 points within 100 days, and the extent of fibrosis on CT scan decreased by a median of 4% FVC improved by a median of 195 ml	Cytokine release syndrome, pneumonia

modulation of mechanisms promoting fibrosis such as the LPA/ATX pathway. Blocking the activity of mPGES-1 and ETRA demonstrate benefit in patients with SSc-RP. Novel T cell targets in SSc include $CD30^+$ Th2 cells and expansion of Treg cells. B cell depletion is a promising target in treating skin and lung fibrosis. Out of 117 clinical trials identified, we only reviewed 14 with available published results. There is a plethora of studies whose results are forthcoming, including results of CAR T therapy. These emerging targeted therapies offer great strides in the treatment of the various clinical manifestations of this potentially devastating disease.

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Conflicts of interest

There are no conflicts of interest.

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Fueling fibrosis: metabolic dysregulation in systemic sclerosis

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Purpose of review
This review examines how metabolic reprogramming drives fibrosis and immune dysregulation in systemic sclerosis (SSc), emphasizing the role of nutrient-sensing and energy pathways in disease progression.

Recent findings
SSc is characterized by a shift from catabolic to anabolic metabolism, defined by reduced AMP-activated protein kinase (AMPK) and enhanced mechanistic target of rapamycin complex 1 (mTORC1) signaling. This promotes biosynthetic activity, with upregulated glycolysis supplying substrates for collagen production and supporting pro-inflammatory immune cell polarization. Remodeling of the tricarboxylic acid cycle yields key metabolites with extrametabolic roles. α-ketoglutarate (αKG) supports epigenetic regulation, collagen maturation, and AMPK activation, offering protective effects. In contrast, succinate and fumarate promote inflammation and fibrotic signaling. Despite increased anabolic activity, oxidative phosphorylation remains elevated in SSc fibroblasts, contributing to excess reactive oxygen species (ROS). Metabolomic analyses consistently show disrupted amino acid and lipid metabolism, including glutamine and tryptophan pathways, linked to immune activation and fibrogenesis. Single-cell transcriptomics reveal diverse fibroblast subtypes with distinct metabolic programs correlating with fibrosis severity.

Summary
SSc is characterized by a metabolic reprogramming that favors anabolic, profibrotic, and proinflammatory states. These interconnected metabolic shifts illustrate how central carbon and nutrient pathways not only sustain energy demands but also actively regulate profibrotic signaling, offering new therapeutic targets for modulating fibrosis.

Keywords
amino acids, anabolism, lipids, metabolism, systemic sclerosis

INTRODUCTION

Metabolic reprogramming has emerged as a pivotal event underlying the pathogenesis of tissue fibrosis [1]. Activated fibroblasts and immune cells undergo a profound reconfiguration of their core metabolic pathways to meet the high energetic and biosynthetic demands required for cellular proliferation, persistent extracellular matrix (ECM) deposition, and sustained immune activation. Recent advancements in metabolomic and transcriptomic data from systemic sclerosis (SSc) patients implicate metabolic alterations across multiple organs, while *in vitro* and animal models reveal widespread metabolic dysregulation involved in SSc pathogenesis [2–4,5▪▪].

Metabolites serve dual roles as substrates in anabolic and catabolic pathways – underpinning essential processes such as protein and nucleic acid biosynthesis – while also functioning as critical modulators of cell fate by influencing cellular behavior, functional phenotypes, and intracellular signaling networks beyond their classical role in energy metabolism. For example, altered lipid metabolism could lead to changes in membrane lipid composition, thereby affecting cell responses to external stimuli through receptor alterations in membrane lipid rafts as well as directly affecting immune signaling through their breakdown metabolites that serve as signaling molecules, such as eicosanoids. Certain metabolites are essential enzyme cofactors, such as α-ketoglutarate (αKG), a cofactor for dioxygenase

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KEY POINTS

- There is consistent shift from catabolic to anabolic metabolism in systemic sclerosis (SSc), driven by dysregulation of key metabolic regulators, including downregulated AMP-activated protein kinase and upregulated mechanistic target of rapamycin complex 1.
- In myofibroblasts, enhanced bioenergetic activity, including increased glycolysis, tricarboxylic acid cycle flux and oxidative phosphorylation supplies energy and biosynthetic precursors for fibrotic processes.
- Metabolomic and transcriptomic studies reveal profound dysregulation of amino acid and lipid metabolism, contributing to immune activation and fibroblast dysfunction in SSc.

enzymes involved in epigenetic methylation and collagen posttranslational modification, both integral to ECM maturation.

In this review, we explore the multifaceted roles of metabolic reprogramming in SSc, focusing on how metabolite availability and metabolic flux contribute to disease pathogenesis. The first part will delineate the dysregulation of catabolic and anabolic metabolism in SSc. The second section will address the enhanced bioenergetic demands in the pathogenesis of SSc. Finally, we will discuss the recent insights from metabolomic and transcriptomic studies with implications of disturbed amino acid and lipid balance contributing to fibrogenesis in SSc.

REGULATION OF CELLULAR BIOENERGETICS – THE CAUSE OR THE CONSEQUENCE

Cells adapt their metabolic processes through two key nutrient-sensing enzymes, AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin complex 1 (mTORC1), that function as counteracting regulators of catabolism and anabolism (Fig. 1) [6]. mTORC1 promotes cell growth and biosynthesis, responding to key fibrotic mediators such as growth factors like TGFβ via noncanonical pathway [7] and amino acids, particularly glutamine, leucine, and arginine, which are elevated in SSc serum (Table 1) [8]. mTORC1 shifts glucose metabolism toward glycolysis but also promotes oxidative phosphorylation (OXPHOS) and enhances protein, nucleotide, and lipid synthesis [7]. Its hyperactivation contributes to fibrosis, as it was shown that its inhibition reduces collagen production in SSc fibroblasts and improves fibrosis in animal models. However, clinical trials with mTORC1 inhibitor, rapamycin, showed limited efficacy, highlighting complex regulatory mechanisms [9]. In contrast, AMPK is activated by increased AMP/ATP ratios, signaling low energy, and promoting catabolic pathways such as fatty acid oxidation and glucose uptake to generate ATP, while inhibiting anabolic processes, including fatty acid, cholesterol, and protein synthesis. Notably, AMPK activity is reduced in fibrosis, and pharmacological activation with metformin or adiponectin alleviates fibrosis in animals models and *in vitro* [10,11].

ATP regeneration relies on OXPHOS, where nicotinamide adenine dinucleotide (NAD^+) donates electrons, received in glycolysis, fatty acid oxidation, and tricarboxylic acid cycle (TCA) to complex I of OXPHOS, resulting in the final synthesis of ATP from ADP at complex V (ATP synthase) (Fig. 2). The NAD^+-dependent enzyme sirtuin 1 (SIRT1) senses cellular energy status and regulates mitochondrial function and metabolism. SIRT1 activity is reduced in SSc, correlating with increased skin and lung fibrosis, while its activation suppresses collagen production, inflammation, and fibrotic remodeling [10,11]. SIRT1 exerts its effects by deacetylating transcription factors like FOXO and PGC1α, which govern lipid metabolism and mitochondrial biogenesis – a process requiring prior AMPK-mediated phosphorylation [12]. Besides sirtuins, NAD^+ is also a cofactor of various enzymes such as PARP and CD38. NAD^+ levels are controlled by CD38, which degrades NAD^+ to nicotinamide (NAM), and NAD phosphoribosyltransferase (NAMPT), which regenerates NAD^+ via salvage pathways (Fig. 1). Elevated CD38 levels observed in SSc tissues and models decrease NAD^+ pool and promote fibrosis, whereas inhibition of CD38 restores NAD^+ levels and confers antifibrotic effects [12]. NAMPT reverses the profibrotic phenotype of dermal fibroblasts [13]. Moreover, adipocytes were identified as a major source of NAMPT, also known as visfatin, while NAM comes from the small intestine [14▪], both tissues that are importantly affected by SSc pathogenesis. NAD^+ levels are also regulated by the enzyme nicotinamide N-methyltransferase (NNMT), which uses the NAD^+ precursor nicotinamide (NAM) and the methyl donor S-adenosylmethionine (SAM). This process lowers both NAD^+ production and the cell's overall methylation capacity, linking NAD^+ metabolism to amino acid metabolism and epigenetic regulation. In idiopathic pulmonary fibrosis , elevated NNMT in fibroblasts is associated with increased ECM production, transformation of lipofibroblasts into myofibroblasts, and resistance to cell death [15▪].

Overall, SSc is characterized by impaired catabolic signaling – marked by decreased AMPK and SIRT1 activity – and enhanced anabolic pathways via mTORC1 activation, driven by TGFβ signaling

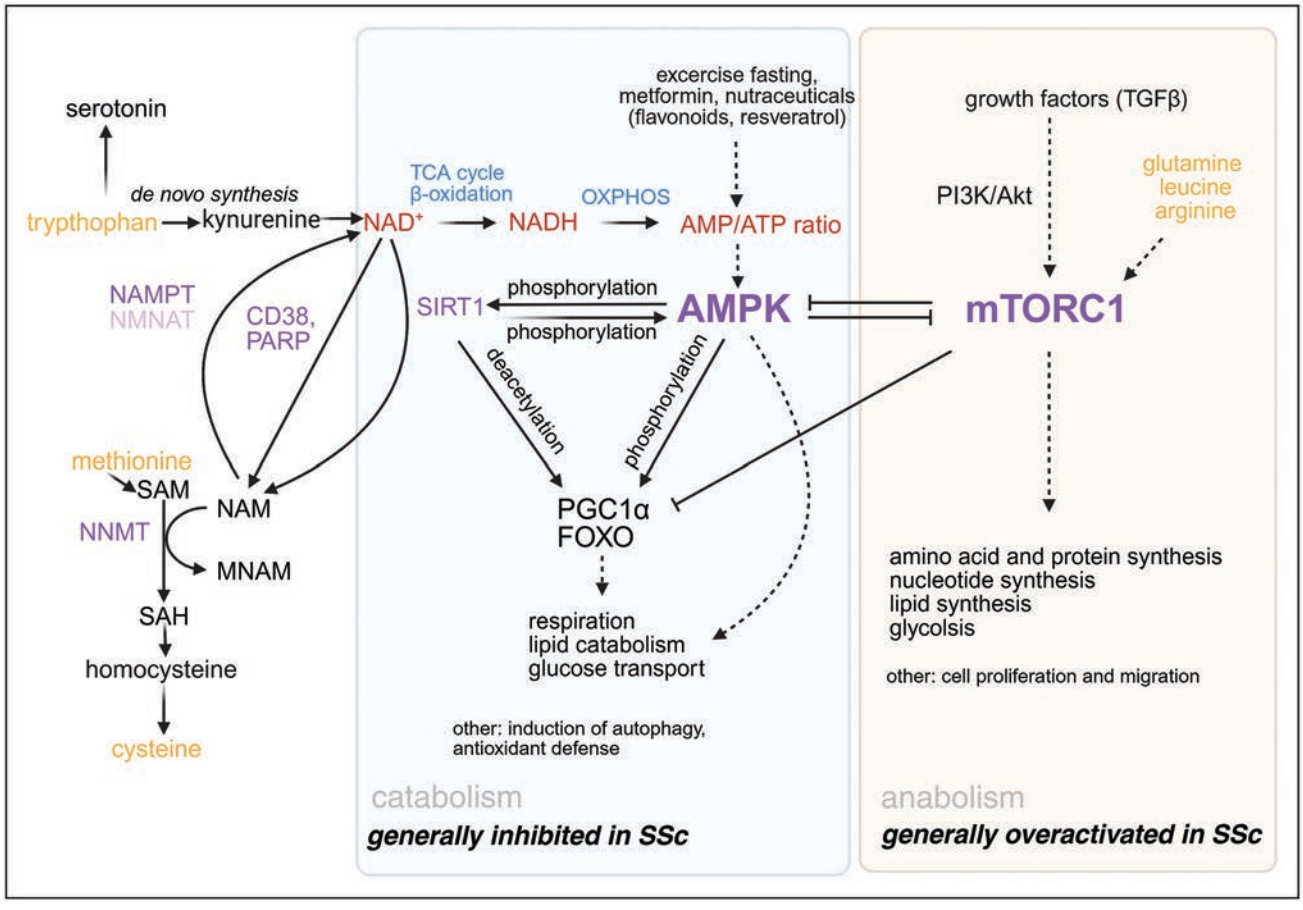

FIGURE 1. Regulation of metabolic pathways in SSc. In SSc, catabolic pathways are generally suppressed, while anabolic metabolism is overactivated. SIRT1 and AMPK regulate transcription factors PGC1α and FOXO to promote mitochondrial biogenesis, lipid catabolism, and glucose transport. AMPK is activated in response to increased AMP/ATP ratios and reciprocally inhibits mTORC1—a key regulator of anabolic processes including protein, nucleotide, and lipid synthesis. Akt, protein kinase B; FOXO, forkhead box O; NAM nicotinamide; MNAM, 1-methylnicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NNMT, nicotinamide *N*-methyltransferase; PARP, poly (ADP-ribose) polymerase; PGC1a, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinases; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; SIRT1, sirtuin 1;TGFβ, transforming growth factor beta.

Table 1. Changes observed in metabolomic studies of SSc patients plasma and serum

Changes observed in	Metabolomics (based on [3,4])
SSc vs. HC	Increased: homocysteine, amino acids kynurenine, glutamine, proline, ornithine; short chain fatty acid carnitines
	Decreased: tryptophan, alanine; long chain fatty acid carnitines
dcSSc vs. lcSSc	Increased: kynurenine, citrulline, ornithine and amino acid metabolites
	Decreased: tryptophan
SSc-ILD vs. SSc-noILD	Increased: homocysteine, valine, arginine, leucine, isoleucine
	Decreased: /
SSc-PAH vs. SSc-no PAH	Increased: asymmetric arginine
	Decreased: arginine

dcSSc, diffuse cutaneous SSc; HC, healthy controls; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; PAH, pulmonary artery hypertension; SSc, systemic sclerosis.

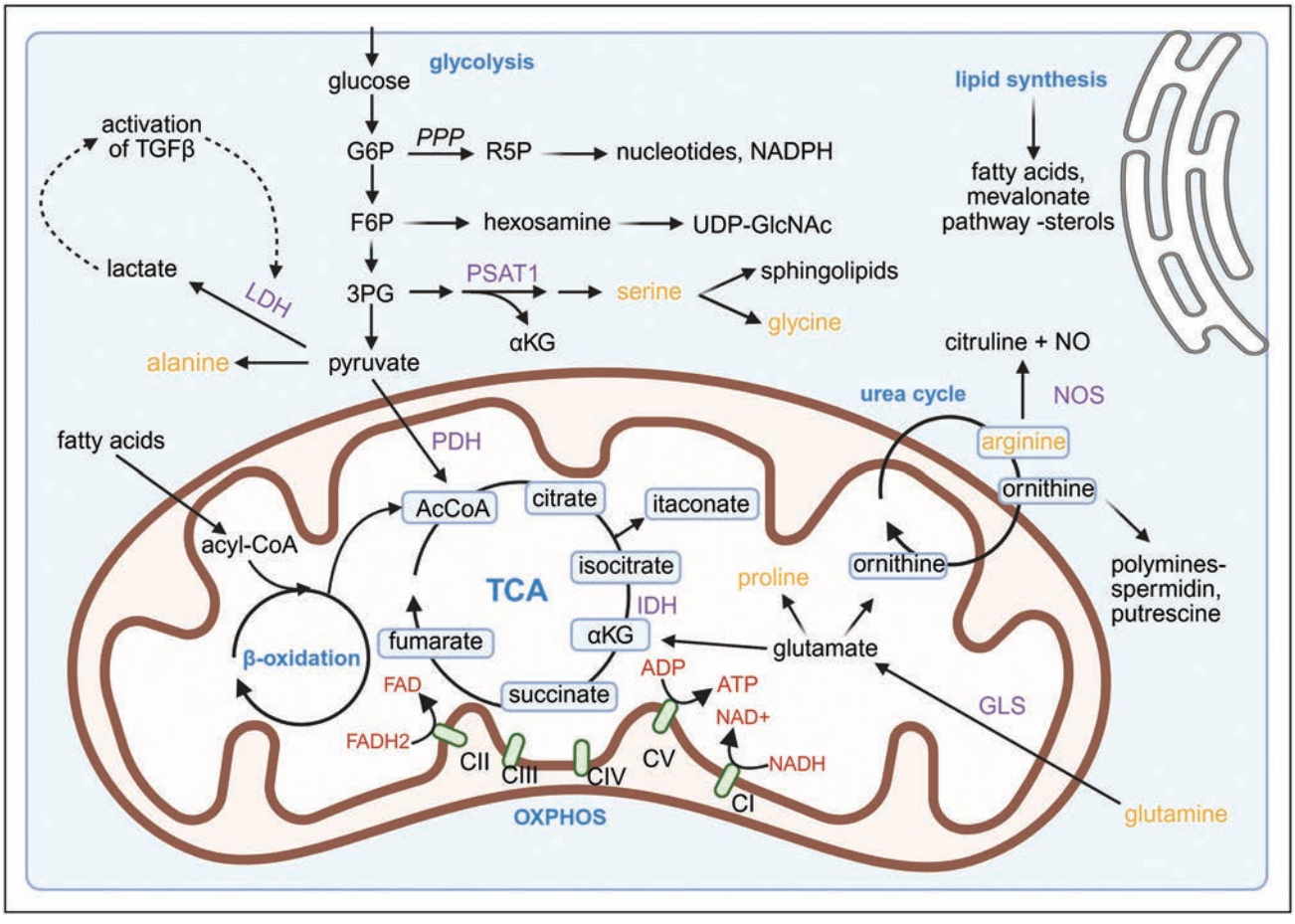

FIGURE 2. Metabolic pathways importantly implicated in SSc. In SSc, key metabolic pathways are altered, including glycolysis, the tricarboxylic acid (TCA) cycle, amino acid metabolism, and lipid synthesis. 3PG, 3-phosphoglycerate; AcCoA, acetyl coenzyme A; CI/II/III/IV/V, complex I/II/III/IV/V; F6P, fructose-6-phosphate; G6P, glucose-6-phosphate; IDH, isocitrate dehydrogenase; GLS, glutaminase; LDH, lactate dehydrogenase; NOS, nitric oxide synthase; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PPP, pentose phophate pathway; PSAT1, phosphoserine aminotransferase; R5P, ribose-5-phosphate; UDP-GlcNAc, uridine diphosphate *N*-acetylglucosamine.

and amino acid availability. NAD^+ depletion from increased CD38 and reduced NAMPT further suppresses SIRT1, contributing to immune activation, fibroblast proliferation, and excessive ECM synthesis.

CHANGES IN BIOENERGETIC CIRCUITS-GLYCOLYSIS, TCA, OXPHOS

Glycolysis is the initial step in cellular energy metabolism, producing limited ATP and pyruvate, which feeds into the TCA cycle. Beyond its role in energy generation, glycolysis intermediates serve a crucial biosynthetic function, particularly in proliferating cells. Glucose-6-phosphate enters the pentose phosphate pathway, generating ribose-5-phosphate for nucleotide synthesis and NADPH for reductive biosynthesis. Fructose-6-phosphate is directed into the hexosamine biosynthesis pathway, producing UDP-GlcNAc, a substrate essential for protein glycosylation. Additionally, 3-phosphoglycerate serves as a precursor for serine and glycine synthesis; notably, glycine comprises approximately 30% of collagen amino acids and is critical for ECM production (Fig. 2).

Unsurprisingly, highly pathogenic active cells undergo metabolic shifts with glycolytic reprogramming. In immune cells, pro-inflammatory Th17 cells and M1 macrophages rely heavily on glycolysis, while Treg and M2 macrophages engage OXPHOS, fatty acid oxidation, and glutaminolysis [16]. In fibroblasts, TGFβ enhances glycolytic enzyme expression, promoting ECM synthesis [17]. Pyruvate is converted to lactate by lactate-dehydrogenase (LDH), which acidifies the microenvironment and activates latent TGFβ. TGFβ also induces LDH in lung fibroblasts, and LDH is elevated in idiopathic pulmonary fibrosis patients' lung tissue [18] and in SSc

serum, correlating with disease progression [19]. Notably, quiescent, contact-inhibited mouse embryonal fibroblasts maintain high activity of pentose phosphate pathway even when glycolytic flux is reduced, reflecting high demand for ECM synthesis [20▪]. Metabolomic profiling of serum from SSc patients revealed an increase in glycolysis-related metabolites, suggesting enhanced glycolytic activity in fibrotic tissues [21]. This is supported by findings at the tissue level, where SSc dermal fibroblasts demonstrate elevated glycolysis that correlates with increased collagen production [22]. Recent integration of spatial transcriptomics with cytometry imaging revealed significant shifts in metabolically defined subpopulations of fibroblasts, endothelial cells, and macrophages in progressive skin fibrosis. These shifts involve a transition from metabolically inactive phenotypes to highly active subsets characterized by elevated glycolytic and TCA cycle/OXPHOS activity across all three lineages. Notably, these metabolically active populations also upregulate hypoxia-inducible factor-1α (HIF1α) and NOX4, indicating their localization in hypoxic, high ROS microenvironments. Metabolically active fibroblasts exhibit the highest expression of prototypical myofibroblast markers, suggesting their direct involvement in the transition from resting fibroblasts to myofibroblasts, thereby promoting fibrotic remodeling [23▪▪].

Proliferating cells often activate glutaminolysis to convert glutamine to αKG, serving as an alternative carbon source for the TCA cycle. Besides supporting mitochondrial metabolism, αKG acts as a cofactor for over 70 αKG-dependent dioxygenases. Examples of these enzymes include chromatin modifiers such as TET and JHDM, a key mediators of metabolic control over cell fate; they hydroxylate HIF1α to trigger its proteasomal degradation, hydroxylate proline to stabilize collagen helices and enable carnitine synthesis [24] (Fig. 3). αKG also binds and inhibits ATP synthase (complex V) causing indirect stimulation of AMPK [25]. Additionally, αKG is produced in the cytoplasm during amino acid biosynthesis, which are essential for collagen production [18], highlighting important extrametabolic roles of this mitochondrial metabolite. Inhibiting αKG-converting TCA enzymes has minimal effect on TGFβ-driven profibrotic activation [18], whereas αKG supplementation rescues cardiac myofibroblast phenotype [26] and improves cardiac fibrosis by enhancing NAD+ and SIRT1 signaling [27].

Itaconate, another important TCA cycle byproduct (Fig. 2), activates anti-inflammatory, antioxidative, and antifibrotic pathways. It is enzymatically produced from cis-aconitate by immune-responsive gene 1 (IRG1/ACOD1) and can also form via reductive carboxylation of αKG by isocitrate dehydrogenase

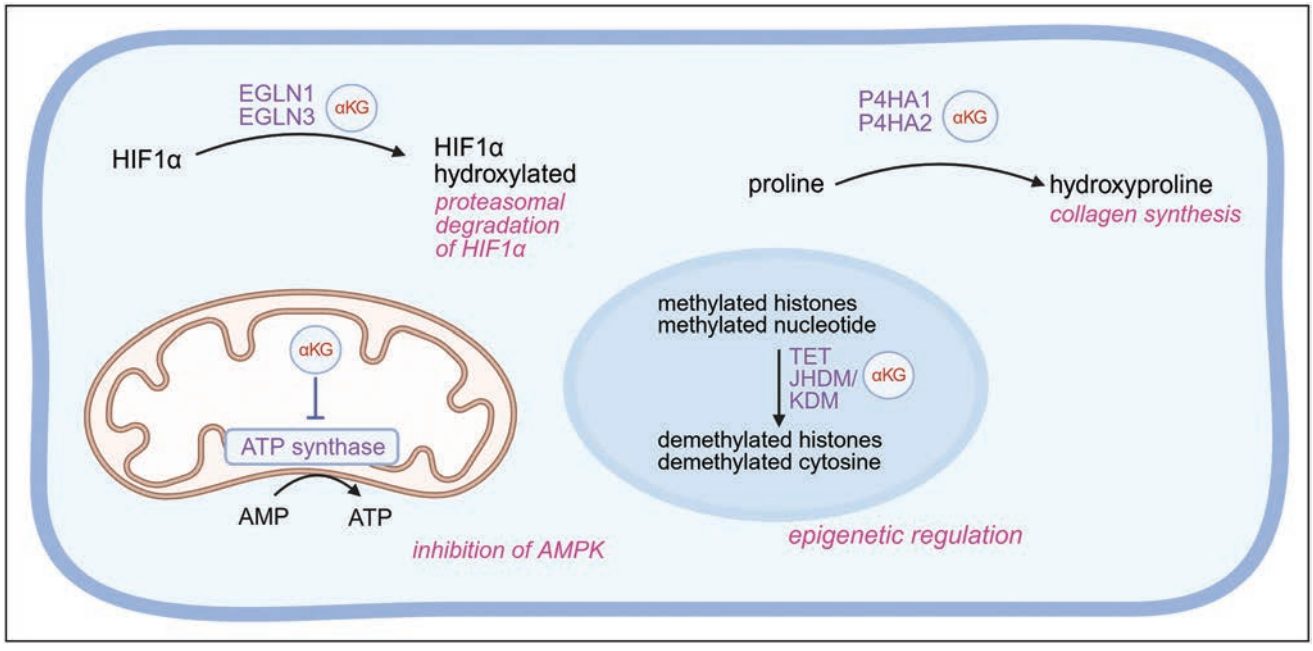

FIGURE 3. αKG as a regulator of cellular processes. Examples of several αKG-dependent enzymes relevant to cellular metabolism and transcription where αKG acts as a cosubstrate (αKG-dependent dioxygenases). αKG promotes HIF1α hydroxylation by EGLN1/3, leading to its degradation, and supports proline hydroxylation by P4HA1/2, a key step in collagen synthesis. αKG also enables demethylations such as translocation methylcytosine dioxygenases (TETs), JmjC domain-containing histone demethylases (JHDMs) and histone lysine demethylases (KDM), which mediate DNA and histone demethylation. In mitochondria, αKG enhances ATP production, resulting in suppression of AMP kinase (AMPK) activation.

(IDH). Itaconate exerts its effects by activating the antioxidant regulator Nrf2, inhibiting the Akt/mTOR and NF-κB pathways, and suppressing succinate dehydrogenase, leading to succinate accumulation and stabilization of HIF-1α [28]. In pulmonary fibrosis, reduced itaconate levels correlate with disease persistence, while treatment with itaconate or its precursor 4-octyl itaconate attenuates fibrosis through Nrf2 activation [29,30] as well as reduces collagen synthesis in dermal fibroblasts [22]. Conversely, TCA intermediates like succinate and fumarate—structurally similar to αKG – block αKG-dependent dioxygenases, prevent HIF-1α degradation and alter histone and DNA methylation [24,31]. Succinate increases in TGFβ-treated fibroblasts and fibrotic lungs, promoting collagen synthesis and stabilizing HIF1α [22,32]. Taken together, TCA cycle metabolites exploit diverse extrametabolic roles directly linked to fibrogenesis, with possible protective (itaconate and αKG) and pathogenic (succinate and fumarate) effects that promote fibrosis and inflammation, especially in pro-inflammatory polarized cells [28].

OXPHOS, which occurs in the inner mitochondrial membrane, is the primary site of cellular ATP synthesis. However, it also generates ROS due to electron leakage primarily from complexes I and III under both normal and stress conditions. Although proteomic analyses indicate a downregulation of OXPHOS components in SSc fibroblasts, mitostress assays paradoxically reveal increased OXPHOS activity accompanied by morphologically hyperfused mitochondria, resulting in elevated ATP production [17]. Consistently, multiple studies report increased ROS levels in SSc skin and cell cultures [33]. OXPHOS function is often disrupted in states of cellular senescence, chronic inflammation, and impaired tissue oxygenation. Complex II, also known as succinate dehydrogenase, plays a crucial role by catalyzing the conversion of succinate to fumarate, thereby linking the TCA cycle to OXPHOS [34]. Under hypoxic conditions, complex II can contribute to ROS generation via reverse electron transport and simultaneously reduce fumarate back to succinate [35]. This leads to an accumulation of succinate and a decrease in fumarate levels, contributing to the profibrotic imbalance previously described in the TCA cycle section.

METABOLIC PERTURBATIONS REPORTED IN METABOLOMIC AND TRANSCRIPTOMIC PROFILING OF SYSTEMIC SCLEROSIS PATIENTS

Plasma and serum samples have been extensively analyzed in metabolomic studies of patients with SSc (Table 1) as compiled in recent reviews [3,4]. While some variability exists across studies and sample types, alterations in amino acid metabolism consistently emerge as a common finding, whereas changes in lipid metabolism tend to be more heterogeneous.

In TGFβ-treated lung fibroblasts production of collagen depends on glutamine and its conversion to glutamate by glutaminase (GLS). TGFβ upregulates GLS in dermal [22] and lung fibroblasts [36] and induces phosphoserine aminotransferase (PSAT1), a key enzyme for *de novo* serine and glycine biosynthesis from glycolytic intermediates [16]. Moreover, besides fibroblasts, aberrant glutamine metabolism is observed in T cells and macrophages of bleomycin-induced lung injury models [16]. Silencing studies reveal that glutamine primarily fuels the synthesis of nonessential amino acids such as glycine and proline, rather than serving as a source for anaplerosis-replenising TCA intermediates extracted for biosynthesis or energy production [36]. Inhibition of GLS attenuated bleomycin-induced pulmonary fibrosis in mice [37], highlighting its therapeutic interference with fibrogenesis.

Metabolomic studies consistently reveal a decrease in tryptophan levels in SSc patients, accompanied by an increased kynurenine-to-tryptophan ratio, indicating enhanced *de novo* NAD^+ synthesis [38,39]. Kynurenine metabolites play important roles in modulating immune responses by influencing T cell proliferation and promoting regulatory T cell (Treg) differentiation [3] and attenuate fibrosis in skin wound healing models [40]. Rise in kynurenine/tryptophan ratio precedes pulmonary artery hypertension in SSc, making it promising prediction biomarker [41▪▪]. Additionally, tryptophan is a precursor to serotonin, a vasoconstrictive mediator implicated in the pathogenesis of pulmonary arterial hypertension and Raynaud's phenomenon. However, therapeutic options targeting serotonin signaling in Raynaud's remain limited, with fluoxetine being the only serotonin-related drug currently used in its management [42]. The paradoxically elevated protective kynurenine levels alongside downregulated profibrotic tryptophan levels likely reflect an inadequate compensatory response to ongoing fibrogenic stimuli, underscoring the intricate and multifaceted nature of metabolic dysregulation in fibrosis and the challenges it poses for targeted therapeutic intervention.

Lipid dysregulation is recognized as one of the key metabolic alterations in human and mice fibrogenesis. In fibrotic mouse models impaired fatty acid (FA) oxidation and induced FA synthesis mediated through mTORC1 activation was necessary for profibrotic effects of TGFβ [37,43]. In plasma and immune cells of SSc patients, significant alterations

in lipid metabolism (FA, carnitine, glycerolipids and sphingolipids) have been reported [4,44–46]. The relevance of lipid metabolism in activated fibrogenesis was also highlighted by early transcriptomic microarray analyses [47] and subsequently corroborated by high-resolution RNA sequencing (RNA-seq) [48] These studies demonstrated that the "normal-like" SSc phenotype exhibited a pronounced transcriptional signature associated with lipid and fatty acid metabolism, which was markedly diminished in the fibrotic state characteristic of the limited cutaneous SSc subtype [47]. This lipid-enriched gene expression program – comprising key regulators of fatty acid and sterol biosynthesis such as HMGCS1, fatty acid desaturases (FADS1, FADS2), and enzymes involved in acyl-CoA metabolism (ACADVL, ACAT2), pointing toward a potentially protective metabolic axis counteracting fibrotic progression. Recent single-cell RNA sequencing (scRNA-seq) analyses have further elucidated the metabolic heterogeneity of fibroblast subsets in SSc, revealing that key profibrotic cell states are distinguished by prominent alterations in lipid metabolism, which correlate with clinical measures of fibrosis. In a study by Zhu *et al.* [5▪▪] profibrotic MYOC^{+} myofibroblasts – recognized as principal effectors of tissue remodeling – exhibited marked transcriptional perturbations in fatty acid and cholesterol metabolism, alongside enhanced oxidative stress response pathways. Conversely, a precursor fibroblast population defined by PI16^{+} expression, which demonstrated an inverse correlation with fibroblast activation and clinical fibrosis, was enriched in cholesterol-rich gene signatures, suggesting a putative protective role of lipid metabolic programs against fibrotic activation. Cholesterol is included in lipid rafts microdomains implicated in signal transduction of tyrosine kinases, including TGFβ. Recent studies have explored how cholesterol content modulates TGFβ and EGF signaling. In hepatocytes, cholesterol depletion did not affect Smad2/3 signaling but altered PI3K/Akt signaling downstream of TGF-β/EGF receptor activation [49]. Furthermore, invaginated type of rafts named caveolae contain caveolin-1, a PPARγ-regulated anti-inflammatory gene enhancing cholesterol efflux. In SSc, caveolin-1 has been shown to modulate TGFβ receptor internalization, suppressing its signaling and ameliorating fibrosis [50].

FACTORS CONTRIBUTING TO METABOLIC ALTERATIONS IN SYSTEMIC SCLEROSIS PATIENTS

The cellular microenvironment, shaped by extracellular nutrients and signaling molecules, critically influences intracellular metabolic pathways and the availability of key metabolites. In SSc, this balance could be disrupted, as evidenced by high prevalence of severe malnutrition among the patients [51], often driven by gastrointestinal disease involvement, where intestinal dysmotility and increased permeability compromise nutrient absorption and systemic metabolite levels. Supporting this, early-stage SSc patients exhibit elevated serum bacterial endotoxins and tight junction proteins, markers that reflect a weakened gut barrier [52]. Such barrier dysfunction contributes to gut microbiome dysbiosis, which further disturbs host metabolism and immune regulation. In SSc, the altered microbial community shifts metabolic outputs, increasing harmful metabolites while reducing beneficial ones. For example, Lactobacillus – frequently elevated in SSc – metabolizes tryptophan via the kynurenine pathway, which promotes pro-inflammatory Th17 cell differentiation. Conversely, the reduced production of short-chain fatty acids like butyrate, propionate, and acetate – metabolites that support regulatory T cell function – is observed in both very early (VEDOSS) and established SSc patients. These microbial and metabolic changes align closely with gastrointestinal symptom severity, highlighting a mechanistic link between dysbiosis and metabolic dysfunction [4,53].

Beyond the gut, nutrient availability is also controlled at the tissue level, where different cells and organs have distinct metabolic roles. Fibroblasts and immune cells, for instance, rely heavily on glutamine [54], while organs such as the lung, adipose tissue, and skeletal muscle serve as glutamine sources through catabolism [55]. In SSc, impaired catabolism in these tissues likely disrupts glutamine supply, contributing to pathological metabolic alterations. Moreover, there are fourteen solute carrier-type transporters capable of transporting glutamine across the plasma membrane [56] and one of them SLC1A5, is highly expressed in fibrotic lung fibroblasts. Its inhibition suppressed mTORC1, HIF1α, glycolysis and ATP production [57▪]. Based on importance of amino acid pools for mTORC1 activity, analysis of other transporters might be crucial. Unraveling these interconnected metabolic dynamics offers promising avenues for developing precision therapies targeting SSc-associated metabolic dysfunction.

CONCLUSION

SSc involves complex metabolic reprogramming characterized by suppressed catabolic and enhanced anabolic signaling, disrupted TCA cycle metabolites, and profound lipid metabolism alterations that collectively drive fibrosis and immune activation. Despite these shifts, intrinsic genetic or epigenetic

changes in metabolic enzymes remain unproven, emphasizing the role of microenvironmental cues and nutrient availability. The intricate redundancy of pathways, exemplified by glutamine transport and mTORC1 regulation, underscores the need for integrative multiomics approaches to unravel regulatory networks. Future research should focus on identifying precise metabolic targets to develop effective, tailored therapies for SSc.

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Conflicts of interest

There are no conflicts of interest.

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The study is investigating how cholesterol depletion and enrichment affect TGFb canonical and noncanonical signaling pathway activation.

A comprehensive review of systemic sclerosis–primary biliary cholangitis overlap: emerging evidence for a distinct clinical subtype

Areeka Memon[a], *Manvitha Nadella*[a], *Morgan Emokpae*[a] *and David N. Assis*[b]

Purpose of review
To synthesize current knowledge on the genetic, immunopathogenic, and clinical presentations of systemic sclerosis (SSc) and primary biliary cholangitis (PBC) with a focus on their co-occurrence as a clinically relevant overlap syndrome. This narrative review summarizes preclinical and clinical studies addressing SSc-PBC overlap.

Recent findings
Genomic studies highlight shared susceptibility loci between SSc and PBC. Furthermore, SSc–PBC overlap patient sera reveals anticentromere antibodies which cross-react with an antigenic motif on pyruvate dehydrogenase-E2 (structural core of pyruvate dehydrogenase complex catalyzing formation of acetyl coA), the most common target of antimitochondrial antibodies in PBC. Similar profibrotic cytokines and T regulatory cell profiles are identified in sera and skin and liver biopsies of patients with SSc and PBC respectively. Analysis of clinical phenotypes reveals that SSc–PBC overlap patients have reduced incidence of pulmonary fibrosis and pulmonary arterial hypertension compared to SSc alone, and less severe hepatic involvement compared to PBC alone.

Summary
SSc–PBC overlap remains an understudied disease process. This review summarizes current knowledge and outlines future directions to guide research and improve care for patients with this distinct clinical overlap.

Keywords
limited cutaneous systemic sclerosis, primary biliary cholangitis, systemic sclerosis–primary biliary cholangitis, systemic sclerosis–primary biliary cholangitis overlap, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is characterized by immune dysregulation, vasculopathy, and multiorgan fibrosis [1]. Primary biliary cholangitis (PBC) is characterized by immune-mediated cholangiocyte loss leading to biliary tract and liver fibrosis [2,3]. SSc–PBC overlap has been described under various names, including Reynold's syndrome, PACK [PBC, ACAs, CREST (calcinosis, Raynaud, esophageal dysmotility, sclerodactyly, and telangiectasias), and keratoconjunctivitis sicca] syndrome, and more generally SSc with PBC or PBC with SSc. Despite differences in primary target organs, similarities between the two diseases include female predominance, shared genetic susceptibility loci, serum autoantibody production and fibrotic mechanisms. Given the shared immunopathogenic mechanisms and clinical phenotypes, this review aims to synthesize current knowledge on SSc–PBC overlap to improve early identification, tailor clinical management and define future research needs.

METHODS

A literature review was conducted to examine the clinical and pathophysiological features of SSc–PBC overlap. Articles published in English through April 2025 were identified using the Ovid MEDLINE database, PubMed, and Google Scholar with search terms including systemic sclerosis, SSc, scleroderma, primary biliary cholangitis, PBC, SSc–PBC, and SSc–PBC overlap. Titles and abstracts were screened for relevance, and full-text articles were reviewed as

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KEY POINTS

- Shared genetic and immunological features including immunoregulatory genes, autoantibodies, profibrotic cytokines, shared T cell responses, and common fibrotic pathways suggest convergent systemic sclerosis (SSc) and primary biliary cholangitis (PBC) pathogenetic mechanisms.
- The presence of less severe hepatic involvement in PBC patients with SSc and less severe lung involvement in SSc patients with PBC is suggestive of a unique overlap disease with a distinct clinical phenotype.
- Clinicians should suspect SSc–PBC overlap if SSc patients present with elevated alkaline phosphatase levels or anti mitochondrial antibodies or if PBC patients demonstrate anticentromere antibodies or abnormal nailfold capillaroscopy.

appropriate. Original research, review articles, and case reports were prioritized. Given the narrative review format, no formal quality assessment or risk-of-bias analysis was conducted.

EPIDEMIOLOGY

Understanding the epidemiology of SSc and PBC provides context for recognizing their overlap and guiding clinical recognition. Both diseases affect women disproportionately with an estimated global prevalence of SSc ranging from 17.6 to 18.9 per 100 000 persons and estimated global incidence at 1.4 to 8.6 per 100 000 person-years [4,5]. The global prevalence of PBC is 14.6 per 100 000 persons and the global incidence is estimated at 1.76 per 100 000 person-years [6]. While recent data suggest a rising prevalence of PBC in the Western Pacific region, epidemiological information from the Mediterranean, Africa, and other underrepresented areas remains limited, similar to SSc [5,7]. As such, reported geographic variation patterns in both diseases may partly reflect differences in surveillance intensity, healthcare access, and diagnostic infrastructure rather than true variation in disease burden.

In a meta-analysis of 20 studies, Liang *et al.* reported a pooled prevalence of SSc in PBC patients of 3.7% (95% CI: 3.1–4.4%), totaling 2130 SSc cases among 73 028 PBC patients [8▪▪]. Data from case–control studies included in their analysis further highlighted a significantly increased risk of SSc amongst PBC patients, with a pooled odds ratio of 7.08 (95% CI: 1.98–25.35) [8▪▪]. Other study results have estimated SSc prevalence in PBC patients to be as high as 12% [9]. Conversely, among patients with SSc, PBC is the most common autoimmune liver disease with a prevalence of 2–3% higher compared to the general population [10▪▪]. Improved understanding of the characteristics of SSc patients who develop PBC will help identify risk factors which can be used to develop targeted screening protocols.

PATHOGENESIS

The pathogenesis of SSc and PBC involves a complex interplay of genetic polymorphisms, environmental triggers, autoantibody production, immune activation, and fibrosis. Vasculopathy, immune activation, and collagen deposition by activated myofibroblasts is characteristic of SSc while PBC is defined by cholestasis due to immune-mediated destruction of cholangiocytes (epithelial cells that line intra- and extrahepatic ducts of the biliary tree whose main physiologic function is modification of hepatocyte-derived bile) in the small intra-hepatic bile ducts [1,11]. Microvascular injury and endothelial cell apoptosis occur early in SSc through activation of innate and adaptive immune systems leading to fibrosis of skin and internal organs [1]. In PBC, decreased activity of Cl^-/HCO_3^- anion exchangers on damaged cholangiocytes leads to disruption of the protective alkaline microenvironment in bile ducts triggering further inflammatory and fibrotic changes [12]. Interestingly, damage to the liver endothelial sinusoidal cells in PBC, previously considered a consequence of cholestatic injury, is now implicated in proinflammatory signaling contributing to pathogenesis, thereby suggesting a component of vasculopathy in the development of PBC [13].

Both diseases are characterized by serum autoantibody production that can follow exposure to environmental triggers and/or infectious agents in genetically susceptible individuals. Silica dust, which is phagocytosed by macrophages and triggers fibrosis, along with organic solvents and heavy metals, are implicated in SSc [14]. Additionally, viral infections, such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpes virus-6, and parvovirus B19, can alter miRNA expression in dermal fibroblasts, triggering fibrotic pathways, and possibly leading to SSc onset [15,16]. In PBC, cosmetics (nail polish, lipstick, and perfume), cigarette smoke, and food additives (microbial transglutaminase and artificial flavoring agents) have been associated with modification of mitochondrial antigens leading to loss of immune tolerance [17,18]. For instance, 2-octynoic acid in some cosmetics and food additives covalently modifies the lysine residue of mitochondrial pyruvate dehydrogenase complex-E2 (PDH-E2) creating neoantigens [18]. Hormone replacement therapy with estrogen can also lead to mitochondrial damage

and upregulation of PDH-E2 in cholangiocytes [19]. Urinary tract infections with *E. coli*, *N. aromaticivorans*, and *L. delbrueckii* have been implicated in PBC pathogenesis, possibly through molecular mimicry between bacterial and human PDH-E2 [20,21]. Reduction in small intestinal mucosa associated bacteria diversity, and overgrowth of *Sphingomonadaceae* and *Pseudomonas* species in the gut, have also been associated with PBC [22].

More than 90% of patients with SSc demonstrate antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on Hep-2 cells, while more specific SSc-related autoantibodies include anticentromere (ACA), antitopoisomerase, anti-RNA polymerase III, anti-U1 ribonucleoprotein, and anti-Th/To antibodies [23]. The hallmark of PBC is loss of immune tolerance to mitochondrial antigens E1, E2, and E3 of the PDH, 2-oxo acid dehydrogenase complex, and the 2-oxoglutarate dehydrogenase complex out of which PDH-E2 is the most common cause of antimitochondrial antibody (AMA) development [9,24,25]. However, at least 5% patients with PBC are AMA-negative, and 10–35% of such patients express antinuclear specific antibodies to sp100 and gp210. IIF is used to detect AMAs (sensitivity: 85%, specificity: 99%) as well as antibodies to sp100 (sensitivity: 23%, specificity: 98%) and gp210 (sensitivity: 27%, specificity: 99%). Enzyme linked immunosorbent assay, immunoblotting, and bead- based assays are other methods for detection of AMAs [26]. Key autoantibodies and antigens are listed in Table 1.

SHARED GENETIC AND IMMUNOLOGIC FEATURES DEFINE SYSTEMIC SCLEROSIS–PRIMARY BILIARY CHOLANGITIS OVERLAP SYNDROME

A cross-phenotype genome-wide association study demonstrated a strong correlation ($r=0.84$) between SSc and PBC risk alleles [27▪]. This analysis identified 44 non-HLA loci that reached genome-wide significance for both conditions, including previously reported genes such as STAT4 and IRF5. To identify potentially shared causal variants, the authors applied Bayesian fine-mapping and colocalization analysis which narrowed the list to nine loci with strong evidence of harboring shared causal variants. Of these, four loci – *TNPO3*, *IL12RB1*, *LOC100506023*, and *HEMGN/ANP32B* – had been previously associated with either SSc or PBC individually but are now supported as causal in both. The remaining five loci – *CD40*, *ERAP1*, *AHNAK2*, *SPPL3*, and *CCDC113* – had not previously reached genome-wide significance in either disease but are now newly identified as shared causal loci. Notably, two of the novel loci (*CD40* and *ERAP1*) are involved in key immunological functions including B cell activation, antigen presentation, and cytokine regulation). Additionally, two novel pleiotropic variants, *rs27524* (single nucleotide polymorphism within an intron of *ERAP1*) and *rs3873182* (downstream of noncoding RNA *RP11-457M11.5*), are associated with the joint phenotype of SSc-PBC [14].

In addition to these non-HLA findings, several HLA class I and II alleles have also been associated with SSc and PBC individually [27▪]. Results of a Mendelian randomization study further supported the association between SSc and PBC by demonstrating that PBC may have a causal effect on the risk of developing SSc with an odds ratio (OR) of 1.399 (95% CI: 1.169–1.674) [28]. Autoantibody cross reactivity between the diseases supports shared immunologic pathological mechanisms. The main antigenic targets of ACAs in SSc are centromeric chromatin (CENP-A and CENP-B) or kinetochore (CENP-C) [29]. However, ACA targeting CENP-A derived from a SSc-PBC patient's sera demonstrated cross-reactivity with an antigenic motif on PDH-E2 [30]. This

Table 1. Key autoantibodies and target antigens

Condition	ACA	ANA	AMA
SSc	chromatin (CENP-A and CENP-B) or kinetochore (CENP-C)	topoisomerase, RNA polymerase III, U1 ribonucleoprotein, Th/To, Pm-Scl antibodies, gp210, sp100	PDH-E1-3, BCOADC-E1-3, OGDC-E1-3
PBC	chromatin (CENP-A and CENP-B) or kinetochore (CENP-C)	gp210, sp100	PDH-E1-3, BCOADC-E1-3, OGDC-E1-3
SSc-PBC Overlap	chromatin (CENP-A and CENP-B) or kinetochore (CENP-C)	topoisomerase, RNA polymerase III, U1 ribonucleoprotein, Th/To, Pm-Scl antibodies, gp210, sp100	PDH-E2 (cross-reactivity in subset of ACA-positive patients) Also PDH-E1 and 3, BCOADC-E1-3, OGDC-E1-3

ACA, anti-centromere antibody; AMA, antimitochondrial antibody; ANA, antinuclear antibody; BCOADC-E1-3, branched-chain 2-oxo acid dehydrogenase complex; OGDC-E1-3, 2-oxoglutarate dehydrogenase complex; PBC, primary biliary cholangitis; PDH-E2, pyruvate dehydrogenase complex-E2; SSc, systemic sclerosis; SSc–PBC overlap, systemic sclerosis–primary biliary cholangitis.

epitope-level cross-reactivity appears to be unique to SSc–PBC overlap and is not seen in ACA-positive SSc patients without PBC [30].

An increase in fibrogenic inflammatory cytokines including interleukin-6 (IL-6), transforming growth factor β (TGF-β), tumor necrosis factorα (TNF-α), and interferon γ (IFN-γ) are consistently observed in the peripheral blood and skin of SSc patients as well as in the liver of PBC patients [31–33]. Analysis of effector and regulatory T cells (T reg) in SSc and PBC patients revealed increased effector Th17 populations and interleukin (IL)-17 production [34]. Specifically, in 17 PBC liver biopsies, the number of IL-17$^+$ T cells per portal area was found to be significantly elevated (mean: seven cells per portal area) compared to five healthy controls, who exhibited nearly no IL17$^+$ T cells in the portal areas of the biopsies (mean: ~0 cells per portal area) [35]. In SSc patients, the percentage of peripheral blood IL17$^+$ T cells was significantly elevated in 57 dcSSc patients by 7% ($P<0.001$) and 78 lcSSc by 5% ($P<0.001$) compared to 16 healthy controls [36]. SSc patients demonstrated quantitative and qualitative abnormalities in CD4$^+$ and CD8$^+$ Treg subpopulations (decreased suppressor responses and numbers of peripheral blood CD4$^+$CD25$^+$ Tregs and CD8$^+$CD28$^-$ Tregs compared to healthy controls), while PBC patients demonstrated similar abnormalities only in CD8$^+$ Treg cells (decreased frequency and phenotypic alterations in CD8$^+$CD28$^-$ Tregs including increased CD127 and decreased CD39 expression in addition to decreased suppressive function of CD8$^+$CD28$^-$ Tregs compared to healthy controls) suggesting a common abnormal CD8$^+$ Treg cell subset involved in both disorders causing fibrosis [34,37,38]. Shared immunogenetic pathways are represented in Fig. 1.

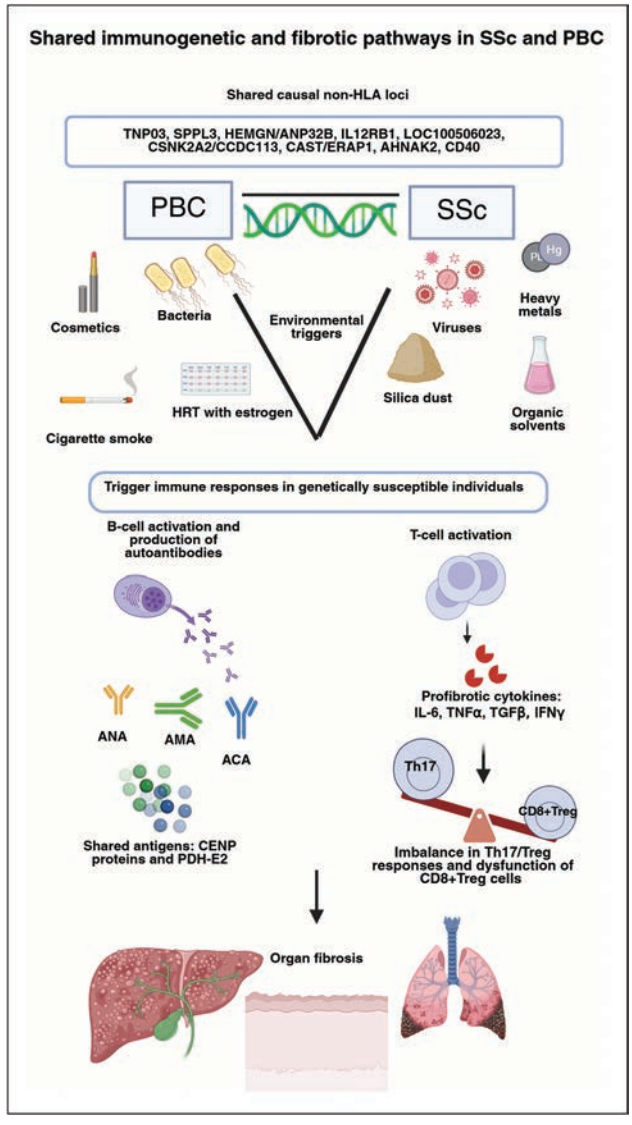

FIGURE 1. Shared immunogenetic and fibrotic pathways in SSc and PBC. The figure describes common pathways of disease, including shared genetic profiles, autoantibodies, immune mechanisms, and profibrotic cytokines. ACA, anticentromere antibodies; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; CENP, centromeric protein; CMV, Cytomegalovirus; EBV, Epstein–Barr virus; HHV-6, human herpes virus-6; HLA, human leukocyte antigen; HRT, hormone replacement therapy; IFN γ, interferon γ; IL-6, interleukin 6; PBC, primary biliary cholangitis; PDH-E2, pyruvate dehydrogenase complex – E2; SSc, systemic sclerosis; TGFβ, transforming growth factor-β; Th17, T helper 17; TNF α, tumor necrosis factor α; Treg, regulatory T cell.

CLINICAL PRESENTATION

The clinical SSc hallmark is skin thickening driven by immune-mediated fibrosis. Histopathologic evaluation reveals sclerosis involving epidermis to hypodermis, hyalinized and thickened dermal collagen bundles, loss of periadnexal fat and adnexal structures, compression of pilosebaceous units, and a perivascular or interstitial infiltrate composed of lymphocytes and plasma cells [39]. By contrast, there are no pathognomonic dermatopathological PBC findings, but 38% of PBC patients present with skin excoriations due to cholestatic pruritus, xanthelasmas, and hyperpigmentation secondary to hyperbilirubinemia [40]. Up to 56% of SSc patients develop small intestinal bacterial overgrowth (SIBO) due to gut dysmotility [41]. Similarly, PBC patients also appear to have gut flora alterations with 33% diagnosed with SIBO despite the disease not being commonly associated with known dysmotility [42]. Fatigue, common to both diseases, negatively impacts health-related quality-of-life [43,44]. Interestingly, fatigue persists despite successful PBC

treatment and improvement in cholestatic liver injury, suggesting an alternative mechanism for this important symptom which is not adequately addressed by current anticholestatic pharmacotherapies [45]. Lastly, PACK is a notable and well recognized phenotype characterized by the presence of PBC, ACAs, and CREST. In a study of 256 PBC patients, 13 (5%) had PACK and of those patients, 5 (36%) also had Sjogren's disease, further demonstrating the heightened concurrence of overlapping rheumatologic disorders in PBC [46].

SSc-PBC overlap patients appear to have milder pulmonary and liver disease compared to those with isolated SSc or PBC. Among 276 patients studied at European Scleroderma Trials and Research group (EUSTAR) centers, 115 (42%) SSc–PBC overlap patients at 10-year follow-up had significantly lower incidence of pulmonary fibrosis and pulmonary arterial hypertension (PAH) compared to 161(58%) SSc alone patients [10▪▪]. Specifically, SSc–PBC overlap patients had 11.6% lower incidence of pulmonary fibrosis compared to SSc alone (95% CI: −19.75 to –3.55) and a 9.86% lower incidence of PAH compared to SSc alone (95% CI: −14.76 to −4.96)[10▪▪]. Furthermore, SSc–PBC overlap is associated with lower rates of liver transplantation and liver-related mortality compared to PBC alone. A retrospective cohort study of 43 SSc-PBC overlap patients showed 16% of the SSc–PBC overlap patients required liver transplantation at follow up compared to 26% in the PBC group (HR: 0.068, *P*: 0.006) [47]. In contrast, telangiectasias, calcinosis, and spontaneous bacterial peritonitis are more commonly observed in patients with SSc–PBC overlap compared to either disease alone [48,49].

Cholestatic liver abnormalities are uncommon in SSc but can be more prevalent compared to the general population. In one small cohort study of 40 SSc patients, 14 (35%) patients had gamma-glutamyl transferase (GGT) and 12 (30%) patients had alkaline phosphatase (ALP) elevation compared to the general population [50]. By contrast, another cohort study of 97 patients including 81 (84%) SSc, 7 (7%)mixed connective tissue disease, or 9 (9%) patients with overlap syndrome revealed hepatocellular liver enzymes in the normal range with median (IQR) [ALT=18 IU/l (IQR: 13.8–26.3) and AST=23 IU/L (IQR: 19–29)] [51]. In a larger study from the Spanish Registro de ESCLErodermia (RESCLE), of 1572 SSc patients 118 (7.5%) were found to have hepatobiliary disease defined as the presence of PBC, primary sclerosing cholangitis, autoimmune hepatitis, nodular regenerative hyperplasia, liver cirrhosis, and/or secondary liver diseases such as viral infection, fatty infiltration, drug toxicity, and thrombotic events. Of these, only seven (0.4%) had hepatobiliary disease attributable to SSc itself, while the most frequent alternative diagnosis was PBC [52]. Given the increased prevalence of PBC in SSc, diagnostic testing for PBC should be performed in all patients with SSc who are found to have elevated cholestatic liver tests, i.e. ALP >1.5× upper limit of normal and elevated GGT levels [53,54▪]. Currently, there are no recommendations for universal routine screening for PBC in patients with SSc, or for screening for SSc in patients with PBC. However, the elevated prevalence of overlapping PBC-SSc raises the need for vigilance regarding symptoms for either condition during routine hepatology and rheumatology clinical visits, respectively. Furthermore, it is reasonable for all patients with SSc to have annual liver tests including ALP given that, in PBC, asymptomatic cholestatic laboratory abnormalities develop years before overt symptoms manifest.

DIAGNOSIS

SSc lacks diagnostic criteria, but the 2013 American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) classification criteria include finger puffiness/skin thickening, fingertip lesions including digital tip ulcers and fingertip pitting scars, telangiectasias, abnormal nailfold capillaroscopy (NFC), PAH or interstitial lung disease (ILD), Raynaud phenomenon, and SSc-related antibodies [55]. In contrast, PBC has defined diagnostic criteria, as published by the American Association for the Study of Liver Diseases, that includes the presence of ≥2 of the following in the absence of other hepatic pathology or extrahepatic biliary obstruction: ALP >1.5× the upper limit of normal, +AMA, and histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium sized bile ducts on biopsy [2]. PACK syndrome also lacks diagnostic criteria but is used to describe the overlap between SSc and PBC with or without keratoconjunctivitis sicca [46]. Notably, PBC diagnostic criteria do not include any dermatologic findings nor NFC abnormalities, although these can be more frequently observed in ACA+ PBC patients [56]. The presence of SSc specific symptoms (% prevalence estimates) in PBC patients such as Raynaud phenomenon (15–20%), skin thickening (2–3%), and calcinosis cutis (<2%) should raise suspicion for SSc–PBC overlap whereas elevated ALP levels (prevalence undefined) in SSc patients should warrant PBC specific diagnostic tests [57,58].

The presence of ACAs are detected in ≥90% of lcSSc patients, 30% of PBC patients, and 80% of SSc-PBC overlap patients [55,59,60]. These antibodies are not exclusive to SSc and PBC and can also be found in Sjogren's disease, rheumatoid arthritis, and other

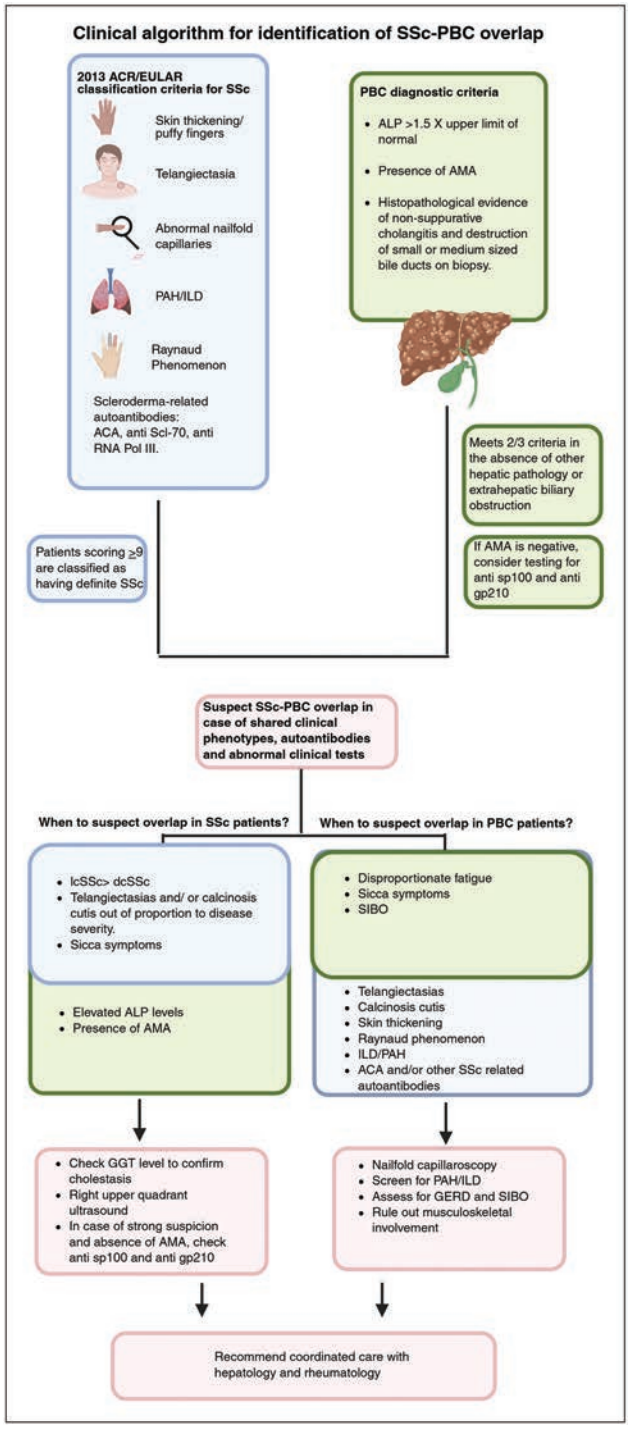

FIGURE 2. Clinical algorithm for identification of systemic sclerosis (SSc)-primary biliary cholangitis (PBC) overlap. Clinical features and serologies for the 2013 American College of Rheumatology/ European Alliance of Associations for Rheumatology classification criteria of SSc and the diagnostic criteria for PBC as per recommendations by the American Association for the Study of Liver Diseases. SSc-PBC overlap should be suspected if patients present with shared clinical and serological criteria. ACA, anticentromere antibodies; ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; GERD, gastro-esophageal reflux disease; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PBC, primary biliary cholangitis; SIBO, small intestinal bacterial overgrowth; SSc, systemic sclerosis.

overlap syndromes. Conversely, AMAs are detected in 90–95% patients with PBC and can be detected in ≥25% SSc patients, with or without evidence of cholestasis [23,61]. Indeed, patients found to be AMA positive but without cholestatic lab abnormalities should be followed with semi-annual liver test monitoring since the presence of AMA can precede the clinical development of PBC by several years. In addition to AMA, sp100 and gp210 antibodies in PBC have a sensitivity of 27% and 23%, and specificity of 99% and 98%, respectively, and should be assayed in patients with suspected PBC who are AMA-negative [62]. Additionally, the sensitivity of AMA and sp100 for detecting PBC amongst SSc patients approaches 100% [63]. While no formal diagnostic or classification criteria for SSc–PBC currently exist, Fig. 2 presents a clinical algorithm for identification of the overlap between these two diseases.

MANAGEMENT

The main indications for immune suppression in SSc are progressive SSc–ILD, rapidly progressive dcSSc, and selected cases of inflammatory musculoskeletal involvement [64]. Despite the autoimmune etiology of PBC, immunosuppression is paradoxically ineffective. Rather, first-line PBC therapy consists of weight-based ursodeoxycholic acid (UDCA) at 15 mg/kg/day. UDCA replaces and dilutes toxic hydrophobic bile acids exerting cytoprotective, antiapoptotic, immunomodulatory, and choleretic effects which improve bile retention in the liver, thereby decreasing cholangiocyte damage, inflammation and fibrosis [3]. Standardization of PBC treatment with UDCA has possibly reduced transplant listings by 50% in a 20-year comparative analysis on PBC patients awaiting liver transplants [65]. However, a meta-analysis found that up to 40% of PBC patients have an incomplete response to UDCA. Although definitions varied across the 16 studies, incomplete response generally referred to failure to achieve full normalization or sufficient improvement in liver function tests [66]. For these patients, UDCA combined with second-line agents including fibrates (fenofibrate and bezafibrate), and peroxisome proliferator activated receptor (PPAR) agonists (seladelpar and elafibranor) are recommended [67,68]. Fibrates interact

FIGURE 2. Continued.

with varying peroxisome proliferator-activated receptors (PPAR) to decrease bile acid synthesis and reduce hepatocyte uptake of bile acids [69]. It has also been suggested that PPARα has an anti-inflammatory effect by downregulating TNFα and IL-1β [70]. Obeticholic acid is also FDA-approved as second-line therapy in PBC. It selectively activates the nuclear hormone receptor farnesoid X receptor and has anticholestatic, anti-inflammatory, and antifibrotic effects [71]. The magnitude of the reduction in cholestasis is more modest compared to fibrates and PPAR agonists, and it is also associated with development of cholestatic itch and portal hypertensive complications in patients with cirrhosis, for whom it is contraindicated.

No specific SSc–PBC overlap treatment guidelines have been published. Of note, bosentan, an endothelin receptor antagonist prescribed for SSc-PAH, can induce mitochondrial toxicity and cholestasis and should be avoided in SSc-PBC overlap patients [72]. SSc–PBC overlap patients are best treated as per existing guidelines for SSc and PBC under combined rheumatology and hepatology care. Individualized treatment should be prescribed for patients with SSc–PBC considering drug toxicities and pathophysiology.

FUTURE DIRECTIONS

SSc–PBC overlap is increasingly recognized in some regions of the world, yet several aspects remain poorly understood, particularly the clinical trajectory, immunologic crosstalk, and underlying genomic risk polymorphisms. Notably, SSc–PBC overlap phenotype demonstrates a milder disease course compared to either condition alone and suggests yet unexplained immunologic derangements and/or fibrotic pathway interactions. Cross reactivity of AMA and ACA antibodies highlights the need for more structural immunology studies to shed light on interactions [30]. On the genomic level, shared loci have been identified of which CD40 and ERAP1 are known immune regulators, however the exact role of the other seven shared non-HLA loci is yet to be determined [27▪].

The field of rheumatology is beginning to recognize the gut microbiome as a critical modulator of autoimmune disease progression. Emerging evidence suggests that patients with PBC exhibit alterations in gut flora with an increased prevalence of SIBO, which has been associated with heightened gastrointestinal symptoms and inflammation [73]. Furthermore, recent innovative work in PBC highlights the impact of microbiota-produced metabolites such as butyrate and its effect on expansion of myeloid-derived suppressor cells through epigenetic and metabolic crosstalk surrounding fatty acid oxidation [74]. This, in turn, may have implications well beyond the liver-gut axis that could extend to extra-hepatic autoimmune disorders such as SSc. Additionally, in both diseases, recent studies of the gut microbiome have hinted at a shared increased association with increase in the phylum Bacteroidetes [73,75]. Therefore, investigating the gut microbiome's role in SSc–PBC overlap may uncover new pathways for disease modulation and open the door to novel interventions such as gut microbiota-directed therapies. Advancing this research will require a multifaceted approach, integrating enhanced serologic profiling with mechanistic immunology studies of circulating PBMCs, and where feasible, liver or skin tissue. Single-cell RNA sequencing, multiparameter flow cytometry, spatial transcriptomics, and paired stool metagenomic/metabolomic analyses could be used to define immune-microbiome interactions and identify genomic and microbial signatures specific to SSc–PBC overlap. Such efforts may improve diagnosis, risk stratification, and therapeutic development for this population.

CONCLUSION

SSc–PBC is a unique clinical entity that is distinct from SSc and PBC phenotypes though there are notable similarities and differences. While the underlying pathogenesis of each entity is not fully understood, common pathogenic features include female predominance, environmental triggers in a genetically susceptible host, shared genetic susceptibility loci, serum autoantibody production, and tissue fibrosis as a key pathologic mechanism. Differences between SSc–PBC, and SSc and PBC include less severe hepatic involvement in PBC patients with SSc and less severe lung involvement in SSc patients with PBC. Clinicians should maintain a high index of suspicion for SSc–PBC overlap when elevated liver function tests occur in patients with SSc, and when patients with PBC manifest NFC changes or Raynaud phenomenon or are found to have +ACA. Vigilant monitoring, early recognition, and tailored management are important for this patient subset. Future research will enable further elucidation of this unique patient subset to improve diagnosis, disease monitoring and treatment.

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Conflicts of interest

There are no conflicts of interest.

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Updates in uricase therapy for gout

Naomi Schlesinger[a] *and Dan Kaufmann*[b]

Purpose of review
Urate-lowering therapy (ULT) plays a pivotal role in treating gout patients. Unfortunately, some patients receiving oral ULT fail to achieve the target serum urate levels of < 6.8 mg/dl, the solubility level of uric acid. Exogenous uricases, considered "enzyme replacement therapy," are a therapeutic option for patients with uncontrolled gout in whom oral ULT has not been efficacious, is not tolerated, or is contraindicated, in some due to underlying comorbidities. Currently, two uricases are available: pegloticase and rasburicase. Pegloticase is indicated for treating uncontrolled gout, while rasburicase is used to prevent tumor lysis syndrome.

Recent findings
The main limitations of pegloticase include gout flares and infusion reactions, which are linked to the formation of antidrug antibodies. Immunomodulation and anti-inflammatory prophylaxis can help reduce these issues. New PEGylated uricases, including nanoencapsulated sirolimus combined with pegadricase (NASP) and PRX-115, are being developed and may offer improved options.

Summary
Exogenous uricases available and those under development are discussed, focusing on immunomodulation and anti-inflammatory prophylaxis to reduce flares, prevent antidrug antibody formation and infusion reactions, and mitigate loss of efficacy in patients with uncontrolled gout needing uricase replacement therapy.

Keywords
antidrug antibodies, flares, gout, hyperuricemia, immunomodulation, infusion reactions, PEGylation, uricase

INTRODUCTION

Gout is an autoinflammatory metabolic disease. It is caused by long-standing hyperuricemia in which serum urate (SU) levels exceed 6.8 mg/dl, leading to monosodium urate (MSU) crystal deposition [1]. Patients with severe gout experience a significant disease burden, marked by frequent gout flares (≥ 2 flares annually), tophaceous deposits, and severe pain. 3% to 4% of gout is chronic severe gout [2]. Severe gout may arise from an inadequate response to oral urate-lowering therapies (ULTs), inconsistent use of ULTs, or failure to receive treatment with ULTs altogether.

Patients with severe gout often use more healthcare resources [3▪]. Uricase enzyme replacement therapy may be advantageous, in patients with severe, uncontrolled gout for whom conventional gout medications are unlikely to rapidly reduce hyperuricemia [4–6]. In this review, we discuss approved and investigational uricases, and the clinical challenges associated with their use, including antidrug antibodies (ADAs), which can lead to loss of efficacy, infusion reactions (IRs), anaphylaxis, and flares. Given the challenges associated with uricase enzyme replacement therapy, adherence to the treatment regimen is recommended to achieve clinically significant outcomes.

THE URICASE ENZYME

In organisms other than humans, the uricase (urate oxidase) enzyme converts uric acid (UA) to allantoin, a metabolite that is 5–10 times more soluble in urine than UA, leading to increased renal excretion [7]. Humans lack a functional uricase, a homotetramer enzyme, due to nonsense mutations that have

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KEY POINTS

- Exogenous uricases, considered "enzyme replacement therapy," are a therapeutic option for patients with uncontrolled gout.
- Exogenous uricases, rapidly reduce the uric acid pool.
- The main limitations of pegloticase include gout flares and infusion reactions, associated with the formation of antidrug antibodies.

occurred throughout evolution, resulting in UA being the final end-product of human purine metabolism [8–11] (Figs. 1 and 2) [11–13].

POLYETHYLENE GLYCOL CONJUGATION

Polyethylene glycol (PEG) is a synthetic, strongly hydrophilic polymer of repeating ethylene glycol units (–CH_2–CH_2–O) [14]. PEGylation involves the conjugation of PEG to biomolecules through covalent bonds. PEGylation increases the size and molecular weight of conjugated biomolecules, thereby improving their pharmacokinetics and pharmacodynamics [14,15]. However, the PEGylated proteins can elicit high levels of anti-PEG antibodies (Abs) [16,17].

Preexisting antibodies (Abs) against the PEG moiety are commonly found in healthy individuals who have not been exposed to PEGylated drugs, and their prevalence in the healthy population ranges from 23% to 72% [18]. The high prevalence results from frequent exposure to everyday products containing PEG, including cosmetics, toothpaste, shampoos, and processed foods [19].

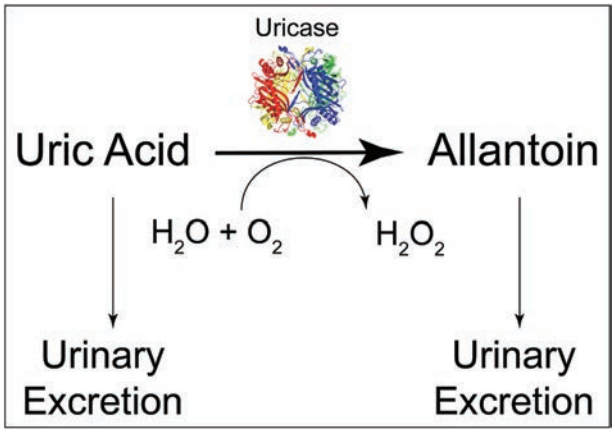

FIGURE 1. Conversion of uric acid to allantoin by uricase.

PEGylation is essential for reducing immunogenicity and extending the enzyme's half-life; however, the opposite effect may occur, where PEGylated enzymes cause the formation of antidrug antibodies (ADAs), which may also result in increased immunogenicity. Factors affecting the immunogenicity of PEGylated drugs include the route of administration, dosing regimen, presence of Abs, patient's immune status, and genetic predispositions [20,21]. ADAs may accelerate the clearance of PEGylated drugs from the bloodstream, and repeated injection of PEGylated proteins can lead to rapid elimination from circulation, known as "accelerated blood clearance" (ABC) [22,23▪▪].

URICASES ARE CONTRAINDICATED IN INDIVIDUALS WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked genetic disorder affecting over 400 million people globally, with a higher prevalence among males of Mediterranean, Asian, and African descent [24,25]. The G6PD enzyme helps prevent cellular damage from reactive oxygen species (ROS). Since erythrocytes are particularly vulnerable to ROS, G6PD deficiency can lead to acute hemolytic anemia when there is an increase in ROS production. This increase can occur due to exposure to certain foods and medications high in oxidative substances, such as uricases [26] (Fig. 1). As a result, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandate G6PD screening before administering the first uricase infusion [27,28].

URICASES

Approved uricases

Rasburicase

Rasburicase, the "naked" (non-PEGylated) recombinant Aspergillus uricase, was approved by the US FDA for children in 2002 and adults in 2009 for short-term use for pediatric and adult cancer patients with tumor lysis syndrome (Table 1) [27,28]. Rasburicase's half-life is 21 h, and it is administered intravenously for 5–7 days with a recommended daily dose of 0.20 mg/kg in patients with hyperuricemia secondary to tumor lysis syndrome [27,28]. Rasburicase has high immunogenicity, leading to Ab formation within 1–6 weeks after treatment begins [20]. IR risk increases with repeated courses of rasburicase [20].

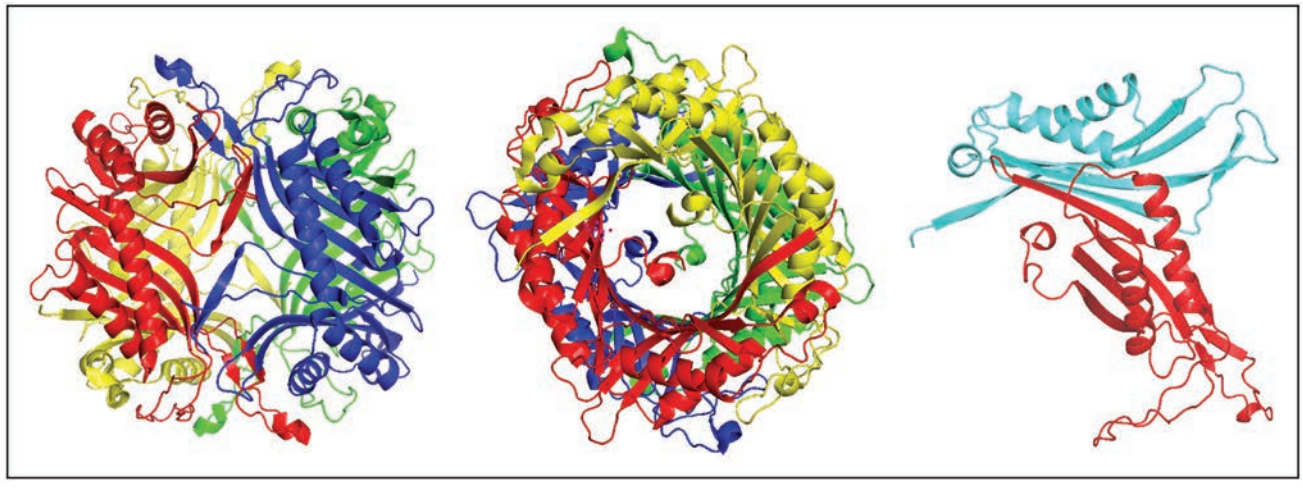

FIGURE 2. Ribbon representation of the Uricase tetramer from a side view (left) and top view (middle). Each monomer is colored distinctly to highlight tetrameric organization. Each monomer is composed of two T-fold domains (right). The first T-fold domain (cyan) contains the strands S1–S4, a pair of helices H1 and H2, plus an extra one-turn helix h1. The second T-fold domain (red) contains the strands S5–S8, a pair of helices H3 and H4, and an extra one-turn helix H2.

Rasburicase has been used off-label in patients with tophaceous gout who are refractory to, have adverse events (AEs), or are contraindicated for treatment with oral ULTs. In a pilot 6-month study by Richette *et al.*, two treatment groups were evaluated: one that received monthly rasburicase ($n=6$) and another that received a 5-day course of treatment ($n=5$) [22]. In the monthly treatment, SU levels were reduced after 6 months, with two patients demonstrating a reduction in the tophus area. The group that received a single 5-day course of treatment showed no significant reduction in SU level at one month.

Pegloticase

Pegloticase was approved by the US FDA in 2010 and by the EMA in 2013 for treating chronic gout in adults refractory to conventional therapy; however, the drug manufacturer withdrew its marketing authorization in the EU in 2016 [4,21]. Pegloticase is a chimera of porcine and baboon liver uricases covalently conjugated to a 10 kDa PEG moiety [5]. Pegloticase was initially administered subcutaneously in a phase 1 study to 13 participants [29]. However, a follow up study [30] determined that pegloticase had a higher bioavailability, tolerability, and efficacy after intravenous administration compared to subcutaneous.

Table 1. Exogenous uricases

Uricase	Approval	Indication	PEGylated	Efficacy with immunomodulation	Half-life	Frequency
Approved						
Rasburicase	FDA, EMEA	Tumor lysis syndrome	No	NA	21 h	Daily up to 7 days
Pegloticase	FDA	Uncontrolled gout	Yes	83%	6–14 days	Biweekly
In trials						
NASP	Completed Phase III BLA Submitted to FDA (7/2024)	Uncontrolled gout	Yes	High-dose group in 2 phase III trials 56% and 46%	3 days	Monthly
PRX-115	Phase 1	Uncontrolled gout	Yes	TBD	TBD	Monthly? (TBD)

Therefore, the recommended pegloticase dose for uncontrolled gout is bi-weekly 8 mg/ml (1 ml) administered intravenously.

The 2020 American College of Rheumatology (ACR) Guidelines and the 2016 European Alliance of Associations for Rheumatology (EULAR) recommend pegloticase for patients with uncontrolled gout, defined as failure to achieve the desired SU target despite using oral ULT and other interventions, and having continued gout flares ($\geq$2 flares/year) or nonresolving subcutaneous tophi [31,32].

Pegloticase is a very potent ULT. The pivotal pegloticase clinical trials demonstrated significant reduction in tender and swollen joint counts and pain, improvements in patients' global assessment and quality of life, and resolution of tophi within months (45% at 6 months (mean time to complete resolution 9.9 months) [5]. However, only 42% of pegloticase-treated patients achieved a complete response, defined as SU levels $<$ 6 mg/dL $\geq$80% of the time in months 3 and 6, compared to 0% in the placebo group ($P < 0.001$) [5]. IRs, as described below, were the most common adverse events, causing withdrawal from this study, which may explain the modest percentage of complete responders [5].

Pegloticase in kidney transplant recipients

Gout is 12 times more common in kidney transplant (KT) recipients than in the nontransplant population. In the US, the prevalence of gout in individuals with chronic kidney disease (CKD) is projected to rise by 29% [33▪▪]. Due to the high prevalence of uncontrolled gout in KT recipients, proper SU management is critical.

The Phase 4 open label PROTECT trial was designed to evaluate the safety and efficacy of pegloticase in KT patients on immunosuppression with chronic gout refractory to conventional ULT. The primary findings of the study demonstrated a high rate of urate-lowering efficacy with pegloticase in KT recipients with no new safety signals [34]. Nonresponse to pegloticase in the PROTECT trial was associated with increased anti-PEG Ab titers and decreased serum pegloticase concentrations. The PROTECT findings showed a high rate of SU-lowering efficacy with pegloticase among immunosuppressed KT recipients.

Polyethylene glycol immunogenicity–antidrug antibodies formation associated with pegloticase

The immunogenicity associated with pegloticase primarily targets the PEG moiety [23▪▪,35]. In contrast to Abs to the PEG portion of pegloticase, Abs to uricase were infrequent and, when present, usually developed after considerable exposure to pegloticase and in subjects with high titers of antipegloticase Abs [36]. In phase 3 randomized controlled studies (RCTs) of pegloticase, ADAs were detected in 89% of patients at least once during the 6-month RCT study period (Fig. 3). 41% (69/169) of patients receiving pegloticase developed high-titer antipegloticase Abs ($>$ 1 : 2430), and 40% (67/169) developed anti-PEG Abs [37]. Antipegloticase Abs developed within 2–3 months of treatment initiation, leading to failure to achieve sustained SU-lowering and increased IRs [38].

Infusion reactions

IRs, by definition, occur during or within 2 h after the conclusion of an infusion. In the pivotal phase 3 trials, IRs occurred in 26% of patients receiving pegloticase every two weeks, compared to 5% in the placebo group. 3% of IRs occurred during the first infusion [5,38]. In 88% cases, the loss of urate-lowering efficacy preceded a patient's first IR, leading to discontinuation of pegloticase administration when SU levels increased to $>$ 6 mg/dl before infusion [33▪▪,35]. IRs were the second most common AEs after gout flares (Fig. 3).

IRs can range in severity from chest discomfort, flushing, dyspnea, to IRs meeting the FDA criteria for anaphylaxis. Although most IRs were rated mild or moderate, 7% of patients who received pegloticase in the open-label extension study experienced serious AEs [39]. Careful monitoring at infusion initiation, recognition, and appropriate assessment of the IR and its severity, followed by immediate management, is required to ensure patient safety and optimal outcome. Slowing the infusion rate or temporarily pausing and resuming the infusion at a slower rate, and using antihistamines, fluids, steroids, and analgesics helped mitigate some of the IR symptoms.

61% of patients $\geq$ 70-year-olds responded to pegloticase compared to 50% of patients $\geq$ 60 years old and only 30% of patients $<$ 60- year-olds who responded ($P = 0.015$) [37]. Hence, age may influence Ab formation and responsiveness.

The pivotal pegloticase trials did not include predefined stopping rules. However, a posthoc analysis identified SU as a biomarker for IRs. Discontinuing oral ULT while on uricase treatment and assessing patients' SU levels before each pegloticase infusion are crucial to track SU, a biomarker for ADAs [40]. If SU levels $>$ 6 mg/dl before two consecutive infusions, discontinuing pegloticase treatment is recommended.

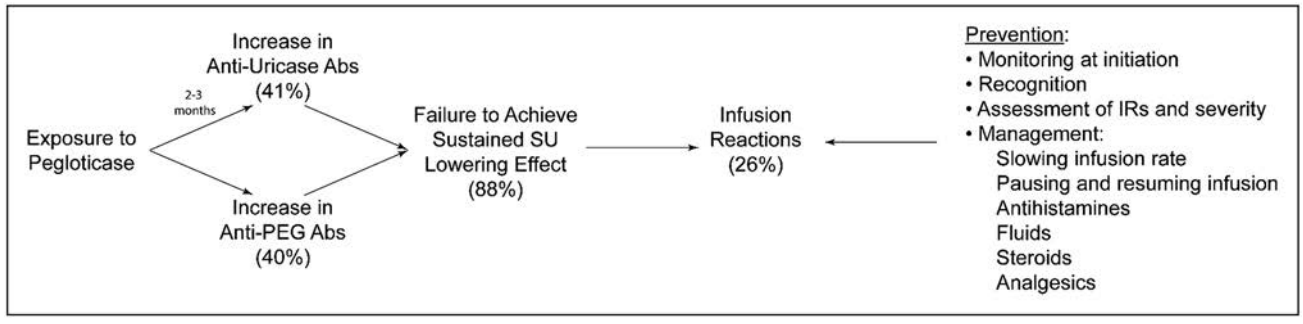

FIGURE 3. Development of antidrug antibodies (ADAs) and associated infusion reactions following pegloticase therapy, with strategies for their prevention.

Immunomodulation

Immunogenicity is the major limitation of pegloticase [37,40]. Co-administration of immune-modifying drugs with pegloticase can enhance the urate-lowering response, minimize IRs, and reduce the likelihood of discontinuing pegloticase therapy [41,42▪▪,43,44▪].

The MIRROR trial (Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase) was a randomized, double-blind, placebo-controlled study evaluating patients with uncontrolled gout [43]. The primary endpoint was the proportion of responders who maintained SU levels < 6 mg/dl for at least 80% of the time during the sixth month of treatment. The combination of pegloticase and methotrexate achieved a response rate of 71%, compared to a 38.5% response rate in those receiving pegloticase and placebo. The co-administration of methotrexate significantly reduced IRs (4% (4/96) compared to 31% (15/49) in the placebo group). The US FDA expanded the pegloticase label to include the co-treatment of pegloticase plus methotrexate in patients with uncontrolled gout based on the MIRROR trial [40,41,42▪▪,43,44▪,45].

The ADVANCE open-label trial assessed the efficacy and safety of co-administering pegloticase with methotrexate in eleven patients who had previously lost their urate-lowering response when treated with pegloticase monotherapy [46▪▪]. The treatment response rate for the combination of pegloticase and methotrexate was only 9%. Most treatment failures occurred within the first three infusions. SU levels gradually decreased, reaching near zero by week 10 and remaining low for the duration of the treatment.

Immunomodulators other than methotrexate may benefit patients who have contraindications to, or cannot tolerate, methotrexate, as seen in studies using mycophenolate mofetil and azathioprine [47,48].

Anti-inflammatory prophylaxis

Up to 80% of patients receiving pegloticase treatment experienced flares during the first three months of therapy [5,49], with a pilot study of rasburicase reporting a similar incidence [22]. Although gout flares during pegloticase treatment are classified as AEs, they represent the drug's efficacy rather than being true AEs.

Colchicine is the only FDA-approved drug used for anti-inflammatory prophylaxis. However, it is often contraindicated, nonefficacious, or intolerable in patients with gout [50]. The choice of anti-inflammatory prophylaxis medication depends on the patient's comorbidities. In patients with CKD stages 3 to 5, colchicine dosage may need to be limited, and in those with CKD as well as heart disease, the use of NSAIDs is not recommended.

Interleukin (IL)-1 is a key cytokine involved in gouty inflammation [51]. Canakinumab, an interleukin (IL)-1β neutralizing monoclonal Ab, is FDA-approved for treating gout flares [52]. A single subcutaneous injection of 150 mg of canakinumab effectively treats flares and provides anti-inflammatory prophylaxis for over three months [53]; however, the use of canakinumab for prophylaxis is currently off-label. A pilot study using a single dose of canakinumab 150 mg for prophylaxis found it efficacious in patients initiating pegloticase with methotrexate [53].

URICASES IN LATE-STAGE DEVELOPMENT

Nanoencapsulated sirolimus plus pegadricase (formerly SEL-212)

Nanoencapsulated sirolimus plus pegadricase (NASP) is a monthly uricase to treat refractory gout. It consists of two components: the first is a nanoencapsulated sirolimus (SEL-110), previously known as SVP-rapamycin or ImmTOR, immediately followed by the

second component, pegadricase (SEL-037), a PEGylated recombinant uricase enzyme derived from *Candida utilis* [54,55▪]. The sirolimus component induces a targeted, antigen-specific tolerance to pegadricase, which helps reduce its immunogenicity. Biologics License Application (BLA) submitted to FDA (July 2024).

The Compare the Efficacy of NASP to Pegloticase in Gout Patients Refractory to Conventional Therapy (COMPARE) is a 6-month RCT phase 2 trial, comparing NASP infused monthly to pegloticase 8 mg biweekly intravenous infusion in patients with uncontrolled gout [56▪]. The primary endpoint was the proportion of participants who reached SU < 6 mg/dl for $\geq 80\%$ of the time during 3 and 6 months. Pegadricase did not meet the primary endpoint. The most common treatment-related AEs with NASP and pegloticase were gout flares (60.2% vs. 50.6%), infections (25.3% vs. 18.4%), and infusion-related reactions (15.7% vs. 11.5%), respectively. Eight participants (9.6%) had stomatitis in the NASP arm, a known AE of rapamycin [56▪].

The phase 3 DISSOLVE trials included two active treatment arms of sequential infusions of SEL-110 and SEL-037 every 28 days compared to a placebo; one treatment arm had a high SEL-110 dose (0.15 mg/kg) and the other a low dose (0.1 mg/kg). The SEL-037 dose was identical in both treatment arms (0.2 mg/kg). The primary endpoint was the percentage of participants who achieved and maintained SU < 6 mg/dl for $\geq 80\%$ of the time during the sixth 28-day treatment period compared to placebo. Response rates in the treatment groups were significantly ($P \leq 0.0015$) greater than placebo [32]. The high dose response rate was 56% in DISSOLVE I and 47% in DISSOLVE II. The stopping rule in the study was SU $<$ 2.0 mg/dl (1 h following treatment in the first treatment period), SU $>$ 1.0 mg/dl on day 21 of the first treatment period, or SU $>$ 6.0 mg/dl on day 21 of each subsequent treatment periods [57▪▪]. For patients $\geq$ 50 years old, the high dose response rate was 65% and 48% in DISSOLVE I and II, respectively. IRs ($\leq$1 h) after NASP administration were reported in 3 (3.4%), 4 (4.5%), and 0 (0.0%) participants who received the high-dose, low-dose group, and placebo, respectively [57▪▪]. 143 (54%) of 265 patients who participated in the main phase of the study completed the 6-month extension. Patients discontinued the study primarily due to the stopping rule [58▪]. Other reasons for discontinuation included withdrawal of consent in 10% of participants and AEs in 13.8%, 6.8%, and 2.2% of participants in the high-dose, low-dose, and placebo groups, respectively. At 12 months, the response rates for therapy were approximately 50% in the high-dose group and 43% in the low-dose group, based on an intention-to-treat analysis. These rates are significantly higher than the 8% response rate observed in the placebo group ($P < 0.0001$). Among participants with tophi at baseline, response rates were 41% in the high-dose group, 43% in the low-dose group, and 9% in the placebo group.

Uricases in early-stage development

PRX-115

Protalix's ProCellEx platform employs plant cell cultures [59,60]. This approach has led to the development of PRX-115, a recombinant PEGylated uricase enzyme expressed in plant cells. This method reduces immunogenicity and extends half-life [59,60].

The PRX-115 phase I single ascending dose clinical trial evaluated the treatment's safety, pharmacokinetics, pharmacodynamics, and immunogenicity in patients with hyperuricemia. This double-blind, placebo-controlled trial randomized 64 participants to eight cohorts; 48 subjects received PRX–115, while 16 received a placebo [61▪▪]. PRX-115 rapidly lowered plasma UA levels to < 6.0 mg/dl after a single administration. Plasma levels remained detectable in the high-dose groups for up to 12 weeks. All randomized participants completed the study, and PRX-115 was well tolerated [62].

CONCLUSION

Currently, two exogenous uricases are available: pegloticase and rasburicase. Pegloticase is indicated for the treatment of uncontrolled gout, while rasburicase is used to prevent tumor lysis syndrome. The main limitations of pegloticase are the occurrence of gout flares and IRs, which are associated with the formation of ADAs. Innovative approaches are necessary to develop PEGylated uricases with enhanced stability, prolonged enzyme half-lives, and reduced immunogenicity. These improvements could enhance urate-lowering efficacy and increase the use of these treatments among patients with uncontrolled gout.

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Conflicts of interest

There are no conflicts of interest.

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OPEN

Gouty inflammation: genetic mechanisms towards flare therapy

Daniel Lyth and Megan Leask

Purpose of review
This review presents evidence for pathways that have genetic underpinnings in gout that should be prioritized for further study and therapeutic development.

Recent findings
Recent genome-wide association studies have identified molecular mechanisms in the pathogenesis of gout that converge on cell metabolism, phagocytosis of crystals and cytokine signalling.

Summary
Understanding how the gene pathways function to influence the gout flare; crystal formation, crystal deposition and the subsequent immune response and inflammation characteristic of the gout flare is critical to developing additional therapies in the gout repertoire.

Keywords
cytokines, genetics, gout, GWAS, immunometabolism, interferon signalling, serum urate

INTRODUCTION

Gout is the most prevalent inflammatory arthritis in the US (3.9% in the general population) [1]. Gout flares impede quality of life [2,3] and while current flare treatments such as NSAIDs, colchicine, and IL-1β targeted biologics exist, all have drawbacks ranging from limited efficacy, off-target effects and expense [4–6] (e.g., hyperglycaemia with prednisone and contraindicated in some gout patients due to comorbidities). To improve quality of life in people that experience gout, new therapies for the management of flares must be developed.

All facets of gout pathogenesis; hyperuricaemia; monosodium urate (MSU)-crystal deposition within the joints; and the associated inflammation characteristic of the gout flare have genetic underpinnings. Supporting this, much is known about the genetics of serum urate (reviewed elsewhere, [7▪,8]) with serum urate GWAS genetically linking the urate transporters and accessory molecules PDZK1 and HNF4A to urate handling in the liver, kidney and small intestine [9]. Crucially the molecular linking of gout GWAS signals to intermediate phenotypes (e.g., gene expression, metabolites and DNA methylation) has uncovered molecular mechanisms and druggable targets that could be evaluated to treat and prevent acute gout flares. Here we present three interconnected broad molecular mechanisms with genetic underpinnings identified in a recent large GWAS of gout [10▪] and corroborated by complimentary mechanistic studies which cement these processes in the pathogenesis of gout - phagocytosis of crystals, immune cell metabolism and cytokine and interferon signalling.

GENETIC MECHANISMS UNDERPINNING MONOSODIUM URATE CRYSTAL INDUCED PHAGOCYTOSIS

Phagocytosis of MSU-crystals by monocytes and macrophages leads to rupture of the phagolysosome membrane [11,12]. This damage results in complex molecular signalling, involving release of cathepsin proteases, mitochondrial damage, K^+ and Ca^{2+} ion dysregulation, and altered lysosome-associated signalling pathways such as mTOR/TFEB and JNK [11,13–16]. Indeed, part of the clinical action of

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KEY POINTS

- The genetics of hyperuricaemia and gout are distinct, with gout genetics impacting the immune system
- Phagocytosis of mono-sodium urate crystals induces pro-inflammatory signalling, but also autophagic signalling which dampens inflammation
- Cellular metabolic genes influence immune cell function via diverse mechanisms, including direct epigenetic modification or formation of substrates for modification
- Cytokines in gout are broadening, with sex-spbecific effects, an emerging role of interferons, and complex genomic regulation via noncoding RNA
- Novel therapeutics could leverage these immunological insights for effective and specific treatment of gout flares for all

colchicine is to prevent phagocytosis, albeit non-specifically by inhibiting microtubule polymerization, contributing to the narrow therapeutic index of the drug [17–19]. Understanding the specific mechanisms that lead to MSU-crystal-specific phagocytosis and rupture and the downstream consequences on the inflammatory response could identify gout-specific therapeutic targets for the treatment of gouty inflammation.

The cellular response phagolysosome membrane damage is twofold, inducing inflammation via NLRP3-inflammasome activation and clearing damaged organelles via autophagy. A recent paper [20▪▪] found that these two programs are mechanistically and transcriptionally separate, with the autophagic response dictated by transcription factor EB (TFEB) [20▪▪] building on previous work showcasing that phagolysosome damage induced inflammation is signalled through JNK [13]. This TFEB driven response activates an autophagic transcriptional program promoting gene expression of genes required for the formation of the key organelle for autophagy, the lysosome. Phagolysosome damage-induced TFEB activation initiates lysosome biogenesis and lysosome acidification likely in a dual attempt to be able to clear the internalized particle, but also to isolate and degrade any damaged phagolysosomes to prevent leakage and damage, i.e. to mitochondrial membranes [11,21]. Inhibition of autophagy in immune cells exposed to MSU-crystals exacerbates inflammation [22▪], which may be due to the lack of autophagic clearance of damaged phagolysosomes [23,24] or mitochondria [25]; both damaged lysosomal membranes and mitochondria are known to activate the NLRP3-inflammasome [26]. A deficit of autophagy is a possible mechanism for the many autophagy-related genes that have been associated with gout.

Autophagy as a starvation response is inhibited by anabolic stimuli, such as insulin and other growth factor signalling which converge on PI3K, as well as nutrient sensing via the mechanistic target of rapamycin (mTOR) [27,28]. Gout associated variants are located at the genes in these pathways such as *IGFR1, IRS1, DDIT4L*, mTOR, PI3K and the autophagy machinery itself, such as *LC3, NRBF2*, and *UVRAG* [10▪]. The PI3K pathway, of which there are many gout-associated genes [10▪] (>40 genes including receptors and ligands activating PI3K, signalling kinases, phosphatases, ancillary molecules, and effector proteins influenced by PI3K activity) is essential for the phagocytosis of particles as large as MSU-crystals [29,30], however many of these genes are broadly expressed and have many more roles than just crystal phagocytosis, targeting these for therapies would likely bring along with them the detrimental effects of PI3K-inhibitors, making benefit unlikely to outweigh the consequences [31].

Another mechanism that can impede phagocytosis is the accumulation of cellular lipids in the form of lipid droplets [32▪,33]. The highly prioritized gout-associated gene *diacyl-glycerol O-acyltransferase 2* (*DGAT2*), which catalyses triglyceride synthesis from diacyl-glycerol and *BSCL2* which codes for seipin an endoplasmic reticulum protein have been shown to have a direct role in lipid-droplet mediated dysfunction of phagocytosis [10▪,33–35]. *DGAT2* appears to be under immune cell-specific regulatory control mediated by DNA methylation and expression of immune-specific lncRNA RP11-535A19.2 [10] and is genetically linked via a long-range enhancer contact to *UVRAG*, implicating possible control of autophagic function of this lipid metabolism gene. Additionally, lipid composition of the cell membrane, membrane fluidity and curvature also impact phagocytosis [36,37] and gout-associated signals have been identified at genes impacting membrane composition, such as *BLTP2, ABCA6, AQP10* and *PITPNB* [38–40].

GENETIC MECHANISMS UNDERPINNING IMMUNE CELL METABOLISM IN THE PATHOGENESIS OF GOUT

Of relevance to gout the phenotypes of immune cells are dictated by their cellular metabolism [41] whereby pro-inflammatory macrophages rely on aerobic glycolysis and anti-inflammatory macrophages rely on oxidative phosphorylation and fatty-acid metabolism [41]. Thus, the consistent genetic associations with cellular metabolic processes [10▪,42,43,44▪] could reflect the importance

of metabolism in the inflammatory role of macrophages and other immune cells.

Glycolysis

MSU and CPP-crystals metabolically rewire macrophages toward the aerobic glycolysis pathway [45] and glycolysis-related genes including *GCKR*, *LDHB, ALDH2, DLAT* and *HK3* are implicated in the control of the metabolomic profile of plasma in gout [10,44▪]. For example, the gout-associated missense variant rs1260326 near glucokinase regulatory protein (GCKR) associates with plasma lactate. Lactate is transported across the kidney tubule membrane by URAT1 (rare Mendelian variants in lactate dehydrogenase (LDHD) [46] raise lactate levels and subsequently raise serum urate likely via increased reabsorption) but lactate levels could also impact immune cell function [44▪]. Lactate impacts gene expression via histone lactylation and/or via providing substrates for histone acetylation which epigenetically promotes a return to a non-inflammatory state [47,48]. *GCKR* is a notoriously pleiotropic locus and therefore the mechanisms underlying this association with both gout and lactate are complex.

Tricarboxylic acid cycle intermediates and epigenetic enzymes and substrates

Key to phagocytic cell function are tricarboxylic acid cycle (TCA)-cycle intermediates, which transcriptionally reprogram the immune cell into pro- or anti-inflammatory polarities [49–51,52▪]. The gout-associated variants at *CPS1* and *GLS2* are the most functionally obvious given they disrupt the protein-coding sequence of these enzymes. The missense variant in *GLS2* and the aforementioned *GCKR* variant rs1260326 [44▪] associate with gout and l-glutamine levels across multiple cohorts. The lead gout missense variant in *CPS1* associates with lower blood arginine indicating a partial loss of function of the enzyme. These two metabolites converge on the TCA cycle - arginine feeds into the TCA-cycle by conversion to glutamate and subsequent transamination into α-ketoglutarate (α-KG) [53]. Other genes encoding proteins associated with TCA-cycle metabolism or transport, IDH2 the enzyme responsible for the conversion of α-ketoglutarate, GLUD1 (glutamate dehydrogenase 1 [54]), PC (pyruvate carboxylase [55]), ABHD11 (a diacylglycerol lipase that regulates α-KG synthesis) are also associated with gout [28[10]]. Mechanistically the process of glutaminolysis and the intermediates of the TCA-cycle including fumarate, succinate and α-KG provide direct substrates for epigenetic modifications, such as histone and DNA methylation [49,50] and have been shown to directly impact phagocytic cell epigenetics altering phagocytic and inflammatory capacity [10▪,48,52▪, 56▪,57,58]. Methylation enzymes, such as the lysine-demethylases KDM6B and JMJD1C which target histone lysines and DNA-methylation modifying enzyme TET2 also have associations of gout. Combining the genetic associations of gout with these metabolic enzymes and epigenetic modifiers provides a potent molecular mechanism for the epigenetic training of immune cells observed in gout [59].

Lipid metabolism

Abnormal lipid metabolism is a hallmark of gout [60] and lipid metabolic pathways are consistently associated with gout [10,42,43]. The aforementioned DGAT2 and enzymes such as abhydrolase domain containing 11 (ABDH11), a diacyl-glycerol lipase [61,62], and transcription factors JAZF1 and HNF4-α which dictate lipid metabolic programs broadly, all impact lipid droplet formation [63,64]. However, many of these genes also impact other areas of lipid function, as diacyl-glycerol levels, impacted by DGAT2 and ABDH11, also provide substrates for arachidonic acid synthesis and activate protein kinase C [65]. The top prioritized gene for gout inflammation, fatty acid desaturase 2 (FADS2), is crucial in the synthesis of long-chain polyunsaturated fatty acids (LC-PUFAs) like EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) which can directly modulate NLRP3-inflammasome activity [66,67]. The gout-associated variant at *FADS2* (*FADS1* and *FADS3* are also located at the same locus) rs61897795 associates with plasma levels of dihomo-γ-linolenic acid, an omega-6 fatty acid eicosanoid precursor for prostaglandins [44▪,68] which modulates NLRP3 [69] lending further credence to omega-three supplementation in people with gout as a therapeutic avenue [70,71]. There is also a gout association at arachidonate 15-lipoxygenase type II (ALOX15B) and the phospholipases PLA2G6 and PLB1 [10▪] which impact NLRP3 inflammasome activity [72▪].

NLRP3-inflammasome assembly is also dependent on translocation from the endoplasmic reticulum to the trans-Golgi network [73] in a lipid specific manner. A protein complex of SCAP and INSIG2 which both have genetic associations of gout is facilitated via association with a cholesterol metabolite, 25-hydroxycholesterol (25-HC). 25-HC retains the NLRP3-inflammasome components at the ER-membrane; the association of the complex is impacted by the level of 25-HC produced [74], which can be induced by type-1 interferon signalling, contributing to the immunosuppressive action of interferons [75]. Finally, there are many fatty-acid derived posttranslational modifications of the NLRP3-inflammasome itself which are essential for proper

function [76,77]. There are many pathways by which these lipid metabolic genes may influence gouty inflammation; however, resolution of individual mechanisms has not been achieved; focus on lipids in immune cell function is likely to be a fruitful avenue for future research.

GENETIC MECHANISMS IMPLICATE CYTOKINES, THEIR RECEPTORS AND THE INTERFERON RESPONSE IN THE PATHOGENESIS OF GOUT

The influence of cytokines in the gout-specific immune response is well documented [4,78,79]. Gout GWAS data indicate that many of these known players have genetic underpinnings and influence gout via alterations in gene expression [10▪]. The most striking genetic association of gout which is not associated with serum urate is at a cytokine gene hotspot containing nine cytokine related genes including *IL1RN* (IL1Ra), *IL1F10* (IL-38), and *IL1B* (IL-1β). It is important to note that the signal is predominantly noncoding in that the linked genetic variants do not disrupt the coding sequence of a gene at the locus. This observation solidifies this region as one that most likely influences gout pathogenesis via gene regulation. Indeed, data from the Gene Tissue Expression database (GTEx) connects this signal of gout association to the expression (eQTL) of genes *IL1RN* and *IL1F10* albeit in tissues (testis and adipose) that do not have obvious links to gout pathogenesis. It is plausible that the association with *IL1RN* expression in testis suggests that the regulatory mechanism could be sex-specific in line with the sex-specific differences in cytokine levels observed in people with gout [80▪▪]. While GTEx has limited blood cell data Gaal *et al.* [81▪▪] mechanistically corroborate these *IL1RN* expression linkages and illustrate that they are gout specific. Individuals with the gout risk variant have lower *IL1RN* expression in PBMCs stimulated with C16/MSU crystal. This lowered *IL1RN* expression also translates to lower concentrations of circulating IL-1Ra for carriers who have and don't have gout. The biologic anakinra (IL1R antagonist) is noninferior compared to alternative oral treatments for the gout flare and in theory could be repurposed for gout but expense precludes it from the anti-inflammatory repertoire and it is not suitable for flare prevention [5]. Identifying other effectors that function in these regulatory pathways and perhaps earlier in the pathways would be a promising avenue of research.

Importantly the *IL1RN* and *ILF10* expression data does not exclude the possibility that the other cytokine genes at this locus are causally linked to gout. Indeed, functional interrogation of the wider locus implicates a novel long non-coding RNA (lncRNA) *AMANZI* in the gene regulation of *IL1B* via long-range chromatin interactions [82▪▪], however the genetic association of the variant explored in this research to gout is within the sub-signal of the genetic association. It is clear that the mechanisms of gene regulation at this locus are extremely complex however publicly available data provide clues as to potential regulatory mechanisms. Some of the most highly gout associated variants at this locus which alter *IL1RN* expression disrupt TFE3 and MTIF transcription factor binding sites [81▪▪] that are influential in the aforementioned immune processes of phagocytosis. While these are excellent candidates further functional experiments are required to uncover the causal variant(s) at this locus. Illuminating the precise regulatory mechanisms that underpin gout specific *IL1RN* expression could uncover additional novel players in gout pathogenesis.

Beyond the cytokine hotspot on Chromosome 2 eQTL data also implicate additional cytokines, their receptors, transcriptional regulators and other proteins in the cytokine signalling cascade including *IL6R, CSF1* and *CSF1R* as likely causal genes in the pathogenesis of gout [10▪]. *CSF1* in particular is also at a locus that has been linked to an immune priming lncRNA [83] and the gene *MAF* is also under genetic control via a scaffolding and gout-associated lncRNA *MAFTRR*[84]. *MAF* regulates expression of IL-10 [85] an anti-inflammatory cytokine involved in resolution of the gout flare and is currently being explored as therapeutic target in other inflammatory disorders [86]. Another highly prioritised gout associated gene promising therapeutic target is *NINJ1* which functions to in pyroptosis and modulates cytokine release [87].

Novel GWAS implicated mechanisms also centre on the molecular pathway linking to type I interferon signalling [10▪]. There are colocalized gout eQTL for the lncRNA *IFNG-AS1* (a.k.a. *NEST)* and *IRF5* (previously associated with other immune conditions [88]) and gene ontology analyses of male and female specific gout signals identify the IFNG pathway as the most significantly associated pathway. RNA-seq indicates that IRF1 in gout $CD14^{+}$ monocytes is more lowly expressed [89▪▪] and Baadii *et al.* found a decrease in IFN1 signalling in the presence of elevated serum urate in PBMCs lending credibility to interferon signalling being suppressed in the context of gout [90]. Population specific analyses also implicate interferon signalling mechanisms. The hematopoietic regulator *ELF1* identified in an East Asian serum urate GWAS is absent in Europeans and functions in the transcription response to interferon-B and type I interferon [91,92]. Functional work in zebrafish indicates that *ELF1* is critical in macrophage behaviour in

response to injury [93▪]. The underappreciated role for interferon signalling to date in gout pathogenesis offers an alternative therapeutic avenue and repurposing of successful interferon therapies.

FUTURE DIRECTIONS FOR GENETICALLY INFORMED THERAPIES FOR GOUT

Genetically validated therapeutics discovered via GWAS and QTL studies increase the chance of successful drug development, (e.g., secukinumab targeting -IL-23R for ankylosing spondylitis) and the FDA are more likely to approve a drug with genetic support [94]. While biologics do exist for some of the key players involved in the immune response to MSUc (e.g., IL1-RA; anakinra, IL-6R; tocilizumab and CSF1R; vimseltinib [95–98]) cost is a massive hindrance. Competition from biosimilars (cheaper, follow-on versions of biologics) may lead to price reductions in the future, but it is unclear whether the overall cost of these types of treatments will decrease substantially owing to factors like manufacturing complexity and regulatory hurdles.

Exemplified by the SARS-COV2 mRNA vaccine, RNA therapeutics are an attractive cheaper alternative to biologics with FDA approved examples and considerable public and private investment [99,100]. Antisense oligonucleotides designed against lncRNA species overactive in gout, or effective delivery of lncRNA mimetics may provide new strategies for gout therapy [101,102]. The *AMANZI* lncRNA as a negative regulator of IL-1β mediated inflammation would be attractive as a mimetic, while the divergent transcript at the *DGAT2* locus (RP11-535A19.2) and other lncRNA found by GWAS will need further characterization prior to targeting. LncRNA like *MAFTRR* are candidates for both diagnostics (e.g., *MAFTRR* and *NEST* levels can differentiate between epileptic and multiple sclerosis cases and controls [103,104] and treatment of hyperuricaemia and gout flare simultaneously, which is not currently achieved by any therapeutic.

Broadly, diet does not play a significant role in serum urate levels [105–107] however research indicates that certain food groups can contribute to gout flares [108] and lipid levels are consistently and causally linked to gout [109–115]. Combined with the genetic linking of polyunsaturated fatty acids to gout (e.g., *FADS2, FADS1* and *DGAT2*) these data suggest that modifying lipid levels, in particular PUFAs, could have therapeutic potential. Supplementation with omega-3 (targeting PUFA levels) needs testing in adequately powered clinical trials in order to assess therapeutic potential.

CONCLUSION

Here in this review we have presented candidate causal pathways in the development and progression of gout with potential therapeutic utility. An essential step in the progression of these targets to therapies is the molecular translation of the genetic signals in order to understand the tissue specific regulatory mechanisms which could lead to more cell-specific targeted therapies.

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There are no conflicts of interest.

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Calcium pyrophosphate crystal deposition: 2025 update to recent epidemiological findings

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Purpose of review
Our objective is to propose an expert opinion focusing on most important and recent developments in calcium pyrophosphate deposition (CPPD) epidemiology. We highlight recent findings published in the past 18 months and their potential implications for research and patient care.

Recent findings
We discuss new understanding of CPPD prevalence through advances in imaging modalities, advances in synovial fluid analyses (SFA), updates on disease phenotypes, and potential sources of misdiagnosis of CPPD. We present recent data regarding extra-articular associations of CPPD, particularly cardiovascular events and osteoporotic fractures. We discuss new therapeutic options. We identify barriers to improving research in CPPD, and tools currently available to overcome certain pitfalls.

Summary
Improved knowledge in the epidemiology of asymptomatic CPPD and symptomatic CPPD disease is crucial to improving recognition of this still underdiagnosed disease, and to understanding patient phenotypes and their outcomes. Future research will require prospective designs to establish the prevalence of CPPD disease phenotypes and to provide more precise data according to each phenotype, both in terms of epidemiological findings and treatment responses, to develop personalized medicine.

Keywords
calcium pyrophosphate deposition disease, clinical outcomes, clinical phenotypes, prevalence, treatments

INTRODUCTION

Calcium pyrophosphate deposition (CPPD) [1] is a condition related to the presence of calcium pyrophosphate (CPP) crystal deposits in articular and periarticular tissues which may be asymptomatic, or can cause acute or chronic inflammatory arthritis and non-inflammatory joint pain, referred to as CPPD disease [2]. Despite being described since the 1960s, the epidemiology of CPPD is still poorly understood, whereas – although direct evidence is scarce – CPPD disease might be the most common cause of inflammatory arthritis in older people (aged > 60 years) [3▪]. Current epidemiological shortcomings, even on basic data such as incidence and prevalence, are directly linked to its inconsistent nomenclature [4,5▪] and to its misdiagnosis. The renewed scientific interest in CPPD disease over the past few years provided advances that pave the way toward more precise epidemiological data [3▪,6,7▪,8▪,9–11].

This narrative review aims to cover the recent updates on the epidemiology of CPPD, and prospects for research and patient care. In this work, 'CPPD' will refer to calcium pyrophosphate deposition (asymptomatic or symptomatic), and 'CPPD disease' will be used as an umbrella term for symptomatic forms of CPPD; the nomenclature used for CPPD clinical states is currently being reconsidered [3▪,4,5▪].

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KEY POINTS

- The epidemiology of calcium pyrophosphate deposition (CPPD) is still poorly understood due to limitations associated with existing tools to identify calcium pyrophosphate (CPP) crystal deposition, unclear nomenclature and considerable clinical heterogeneity.
- CPPD disease presents a wide variety of clinical phenotypes that can mimic or overlap with other rheumatic diseases, and recent studies have shown that almost one fifth of seronegative RAs meet diagnostic criteria for CPPD disease, hence the importance of taking into account combined clinical, biological and imaging data.
- The descriptive terms 'recurrent' and 'persistent' phenotypes are increasingly used: the hospital-based cohort from which the ACR/EULAR 2023 diagnostic classification criteria were developed showed that 50% of patients who presented with at least one acute episode had a recurrent phenotype, and that nearly 25% of this cohort had a persistent phenotype.
- As a systemic disease, CPPD disease undoubtedly has significant clinical outcomes, which are increased cardiovascular morbi-mortality, an increased risk of osteoporotic fracture, and a probable increased risk of worsening cartilage structural lesions and pain in OA patients, which warrant appropriate prevention.
- Although chronic CPPD disease management mainly relies on off-label prescriptions, it is becoming more and more specific with the growing use of targeted therapies, as shown by ongoing clinical trials involving Tocilizumab and Baricitinib.

CPPD AND CPPD DISEASE PREVALENCES, BASED ON RECENT PROGRESS IN CRYSTAL DETECTION ON IMAGING

CPPD disease incidence and prevalence gaps are fostered by diagnostic challenges [12,13▪], and by the confusing use of imaging evidence of CPPD disease – most often of radiographic chondrocalcinosis – as a surrogate for the presence of the deposition or of the symptomatic disease, the latter requiring a knowledge of the clinical context. As a result, prevalence data is mostly available for CPPD and not for CPPD disease. The data available for CPPD is summarized in Table 1, and needs to be updated to improve the knowledge on CPPD epidemiology.

For this update, current crystal detection methods and their performance have been the focus of numerous recent studies [14,15,17,18].

Conventional radiography of the appendicular skeleton is the conventional modality used to estimate CPPD prevalence. It offers many advantages in everyday practice: standardized imaging procedures, high accessibility, independence from the operator, low cost, and fast acquisition. As a result, even if more sensitive modalities are available, it will continue to be used in the assessment of CPPD in everyday practice. Additionally, due to its widespread use, it is quite amenable for the application of new methods, such as artificial intelligence. For example, Hu?gle *et al.* aimed to develop a deep-learning algorithm for automatically and reliably detecting features of CPPD in hand radiographs [19]. After testing models with different combinations of articular sites, they found that a combined deep-learning model detecting imaging features of CPPD on hand radiographs at the TFCC and MCP-2/3 joints provides the highest diagnostic performance [19]. The long-term goal of this study was to validate an algorithm that meets the ACR/EULAR criteria for large-scale detection of CPPD disease cases in databases or electronic medical records using radiography and patient-reported information, and perhaps develop the same kind of algorithm for other frequently affected joints [19].

After radiography, ultrasound (US) – more sensitive – is the preferred technique for CPPD diagnosis [20,21▪▪]. In a study in patients with end stage OA (mean age 71 years), CPPD prevalence on ultrasound was 50% (reference standard was microscopic analysis) [22]. More recently, in an ultrasound study of painful knees (21–90 years), an overall CPPD prevalence of 22.4% in fibrocartilage and 9.8% in hyaline cartilage (respectively 23.3% and 46.7% after 80 years of age) was reported, with an overall CPPD prevalence coexisting in fibro- and hyaline cartilage of 9.5% [23]. Also, Cipolletta *et al.* recently proposed a reduced US scanning protocol for detecting CPPD: the bilateral assessment of knees, wrists and hips, compared to a synovial fluid analysis (gold standard), provides satisfying results with a sensitivity of 96.7% (95% CI: 82.8, 99.9) and a specificity of 100% (95% CI: 88.8, 100.0) for the diagnosis of CPPD, and had good feasibility [mean (S.D.): 12.5 (5.3) min] among 102 participants with CPPD and 102 controls [24▪]. However it should be kept in mind that specific training is essential for correct use of US in microcrystalline arthritis [20,25].

Validated CPPD imaging modalities also include conventional computed-tomography (CT) and dual-energy computed tomography (DECT) [7▪,15]. CT is the most appropriate tool to identify the axial phenotypes of CPPD [21▪▪]. DECT is not more sensitive than conventional CT for calcium-containing crystal detection, and does not adequately discriminate between two main calcium-containing crystal types, CPP and basic calcium phosphate (BCP) [26,27]. Definitions have been proposed by an expert group on imaging features [15], and recommendations for their use were suggested by EULAR in 2023 [21▪▪]. As

Table 1. CPPD prevalence according to the geographical region: summary of available data

Study	Geographical region	Population	Diagnosis modality	Prevalence
Bergström *et al.*, 1986 [65]	Switzerland	81 women and men (79 years)	X-ray of the wrists and knees	23% in women 6% in men
Sanmarti *et al.*, 1993 [66]	Catalonia, Spain	141 women and 120 men (≥ 60years)	X-ray of the wrists and knees	14% in women 6% in men
Malaviya *et al.*, 2001 [67]	Kuwait (Gulf region)	100 consecutive adult patients presenting with knee arthritis (70 men, 30 women, median age 50 years)	X-ray of the knees	0.5%
Al Arfaj *et al.*, 2002 [68]	Saudi Arabia	63 women and 90 men (50–93 years)	X-ray of knees, wrists and hands	3.9%
Neame *et al.*, 2003 [69]	United Kingdom	1084 women, 643 men; mean age 63.7; 999 (58%) with knee pain	X-ray of knees	4.5% (no sex-related predisposition)
Salaffi *et al.*, 2005 [70]	Italy	2155 subjects (≥ 18 years) in patients with arthralgia	X-ray (not specified)	0.42%
Zhang *et al.*, 2006 [71]	China	Random sample of Beijing residents (> 60 years)	X-ray of knees, wrists and hands	2.7% in women 1.8% in men
Zhang *et al.*, 2006 [71]	USA	White US subjects from Framingham cohort (> 60 years)	X-ray of knees, wrists and hands	7.7% in women 6.2% in men
Ramonda *et al.*, 2009 [72]	Italy	946 women and 683 men (≥ 65 years)	X-ray of knees and pelvic basin	12.8% in women 7.0% in men
Balderrama *et al.*, 2017 [39]	USA	5082,696 US veterans (~ 69±12 years, 95% men)	ICD-9 codes	5.2 per 1000
Karimzadeh *et al.*, 2017 [73]	Dubai	357 women and 243 men referred to the radiology units for joint radiography for any reason (50–90 years)	X-ray of joints (not specified)	3.83%
Garza *et al.*, 2019 [74]	Mexico	1253 women and 348 men from a tertiary care center	X-ray of knees, wrists and hands	2.9% in women 3.2% in men
Hameed *et al.*, 2019 [75]	Southern Sweden	1.3 million with at least one visit of interest, 20–102 years and 56% men	ICD-10 codes	0.09%
Lu *et al.*, 2020 [76]	China	2556 patients from a tertiary center (71 (54–86) years)	Odontoid calcification on cervical CT-scan	2.7%

CPPD, calcium pyrophosphate deposition.

for conventional radiography and US, validated definitions of CT-based imaging features in CPPD should be developed [26,28].

RECENT PROGRESS IN CALCIUM PYROPHOSPHATE CRYSTAL DETECTION IN SYNOVIAL FLUID ANALYSIS

Recent advances have also been made regarding CPP crystal detection in synovial fluid (SF). Raman spectroscopy is proposed as a next-generation method for the characterization of CPP crystals in SF, with good capabilities of discriminating from other crystal types [29]. This method requires expertise and is currently a research-only device not yet transferred to clinics. However, Niessink *et al.* recently developed an approach to demonstrate that the identification process can be automated with the use of machine learning techniques, which could lead to a more accurate and objective diagnosis of the type of arthritis in a point-of-care-setting, independently of the rheumatologist's opinion [30▪]. Finally, regarding the standard compensated polarized light microscopic method (operator dependent), Fitzgerald *et al.* proposed to adapt it with a polarized digital camera and multifocal depth imaging capabilities to create digital images from synovial fluid mounted on microscope slides: crystal detection rates for CPP were higher with this adapted digital method than with the standard polarized light microscopy (51%. vs. 28%) [31]. This finding supports further development and validation of an automated crystal

detection system to improve CPP detection and characterization, and therefore the sensitivity and specificity of identifying CPPD in individuals.

CLINICAL PHENOTYPING OF CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

The clinical phenotypes of CPPD disease have evolved over the years, from 6 main phenotypes in 1985 to 4 main phenotypes in 2023 [32], and seem to have different prevalences [8▪]. The common ones were those recognized in 2011 by the EULAR task force, under the umbrella term *"calcium pyrophosphate deposition (CPPD)"*: *"asymptomatic CPPD (isolated CC)"*, *"OA with CPPD" causing mechanical pain attributed to cartilage degradation and/or CPPD*, *"acute CPP crystal arthritis"* and *"chronic CPP crystal inflammatory arthritis"*[33], recently updated through the publication of the ACR/EULAR in 2023 [7▪]. The 'recurrent' form of CPPD disease, belonging to the 'acute' and/or 'chronic' forms depending on authors, and the 'persistent' form that belongs to the 'chronic' form for some authors, are currently emerging terminologies [8▪]. Other phenotypes are less described, mostly in case reports [34▪], and include axial involvements (e.g., crowned dens syndrome (CDS)), and anectodical extra-articular tophaceous CPP depositions, pseudoneuropathic arthropathy, and mixed crystal depositions [6,35–37]. Those imprecise phenotypes are directly linked to the heterogeneity of the disease. A consensus on the clinical features of the main CPPD disease phenotypes, then formalized through consensus-derived nomenclature, would make it possible to work on homogeneous groups of patients. This phenotype nomenclature project will follow the current nomenclature project on disease elements and states, which currently constitutes the G-CAN Nomenclature project [4,5▪].

The characteristics of the different inflammatory phenotypes of CPPD disease have been reported in a study using data from the international cohort assembled to develop the ACR/EULAR CPPD classification criteria [8▪]. Acute CPP crystal arthritis was reported in almost all participants, either as a single or recurrent episodes, and disease duration was associated with recurrent flares. Chronic CPP crystal inflammatory arthritis was present in 25% of cases, and was associated with acute wrist arthritis, metacarpophalangeal and STT joint OA, and negatively associated with either metabolic or familial risk for CPPD. Crowned dens syndrome was associated with male sex, STT joint OA, and more joints affected with chondrocalcinosis [8▪].

One of the remaining questions is whether asymptomatic CPP crystal deposition (whatever their method of identification) constitutes a 'preclinical stage' itself (i.e., if it can be considered as a phenotype itself), and whether only a small portion of patients evolve into a clinical stage, in the same way as asymptomatic hyperuricemia can evolve into gout [9].

OTHER RHEUMATIC CONDITIONS AS POTENTIAL SOURCES OF MISDIAGNOSIS AND DIAGNOSTIC DELAY

CPPD disease is a classic mimicker of other rheumatic conditions, which commonly leads to diagnostic delay. The main potential source of misdiagnosis is gout [38], due to the fact that microcrystalline arthropathies share many common clinical features, even if the joints affected are somewhat different. Symptomatic OA is another main differential diagnosis that has been reported for years, as an acute swollen joint linked to an episode of acute CPP crystal arthritis can be easily mistaken as an OA flare. Other potential sources of misdiagnosis are rheumatoid arthritis (RA) and particularly in its seronegative form [13▪,39,40], polymyalgia rheumatica [36,41], psoriatic arthritis [42], and axial spondyloarthritis [43]. Although they represent differential diagnoses, these are not exclusive, and a patient can have both a CPPD disease and one of the above-mentioned diagnoses. But given the number of publications on this subject, it seems that seronegative rheumatoid arthritis is a very common misdiagnosis, as recently re-highlighted by Codes-Méndez *et al.* [44▪]. Codes-Méndez *et al.* proposed to apply the 2023 ACR/EULAR classification criteria for CPPD disease in a seronegative rheumatoid arthritis cohort from a real-world clinical setting [7▪] to evaluate the proportion of patients diagnosed with seronegative-RA who met the CPPD disease classification criteria [44▪]. Among the 95 patients included with seronegative RA, 18 (18.9%) met ACR/EULAR criteria. The authors emphasize the importance of taking account all clinical, biological and imaging data to avoid misdiagnosis and consequently inappropriate therapeutic implications [44▪]. It is very likely that to better decipher the epidemiology of CPPD disease we must extract correct diagnoses from the population of patients mislabeled with these alternate diagnoses. Further studies are needed to determine the frequency of CPPD disease and all its mimickers, among all causes of arthralgia, in patients over 60 years of age (some prevalences are reported in Table 2).

CALCIUM PYROPHOSPHATE DEPOSITION AS A RISK FACTOR FOR COMORBIDITIES

As a systemic condition, CPPD disease is associated with comorbidities, which were first documented only a few years ago, explaining the sometimes incipient nature of available results [45].

Table 2. Prevalence of CPPD among the most common conditions associated with secondary CPPD, and the prevalence of those conditions in CPPD patients (original table)

Condition	Prevalence of CPPD among patients with a condition of interest	Prevalence of the condition of interest among CPPD patients	Prevalence of the condition of interest in the general population
Osteoarthritis (OA)	17.7–50% [22,77,78]	*Not available*	3.0% [79]
Seropositive rheumatoid arthritis (RA)	3–16.6% [13▪,77,80]	*Not available*	0.30% [81,82]
Seronegative rheumatoid arthritis (RA)	3.9–32.3% [12,13▪]	*Not available*	0.15% [81,82]
Gout	7.7% [38]	*Not available*	<1% to 14.5% [83–85]
Polymyalgia rheumatica (PMR)	*Not available*	*Not available*	0.7 to 2.3% after 50 years [86]
Psoriatic arthritis (PsA)	*Not available*	*Not available*	0.05 to 0.3% [87]
Axial spondyloarthritis	*Not available*	*Not available*	0.5% [88]

These results are given for the general population, and should be interpreted with caution due to the small amount of data available. These results were obtained through various diagnostic techniques (SFA and different imaging techniques).
CPPD, calcium pyrophosphate deposition.

Cardiovascular outcomes represent the best documented outcome domain for CPPD disease [46,47▪,48–52]. Brikman *et al.* investigated the association of vascular calcifications (VC) detected on knee and wrist radiographs of 98 older patients diagnosed with at least one episode of acute CPP crystal arthritis, compared with 98 controls with OA [48]. They found that VC adjacent to the affected joint were detected in 69 patients in the CPP group and 19 patients in the control group ($P < 0.001$), highlighting a strong association between VC on radiographs and acute CPP crystal arthritis [48]. Bashir *et al.* recognized CPPD as a novel risk factor for myocardial infarction, acute coronary syndrome and stroke [53]. Tedeschi *et al.* then identified that acute CPP crystal arthritis was significantly associated with increased risk for major adverse cardiovascular events in years 0–2 [HR (95%) 1.32 (1.01, 1.73)] and nonfatal cardiovascular events in years 0–2 [HR (95%) 1.92 (1.12–3.28)] and years 2–10 [HR (95%) 2.18 (1.27–3.75)], but not death [46]. The same team examined the atherosclerotic burden, using coronary artery calcium (CAC) scores, and compared 10-year atherosclerotic CV (ASCVD) risk scores in patients with vs. without chondrocalcinosis, among 756 patients with chondrocalcinosis matched to 1554 comparators on sex and age [51▪]. The 10-year ASCVD score was higher in the chondrocalcinosis cohort, but not the CAC score, suggesting that factors beyond coronary artery calcification contribute to the increased cardiovascular event rate in patients with CPPD disease [51▪]. Parperis *et al.* examined the outcomes of patients admitted for acute coronary syndrome (ACS) with and without CPPD in the US National Inpatient Sample (NIS) Database, and found that ACS in CPPD patients was associated with higher healthcare utilization and lower in-hospital mortality than non-CPPD patients [50].

From a bone health perspective, Abhishek *et al.* found an independent association between CPPD and low cortical BMD [52], and Balderrama *et al.* found a positive association between CPPD and osteoporosis [39]. Recently, Tedeschi *et al.* confirmed an increased risk of fracture among 1148 patients with acute CPP crystal arthritis versus 3730 matched comparators (mean age 73 years), using electronic health records, with an adjusted HR (95%) 1.8 (1.3, 2.3) [47▪]. They also highlighted an adjusted relative risk of fracture twice as high in the acute CPP crystal arthritis cohort (HR 1.8, 95% CI 1.3, 2.3) [47▪].

Regarding OA and its association with CPPD, the direction of causality between the two, and their potential for mutual exacerbation, has been debated for years among researchers from basic science to the clinical point of view, and OA is at least considered as a major CPPD co-morbidity [3▪,17]. Recently, Nielson *et al.* explored in a cross-sectional fashion, whether overweight individuals with knee OA and intra-articular calcium crystal (CaC) deposits (assessed on CT) experienced more knee joint inflammation (assessed on MRI) and knee pain compared with individuals without CaC deposits, and no association was found [54]. However, in another 2-year observational study, still using CT to detect CaC, and MRI for cartilage worsening, they found that CaC in the cartilage was associated with a higher risk of MRI cartilage worsening in the same compartment and subregion over two years [55▪]. Also, a longitudinal analysis in the MOST study, using CT to detect intra-articular CaC, was associated with the risk of having more frequent, persistent, and worsening knee pain over two years [56]. These findings are of great

importance because they contradict the general consideration for years that CPP crystal deposits in OA are "asymptomatic".

The association with nephrolithiasis was studied by Mirza *et al.* who implemented a study in the National VA Corporate Data Warehouse, in a cohort of 18 761 CPPD patients matched by age and sex to 75 043 controls [57]. They found an adjusted odds ratio of 1.66 (95% CI 1.56, 1.76) for nephrolithiasis in CPPD patients, and this result remained significant after removing patients with hyperparathyroidism [57].

Finally, comorbidities associated with CPPD disease may depend on the clinical states and phenotypes of the disease to focus on homogeneous groups of patients, and with prospective design if possible. Moreover, it could be interesting to compare clinical outcomes of asymptomatic CPPD and symptomatic CPPD (i.e., CPPD disease). Those results have a direct clinical impact, particularly in terms of prevention, for example when discussing the duration of colchicine after an acute episode for potential cardio-protective purposes.

CALCIUM PYROPHOSPHATE DEPOSITION TREATMENTS

Acute CPPD crystal arthritis is rarely difficult to treat, with several publications in recent years showing the efficacy of anti-IL1 in cases where conventional treatments (colchicine, prednisone, or even NSAIDs) have failed and/or are contraindicated [3▪,58]. The COLCHICORT randomized controlled trial compared the efficacy of colchicine and prednisone (prescribed for 2 days) in patients who were experiencing acute CPP crystal arthritis for <36 h, and showed that more than two-thirds of patients responded within 48 h, regardless of treatment [59▪].

The range of treatments used to manage chronic forms of CPPD disease is wider than in the acute form, and all of them are prescribed off-label [60▪]. These are the long-term prescription of colchicine (0.5 mg or 1 mg/day, effective in 50% of patients), rarely hydroxychloroquine, sometimes methotrexate at 15 mg/week, and more recently biologics (anti-IL1 and anti-IL6 antibodies) [60▪]. A recent retrospective study was carried out on a French bicentric cohort of 55 patients (70% persistent forms and 25% recurrent forms) who received Tocilizumab (mainly intravenously) [61▪]. A significant improvement in pain was observed at 3 and 6 months, prompting the submission of a prospective study protocol for Tocilizumab in chronic CPPD disease (TociCCAre study, currently funded and being set up) [61▪]. Finally, the involvement of the JAK/STAT pathway in microcrystalline inflammation suggests the theoretical relevance of JAK inhibitors: an Italian study is underway with baricitinib, the BAPTIST study.

PROSPECTS FOR IMPROVEMENT IN EPIDEMIOLOGICAL STUDIES ON CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

Recent efforts have been made to remove barriers hindering current epidemiological studies, like the publication of the 2023 ACR/EULAR classification criteria [7▪], the homogenization of imaging definitions [16], and the consensus project by the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) to develop a nomenclature for CPPD [4,5▪]. In parallel, efforts are being made in coding systems, as ICD-10 did not provide specific codes for CPPD disease, but the ICD-11 version currently in development will separate "chondrocalcinosis" (FA262) and "calcium pyrophosphate deposition disease" (FA260) conditions [32]. To try to better identify acute CPP crystal arthritis in clinical practice, Cipolletta *et al.* developed and validated a patient-reported definition of acute CPP crystal arthritis in people with crystal-proven CPPD disease [62]. They collected patient-reported outcomes from 246 individuals in 7 centers. The most informative variable was patient-reported acute CPP crystal arthritis, followed by patient-reported joint swelling, and patient-reported joint warmth. The aim of this validated definition is to use it in clinical trials and observational research in CPPD, notably to record the occurrence of acute CPP crystal arthritis as the outcome of interest in long-term studies of patients with CPPD disease [62]. Other methods had been previously developed, like a billing code algorithm [63], and a combination of natural language processing, machine learning methods, and synovial fluid lab results to yield an algorithm that significantly boosted a positive predictive value for 'pseudogout' identification [64].

All these tools will no doubt have a positive impact on the accuracy of CPPD epidemiology.

CONCLUSION

The current main limitations of epidemiological studies on CPPD are its under-diagnosis, and the lack of specific incidence and prevalence studies on large cohorts, which should be more feasible now due to improved diagnostic tools (e.g., advances in imaging, automated crystal detection) and the first classification criteria. Creating a clear nomenclature and consensus-based definition of clinical phenotypes, developing new tools to efficiently identify patients in databases, and conducting prospective epidemiological studies will help to improve diagnosis, prevention, care and treatment.

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Conflicts of interest

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Updates in juvenile dermatomyositis: pathogenesis and therapy

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Purpose of review
This review provides updates on juvenile dermatomyositis pathogenesis and treatment.

Recent findings
JDM pathogenesis research updates in genetic risk factors include C4 copy number. Studies clarify myositis-specific autoantibodies' (MSA) role in disease pathogenesis and more myositis-associated antibody (MAA) clinical associations. Recent studies validate an interferon (IFN)-regulated gene score and an IFN-related monocyte surface protein marker, SIGLEC-1. Vasculopathy and mitochondrial dysfunction evidence increases, both with ties to IFN. Studies point to not only T and B cells, but monocytes, macrophages, and neutrophils as dysregulated in JDM. Regarding treatment, there are growing reports of success with therapies targeting IFN-signaling (Janus kinase inhibitors), dazukibart (anti-IFN-beta), and anifrolumab (anti-IFNAR1). Chimeric antigen receptor (CAR) T-cell therapy targeting B-cells in a growing number of adult myositis patients and one JDM patient have dramatic reports of achieving drug-free remission.

Summary
Growing evidence show genetic markers, MSA, IFN, vasculopathy, varied immune cells, and mitochondrial dysfunction having important roles in JDM pathogenesis. Some refractory patients show benefit with newer IFN pathway-targeted therapies and cellular CAR-T-cell therapy. Further collaborative research on disease pathogenesis, treatment targets, and innovate clinical trial design is needed to increase access to more efficacious treatments in JDM.

Keywords
autoantibody, interferon, juvenile dermatomyositis, mitochondria, myositis autoantibody, pathogenesis, treatment, vasculopathy

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare inflammatory systemic autoimmune disease characterized by vasculopathy, muscle weakness, and skin rash. It is by far the most common juvenile idiopathic inflammatory myopathy (JIIM). Myositis-specific autoantibodies (MSA) define clinical subgroups within JDM. Most patients have a chronic or polycyclic disease course, and some patients are refractory to many standard treatments, such as corticosteroids and methotrexate. Although research has progressed on JDM, the cause remains incompletely understood [1]. Here we will review recent updates in pathogenesis and treatment.

PATHOGENESIS

Genetics

Genomic investigations have revealed variants associated with idiopathic inflammatory myopathies (IIM), with some specific to myositis subtypes, including JDM. Most recently, Zhu *et al.* [2▪], as a part of the Myositis Genetics Consortium, published a meta-analysis of two prior large myositis genetic studies [3,4] that strengthened prior evaluations and

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KEY POINTS

- Genetic markers (e.g. HLA associations and C4 copy number variation) and both adaptive (e.g. T cell and B cell) and innate (e.g. monocyte, macrophage, and neutrophil) immune cell dysfunction play important roles in JDM pathogenesis.
- Beyond the clinical associations of myositis-specific antibodies (MSA), studies show a more direct connection of MSA to disease pathogenesis. Myositis-associated antibodies also have demonstrated clinical associations in juvenile myositis. Specific MSA testing has varied accuracy based on testing methodology.
- Vasculopathy and mitochondrial dysfunction have important roles in JDM, both tied to IFN. IFN-related gene and protein markers show disease-activity association and can be considered for broader use as a biomarker in JDM.
- IFN pathway-targeting therapy [Janus kinase inhibitors, dazukibart (anti-IFN-beta), and anifrolumab (anti-IFNAR1)] and cellular chimeric antigen receptor (CAR) T-cell therapy targeting B cells show impressive efficacy in refractory patients, but further study is needed.
- More collaborative research is needed in this rare disease to identify promising biomarkers, treatment targets, and innovative clinical trials to increase access to better treatments for JDM patients.

revealed significant overlap in risk alleles identified by two different methods (Immunochip, Genome-Wide Association Study or GWAS).

Human leukocyte antigen region

Despite analyses confounded by linkage disequilibrium, genetic density, and heavy reliance on imputation, HLA have repeatedly been shown to be the strongest risk alleles for inflammatory myopathies, including JDM [3,4]. The most notable associations emerge when patients are stratified by autoantibody status [5–9], which may represent distinct pathogenic pathways [10]. Zhu *et al.* re-demonstrated several HLA associations, including HLA-DRB1*03:01, also known as DR3, the strongest HLA risk allele in total IIM, HLA-B*08:01, part of the ancestral haplotype 8.1, and a variant near HLA-DRB5/HLA-DRB6 (rs1894553), which was specific to JDM.

Non-human leukocyte antigen variants

Zhu *et al.* confirmed some previously reported risk loci (e.g. *PTPN22*, *STAT4*) but did not validate some others (e.g. *NAB1, DGKQ, YDJC*) [11]. They also uncovered novel loci (e.g. *FCRLA, NFKB1, IRF4*, and *ATXN2*) in IIM overall. In JDM, the *IRF4* variant (rs12203592) had the strongest effect size, though it was only sequenced by Immunochip.

Copy number variation and complement in juvenile dermatomyositis

Complement genetics, specifically *C4* gene copy number (GCN) variation, demonstrate striking correlation with the IIM in general and JDM in particular [12–15]. GCN variation analyses suggest that lower *C4* GCN, expected to cause lower serum C4, is associated with an increased risk of developing myositis [12,13], though the exact risk mechanism is not fully understood. Nomura *et al.* [16] recently showed that C3 and C4 serum levels were lower in adult Japanese patients with IIM and interstitial lung disease (ILD). Serum complement levels vary with consumption and GCN for C4, though the latter was not assessed in that study. Complement consumption has not been well characterized in myositis versus in systemic lupus erythematosus (SLE), which may indicate an independent role of C4 GCN in IIM.

Epigenetic contributions to juvenile dermatomyositis

Epigenetic changes likely contribute to autoimmune diseases, though this is not well studied in IIM [17]. Recently, two studies in JDM specifically focused on nonsynonymous single nucleotide polymorphisms that affect downstream gene expression by altering protein phosphorylation or N6-methyladenosine RNA modification [18,19]. These single-nucleotide polymorphisms (SNPs) were correlated with altered gene expression levels of key immunologic factors such as class I and II HLA molecules and *C4A,* indicating this as an exciting area for further research.

Myositis autoantibodies

Myositis-specific autoantibodies (MSA)

MSA, found only in myositis, have been associated with clinical subgroups within JIIM, as summarized elsewhere [20–25]. Antitranscriptional intermediary factor (TIF1), antinuclear matrix protein 2 (NXP2), and antimelanoma differentiation-associated protein 5 (MDA5) are most common in JDM [20–25]. Briefly, anti-TIF1 is associated with photosensitive rashes and a chronic disease course, while anti-NXP2 is associated with more severe muscle disease and increased risk of calcinosis. Anti-MDA5 is associated with ILD and is more prevalent in Asian cohorts [26,27]. There is no cancer association for any MSAs in JDM (e.g. TIF1 and NXP2) as there is in adults [24,25]. Antisynthetase autoantibodies (transfer or tRNA synthetases) are the most common in adult IIM [28] and rare in children [24,25].

There is increasing research pointing to the role MSAs play in pathogenesis [29▪,30▪]. Subtypes of adult IIM, including those defined by MSA, demonstrate distinct gene expression profiles in muscle [31]. Pinal-Fernandez *et al.* recently showed that MSA–autoantigen complexes are present in muscle cells from myositis patient biopsies, providing insight for how autoantibodies against ubiquitous intracellular machinery could lead to muscle-specific disease [32]. Several MSA, including anti-TIF1 [33], anti-Jo1 [or histidyl-transfer RNA synthetase (HRS)] [34], and anti-MDA5 [35,36] have been shown to induce myositis in experimental mouse studies [37].

Myositis associated autoantibodies (MAA)

MAAs are associated with IIM and overlap myositis, as well as other conditions without myositis. Anti-Ro52 confers increased risk of ILD and a chronic disease course in myositis [38]. Sherman *et al.* found MAA positivity (Ro60, Ro52, La, Pm/Scl, Ku, Smith, U1RNP, U-RNP other, TMG cap and/or NT5C1A) was associated with a chronic disease course and increased mortality. Importantly, this study identified that the number of positive MAAs was associated with mortality and proposed that early detection of MAAs may lead to improved outcomes for patients with juvenile myositis [39▪▪].

Myositis autoantibody testing methodology

Despite the well demonstrated benefit of MSA and MAA identification regarding diagnosis and prognosis, there are caveats to result interpretation based on testing methodology. Immunoprecipitation is considered the reference standard method. However, it is expensive and takes months to result. Commercial immunoassays of varied methods are not only lower cost, more widely available and have shorter turnaround times, but also have more false positives and negatives [40]. Patients generally have a single MSA, so multipositivity in commercial immunoassays may indicate a false positive. In one study including 321 samples, most commercial assays performed reasonably well versus immunoprecipitation; however, anti-TIF1 had low sensitivity in line blot and very low sensitivity in dot blot assays [41,42], with similar findings by others [40,43▪]. This is notable, as anti-TIF1 is one of the most common MSAs in JDM. Consideration of pretest probability by clinical context and testing methodology are essential when interpreting results.

Interferon

Initial microarray transcriptomic studies in muscle identified interferon (IFN) or IFN-related genes (IRG) as most differentially expressed, with similar findings of IRG in blood and skin of JDM and adult dermatomyositis (DM) patients [44–47]. Recently, Turnier *et al.* [44] found IFN to be the top dysregulated pathway in JDM noninvasive tape-stripping skin samples. Many IRG expression or scores in muscle [48,49] and blood correlate with disease activity, highlighting its importance in JDM and its potential use as a disease biomarker [44,45,48,50,51,52▪,53▪].

Interferon type

In pathway analysis, type I IFN (e.g. IFN-alpha and IFN-beta) is usually top-ranked in JDM, but type I IFN downstream markers (e.g. genes and proteins) greatly overlap with type II (IFN-gamma) and III IFNs (IFN-lambda), so the specific IFN trigger can be difficult to specify. Direct IFN measurement is difficult, as IFNs are in quite low concentration in blood [48], but peripheral IFN-alpha was found to be increased in JDM versus controls. Peripheral IFN-beta was found to be elevated in adult DM versus other myositis types, and had higher significant correlation with the IRG score in blood versus other IFNs. In adult DM skin, IFN-beta RNA transcripts correlated better with the IFN score, and IFN-beta protein correlated better with a clinical DM skin activity score, Cutaneous Dermatomyositis Area and Severity Index Activity Score (CDASI-A). These may mean the IFN-beta drives more of the downstream IFN score in adult DM skin and blood [54,55].

Interferon biomarkers: interferon-response gene (IRG) scores

From a large ($n=57$), well characterized cross-sectional cohort of JDM patients, a 28-gene IRG score had moderate correlation with various validated JDM disease measures, with higher correlation to skin disease activity in anti-TIF1 JDM. Weakness and joint disease were most predictive of having a high IRG score [51]. In 43 JDM patients with 87 longitudinal samples, including 18 treatment-naive samples, McMahon *et al.* found the same IRG score to have strong correlation with the modified Disease Activity Score that persisted over time [51], demonstrating promise as a monitoring biomarker [56].

While some centers are starting to routinely measure IRG scores in clinical settings, the European Alliance of Associations for Rheumatology (EULAR) task force has several recommendations to consider when incorporating an IFN-related biomarker into clinical practice including assay methodology, clinical validation, and consistent reporting for broad interpretability across sites, which should also be considered in JDM [52▪,57,58].

Interferon biomarkers: interferon-related proteins

IFN-related protein biomarkers identified in JDM have included Eotaxin, MCP-1, galectin-9, neopterin, CXCL10, and CXCL11 [59–62]. The most extensive validation has been done with CXCL10 (IP-10) and galectin-9, which were corelated with disease activity in multiple, independent longitudinal cohorts [63]. SIGLEC-1, an IFN-induced protein on the surface of $CD14^+$ monocytes, was associated with the IRG score and JDM disease activity including skin and muscle, with high levels predictive of treatment intensification [64]. Another study found SIGLEC-1 protein expression in $CD14^+$ monocytes to correlate with disease activity and the IFN signature in JDM [65▪▪]. In adult DM, SIGLEC-1 was found to be highest on intermediate monocytes versus controls and highly correlated with overall disease and organ-specific disease activity, supporting its utility in stratifying patients [66]. Veldkamp *et al.* [67▪▪] identified SIGLEC-1 as reliable in-vitro marker for type I IFN responses, also demonstrating inhibition with chemical IFN blockade, which may be useful to identify patients for IFN-blocking therapies. SIGLEC-1 may be more accessible across sites, as it is assessed by flow cytometry, which is relevant for EULAR IFN-biomarker task force considerations for potential clinical use.

Model of interferon in muscle

Covert *et al.* explored JDM pathogenesis by looking at the effect of two types of type I IFN (IFN-alpha, IFN-beta) in a three-dimensional in-vitro muscle model (myobundles) with contractile function derived from pediatric healthy muscle. They found IFN-beta (not IFN-alpha) was associated with decreased contractile force and slowed twitch, with effects most prominent with exposure during the differentiation period [68,69]. Gene expression (RNA-seq) found that IFN-beta had more significant upregulation of IFN-response and proinflammatory genes than IFN-alpha, with decreased oxidative phosphorylation and myogenesis genes. Both function and gene expression patterns reversed with Janus kinase (JAK) inhibition [68,70▪].

Vasculopathy

Children with JDM have impaired microvascular function. The pathologic severity of vasculopathy associates with cutaneous and muscular disease severity and extra-muscular manifestations (e.g. gastrointestinal ulcerations, calcinosis, ILD, cardiac involvement) [59,61,71]. The cause of vasculopathy in JDM remains incompletely understood. Vessels have altered expression of cell adhesion molecules, immune complex and complement deposition, and increased expression of MHC class I and class II [72–75]. Specifically, CXCR3, VCAM-1, and ICAM-1 expression in muscle endothelial cells reflect activation, facilitating the attraction and invasion of immune cells [76]. Co-expression of MxA and VCAM-1 in muscle endothelial cells suggests the activation of the IFN pathway, tying IFN and vasculopathy together [77,78]. Pathologic neoangiogenesis, capillary drop out, and luminal occlusion are seen in later stages of disease [79–81]. Focal vasculopathy and capillary loss cause ischemia in perifascicular lesions, likely resulting in perifascicular atrophy [82]. Ultrastructural studies have shown abnormalities in arteriole and venous capillary endothelial cells [82,83] with loss of intramuscular microvessels and impaired vascular regeneration [83].

Looking within specific MSA groups, anti-TIF1 adult DM had decreased capillary density, increased capillary microhemorrhages and disorganization on nailfold video capillaroscopy (NVC) [84]. Zhao *et al.* described increased clinical vascular damage in adult anti-MDA5 DM, and in-vitro increased endoplasmic reticulum (ER) stress/unfolded protein response in lung microvascular endothelial cells (MVECs) treated with anti-MDA5 sera [85]. *In vitro*, anti-Jo-1 myositis immunoglobulins caused complement-dependent cellular cytotoxicity and increased TREM-1 expression in muscle endothelial cells [86].

Immune cells

In JDM muscle biopsies, infiltrate of adaptive immune cells, including T and B cells, is well documented, and also incorporat

ed into JIIM muscle biopsy scoring [87,88]. Multiple studies support a role of B cells in JDM pathogenesis [89–92]. Growing evidence underscores the involvement of monocytes and macrophages in the initiation, progression, and resolution of muscle inflammation [93,94,95▪,96,97]. Neutrophils are also increasingly recognized as pathogenic mediators in JDM, and neutrophil extracellular traps (NETs) are associated with disease activity in JDM and adult IIM [98–103].

Mitochondria

More studies recognize mitochondrial dysfunction in the pathogenesis of JDM. Duvvuri *et al.* found elevated peripheral mitochondrial markers in JDM associated with muscle damage and calcinosis. They found IFN-alpha induced skeletal muscle cell mitochondrial calcification via the generation of mitochondrial reactive oxygen species (mtROS), emphasizing the role of mtROS in pathogenesis [104]. Another study used a

murine model of IFN-gamma-driven myositis to demonstrate myofiber metabolic dysregulation, muscle mitochondrial abnormalities and oxidative stress [105▪]. Zhao *et al.* found increased risk of myositis associated with mitochondrial DNA copy number and SNPs in the mitochondrial displacement loop (part of the noncoding region of mitochondrial DNA) and increased ROS in adult DM/polymyositis (PM) versus controls [106]. Finally, Wilkinson and colleagues demonstrated that $CD14^+$ monocytes in JDM have dysregulated mitochondrial-associated gene expression that correlates with increased IRG expression and paralleled altered mitochondrial biology and increased oxidized mitochondrial (oxmt) DNA production. They showed JDM patient oxmtDNA induces IRG expression in healthy peripheral blood mononuclear cells, which was blocked by targeting oxidative stress pathways [107]. Together, these data support a role of altered mitochondrial metabolism in JDM pathogenesis.

TREATMENT

Current treatment

In general, high-quality data regarding medical therapy (e.g. randomized controlled trials or RCT) in juvenile myositis is lacking, limited to one dedicated JDM RCT (2016) studying prednisone versus prednisone with methotrexate (MTX) or cyclosporine finding the latter options better with MTX preferred given less side effects [108]. The only other RCT including JDM [Rituximab in Myositis, majority adult myositis patients (2013)] did not meet its primary endpoint but found benefit with rituximab, particularly in the JDM subgroup [109,110].

Treatment is largely guided by lower quality evidence (e.g. case reports/series, retrospective studies, uncontrolled prospective studies) with treatment guidelines and consensus treatment plans by different organizations or countries including Childhood Arthritis and Rheumatology Research Alliance (CARRA) from North America reviewed elsewhere [1,53▪]. Briefly, initial medical treatment generally includes daily oral prednisone and MTX, with an option to add pulse intravenous methylprednisolone (IVMP) and/or intravenous immunoglobulin (IVIG). For refractory disease, options are varied with limited head-to-head comparisons including cyclosporine, mycophenolate mofetil (MMF), azathioprine as well as biologic agents. The biologic disease-modifying antirheumatic drug (bDMARD) consensus treatment plans from CARRA include tumor necrosis factor alpha (TNFa) inhibitors (adalimumab, infliximab), abatacept, rituximab, and tocilizumab [111]. Cyclophosphamide is also noted in several guidelines as a consideration for severe disease [1,53▪]. Nonpharmacologic management of juvenile myositis includes exercise, optimizing mental health, sun protection to limit UV exposure, as well as calcium and vitamin D, which have been reviewed elsewhere [1,24].

Given that many patients have suboptimal response to current therapies, treat to target recommendations endorsed by the Paediatric Rheumatology European Society (PReS) and CARRA were recently published based on consensus from a 36-member international task force including two patients and a parent. There were seven overarching principles and 12 recommendations including that parents and treaters should share decisions in setting treatment targets and therapeutic strategies. Inactive disease is the preferred target with minimal disease activity as an alternative target. Timeline for target goal achievement is within 12 months after treatment start. Interim targets include minimal and moderate clinical improvement within 6 weeks and 3 months, respectively, as well as normalization of muscle strength within 6 months. Although high-dose glucocorticoids remain key to initial treatment, progressive tapering and discontinuation of glucocorticoids within 12 months through optimization of concomitant immunomodulatory medications was also advised [112▪▪]. Notably, the task force recognized that current available evidence is not strong and needs to be expanded by future research.

Emerging therapy targeting the interferon pathway

Janus kinase (JAK) inhibitors

Given the prominence of IFN pathways in JDM, they have been identified as a treatment target. JAKs signal for multiple different cytokines including type I, II, and III IFNs [113]. By inhibiting JAK, IFN-signaling can be decreased. JAK inhibitors (JAKi) have been used with clinical improvement in refractory patients in JDM, first reported in 2018 [48,114]. Most recently, reviews note in over 270 JDM patients (primarily refractory, three new-onset) with 2–35 months of follow-up. Most are retrospective case reports/series, with three open-label prospective studies ($n=10$). The most frequently reported JAK inhibitor in JDM was tofacitinib, but there is no evidence to indicate one JAKi outperforms another in JDM. Skin disease was the most common indication for JAKi with JDM and 115 of 158 (73%) with active skin disease improved. Muscle disease activity (weakness) was less common, but a greater percentage improved (55/57, 96%). There were cases with interstitial lung disease, most commonly MDA5, who improved (65/65, 100%) as well as with

calcinosis (34/36, 94%). A subset of JDM patients had IFN pathway markers that decreased or normalized as a proof-of-concept with JAKi treatment. Reported individuals had varied myositis-specific autoantibody groups, different dosing of JAKi, and varied clinical features [115,116,117▪].

Regarding safety of JAKi in JDM, limited reports systematically collected safety information but in general, infections were most common adverse event including herpes viral infections, followed by laboratory changes. Cell count changes, and ALT and CK elevation have been reported. These adverse events have been reported with JAKi use for other indications [e.g. rheumatoid arthritis (RA)]. Inconsistent elevation in muscle enzymes including LDH and aldolase requires more careful monitoring of muscle disease activity in JDM. Black box warning events for JAKi use for adult RA (thromboembolic events, cardiovascular events, and malignancy) have not been noted in JDM [115,116,117▪].

An international survey of CARRA and PReS JDM groups (2024) found 150/229 (66%) have used JAKi for over 450 patients, with 77% noting clinical improvement in most or all patients, and 17% reporting side effects. The highest ranked perceived barriers to JAKi use were lack of clinical data and inability to obtain insurance approval. The highest ranked clinical indications for starting JAKi were refractory skin disease, refractory muscle disease, inability to wean steroids, and intolerance to other steroid-sparing agents [118]. Thus, based on published reports and international survey, most treatment refractory JDM improved with JAKi, but further unbiased study is needed to better determine which patients are most likely to benefit and to improve access to JAKi for JDM patients.

Dazukibart

As mentioned above, there is some indication that IFN-beta may play a particularly important role in DM and the myositis model. Dazukibart (PF-06823859), a monoclonal antibody to IFN-beta, has been studied in adult DM in a multicenter double-blind RCT at different doses ($n=52$, 150 or 600 mg every 4 weeks) versus placebo (n = 23). They demonstrated significantly lower skin disease by CDASI-A with dazukibart and dazukibart was generally well tolerated. Notably, patients had more dramatic decreased IRG score in skin than blood [119▪].

One 9-year-old girl with anti-NXP2 JDM, characterized by severe muscle disease, including wheelchair reliance and swallowing difficulties, and skin ulcers, developed gastrointestinal ulcers and ILD on varied treatment including prednisone, MTX, MMF, IVMP, and IVIG. She was then given compassionate use intravenous dazukibart at 20 mg/kg (600 mg) and had subjective strength improvement by 2 weeks and ability to ambulate independently by 4 weeks with decreased edema on MRI. Skin ulcers resolved by week 8. She also had resolution of abdominal pain and was able to switch from parenteral nutrition to a full oral diet. She has continued on dazukibart (10 mg/kg) every 4–6 weeks since initiating this therapy with IVIG. She has not had any safety events, though CK and aldolase elevations were noted without decreases in strength. At last follow-up (14 months after starting dazukibart), she was able to walk up three flights of stairs and had started running. Her ILD has resolved, and she has not had any further skin or gastrointestinal ulcers [120▪].

Anifrolumab

There have also been cases of refractory JDM despite JAKi treatment. Some have been treated with anifrolumab, a monoclonal antibody targeting the type I IFN receptor, which includes IFN-alpha and IFN-beta. This is approved for adult SLE [121,122].

There are three case reports of anti-TIF1 JDM with refractory skin disease after multiple treatments, including JAKi, who improved on anifrolumab. A 14-year-old girl had improvement of muscle findings but persistent skin disease despite 6 years of treatment including tofacitinib (JAKi) (10 mg twice daily) with an elevated IFN-beta level. She stopped tofacitinib and started anifrolumab (300 mg intravenously every 4 weeks, FDA-approved dose for adult SLE). She had a rapid and dramatic improvement in skin findings within 72 h and a clinically significant reduction of CDASI-A by about 2 months [123]. A 9-year-old girl had improvement of muscle disease but persistent skin disease despite treatment including rituximab and 3 JAKi (tofacitinib, baricitinib, and upadacitinib) over about 3 years. With anifrolumab (5 mg/kg or 200 mg every 4 weeks), she had rapid complete resolution of skin disease including improvement of a skin ulceration on the foot, and a decrease in IRG expression. She fully weaned off steroids after about 3–4 months. An 11.5-year-old boy with common variable immune deficiency that had some improvement on treatment flared with steroid wean, without response to upadacitinib (JAKi). Subsequently, intravenous anifrolumab (6 or 200 mg every 4 weeks) led to rapid resolution of skin ulceration and facial rash and a decrease in IRG expression. He had a new skin ulcer appear on anifrolumab, but it subsequently healed [124].

There were also two cases of refractory JDM who had response in both skin and muscle disease to anifrolumab. A 16-year-old boy had initial response to standard therapy but flared 2 years later without response to retreatment. Family opted to try anifrolumab (adult SLE dose) with dramatic improvement.

Muscle enzymes normalized and MRI edema resolved at 6 months, with significant decrease in CDASI-A score by 8 months. A 25-year-old woman diagnosed with JDM at 6 years old had recurrent disease flares on multiple treatments including high-dose tofacitinib (10 mg BID). She then stopped tofacitinib and started anifrolumab (adult SLE dose). After two infusions, she also had a significant CDASI-A improvement and subjective improvement in strength. After five infusions, she had improvement of muscle edema on MRI [125▪▪].

Overall, there are multiple IFN-targeting treatment options that have shown efficacy in refractory JDM patients. Anifrolumab may be a more effective or more complete blocker of IFN-signaling than JAKi. This is consistent with reports from Mendelian interferonopathies noting clinical improvement and decreased IRG scores with anifrolumab versus JAKi [126,127].

Emerging chimeric antigen receptor T-cell therapy targeting B cells

B cells have been established as dysregulated in JDM [90–92]. While rituximab, a B-cell-targeting chimeric anti-CD20 monoclonal antibody, has shown benefit, not all JDM patients respond. This is thought to at least partially be due to pathogenicity of plasmablasts expressing CD19 and lack of depletion of tissue-based B cells [109,128–130].

CAR-T cells are an immunotherapy involving genetically engineered T cells to target a specific marker, in this case B-cell markers [CD19 or BCMA (B-cell maturation antigen)]. This type of therapy has been impressively successful with pediatric B-cell malignancies. Refractory adult myositis patients (three antisynthetase syndrome patients, three anti-SRP immune-mediated necrotizing myopathy patients) with anti-CD19 ($n=5$) or anti-BCMA ($n=1$) B-cell targeting CAR-T-cell therapy with 5–18 months of follow-up have been reported to all successfully achieve drug-free remission, other than one patient who was limited to just MMF treatment [131–135].

Another antisynthetase patient who received anti-CD19 CAR-T-cell therapy [136] and achieved drug-free remission, had a disease flare after 9 months with weakness and elevated CK. After reinfusion of the same CAR-T-cell product, he did not have expansion of CD19 targeting T cells and did not respond clinically. He received bridging anti-CD38 therapy (daratumumab) which can target plasma cells, distinct from CD19 cells, and then anti-BCMA CAR-T-cell therapy, which can also target plasma cells. CD138 plasma cells present in an inguinal lymph node prior were not detectable afterwards. He was able to re-achieve drug-free remission through 9 months of follow-up [137].

Finally, there is one 10-year-old refractory JDM patient who received anti-CD19 CAR-T-cell therapy with significant improvement in muscle and skin disease including resolution of ulcers and improvement in calcinosis with drug-free remission maintained at 8 months of follow-up [138▪▪]. Thus, despite generally limited follow-up time with B-cell targeting CAR-T-cell therapy, it has generally allowed for drug-free remission, an ultimate goal for providers and patients, in eight myositis cases including one JDM case. Anti-BCMA CAR-T-cell therapy may be an option for those without response to anti-CD19 CAR-T-cell therapy with additional targeting of plasma cells.

Current and upcoming clinical trials

As mentioned above with treat-to-target, more research and high-quality data is needed to guide treatment in juvenile myositis. One of the limitations of traditional RCTs in JDM is the rarity of the condition and the patient numbers necessary to demonstrate differences between treatment arms. Current recruiting clinical trials open to JIIM patients at the time of this review (Table 1) are all open-label, nonrandomized with one baricitinib (JAKi) study and four anti-CD19 CAR cell therapies.

For an upcoming study not yet recruiting, a Bayesian design was utilized to maximize information from a limited number of patients. Consensus expert prior opinion by 10 expert clinicians in a Bayesian prior elicitation meeting was that the probability of newly diagnosed JDM patients to achieve clinically inactive disease off glucocorticoids within 12 months was 0.55 on baricitinib (JAKi) and 0.23 on MTX, indicating baricitinib is superior to methotrexate. However, they found sufficient uncertainty to warrant a RCT. As more is known about MTX, a 2 : 1 (baricitinib ($n=20$) : MTX ($n=10$)) randomization was proposed. This BARJDM study will be planned as a multicenter, open-label randomized controlled superiority trial to assess the effectiveness and safety of baricitinib with glucocorticoids to be superior to MTX with glucocorticoids [139]. Prior distributions will be combined with the trial data from BARJDM to determine posterior distributions of the two treatments, with a smaller number of patients needed versus a traditional RCT study [140▪▪].

CONCLUSION

Juvenile dermatomyositis is a complex disease, but recent research has increased knowledge about its pathogenesis (Fig. 1). HLA and non-HLA genetic

Table 1. Interventional therapeutic studies for juvenile myositis currently recruiting

NCT number	Study title	Diseases included	Intervention	Sponsor	Age range (years)	Phases	Enrollment	Location(s)
NCT06686524	Clinical Study of CD19 Targeted Universal Chimeric Antigen Receptor T Lymphocytes (UCAR-T) for the Treatment of Refractory Juvenile Dermatomyositis (RJDM)	DM, JDM	Anti-CD19 UCAR-T cell therapy	Chongqing Precision Biotech Co., Ltd	≥5	PHASE1	18	Hangzhou, Zhejiang, China
NCT05524311	Baricitinib in the Treatment of New-onset Juvenile Dermatomyositis (MYOCIT)	JDM	Baricitinib (2 mg <6yo, 4 mg 6yo+)	Assistance Publique - Hôpitaux de Paris	5–18	PHASE2	16	Multisite in France
NCT06569472	Clinical Trial of CD19-targeted CAR-T Therapy for Refractory Juvenile Dermatomyositis	JDM	Anti-CD19 CAR-T cell therapy	Chongqing Precision Biotech Co., Ltd	5–16	PHASE1	10	Hangzhou, Zhejiang, China
NCT06154252	RESET-Myositis: An Open-Label Study to Evaluate the Safety and Efficacy of CABA-201 in Subjects With Active Idiopathic Inflammatory Myopathy or Juvenile Idiopathic Inflammatory Myopathy	IIM, DM, ASyS, IMNM, JDM, JIIM	CABA-201 anti-CD19 CAR-T cell therapy	Cabaletta Bio	Juvenile cohort: 6–17, Adult cohort: 18–75	PHASE1/ PHASE2	24	Multisite International
NCT06308978	A Phase 1 Study of FT819 in B-cell Mediated Autoimmune Disease	AAV, IIM, SSc, SLE	FT819 (anti-B-cell)	Fate Therapeutics	12–70	PHASE1	244	Multisite in USA
NCT06255028	A Study of CNTY-101 in Participants With Refractory B Cell-mediated Autoimmune Diseases (CALiPSO-1)	SLE, LN, IIM including JIIM, SSc	CNTY-101, CD-19 targeted CAR iNK Cell Therapy	Century Therapeutics, Inc.	≥17	PHASE1	48	Multisite in USA

All of these studies are open-label and not randomized. This was based on clinicaltrials.gov at the time of this review. AAV, ANCA-associated vasculitis; ASyS, antisynthetase syndrome; CAR, chimeric antigen receptor; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; JIIM, juvenile idiopathic inflammatory myopathy; LN, lupus nephritis; iNK (CAR iNK), induced pluripotent stem cells are genetic modified to express a chimeric antigen receptor and differentiated into natural killer cells; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UCAR, universal chimeric antigen receptor; USA, United States of America.

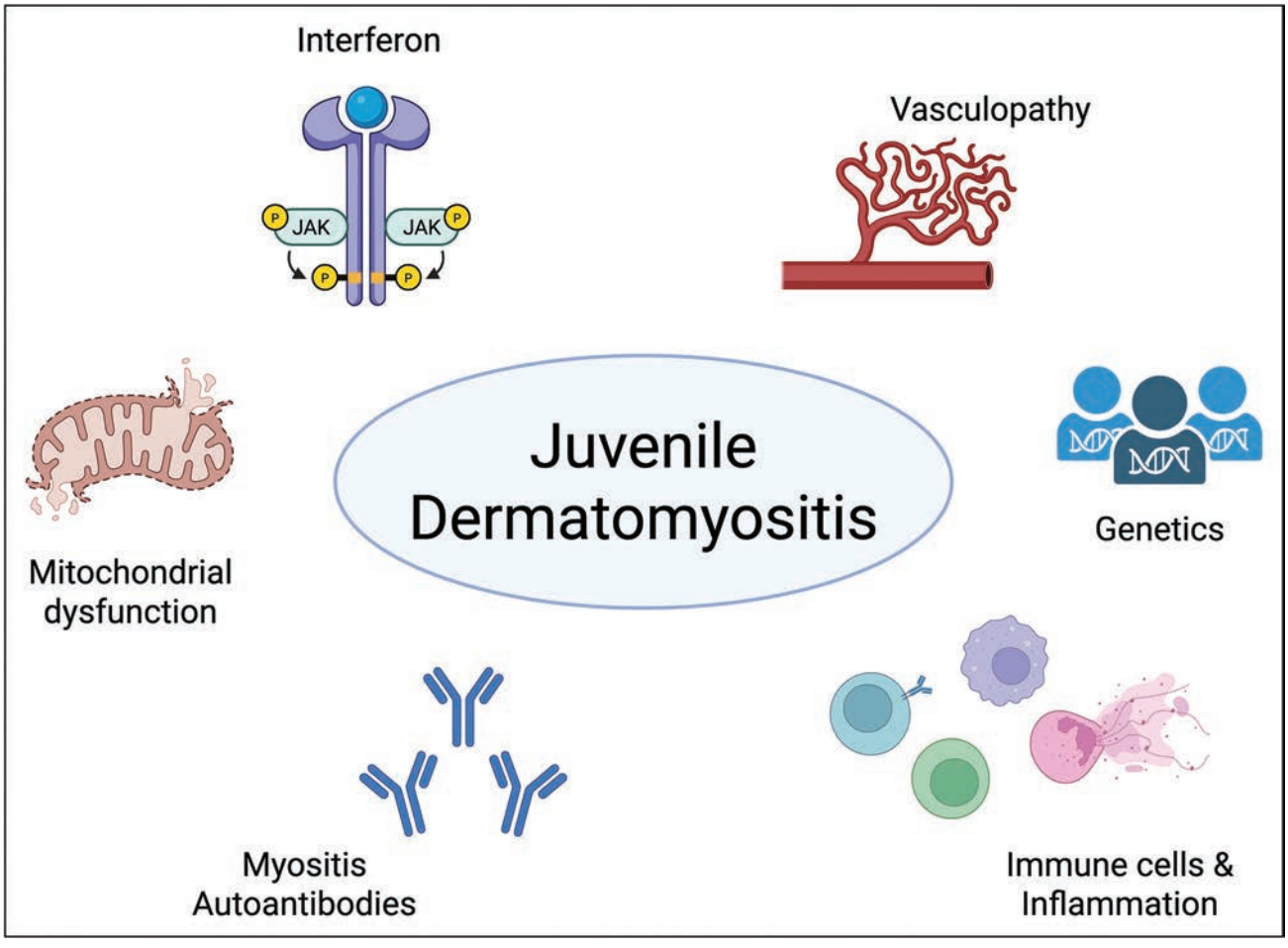

FIGURE 1. Some key components in juvenile dermatomyositis pathogenesis. Created in BioRender.

markers and C4 copy number variation have been validated as risk factors in JDM, with recent studies identifying epigenetic changes as well. Although MSA were previously established to define clinical subgroups within JIIM, additional clinical associations with MAA have been uncovered. The observation of MSA–autoantigen complexes in patient muscle cells has provided interesting new insights MSAs' more direct role in disease pathogenesis. With more widespread autoantibody testing, variability in testing accuracy based on MSA/MAA testing methodology has been demonstrated, some with decreased sensitivity for anti-TIF1, one of the most common MSA in JDM. Clinicians need to be aware of specific limitations of myositis autoantibody testing and interpret results with testing limitations and clinical context in mind.

IFN remains prominently dysregulated in JDM, with recent studies validating that IFN-related markers (gene score, protein) correlate with disease activity such as IRG scores and SIGLEC-1, a cell-surface marker on monocytes. They are promising disease-activity biomarkers, though EULAR IFN-biomarker considerations should be evaluated before broad clinical use. There is increasing evidence of the importance of vasculopathy, adaptive and innate immune cells, and mitochondrial dysfunction in JDM with IFN interplay.

Emerging treatments beyond standard immunomodulatory therapies include those targeting IFN (JAKi), dazukibart (anti-IFN-beta), and anifrolumab (anti-IFNAR1) with promising reports of efficacy in refractory patients. Novel use of CAR-T-cell therapy from oncology targeting B cells in autoimmune disease, including adult and juvenile myositis, demonstrated a small number of patients were able to achieve drug-free remission. Further study is needed to validate these emerging therapies. Clinical trials remain limited in JDM and innovative alternatives to RCT study design such as Bayesian design may help advance therapies. More research on pathogenesis is needed to refine biomarkers and treatment targets in JDM. Continued collaborative research on this rare disease will help us understand the heterogeneity within JDM and increase access to targeted therapies for each JDM patient in the future.

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