



Skin involvement in early diffuse cutaneous systemic sclerosis: an unmet clinical need

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Abstract | Diffuse cutaneous systemic sclerosis (dcSSc) is associated with high mortality resulting from early internal-organ involvement. Clinicians therefore tend to focus on early diagnosis and treatment of potentially life-threatening cardiorespiratory and renal disease. However, the rapidly progressive painful, itchy skin tightening that characterizes dcSSc is the symptom that has the greatest effect on patients' quality of life, and there is currently no effective disease-modifying treatment for it. Considerable advances have been made in predicting the extent and rate of skin-disease progression (which vary between patients), including the development of techniques such as molecular analysis of skin biopsy samples. Risk stratification for progressive skin disease is especially relevant now that haematopoietic stem-cell transplantation is a treatment option, because stratification will inform the balance of risk versus benefit for each patient. Measurement of skin disease is a major challenge. Results from clinical trials have highlighted limitations of the modified Rodnan skin score (the current gold standard). Alternative patient-reported and other potential outcome measures have been and are being developed. Patients with early dcSSc should be referred to specialist centres to ensure best-practice management, including the management of their skin disease, and to maximize opportunities for inclusion in clinical trials.

Contractures

Deformities resulting from tissue shortening or hardening; in patients with SSc contracture is caused by tightening of the skin.

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Systemic sclerosis (SSc) is a multisystem connective-tissue disease characterized by fibrosis, and by vascular and immunological abnormalities. The two main subtypes of SSc, defined according to the extent of skin involvement (scleroderma, meaning 'hard skin'), are diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc¹. dcSSc is the subtype of greater concern, because it is characterized by rapid progression and a high prevalence of early internal-organ involvement (including lung, heart and kidney), which can be life-threatening. dcSSc is therefore associated with high mortality^{2–4}, with a 5-year survival rate of around 70%, and clinicians understandably tend to focus their attention on early identification and treatment of internal-organ disease. However, on a day-to-day basis, in patients with early dcSSc (those within the first 3–5 years of the onset of symptoms), it is skin thickening that has the greatest impact on quality of life, causing pain, intractable itching and functional limitation.

Skin involvement in early dcSSc is an important topic, not only because of the effects of skin disease on the patient, but also because the skin is a very visible and accessible 'window' into the dcSSc disease process. Therefore, examining the skin enables the prediction and monitoring of disease progression and of treatment

response. A Review of this topic is timely because of developments over the past 5 years in benchmarking of the burden of skin disease in patients with dcSSc and in understanding of how to identify 'progressors' (patients with progressive disease), not only on the basis of clinical features, but also through advances in molecular technologies applied to skin biopsy samples. In addition, controversies exist with regard to how best to measure the extent and consequences of skin disease, as highlighted by results from clinical trials, and there is an ongoing need to promote best-practice management of skin disease, as well as of internal-organ disease.

The aim of this Review is to provide a comprehensive description of the clinical and scientific implications of skin involvement in dcSSc. First, we describe skin involvement, patterns of progression and the associated clinical burden, including contractures and ulceration. Second, we outline how skin-disease progression can be predicted by consideration of clinical features (including disease duration, extent of skin disease and autoantibody status) and potentially by gene-expression profiling of biopsied skin. Identifying progressors is especially relevant now that autologous haematopoietic stem-cell transplantation (HSCT) is an option for patients at high risk of progression, so that only those patients most in

Key points

- Much of the pain and disability of early diffuse cutaneous systemic sclerosis (dcSSc) results from skin thickening (scleroderma), which can be rapidly progressive, commencing distally then extending proximally.
- 'Progressors' in terms of skin disease can now be identified by considering disease duration, extent of skin disease, autoantibody status and (potentially) gene-expression profiling of skin biopsy specimens.
- Improvement in the ability to predict progressive skin disease will inform the selection of patients for haematopoietic stem-cell transplantation, as well as more targeted inclusion of patients in clinical trials.
- Limitations of the modified Rodnan skin score are stimulating development of other outcome measures of skin disease, including patient-reported outcome measures, non-invasive imaging methods and composite scores.
- Best-practice management of early dcSSc includes early referral to a specialist centre, pain management, multidisciplinary input, immunosuppressive therapy and, when at all possible, inclusion in a clinical trial.

need are exposed to the potential toxicity (and even lethality) of HSCT. Third, we discuss outcome measures of skin disease, specifically the modified Rodnan skin score (mRSS), but also patient-reported outcome measures and non-invasive imaging techniques. Fourth, we describe best-practice management, including general measures, immunosuppressant treatment and HSCT, and discuss the controversial topic of whether or not glucocorticoids should be prescribed. We do not discuss recent, ongoing or proposed studies of new targeted therapies (including biologic agents such as tocilizumab and rituximab), as these have been reviewed elsewhere⁵. However, the information we present reinforces that patients with early dcSSc should, whenever possible, be recruited into clinical trials, to maximize the chances of identifying an effective disease-modifying therapy for this currently incurable disease.

Clinical features and disease burden

Clinical features

In patients with early dcSSc, skin involvement commences distally, usually first affecting the fingers, which often become swollen and painful. This early oedematous phase is sometimes misdiagnosed as inflammatory arthritis and can be associated with carpal tunnel syndrome, but over a few weeks the skin hardens and the diagnosis of SSc usually becomes obvious. A defining feature of the dcSSc subtype is the (often rapid) progression of skin involvement to proximal to the elbow or knee and/or involving the trunk. Conversely, in limited cutaneous SSc, skin involvement is confined to the extremities (distal to the elbows and knees) and to the face and neck⁶.

During the early (inflammatory) phase of dcSSc, when the skin disease is progressing, the skin is often itchy and painful. Pigmentary change can occur^{7,8} and can be distressing to patients, especially those with darker skins. Skin tightening commonly leads to contractures, particularly fixed flexion deformities of the fingers⁹ (FIG. 1a), but also of the elbows and sometimes knees. Range of movement is often substantially reduced, for example, at the shoulder or at the ankle, subtalar and mid-tarsal joints. The flexion contractures predispose to overlying ulcers, which can be refractory to

treatment and which can lead to underlying osteomyelitis. Rarely, the skin is so tightened that small superficial ulcers appear, unrelated to pressure points (FIG. 1b).

Itch, which is often described as the most troublesome skin symptom of early dcSSc, resolves when the early inflammatory phase subsides. In those patients who survive, the severity of the skin disease (as assessed by the mRSS) will generally plateau (usually within 3–5 years of onset)¹⁰, followed by gradual softening and atrophy of the skin, to the extent that years later, there might no longer be any skin thickening. The contractures, however, persist and are usually irreversible⁹ (FIG. 1c).

Associated morbidity

Although it has long been recognized that the skin involvement in early dcSSc is painful, disabling and disfiguring, these elements of the disease burden have only been quantified in the past few years. The European Scleroderma Observational Study (ESOS)¹¹ involved 326 patients with early dcSSc from 19 countries (with a median disease duration from onset of skin thickening of 11.9 months), and although the main aim was to assess treatment outcomes, ESOS also provided the opportunity to examine associations between severity of skin involvement and both functional ability and quality of life. Severity of skin involvement was measured with the mRSS. At the baseline visit, high mRSS was associated with high levels of disability (with 'grip' and 'activity' being most affected) as assessed by the Health Assessment Questionnaire disability index (HAQ-DI) (Spearman's $\rho = 0.34$, $P < 0.0001$), and specifically with high levels of hand disability, as assessed by the Cochin Hand Function Scale ($\rho = 0.35$, $P < 0.0001$)¹². Fine finger movements were particularly affected. mRSS was also associated with severity of pain, as assessed on a 0–100 visual analogue scale ($\rho = 0.17$, $P = 0.002$), and severity of fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy fatigue score ($\rho = -0.20$, $P = 0.0005$). Examining changes over 12 months, increases in the mRSS were associated with worsening disability as measured by HAQ-DI ($\rho = 0.40$, $P < 0.0001$). In summary, ESOS demonstrated that the greater the degree of skin thickening, the greater the disability (with an emphasis on hand disability), pain and fatigue, and that if skin thickening progresses then so too does disability. This association in early dcSSc has since been confirmed in other studies: in a single-centre retrospective study¹³, an increase in mRSS was associated with worsening disability as measured by HAQ-DI in the subgroup of patients with early dcSSc ($\rho = 0.36$, $P = 0.004$), and in a study of 154 patients from Canada with early dcSSc¹⁴, changes in mRSS correlated with changes in HAQ-DI (Pearson's $r = 0.43$ for 1-year data, $r = 0.41$ for 2-year data).

Predicting progression of skin disease

Associations with skin-disease severity

Among patients with early dcSSc, various trajectories of skin involvement are observed: skin score can progress (sometimes rapidly), stabilize or improve. An important aim is to identify those patients with progressive skin

Ulcers

Skin lesions with discernible depth and loss of the epithelium.

Scleroderma renal crisis

A complication of SSc that involves sudden onset of hypertension accompanied by renal failure.

Tendon friction rubs

Palpable rubs that are found, for example, over wrists, ankles and knees, and are thought to result from inflammatory change in the tenosynovium.

involvement, not only because it is painful and disabling, but also because extensive and/or progressive skin disease portends a poor outcome. Survival is reduced in patients with high skin scores^{15–17}. A high ‘skin-thickness progression rate’ (the mRSS at first visit divided by patient-reported duration of skin thickening) is a predictor of early mortality and of scleroderma renal crisis¹⁸. Researchers who conducted an analysis of the European Scleroderma Trials and Research (EUSTAR) database identified reduced survival of progressors among patients with dcSSc: a group of 78 ‘skin progressors’ had lower survival (and more decline in lung function) than 943 ‘non-progressors’¹⁹. Conversely, a reduction in skin thickening is reassuring, because it is associated with improvement in survival²⁰ and reduction of internal-organ involvement²¹.

Predictors of progression

Accurate prediction of progressive skin involvement would enable clinicians to make informed decisions regarding whether or not to initiate potentially toxic treatments, usually an immunosuppressant but potentially (in highly selected patients) HSCT. Although treatment-related mortality with HSCT has fallen considerably since the introduction of the technique, it remains a concern, so the procedure should only be carried out in those at highest risk. Prediction of progressive skin disease is also important for researchers designing clinical trials of potential disease-modifying therapies; inclusion and exclusion criteria should be selected to include progressors rather than non-progressors, who are less likely to benefit from treatment. Progressors are often defined as those experiencing a 5-unit and 25% increase in mRSS over 12 months^{22–24}.

Tendon friction rubs are an indicator of disease that is very likely to progress^{25,26}. In a study of an inception cohort from the University of Pittsburgh (reported in 2011)¹⁸, anti-RNA polymerase III antibody positivity was associated with rapid skin-disease progression. More recently, several groups have investigated other

predictors of progressive skin disease. Low mRSS, short disease duration and joint synovitis were predictors of disease progression in an analysis from the EUSTAR database²², whereas a high baseline mRSS (and absence of friction rubs) predicted improvement²⁷. These results led to the suggestion that only patients with an mRSS of ≤ 22 should be included in clinical trials of early dcSSc, because patients with higher scores are unlikely to have progressive skin disease²². This fairly stringent cut-off excludes many patients. An analysis of the ESOS cohort²³, in whom mRSS was assessed at 3-month intervals (enabling detailed assessment of disease trajectory), demonstrated that patients with higher skin scores could reasonably be included in clinical trials if their disease duration was short. Among the 293 patients with sufficient data to assess their status, the 66 progressors had shorter disease duration than the 227 non-progressors (median 8.1 months versus 12.6 months, $P=0.001$), as well as lower mRSS (median 19 units versus 21 units, $P=0.030$), with those patients who were anti-RNA polymerase III antibody positive going on to have the highest skin scores and peaking earliest. Two predictive models were derived for progressive skin thickening²³: the first included mRSS, duration of skin thickening and their interaction, and the second added anti-RNA polymerase III antibody positivity. Both models were more accurate than a model with an mRSS cut-off of 22, and for a given skin score were more flexible, enabling a higher baseline skin score to be compensated for by a shorter disease duration²³. Application of these models should maximize numbers of the most informative patients (progressors) to be included in clinical trials. Subsequently, results from other studies have confirmed the role of skin score and disease duration as predictors of progression. A 2021 analysis from the Pittsburgh cohort²⁸ led to the conclusion that ideally only patients with a disease duration of <18 months should be included in clinical trials, although the findings from ESOS²³ suggest that some flexibility in disease duration could be permitted in the

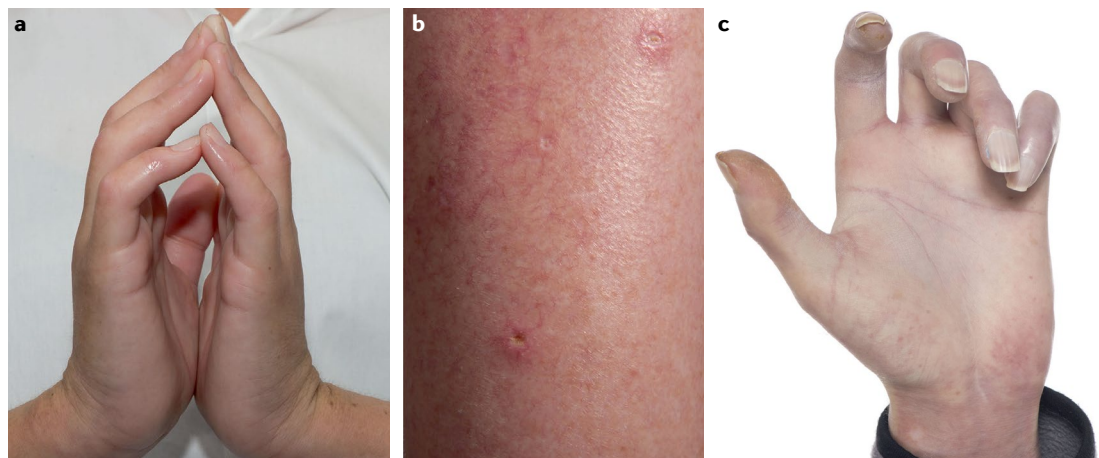


Fig. 1 | Skin involvement in diffuse cutaneous systemic sclerosis. a | Flexion contractures of the fingers in early diffuse cutaneous systemic sclerosis (dcSSc). **b** | Superficial cutaneous ulceration in early dcSSc. **c** | Late-stage dcSSc with persisting contracture (note the scar from carpal tunnel decompression, performed soon after the onset of symptoms of dcSSc). Images copyright of Northern Care Alliance NHS Foundation Trust.

presence of low skin scores. Findings from the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS)²⁴ cohort suggested that an mRSS of ≤ 27 was predictive of progression, despite a mean disease duration of 2.4 ± 1.5 years (which is longer than the disease duration of the ESOS cohort²³). In a Japanese multi-centre prospective cohort study²⁹, disease duration of ≤ 12 months and an mRSS of ≤ 19 predicted progression (sensitivity 73.9%, specificity 81.1%), which is consistent with the findings from ESOS²³.

Results from skin global gene-expression studies indicate that SSc skin has a distinct transcript profile (although considerable heterogeneity exists). Although these results demonstrate the presence of prominent fibrotic and inflammatory signatures (which can co-occur in individual patients), a subgroup of SSc skin samples has a gene-expression pattern that resembles the transcript profile of healthy individuals (a 'normal-like' pattern)^{30–32}. In addition, evidence increasingly indicates that the skin gene-expression profile of a patient with SSc changes over time, in parallel with the clinical course of skin involvement^{31,33}. SSc skin gene-expression signatures might help to predict outcomes of dcSSc. Higher 'fibroinflammatory' scores are associated with higher skin scores (both mRSS and locally at the biopsy site)³⁰. Results from a study of the Prospective Registry of Early Systemic Sclerosis (PRESS) cohort, published in 2020, suggest that gene-expression profiles in samples from forearm skin biopsies of patients with early dcSSc are associated with prior skin-disease progression, but are not predictive of future progression³¹. These findings contrast with those from a phase 2 trial of tocilizumab, in which expression of five fibrotic and inflammatory genes in forearm skin biopsy samples from patients treated with a placebo was associated with mRSS progression³⁴. Inflammatory, fibroproliferative and normal-like skin gene-expression subsets were identified using a machine-learning approach³², and might help to explain the variable response to immunomodulatory therapies. In a randomized controlled study of treatment with abatacept in dcSSc, the results of which were published in 2020, patients with the inflammatory or normal-like expression profiles responded to treatment, whereas no statistically significant treatment effect occurred in the overall study population³⁵. Results from other studies (published from 2018 to 2021) have indicated that patients with an inflammatory skin gene-expression profile have shorter disease duration and higher skin score than individuals with other expression profiles^{31,36,37}. Consistent with these findings, results published in 2021 from a longitudinal study indicated that immune cell and fibroblast signatures decline over time, and overall skin gene expression trends towards normalization in patients with early diffuse SSc³³. Currently, it is not known to what extent skin gene-expression profiling can help to predict response to treatment beyond the information provided by easily obtained clinical predictors such as disease duration, baseline skin score and anti-RNA polymerase III antibody positivity status. Anti-RNA polymerase III antibody is one of the SSc-specific autoantibodies that are associated with the diffuse cutaneous subtype of SSc, another

is anti-topoisomerase I antibody¹¹. As mentioned above, patients with dcSSc with anti-RNA polymerase III positivity experience more rapidly progressive skin involvement than the overall population of patients with dcSSc¹¹. Notably, differences in gene expression and pathway enrichment between major autoantibody subgroups in early dcSSc³⁸ might reflect both distinct and overlapping biological mechanisms determining progression and regression of skin disease at the patient level. Integration of high-dimensional gene and protein expression data by weighted gene co-expression network analysis (WGCNA) elucidates likely pathogenic mechanisms³⁹ and points towards the potential to better define longitudinal differences to link gene³³ and protein expression to clinical changes (FIG. 2). This analysis should provide additional insights into local pathogenesis of skin fibrosis³⁹, and might help to identify candidate biomarkers that can be used for inpatient stratification or assessment of outcome, building upon results from studies of biomarkers validated in conditions such as liver cirrhosis, including the enhanced liver fibrosis score, which correlates with skin severity and progression^{40,41}.

In summary, we now have a much better insight than 5 years ago into the factors that predict disease progression, and progress is being made towards a stratified approach to therapy. As we continue to advance our knowledge, it will be possible to build upon the conceptual framework for the association between skin-score trajectory and the biology of progression and regression, as outlined in FIG. 2.

Outcome measures

Reliable outcome measures that are sensitive to change are a prerequisite to monitoring both disease progression and the response to treatment. However, identification and/or development of reliable outcome measures for SSc skin disease has proved to be a major challenge, leading to much discussion between clinicians and industry partners, and demonstrating the need for further research. Here, we describe the main outcome measures used for the assessment of skin involvement⁴². The current outcome measures are not ideal, but efforts are ongoing to improve them through modification of existing tools and development of new measures, including (at least for early-phase studies) non-invasive imaging techniques.

The mRSS

Measurement of the extent of skin involvement is complex, and needs to take into account the surface area affected and the degree of involvement at various body sites. The mRSS⁴³, which involves skin palpation at 17 sites, has been fully validated as per OMERACT principles⁴⁴, but presents challenges. The mRSS is described in detail elsewhere⁴³, and key points relating to its use and limitations are presented in BOX 1.

Self-assessment of skin involvement

The 'hands on' nature of the mRSS has implications for both clinical practice and clinical trials in the era of COVID-19, when patient visits to hospital are being minimized. Therefore, patient self-assessment of skin

involvement, which was previously proposed^{45,46}, but not widely applied, is now an attractive option. An exciting development is the Patient Self-Assessment of Skin Thickness in Upper Limb (PASTUL) questionnaire⁴⁷. In an initial study of 104 patients with SSc, 78 (75%) of whom also had an mRSS assessment, there was moderate correlation between PASTUL scores and both total mRSS ($r=0.56$) and upper-limb mRSS ($r=0.58$). PASTUL scores also strongly correlated with results from the Scleroderma Skin Patient-Reported Outcome (SSPRO)⁴⁸. Once fully validated, PASTUL could be an important addition to clinical trials, bringing the possibility of more-frequent skin scoring during trial treatment than has previously been possible (and in the patient's own home).

Other outcome measures

The limitations of the mRSS have resulted in exploration of the use of other outcome measures of skin involvement, including composite measures. These measures are attracting increasing interest for application in trials of early dcSSc.

Patient-reported outcomes. The SSPRO⁴⁸ is an 18-item questionnaire for the assessment of skin-related quality of life in patients with SSc. Researchers have already applied the SSPRO in clinical trials⁴⁹, and its further use is likely. The HAQ-DI, although not specific to the skin involvement of early dcSSc, captures much of the associated disability and has the advantage that most clinicians are familiar with it. In the past 5 years, several trials have included the HAQ-DI as an outcome measure^{35,49-55}. Because itch can be a very prominent feature in early dcSSc, itch assessment should also be considered, for example, with the 5-D itch scale⁵⁶, which researchers included in a 2020 phase 2 study of the safety and efficacy of the cannabinoid receptor 2 agonist lenabasum for the treatment of patients with SSc⁴⁹.

Non-invasive imaging methods. The two main methods in this category are high-frequency ultrasonography and optical-coherence tomography (OCT). Ultrasonography reliably measures skin thickness, according to results from several cross-sectional studies⁵⁷⁻⁶⁰, and a 2021 study advocated ultrasonography as an outcome measure⁶¹.

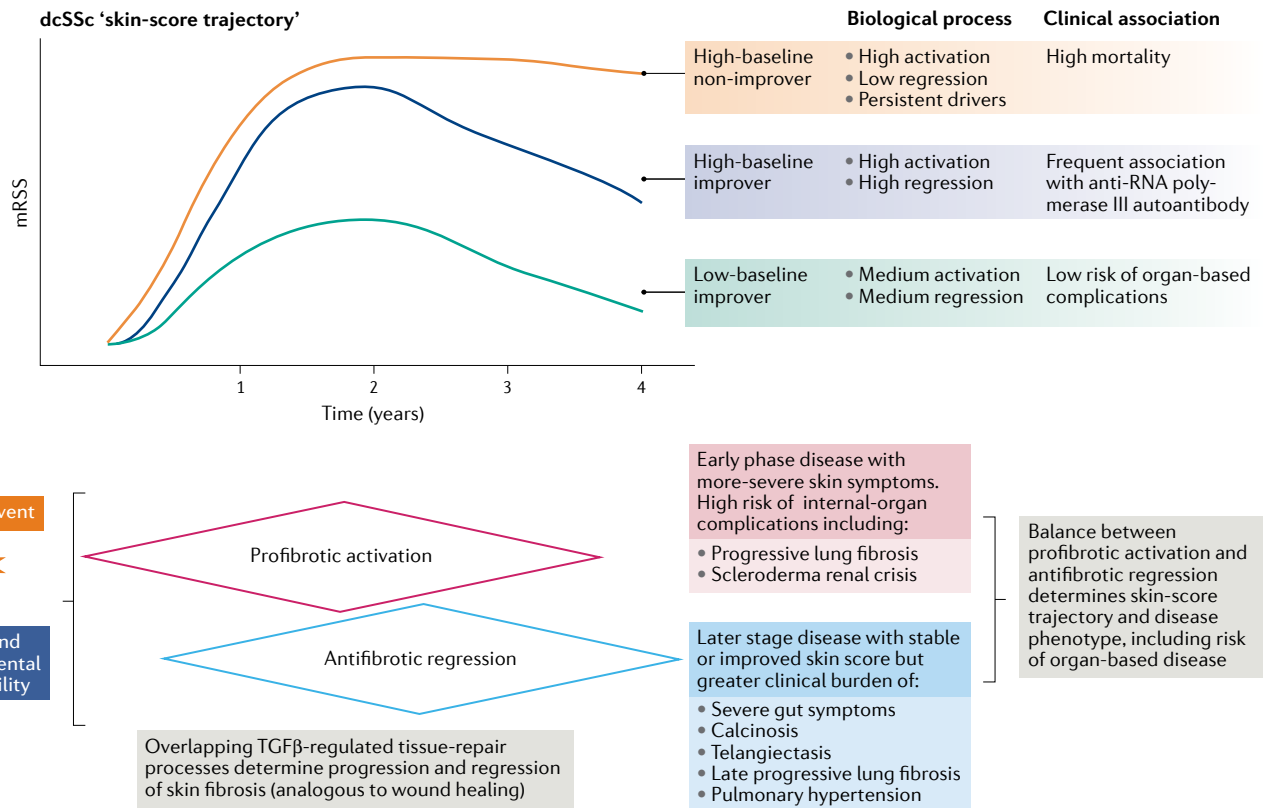


Fig. 2 | Conceptual framework for skin-score trajectory and clinical diversity in diffuse cutaneous systemic sclerosis. Although at a group level, cohort studies and clinical trials of systemic sclerosis (SSc) almost always show improvement in average skin score over 1–3 years, this group-level behaviour does not reflect differences in modified Rodnan skin score (mRSS) change over time for individual patients. Operationally, SSc can be differentiated into three subgroups, characterized by high peak mRSS followed by regression, high peak mRSS without disease regression or lower peak mRSS tending to improve over 2–5 years of follow-up. This pattern of subgroups is likely to reflect interplay between the effectors of progression and fibrosis and the counteracting influence of the mechanisms that determine spontaneous regression, which is a hallmark of normal skin

wound healing. Molecular and cellular determinants of these processes are likely to interact and to underlie the distinct patterns of skin disease, and might also determine the development and severity of internal-organ complications in SSc. Greater understanding of the biological basis of heterogeneity in skin-score change could facilitate clinical trial design and a more stratified approach to patient care. Notably, in normal skin, wound-healing mediators such as TGFβ regulate both profibrotic mechanisms and processes involved in regression of fibrosis, such as induction of matrix-degrading metalloproteinases. The balance between these processes of activation and regression and the persistence of local mediators of fibrosis might underlie the distinct skin-score trajectories observed for individual patients with SSc^{16,23,38}.

Box 1 | Modified Rodnan skin score

What is the modified Rodnan skin score?

To determine the modified Rodnan skin score (mRSS), skin is assessed by palpation at 17 sites and scored on a 0–3 scale (0 = uninvolved, 1 = mild involvement, 2 = moderate involvement, 3 = so severely affected that the skin can hardly be moved), giving a total score of 0–51. The minimal clinically important difference for improvement at 12 months, in the context of a clinical trial, is 5 units¹⁰⁶.

Limitations

- Substantial inter-observer variability occurs with the mRSS¹⁰⁷, although in a study in which ten rheumatologists assessed seven patients, inter-observer and intra-observer reliability were high (0.81 and 0.94, respectively)¹⁰⁸. A major contributor to inter-observer variability is that some raters tend to ‘maximize’ (select a score based on the most severely affected area), some choose a ‘representative’ score (select the score that seems more representative) and some choose an ‘average’ score^{43,109}. Standardized training can reduce variability in skin scoring^{110,111}.
- With the mRSS, the skin is very difficult to assess in later-stage disease¹¹², because although the skin is then softening it can remain tethered, making it impossible to pinch.

Applicability**In clinical practice**

- Without doubt, the mRSS is useful in the outpatient clinic, because it is quick and easy to perform and will help the clinician to decide whether to intensify or to begin withdrawing immunosuppressant treatment. The mRSS associates with patient-reported worsening of skin involvement¹¹³.

In clinical trials

- The mRSS has tended to be the primary outcome in clinical trials of potential disease-modifying therapies in patients with early dcSSc, given that the degree of skin involvement reflects the ‘overall’ early dcSSc disease process. Several of these trials^{35,49–53} have failed to meet their primary end points, although signs of efficacy have come from secondary end points. For example, in the FocuSSed phase 3 randomized placebo-controlled trial of tocilizumab⁵¹, patients on active treatment showed no improvement in mRSS, but lung function did improve. In a randomized controlled trial of abatacept³⁵, active treatment resulted in improvement of scores for the Health Assessment Questionnaire–Disability Index (HAQ-DI)¹¹⁴ and ACR Composite Response Index in dcSSc (a composite measure including the mRSS)⁷¹, but not for mRSS alone. Experience in these and other studies raises the question of whether improvement in skin disease was ‘missed’ because of the limitations of the mRSS.

Ultrasonographic measurement of skin thickness with a 4–15 MHz linear probe correlated well with histological assessment ($r = 0.6926$, $P = 0.009$) and with local (forearm) mRSS ($r = 0.7961$, $P = 0.001$) in 13 patients with SSc (nine of whom had dcSSc) who underwent forearm skin biopsy⁶². As the imaging resolution with ultrasonographic devices improves and ultrasonography-based elastography becomes available in a clinical setting, additional studies will be needed to assess the reliability and validity of improved ultrasonographic skin-thickness measurement modalities in SSc⁶³. Moreover, accurate measurement by ultrasonography requires training and is time-consuming if performed at multiple body sites in individual patients, which probably explains why ultrasonography has not been adopted as an outcome measure in later-phase multicentre studies.

The technical challenges associated with ultrasonography will most likely also apply to OCT, which is another promising tool for the assessment of skin thickness that is currently in early-phase proof-of-concept studies. OCT essentially takes *in vivo* ‘optical biopsy’ images of the skin⁶⁴ to visualize skin structure. In this way, epidermal thickness can be measured at high resolution ($<10\ \mu\text{m}$). Very few studies have so far examined

the use of OCT in patients with SSc^{65,66}. Although OCT can provide higher imaging resolution than ultrasonography-based techniques, currently it has limited imaging depth, which complicates assessment of lower layers of dermis in certain body areas, underscoring the need for further development in this area. Polarization-sensitive OCT (PS-OCT)⁶⁷ is an extension to OCT that involves the measurement of birefringence (an optical property of collagen) in addition to skin thickness. Birefringence can be considered a measure of skin ‘heterogeneity’ and, therefore, potentially a measure of fibrosis. Epidermal thickness measured by PS-OCT correlated with histological thickness in a study that involved ten patients with SSc and ten healthy individuals⁶⁸. Larger prospective studies that examine change over time are required to validate both ultrasonography and OCT as possible outcome measures.

Durometry. As a measure of skin hardness, durometry has long been advocated as a possible outcome measure in clinical trials of early dcSSc⁶⁹, but not widely adopted. However, in 2020 durometry was revisited⁷⁰, and it deserves further investigation, including in longitudinal studies with examination of sensitivity to change. A durometer is hand-held, portable and relatively easy to use, making durometry a potentially useful additional outcome measure in multicentre studies.

Composite scores. Composite scores incorporate multiple elements and might therefore be more representative of disease status than individual measures. At present there are no composite scoring systems specifically for skin disease in patients with SSc. However, the ACR provisional composite response index in dcSSc (CRISS)^{71,72}, which is heavily weighted by the mRSS, was used in patients with dcSSc in several studies that had results published in 2020 (REFS^{35,49,51–53}). The ACR-CRISS includes five measures: the mRSS, percentage predicted forced vital capacity, the HAQ-DI, and patient and clinician global assessments.

Dynamic biomarkers. Longitudinal measurements of expression in skin of two genes, *THBS1* and *MS4A4A*, correlate with mRSS measurements⁷³. However, no studies have yet produced evidence of changes in skin gene expression that correlate with how patients with dcSSc ‘feel, function and survive’, to establish them as surrogate outcome measures.

Serum is another possible source of composite biomarkers, such as those used for the enhanced liver fibrosis score^{38,41}, as well as novel proteomic markers that are currently being explored as candidates for the assessment of treatment response⁷⁴. However, evidence suggests that substantial heterogeneity could exist in the longitudinal relationships between serum markers and mRSS³⁸.

Best-practice management

Although there is currently no cure for SSc (so it is important that whenever possible patients are recruited into clinical trials), there is no room for nihilism, as much can be done to support patients through the worrying phase of early dcSSc. Management options include

Elastography

Assessment of the elasticity and stiffness of soft tissues, usually by ultrasonography.

Raynaud phenomenon
Colour change of the fingers on exposure to cold or to emotional stress: the classic triphasic change is white to blue to red.

symptomatic treatment for progressive skin disease and (in most patients) immunosuppression. Notably, the evidence base in favour of immunosuppression is weak¹¹. In addition, a small minority of patients are candidates for HSCT⁶. Despite recent interest in the tyrosine kinase inhibitor nintedanib as a treatment for SSc-related interstitial lung disease, the SENSICIS trial provided no evidence of an improvement in skin score⁷⁵, although it was primarily a trial investigating lung disease rather than a study of patients with early dcSSc.

Here, we describe aspects of best-practice management of skin thickening in early dcSSc, as shown in FIG. 3. Decisions on treatment (particularly on the choice of immunosuppressant) are influenced by the presence or absence of other SSc ‘complications’, such as concomitant myositis or interstitial lung disease⁷⁶.

Early recognition

Diagnosis of early dcSSc is often delayed⁷⁷, which prevents timely identification and early treatment of (for example) internal-organ involvement and delays patient education. These delays can be addressed by raising physicians’ awareness of the signs and symptoms of dcSSc. Any patient with new onset of skin thickening that could indicate early dcSSc should be referred to a specialist centre, especially if the skin thickening has rapidly progressed. Although Raynaud phenomenon is a symptom in most patients with early dcSSc, in some individuals it develops only after skin thickening, so the use of Raynaud phenomenon as a ‘red flag’⁷⁸ does not always apply to dcSSc, in contrast to the situation in limited cutaneous SSc, in which the onset of Raynaud

phenomenon usually precedes the diagnosis of SSc by many years⁶.

General measures

The four main general measures for the management of skin involvement in early dcSSc are analgesia, treatment of itch, physiotherapy and occupational therapy. Clinical psychology input is an additional consideration.

Analgesia. The pain of skin disease in early dcSSc is often insufficiently recognized, even though it has a considerable effect on quality of life. Among the 326 patients recruited into ESOS¹², the mean and median scores for the sHAQ pain scale (which has a range of 0–100, with 100 indicating the greatest disability) were 32.9 (standard deviation 26.9) and 29.0 (interquartile range 8.7–52.7), and skin thickening correlated with pain ($\rho = 0.17, P = 0.002$). Development of contractures and ulcers further contributes to pain. Analgesia is therefore a key aspect of management. The pain might have a neurogenic component⁷⁹, so treatment with gabapentin or pregabalin can be considered. Some patients will benefit from referral to a pain-management clinic.

Management of itch. Management of this symptom is very challenging. Antihistamines can be tried, but seldom seem to be helpful. Some patients find benefits with 1% menthol in aqueous cream. Anecdotally (A.H., unpublished observations), low-dose prednisolone can relieve itch. Prednisolone is, however, a risk factor for scleroderma renal crisis, as discussed below.

Physiotherapy and occupational therapy. Researchers have given little attention to the roles of physiotherapy and occupational therapy in early dcSSc, even though it seems logical that these approaches could be helpful to maintain range of movement and maximize function. Anecdotally, patients benefit from stretching exercises to maintain range of movement, and many enjoy hydrotherapy (A.H., unpublished observations). In a 2021 study that included 34 patients with dcSSc, but with unspecified disease duration, results suggested a benefit from hand exercises⁸⁰. Ideally, all patients with early dcSSc should be assessed by an occupational therapist, as almost all patients have considerable functional disability, including impairment of hand function¹². ‘Remote’ occupational therapy via a mobile app⁸¹ could be a way forward, at least in some patients.

Clinical psychology input. Patients with early dcSSc report feeling overwhelmed by their disease, with loss of control. This feeling relates in large part to the disability, pain and fatigue that are directly or indirectly related to skin disease. Clinical psychology referral should be considered.

Immunosuppressant therapy

Both the British Society for Rheumatology (BSR)–British Health Professionals in Rheumatology (BHPR)⁸² and EULAR⁸³ recommend immunosuppressant therapy for the skin disease of SSc. The BSR–BHPR guidelines suggest the use of mycophenolate mofetil (MMF),

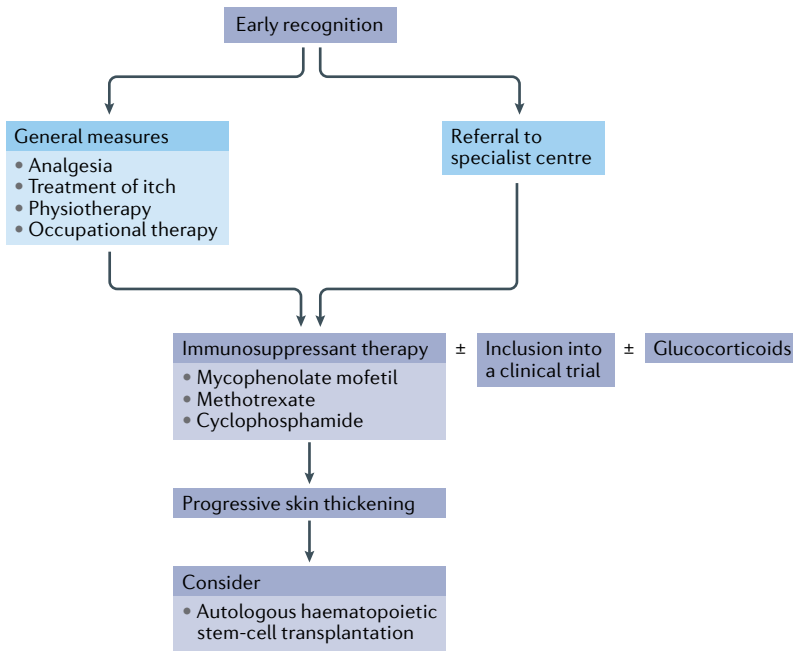


Fig. 3 | Management of skin disease in patients with early diffuse cutaneous systemic sclerosis. Early recognition and referral to a specialist centre are the first principles of management. Pending specialist review, ‘general measures’ should be initiated. In most patients, immunosuppressant therapy should be prescribed. If at all possible, patients should be offered the opportunity to participate in a clinical trial. For patients who continue to progress, haematopoietic stem-cell transplantation should be considered.

methotrexate or cyclophosphamide, whereas the EULAR recommendation is for methotrexate. Among the few clinical trials of immunosuppressants that have specifically examined skin disease primarily in early dcSSc, two used methotrexate^{84,85}, none used MMF (despite results from several early retrospective and prospective observational studies that suggest benefit^{86–88}) and none used cyclophosphamide. In ESOS¹¹, the researchers examined the relative effectiveness of commonly used immunosuppressants in patients with early dcSSc. The treatment options in this observational study were methotrexate (oral or subcutaneous at a target dose of 20–25 mg weekly), MMF (target dose 1 g twice daily), cyclophosphamide (intravenous or oral) or no immunosuppressant. A trend in favour of immunosuppression was seen, as after 12 months, mRSS fell in all groups, but more so in the immunosuppressant groups: for methotrexate ($n=65$) -4.0 units (95% CI -5.2 units to -2.7 units), for MMF ($n=118$) -4.1 units (95% CI -5.3 units to -2.9 units), for cyclophosphamide ($n=87$) -3.3 units (95% CI -4.9 units to -1.7 units) and for no immunosuppressant ($n=56$) -2.2 units (95% CI -4.0 units to -0.3 units) (P -value for between-group differences = 0.346). The conclusion from ESOS was that immunosuppression conferred benefit, but that this benefit was modest. Improvements in mRSS in patients with dcSSc (although not specifically early dcSSc) also occurred in the Scleroderma Lung Study I (cyclophosphamide compared with placebo) and the Scleroderma Lung Study II (cyclophosphamide and MMF compared with patients treated with placebo in Scleroderma Lung Study I) at 12, 18 and 24 months ($P < 0.05$)⁸⁹. Further support for the use of MMF comes from the results of an Australian observational study⁹⁰ and from a report of five patients with recurrence of progressive skin involvement after either discontinuation or dose reduction of MMF⁹¹.

Glucocorticoids

The use of glucocorticoids in early dcSSc is highly controversial⁹², and although some clinicians prescribe them, others do not, as demonstrated by the observation that 44% of patients who were recruited into ESOS had been prescribed them¹¹. Glucocorticoids are likely to reduce the itch and pain (from the skin) that occur in patients with early dcSSc because these symptoms are thought to result from skin inflammation. However, glucocorticoids are a risk factor for renal crisis, especially when used in high doses^{93–95}. Many clinicians are, therefore, understandably reluctant to prescribe glucocorticoids for patients with early progressive dcSSc, who are already at high risk of renal crisis, a risk that is further increased with anti-RNA polymerase III antibody positivity^{96,97}. Notably, patients who are anti-RNA polymerase III antibody positive often have rapidly progressive disease²³ and are therefore particularly likely to have itchy, painful skin that might benefit from glucocorticoid treatment. This controversial issue is currently being investigated in a randomized placebo-controlled trial of the use of prednisolone in patients with early dcSSc (ClinicalTrials.gov identifier: NCT03708718)⁵⁵.

Intravenous iloprost

Intravenous iloprost is widely used in the treatment of SSc-related digital vasculopathy, but might have other beneficial effects, such as the downregulation of expression of connective-tissue growth factor⁹⁸. In our experience (C.D. and A.H., unpublished observations), intravenous iloprost can help to heal the superficial ulcers that can occur in patients with very tightened skin (FIG. 1b), suggesting that there is an ischaemic element to these ulcers.

Autologous HSCT

HSCT should be considered in highly selected patients with rapidly progressive dcSSc. In all three trials that provided the evidence base for this recommendation (ASSIST⁹⁹, ASTIS¹⁰⁰ and SCOT¹⁰¹), patients who underwent HSCT demonstrated benefit in terms of mRSS compared with patients treated with cyclophosphamide, although mRSS was not the primary end point (mRSS was, however, part of the composite primary end point in the ASSIST study⁹⁹). Improvement in mRSS was also reported in a prospective 'real-world' study of 80 patients who underwent HSCT¹⁰². The treatment-related mortality of HSCT in the SCOT study was 3% at 54 months and 6% at 72 months¹⁰¹, and therefore lower than previously reported (a 2001 phase 1/2 trial reported a procedure-related mortality of 17%)¹⁰³, most likely reflecting careful patient selection and adjustments to the transplantation regime. A key question that is currently being addressed¹⁰⁴ is whether HSCT should be recommended as a first-line therapy as opposed to being reserved for patients who do not respond to immunosuppressant therapies. This difficult decision will be informed by the stratified medicine approach referred to earlier (taking into account advances in our ability to predict those patients most likely to have progressive disease), and by ensuring that individualized care is tailored to patients' needs and expectations¹⁰⁵.

Conclusions

The past 5 years have provided new insights into the most visible and characteristic manifestation of early dcSSc — skin thickening (scleroderma) — which is often rapidly progressive. Importantly, we now recognize the burden of skin disease, which has a very considerable effect on quality of life; previously, it was often overlooked. We are now in a good position to predict which patients will develop rapid progression of skin thickening, thereby enabling early intervention with immunosuppressive therapies or with HSCT, and/or inclusion into clinical trials. The lack of reliable outcome measures of skin disease represents a major unmet need. However, the challenges of monitoring skin disease, both in the clinic and in the setting of clinical trials, are now better understood, and research is ongoing. Better outcome measures (and improved identification of progressors) will maximize the efficiency of future clinical trials of the many promising new targeted therapies. Pending identification of a safe and effective treatment, clinicians should not forget current best-practice guidelines, which can provide at the very least some symptomatic relief from painful, disabling skin disease.

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