Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc) is a multisystem autoimmune disease in which there is increased fibroblast activity resulting in abnormal growth of connective tissue. This causes vascular damage and fibrosis. Fibrosis occurs in skin, the gastrointestinal (GI) tract, heart, lungs and other internal organs. Vascular manifestations include secondary Raynaud’s phenomenon, ischaemia of extremities, pulmonary arterial hypertension and renal disease.

The name scleroderma is derived from the Greek for ‘hard skin’ and emphasises the dermatological component of the disease. It was described by Hippocrates. There is a localised form of scleroderma, also known as morphoea. See separate Morphoea article.

Types of systemic sclerosis[1]

SSc is classified into two main types, according to the extent of skin involvement. Classification is important as the development of the condition - and therefore early management - will depend upon which type is diagnosed.

Limited cutaneous systemic sclerosis (lcSSc), or limited scleroderma

- The more common type of SSc.
- Areas of skin affected include only the face, forearms and lower legs up to the knee.
- The older term for limited scleroderma is CREST syndrome (Calcinosis, Raynaud’s disease, O Esophageal dysmotility, Sclerodactyly, Telangiectasia).

Diffuse cutaneous systemic sclerosis (dcSSc), or diffuse scleroderma

- This is less common.
- Skin areas involved include also the upper arms, thighs or trunk.
- There is higher risk of mortality.

Other types

Overlap SSc is thought to account for up to 20% of cases.

There are rarer types, including systemic sclerosis sine scleroderma, in which there is internal organ involvement without the skin changes.

Epidemiology[1, 2]

SSc is present throughout the world and is represented in all ethnic groups. Incidence and prevalence figures vary widely and there appears to be a large geographical variation. In the UK, annual incidence is reported to be 3.7 per million and prevalence 31-88 per million. Around the world, prevalence is reported to vary from 30-240 per million. It seems to be more common in North America and Australia than in Europe. Women are affected more often than men, and those of African origin are also more affected. The peak age of onset is 40-50 years but it can affect any age group. It is rare in children.

Aetiology[3, 4]

The cardinal features of SSc are:

- Excessive collagen production and deposition.
- Vascular damage.
- Immune system activation via autoantibody production and cell-mediated autoimmune mechanisms.

These three pathogenic factors cause the heterogeneous clinical manifestations.

The cause is unknown; however, genetic, infectious and environmental factors all appear to play a role. Possible factors which have been implicated include:

- Genetic predisposition. A family history of SSc increases the risk.
- Infectious agents. Various agents, including cytomegalovirus, parvovirus B19, Helicobacter pylori, hepatitis B virus, Epstein-Barr virus, Toxoplasma gondii and chlamydia have been implicated as possible triggers.
- Chemicals (such as polyvinyl trichloroethylene, some pesticides, organic solvents, hair dyes and silica).
- Drugs (such as cocaine, pentazocine, bleomycin, penicillamine and vitamin K).
- Radiation therapy.
- Physical trauma.
- Vitamin D deficiency. There is a strong association and many people with SSc have documented vitamin D deficiency.
Clinical features \[5, 6\]

Common presenting symptoms are Raynaud's phenomenon (which may precede other symptoms by some years), skin hardening in hands or face and oesophageal symptoms. Early symptoms can also be nonspecific - eg, fatigue, musculoskeletal pains and hand swelling. Both limited and diffuse scleroderma can involve internal organs; the severity of skin changes does not necessarily reflect the severity of internal organ involvement.

LcSSc

- Generally a milder disease, with less skin involvement, slow onset and slow progression.
- The slow onset may mean that symptoms are relatively unnoticed until internal complications occur.

DcSSc

- Usually a more rapid onset, with skin thickening and Raynaud's phenomenon occurring together or within a short interval. The skin changes may spread rapidly, within a few months of disease onset.
- Symptoms tend to be at their worst in the first 3-5 years of the disease, after which there is a stable phase and further deterioration is unlikely. The disease may then reverse to some extent, with softening of the skin and improved mobility.
- Internal organ involvement is more common.

General features

- Fatigue.
- Weight loss.

Skin features

- Signs in the hand:
  - Swelling (non-pitting oedema) of fingers and toes - a common early sign; digits may look sausage-like; hand movement may be limited.
  - Skin becomes hard and thickened - this may limit joint movement or cause joint contractures; in the fingers, this is known as sclerodactyly.
  - Swelling and sclerosis reduce hand movements, so patients may be unable to make a fist, or to place the palmar surfaces together - the 'prayer sign'.
  - Fingertips may have pitting, ulcers or loss of bulk from finger pads. Digital ulcers are common, occurring in nearly half of cases \[7\].
  - Raynaud's phenomenon. This is the most common symptom and is present at some point in 90% of cases. Raynaud's phenomenon with puffy fingers is thought to be a cardinal sign of likely SSc \[8\].
  - Calcinosis - nodules or lumps of chalky material which may break through the skin.
  - Face and mouth:
    - Tightening of facial skin.
    - Tight lips (microstomia) - can make dental hygiene difficult.
  - Telangiectasia.
  - 'Salt and pepper' appearance of skin, due to areas of hypopigmentation and hyperpigmentation.
  - Dry or itchy skin; reduced hair over affected skin areas.

Musculoskeletal features

- Joint pain and swelling.
- Myalgia (due to inflammatory myopathy).
- Restriction of joint movement, contractures and muscle atrophy due to skin sclerosis.
- Tendon friction rubs - palpable/audible over the flexor/extensor tendons of the hands, knees and ankles.

GI features

GI symptoms are extremely common in SSC, occurring in the majority of cases and are often one of the earlier manifestations \[7\]. Symptoms are primarily due to dysmotility due to collagen deposition and loss of smooth muscle function. Any section of the GI tract can be affected. Potential GI manifestations include:

- Heartburn and reflux oesophagitis.
- Oesophageal scarring and dysphagia.
- Delayed gastric emptying - eg, fullness after meals.
- 'Watermelon stomach' (gastric antral vascular ectasia) - may cause GI bleeding and anaemia.
- Reduced small bowel motility - can cause bacterial overgrowth, with bloating, malabsorption, diarrhoea and malnutrition. (Malnutrition may also be caused by swallowing problems.)
- Constipation due to reduced colonic motility.
- Obstruction and pseudo-obstruction can occur due to reduced motility and bacterial overgrowth. These can be followed by perforation and peritonitis.
- Anorectal dysfunction: In some cases, the rectum and anus are involved, causing faecal incontinence or rectal prolapse.

Pulmonary features
The two main pulmonary problems associated with SSc are:

- **Pulmonary fibrosis (interstitial lung disease):**
  - Occurs in as many as 80% and it is clinically significant in around a third \(^1\).
  - Causes restrictive lung disease.
  - Symptoms and signs: exertional dyspnoea, cough, coarse basal crackles.

- **Pulmonary arterial hypertension (PAH):**
  - Occurs in up to 12% of patients with scleroderma \(^9\).
  - A leading cause of death in SSc. The presence of PAH drastically reduces survival rate (50% mortality within three years of diagnosis of PAH \(^9\). Outcome is worse than for other causes of PAH).
  - Symptoms and signs: exertional dyspnoea, syncope, right ventricular strain features.
  - Research has attempted to define predictive screening tools. These include monitoring lung function, ECG, echocardiogram, urate levels and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and by taking into account anti-centromere antibody (ACA) presence and history or presence of telangiectasia \(^10\).

Other potential pulmonary complications include:

- **Aspiration pneumonia** from severe reflux.
- Respiratory muscle weakness if there is severe myositis or extensive skin disease involving the chest.
- **Pneumothorax.**
Cardiac features\[7\]
The wide variety of abnormalities makes it difficult to assess prevalence. It is likely that the subclinical cardiac involvement rates are very high. Cardiac problems are more common in the diffuse subtype and are associated with poor prognosis. Cardiac disease is due to myocardial fibrotic change or secondary to PAH or renal problems. It may be asymptomatic until well developed. Presentation includes palpitations, exertional chest pain/dyspnoea, dizziness, and peripheral oedema, or it may be detected through echocardiogram monitoring. Potential cardiac problems due to SSc include\[11, 12\]:

- Microvascular coronary artery disease (resulting in myocardial ischaemia).
- Accelerated atherosclerosis with subsequent coronary heart disease.
- Myocardial fibrosis.
- Left ventricular (LV) systolic dysfunction, LV diastolic dysfunction.
- Pericarditis or pericardial effusion: these may cause cardiac impairment or congestive cardiac failure.
- Arrhythmias and conduction defects (including bradyarrhythmias and tachyarrhythmias).
- Endocarditis.
- Cardiac changes secondary to PAH or severe hypertension due to renal crisis.

Renal features\[13\]
Renal presentations include signs of development of:

- Antineutrophil cytoplasmic antibodies-associated glomerulonephritis.
- Reduced renal functional reserve - proteinuria, microalbuminuria or reduced glomerular filtration rate (GFR).

Scleroderma renal crisis. This is a serious condition with features of accelerated hypertension, which can lead to renal failure if not treated promptly. It occurs in 2-15% of patients with SSc and is more common in those with diffuse, rapidly progressive disease\[14\]. It usually presents as accelerated hypertension with oliguria, headache, fatigue, oedema, rapidly rising serum creatinine levels, proteinuria and microscopic haematuria. Scleroderma renal crises can occur with apparently normal blood pressure but the blood pressure is higher than baseline values - hence the importance of regular blood pressure monitoring.

Genitourinary features
- Erectile dysfunction occurs in 80-90% of men with the condition, due to vascular changes\[15\].
- Women may have dyspareunia.

Investigations

General blood tests
- FBC.
- ESR and CRP.
- Baseline biochemistry and renal function.

Autoantibodies\[6, 7\]
These are now considered crucial for classification. Autoantibodies are heterogeneous, reflecting the nature of the condition. They are helpful in subtyping the disease, are linked to clinical features and prognosis and are now included in the diagnostic criteria. Antinuclear antibody is positive in the majority but is not specific to SSc.

The main SSc-specific autoantibodies, included in the diagnostic criteria, are:

- Anti-topoisomerase 1 (also known as anti-Scl 70) - strongly associated with lung fibrosis and with renal disease and a poor prognosis.
- Anti-centromere antibody (ACA) - seen almost only in patients with lcSSc and is associated with increased risk of pulmonary hypertension but relative protection from lung fibrosis and kidney involvement.
- Anti-RNA polymerase III antibody - associated with dcSSc and especially with kidney involvement. There is a strong association between presence of anti-RNA polymerase III antibodies and the development of scleroderma renal crisis which helps to identify at-risk patients\[13\]. Conversely, it is associated with a relatively low rate of interstitial lung disease.

Other autoantibodies associated with SSc include:

- Anti-fibrillarin (anti-U3RNP) antibody - associated with heart involvement, pulmonary hypertension and fibrosis, kidney involvement and myositis.
- Anti-Th/To antibody - associated with an increased risk of interstitial lung disease .
- Anti-Ro52/TRIM21 antibody - also associated with an increased risk of interstitial lung disease and poorer prognosis\[16\].
- Anti-U11/U12 RNP antibody - associated with an increased risk of interstitial lung disease and seen in both limited and diffuse subtypes.
- Anti-PM-Scl antibody - associated with the combination of myositis and scleroderma.
- Anti-U1RNP (anti-nRNP) antibody - associated with joint involvement and overlap syndromes.

Other investigations
- Urine protein - as baseline or if there are renal complications.
- Nailfold capillaroscopy - helps to assess the likelihood of scleroderma in patients with Raynaud's phenomenon or swollen fingers. This is also useful in predicting risk of developing ulcers\[17\].
Hand X-ray may show calcinosis.
Thermography with cold challenge helps to assess the severity of Raynaud's phenomenon.
Endoscopy and/or barium studies, depending on GI symptoms.

**Monitoring and further investigations**[7]

Because of the multi-system nature of the disease and the potential for severe complications, ongoing investigation potential is extensive and will be based on symptoms, typing, autoantibodies, etc, but may include:

- Renal function.
- B-type natriuretic peptide (BNP) and N-terminal proBNP.
- Lung function tests.
- High-resolution chest CT scan.
- ECG and echocardiography.
- Cardiac MRI.
- Oesophageal manometry and 24-hour pH studies.
- Endoscopy.
- Hydrogen breath testing or jejunal aspirates may be used to diagnose small intestinal bacterial overgrowth (SIBO).

**Diagnosis**[6]

Early diagnosis is important as early treatment is thought to influence outcome. Diagnostic criteria have traditionally been proximal scleroderma (proximal to the metacarpophalangeal (MCP) joints, sclerodactyly, digital pitting scars or pulp loss, and bilateral basilar pulmonary fibrosis. In 2013, the collaboration of the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) proposed a new set of criteria. Further items are given a weighted score. A score of 9 or more is diagnostic of SSc. The traditional 'major' criterion of skin thickening extending proximal to the MCP joints is given a score of 9 and is therefore sufficient on its own to make a diagnosis. The following features are included in the new system:

- Skin thickening extending proximal to the MCP joints (score 9).
- Skin thickening of the fingers (score 2 for puffy fingers, 4 for sclerodactyly).
- Fingertip lesions (score 2 for ulcers, 3 for fingertip pitting scars).
- Telangiectasia (score 2).
- Abnormal nailfold capillaries (score 2).
- Pulmonary arterial hypertension and/or interstitial lung disease (score 2).
- Raynaud’s phenomenon (score 3).
- SSc-related autoantibodies (score 3).

**Early diagnosis - the VEDOSS initiative**[18]

The VEDOSS (Very Early Diagnosis Of Systemic Sclerosis) initiative in Europe identified the following features as being key to diagnosing SSc in the very early stage:

- Antinuclear antibodies.
- Scleroderma-specific antibodies.
- SSc pattern on nailfold capillaroscopy.
- Puffy fingers in Raynaud's syndrome patients.

**Differential diagnosis**[5]

Several other diseases can present in a similar way to SSc, including:

- Raynaud's phenomenon from other causes.
- Vibration injury.
- Other connective tissue disease or mixed connective tissue disease - eg, with features of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).
- Undifferentiated connective tissue disease.
- Amyloidosis.
- Chronic graft-versus-host disease.
- Paraneoplastic syndromes.

**General approach to management**[1]

There is no cure for SSc. Management consists of controlling symptoms and preventing complications. It is a complex, uncommon, multi-system disease with significant risk of serious complications. It must therefore be managed by SSc specialists working as a multidisciplinary team with allied professionals and organ-based specialists. The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHRP) published guidelines in 2016 for the management of SSc. They note that these recommendations are based on weak evidence, as the nature and progression of the condition is heterogeneous, it is uncommon and, as a result, there are not high-quality studies upon which to base advice. The importance of defining the subtype (local or diffuse) is stressed, as management differs. In particular, those with early diffuse disease should be considered for early immunosuppressive therapy.
Regular monitoring and reviews are aimed at early detection and treatment of complications. Monitoring includes reviewing symptoms, monitoring blood pressure and renal function and monitoring lung and cardiac function, etc.

**Non-pharmacological treatments**

- **Patient involvement and education:**
  - 'Expert patient' programmes and the Scleroderma Society (now Scleroderma and Raynaud's UK)[20].
  - Awareness of urgent problems such as renal crisis or intestinal obstruction symptoms.

- **Physiotherapy to promote joint mobility and muscle strength.**
- **Home exercises to maintain range of motion** (such as gentle mouth, face and hand stretches).
- **Avoid tobacco and maintain healthy weight.**
- **Nutritional advice, and supplements if needed.**
- **Emollients for skin dryness and itching.** Short courses of topical steroids or antihistamines if required.
- **For Raynaud's phenomenon:**
  - Prevention - avoid cold and trauma; use warm clothing or heated clothing.
  - For an attack - warm the body, hands and feet gently (the skin may be numb and unable to feel if the heat source is too hot); use gentle arm movements or gentle massage to help restore circulation.

- **Occupational therapists** - for adaptations to assist in daily living.
- **Camouflage products** - for cosmetic help with skin changes.
- **Laser or pulsed light therapy** as well as camouflage may be useful for telangiectasias.

**Immunotherapy**

The BSR/BHPR guidelines advise that anyone with dcSSc of less than three years' duration should be considered for treatment with a broad-spectrum immunosuppressive agent. Agents used are methotrexate (MTX), mycophenolate mofetil (MMF) or cyclophosphamide (CYC). Autologous stem cell transplantation (ASCT) may later be appropriate in some cases, particularly in those considered to be at high risk of progression.

Skin involvement may be treated with either MTX or MMF. Other options include CYC, oral steroids (in as low a dose as possible and with close monitoring of renal function) and rituximab. Azathioprine (AZA) or MMF may be used after CYC to maintain improvement in skin sclerosis and/or lung function.

**Management of organ-based disease**[1]

**Management of skin problems**

**Raynaud’s phenomenon symptoms and ulcers**

- **Nifedipine** is currently the only drug licensed for Raynaud's phenomenon in the UK. Guidelines advise the use of further possible treatments for Raynaud’s phenomenon which may be effective but are not yet licensed in the UK.
- **First-line treatment** should be a calcium-channel blocker such as nifedipine, or an angiotensin II receptor antagonist (such as losartan).
- **If first-line treatment does not work,** one of the following may be considered:
  - Selective serotonin reuptake inhibitors (SSRIs).
  - Alpha-blockers.
  - Statins.
  - Phosphodiesterase type-5 inhibitors.

- **In severe cases:**
  - Intravenous (IV) prostanoid (iloprost).
  - Digital sympathectomy +/- botulinum toxin A injection.

- **In addition for ischaemic ulcers:**
  - Management by a multidisciplinary team.
  - Antibiotics if infected.
  - Analgesia.
  - Vasodilators.
  - Sildenafil specifically recommended before trial of IV or surgical treatment.

**Calcinosis**

- **Infection** should be recognised and treated promptly.
- **Pharmacological options** that have been tried include aluminium hydroxide, bisphosphonates, calcium-channel blockers, colchicine, infliximab, IV immunoglobulin, minocycline, rituximab and warfarin.
- **Interventional options** that have been used include extracorporeal shock wave lithotripsy and intralesional steroid and laser therapy.
- **Surgical removal** should be considered if severe or impacting on function/quality of life.

**Management of musculoskeletal symptoms**
Immunosuppressant therapy may be considered.

Surgical procedures for specific indications such as:

- Release of contractures.
- Removal of troublesome calcinosis.

Myalgia, arthralgia and painful oedema:

- Non-steroidal anti-inflammatory drugs (NSAIDs), if tolerated.
- Simple analgesics.

Management of GI symptoms

For upper GI symptoms:

- Lifestyle measures are often advised (such as maintaining upright posture after meals, raising the head of the bed, limiting alcohol) but medication is usually required.
- Proton pump inhibitors. High-dose and long-term therapy may be needed.
- May also need H$_2$-receptor antagonists and/or pro-motility agents (metoclopramide or domperidone).
- Dilatation of oesophageal strictures if required.
- Those with watermelon stomach may require endoscopic laser coagulation to prevent bleeding.

For intestinal bacterial overgrowth and malabsorption:

- Cytocyc antibiotics.
- Nutritional advice and nutritional supplements; rarely, parenteral nutrition is required.

For constipation:

- Dietary fibre and good fluid intake.
- Softening laxatives (such as lactulose) and/or soluble fibre (such as ispaghula).
- At times, diarrhoea may be the prominent symptom and anti-diarrhoeal agents may be required. Constipation and diarrhoea may alternate.

Pseudo-obstruction is treated initially by bowel rest and antibiotics. Laparotomy may be needed. Surgery may be required for rectal prolapse.

Management of pulmonary disease

Pulmonary fibrosis (interstitial lung disease)

- Treatment should be by CYC infusion, with MMF as an alternative or following CYC.
- Supportive treatment: prompt treatment of chest infections - oxygen if needed.

Pulmonary arterial hypertension (PAH)

- Evaluation includes right heart catheterisation and assessment of co-existent cardiac and lung conditions.
- Treatment of PAH has improved recently and includes:
  - Endothelin receptor antagonists - eg, bosentan or ambrisentan.
  - Phosphodiesterase type-5 inhibitors - eg, sildenafil, tadalafil.
  - Prostaglandin derivatives - eg, iloprost or epoprostenol.
- Supportive treatment - eg, oxygen, diuretics.

Management of renal conditions

- Treatment of scleroderma renal crisis is with ACE inhibitors, plus dialysis if necessary. Additional anti-hypertensive agents may be required.
- Testing patients with scleroderma for anti-RNA polymerase III antibodies may help identify at-risk patients[13].

Management of cardiac conditions

Treatment for many of the cardiac conditions which occur is according to the clinical features.
Systolic heart failure

Options include:
- Immunosuppression with or without a pacemaker.
- Implantable cardioverter defibrillator.
- Angiotensin-converting enzyme (ACE) inhibitors and carvedilol.

Diastolic heart failure with preserved left ventricular ejection fraction

- Diuretics.
- Calcium-channel blockers.

Management of erectile dysfunction\[15\]

On demand phosphodiesterase type-5 inhibitors are not usually effective in men with SSc, but regular or alternate day treatment may be more successful. Intracavernous prostaglandin E1 injections and penile prostheses may also be considered.

Complications

Many complications are part of the diverse and complex clinical presentation, and are discussed in the clinical features section above.

Malignancy\[21\]

SSc is associated with a higher risk of malignancy. The highest risk is associated with lung cancer, breast cancer and haematological malignancies. It is not known yet who and how to screen.

Sjögren’s syndrome

- This may occur in patients with an 'overlap syndrome', where there are both scleroderma and Sjögren’s syndrome features.
- Common symptoms are dry eyes and mouth; other mucous membranes (eg, vagina) may be symptomatic.
- Can cause eye irritation, dysphagia, dysphonia and increased dental decay.
- Treat with lubricants (eg, artificial tears and saliva) and with dental care.

Other complications

- Depression.
- Osteoporosis - due to reduced blood flow.
- Hypothyroidism may be associated.

Pregnancy\[22, 23\]

Successful pregnancy is possible. It should be planned when the disease is stable to avoid complications. Teratogenic medication should be stopped. Close monitoring, multidisciplinary care and individually tailored treatment are needed. Reflux is the most common problem. The most dangerous complication is scleroderma renal crisis. ACE inhibitors may be used in pregnancy if renal crisis is suspected. Outcomes on the whole are good although there is a risk of prematurity. Pregnancy should be avoided in the presence of PAH, in severe organ involvement or in the early stages of rapidly progressive diffuse disease as these situations are associated with high risk.

Prognosis

The disease course varies with each individual. The prognosis depends on the extent of complications. Therefore, mortality figures vary enormously. Overall, five-year survival is around 75% and ten-year survival is around 62.5%\[24\]. Deaths from kidney disease have dropped over recent years and the most common causes of death are now pulmonary fibrosis and PAH\[2\]. Survival at one year after renal crisis is 70-80% but this drops to 50-60% at five years\[14\].

Further reading & references

- BSR and BHPR guideline for the treatment of systemic sclerosis; British Society for Rheumatology (2016)


19. SRUK - Scleroderma & Raynauds UK


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