Raynaud's Phenomenon and Digital Ulcers in Systemic Sclerosis

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Abstract

Raynaud's phenomenon (RP) is a symptom complex related to impaired digital perfusion and can occur as a primary phenomenon or secondary to a wide range of underlying causes. RP occurs in virtually all patients with systemic sclerosis (SSc) and is often the earliest clinical manifestation in the natural history of the disease. Careful assessment is required in RP patients to avoid missing secondary causes of RP, including SSc. Digital ulcers (DUs) are a painful and disabling visible manifestation of the digital vascular injury. Significant progress has been made in the definition and assessment of DUs and understanding ulcer pathogenesis. There are a wide range of available treatments to both prevent and heal DUs; some of which are also used in RP management. The present review shall consider the assessment of patients with RP, including 'red flags' suggestive of SSc. We shall review the pathogenesis, definition and classification across the spectrum of SSc-DU disease, alongside a review on management approaches including drug therapies and surgery for SSc-RP and ulcers. We also highlight unmet needs and research priorities in SSc-RP and SSc-DUs and introduce the concept of a unified vascular phenotype in which vascular therapies may support disease modification strategies.

Introduction

Systemic sclerosis (SSc) is a complex connective tissue disease which is characterised by autoimmunity, progressive generalised obliterative vasculopathy and widespread aberrant tissue fibrosis.[1,2] Digital vascular disease (vasculopathy) occurs in virtually all patients with SSc, ranging from symptoms of Raynaud's phenomenon (RP) (Figure 1) to irreversible ischaemic tissue injury causing digital ulcers (DUs) (Figure 2) and sometimes gangrene. Although SSc is a very heterogenous disease, RP is experienced by the majority (>95%) of patients, and is the most common symptom and clinical sign of the disease.[2,3] Whereas, in primary RP tissue ischaemia is transient/reversible, in secondary RP (in particular SSc-RP) persistent tissue ischaemia can occur resulting in digital ulceration and/or gangrene. However, there are only limited to data to suggest an association between the severity of RP and DUs[4], which likely reflects the complexity of vascular (and skin involvement) in SSc.

The purpose of this review is to highlight 1) when to suspect SSc in the setting of RP, including how to assess the patient with Raynaud's to identify 'red flags' indicating potential SSc; 2) the spectrum of RP and DU disease in SSc encompassing relevant pathophysiology, diagnosis and classification, and management. We will also highlight current unmet needs and research priorities in RP and DU disease and discuss the concept of a unified vascular phenotype in which vascular therapy could be a disease modifying strategy.

Epidemiology

Endothelial injury is an important initiating event in SSc, often manifesting clinically as RP. Registry analyses suggest ~95% of patients with SSc experience RP.[3] The remaining 5% may not fulfil strict definitions of RP (often necessitating bi-phasic digital colour change) but digital microangiopathy is usually still evident by the presence of abnormal capillary morphology at the nailfold. In patients with limited cutaneous SSc, RP may predate the diagnosis of SSc by many years (sometimes decades).[5] Whereas, in patients with diffuse cutaneous SSc, RP typically develops in closer proximity to the onset of skin sclerosis.[5]

DUs are common in patients with SSc and are a major cause of disease-related pain and morbidity.[6] Approximately half of patients with SSc experience DU[7–10] with a point prevalence of 5 to 10%.[10,11] In a study from the European Scleroderma Trials and Research cohort

database, the probability of developing DUs was 70% by the end of the 10-year observation period.[12] Several studies have reported that fingertip DUs have a higher prevalence than extensor ulcers.[13–15] In contrast, Ennis et al, reported that extensor ulcers had a similar prevalence (of 6%) and were as similarly disabling as fingertip DUs.[11] Patients often develop ulcers affecting multiple digits simultaneously, including both fingertip and extensor-aspect DUs.[15] Despite the availability of a number of advanced therapies to prevent and treat DUs, around one third of patients with SSc may develop recurrent ulceration.[16]

Clinical presentation

RP is a highly variable symptom complex which results from aberrant digital perfusion. Digital colour changes (Figure 1) are the cardinal symptom of RP, although other body sites/vascular beds can be affected including the toes, lips, ears, nose and nipples[17] The stereotypical series of colour changes (physiological basis in parentheses) from attacks of RP consists of initial white/pallor (vasoconstriction/occlusion of pre-capillary arterioles), then blue/purple (cyanosis from deoxygenation of sequestered blood), and finally red (post-ischaemic hyperaemia).[17] Digital ischaemia results in significant pain and paraesthesias. In general, the majority of patients with primary RP will develop symptoms by 30 years of age, whereas, after 40 it is almost always secondary. SSc patients can identify with distinct patterns of RP over time (that may reflect progression of vasculopathy) with established disease being associated with fewer 'stereotypical' attacks of RP, and more persistent features of tissue ischaemia.[18] Cold exposure is an important trigger for attacks of RP. However, most patients with SSc experience symptoms throughout the year, given a lower threshold for cold sensitivity in SSc patients.[19] Another important trigger of attacks is emotional stress, both in primary and secondary RP. A number of classification and diagnostic criteria for RP have been proposed.[20–24] In general, these are based on patient reported episodic digital colour changes in response to cold exposure, most of which have required at least two-colour changes in order to diagnose or classify RP.

Approximately, 75% of patients with SSc will develop their first DU episode within 5 years of their first non-RP symptom[7]. Moreover, progressive vasculopathy in patients with SSc can progress to critical ischemia and gangrene, which may necessitate digital amputation, and can affect approximately 1.5% of patients per year.[25] SSc-DUs are associated with significant

pain[11,26] with higher analgesia requirements[27], reduced health related quality of life[28] and hand-related disability including negative impact on occupation.[8,26,29,30] Data from the Digital Ulcers Outcome (DUO) registry identified that patients with 'chronic' and 'recurrent' DUs had greater rates of impairment in activity including occupation, and need for both paid and unpaid help.[16] In addition, these patients also had the greatest need for interventions including hospitalisation and analgesia.[16] The mean annual cost per patient in the European Union of SSc-DU has been estimated to be €23,619, was higher with complications (€27,309), and approximately 10% as a result of lost work productivity from patients and/or their care givers.[31] The availability of non-proprietary medications should see this cost fall in the future. SSc-DUs are typically very slow to heal. In an observational study which included 1,614 digital lesions, the mean (minimum and maximum) time to healing for 'pure' (ischaemic) DUs was 76.2 (7 and 810) days, and for DU derived from calcinosis was 93.6 (30 and 388 days).[14] The DU characteristics associated with a significant delay in ulcer healing included the presence of fibrin, wet or dry necrosis, eschar, exposure of bone and tendon, and gangrene.

DU infection can be associated with delayed ulcer healing and osteomyelitis. The most common (approximately 50%) organism is *Staphylococcus aureus*.[32,33] Enteric organisms (*Escherichia coli* and *Enterococcus faecalis*) have also been reported in around 25% of patients with SSc-DUs, which highlights the need for patient education about the need for meticulous wound care.[32] Infection has been reported to be associated with greater perfusion (as assessed by laser speckle contrast imaging) to both the ulcer centre and surrounding area, and is highly (negatively) correlated with the time to healing.[34]

Pathophysiology

Primary RP ('idiopathic'), is considered an isolated functional vasospastic condition. Whereas, the aetiopathogenesis of SSc-RP includes (amongst other factors) endothelial cell injury (possibly autoantibody mediated), an imbalance between vasoconstrictor and vasodilator factors (e.g. endothelin-1 and nitric oxide, respectively), structural microvascular changes from progressive microangiopathy, and intravascular factors leading to luminal occlusion and increased vasoconstriction (e.g. platelet activation and impaired fibrinolysis).[2,35]

In general, DUs which occur on the fingertips are considered to be ischaemic (Figure 3). Whereas, those which occur over the extensor aspects, in particular over the small joints of the hands, are also related to recurrent trauma at exposed sites, and potentially due to increased skin tension (Figure 3). Patients can also develop digital ulceration in relation to underlying subcutaneous calcinosis (Figure 3). The pathogenesis of calcinosis-associated ulceration may differ significantly (e.g. to ischaemic ulcers) and local mechanical and inflammatory phenomena may play a significant role.[7] Whether SSc-DU can be considered the consequence of 'severe Raynaud's' is debateable but DU are generally considered a manifestation of more advanced vasculopathy. Patient-reported RP severity has been noted to be higher in patients with active DU.[4] SSc-associated microangiopathy as assessed by capillaroscopy (namely capillary drop) is strongly associated with the severity of DU disease (e.g. new ulceration).[36] However, relatively little (if anything) is known about the pathophysiology of ulcers which occur at other sites of the hands which are less frequent including at the base of the nail and lateral aspect of the digits. Lower limb large vessel disease is well-recognised, in particular in patients with limited cutaneous SSc and positive anticentromere antibody, and can result in severe ischaemic complications including gangrene.[37,38] Irrespective of the underlying cause, DUs can result in significant irreversible tissue loss (Figure 3).

Assessment

Early recognition of SSc-related RP is important to facilitate earlier diagnosis and management of SSc disease-related manifestations. Clinicians should be aware of a number of 'red flags' (Box 1) which are strongly suggestive of secondary causes such as SSc. Important red flags are included in the proposed 'very early diagnosis of SSc' [VEDOSS] criteria that includes RP, puffy fingers and positive antinuclear antibody[39] and further validation is ongoing. The identification of SSc-specific autoantibodies and/or the SSc pattern on nailfold capillaroscopy strengthens the likelihood of future SSc.[39] The second objective of assessment is to determine the impact of RP including the development of persistent tissue ischaemia (e.g. DUs).

Key investigations in the assessment of patients with RP exhibiting any suspicion of secondary Raynaud's include the detection of autoantibodies and performing nailfold capillaroscopy,

which are strong independent predictors of progression from isolated RP to SSc.[40] In a large prospective study of 586 RP patients who were followed up over 3,197 patient years, 12.6% developed definitive SSc.[40] Multivariate analysis revealed that predictors of progression to definitive SSc included positive antinuclear antibody (ANA) (Hazard ratio [HR] 5.67) and SSc-specific autoantibodies (HR 4.7), as well as the SSc pattern on nailfold capillaroscopy (HR 4.5), and all of which have a high negative predictive value.[40]

Clinical investigations

A detailed examination of the hands should be performed including seeking evidence of SSc skin involvement (e.g. sclerodactyly), signs of persistent digital ischaemia (e.g. digital pitting scars and ulcers) and other stigmata of SSc (e.g. telangiectasia and calcinosis). The number, size and distribution of DUs should be assessed including signs of infection (e.g. discharge and erythema) and deeper progression (e.g. visualisation of underlying tendons and bone). Asymmetry in RP symptoms and/or DUs may indicate proximal (large) vessel involvement, which could be amenable to therapeutic intervention.

Routine investigations also include testing a full blood count, and ESR or CRP.[41] Routine biochemistry (e.g. renal and liver function) and thyroid function can suggest alternative secondary causes of RP.[41] Other investigations are guided by the clinical picture, including testing of creatine phosphokinase, complements C3 & C4, immunoglobulins with serum protein electrophoresis, fasting lipid profile (in patients at risk of atherosclerosis), and performing a chest radiograph to exclude (a bony) cervical rib.[41]

As previously described, autoantibodies can help to identify those patients who are at the greatest risk of developing autoimmune rheumatic diseases, including SSc. Therefore, testing for autoantibodies should be part of the initial assessment of patients with RP, including those with symptoms and/or signs of an underlying autoimmune connective tissue disease. The standard primary method for detecting ANA uses indirect immunofluorescence (IIF) and anti-centromere antibodies are often confirmed by the IIF staining pattern alone. SSc-specific antigenic targets include anticentromere, anti-Scl-70 (which are commonly available), anti-RNA polymerase (I-III), U3-RNP, Th/To and EIF-2B (which are less frequently available specialist-/research-antibodies). Scleroderma overlap syndromes can occur with anti-

RUVBL1/2, U1-RNP, anti-SS-A/Ro60, anti-Ro52, and anti-Ku and anti-PM/Scl.[42] SSc sometimes occurs in the presence of anti-synthetase antibodies such as anti-Jo-1, anti-PL7 and anti-PL12.[43] Commercially available tests to detect SSc-associated antibodies (e.g. by ELISA) can sometimes yield a false positive result and therefore a high index of suspicion should be maintained, and further confirmatory testing requested (e.g. IIF), in patients with possible SSc.[44]

Assessment of digital vascular structure and function

A range of non-invasive methods can be used to assess digital vascular structure and function. Microvascular alterations are central to the early pathogenesis of SSc and many of the later disease complications, including DUs. There is also a strong need to assess the macrovascular system in patients with SSc. Some patients develop a disease-related SSc macroangiopathy, whereas, others develop macroangiopathy related to atherosclerosis[4546] particularly when classical cardiovascular risk factors coexist. Furthermore, involvement of the ulnar artery has been reported to be strongly predictive of future DUs.[47,48]

Nailfold capillaroscopy

Nailfold capillaroscopy is a non-invasive imaging technique which allows the microcirculation to be visualised in *situ* including examination of capillary morphology and architecture. The key importance of performing nailfold capillaroscopy is reflected by the inclusion of capillaroscopy in the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc.[49] Nailfold capillary abnormalities have also been reported to be predictive of future DUs and other manifestations of SSc.[50–53]

Capillaroscopy is performed at the nailfold where the capillaries of the distal row lie parallel (compared to perpendicular) to the surface of the skin, and therefore allows them to be visualised in their entirety. Nailfold capillaroscopy can be performed using a wide range of low- and high-magnification devices. Low-magnification devices[54,55] including the dermatoscope, stereomicroscope and ophthalmoscope allow for a global (wide-field) assessment of the nailfold area. Assessment at low-magnification allows the user to assess whether the nailfold capillaries and architecture are broadly normal or abnormal. In the future, the availability of low-cost, low-magnification USB-microscopes may broaden access

to capillaroscopy. High-magnification (x200-600) videocapillaroscopy is considered the 'gold standard' and allows detailed examination of individual capillaries. Semi-quantitative assessment (e.g. measurement of capillary diameter and numbers) can also be performed and has been proposed as a promising future tool/biomarker to assess disease activity, and possibly as an outcome measure for therapeutic trials of SSc-vasculopathy.[56]

Normal nailfold capillaries (Figure 4) have a homogeneous, 'hair-pin' like appearance with a regular distribution. In SSc-spectrum disorders the 'scleroderma' capillaroscopic pattern (Figure 4) includes enlarged (including 'giant' capillaries), capillary loss ('loop dropout') and microhaemorrhages. Characteristic microvascular alterations can also be identified in other connective tissue diseases, in particular, dermatomyositis (Figure 4). Cutolo proposed classification into the 'early', 'active' and 'late' scleroderma patterns.[57] Initially there are a few giant capillaries and microhaemorrhages ('early'), which subsequently increase in number, with moderate loss and mild disorganisation of capillaries ('active'). Finally, there is severe loss of capillaries with gross disorganisation of the capillary architecture with extensive avascular areas and marked evidence of aberrant neovascularization ('late' changes). The recently externally validated 'fast track' decision algorithm allows individuals with a range of prior capillaroscopic experience to successfully differentiate between abnormal (i.e. scleroderma patterns) from non-scleroderma patterns, with excellent reported reliability.[58]

Microvascular structural abnormalities (as assessed by capillaroscopy) have been reported to be associated with functional microvascular disease (i.e. lower perfusion) in patients with SSc.[59,60] The agreement between objective non-invasive microvascular imaging and patient-reported assessment of digital vascular function is poor and explanations for such findings have not yet been fully elucidated.[61] Future research is indicated including to assess the potential benefit of combining assessment of microvascular structure and function for use as a combined outcome measure in future clinical trials of SSc-vasculopathy.

Laser-based techniques

Laser Doppler imaging (LDI) has been widely used in research to investigate the pathophysiology of RP and SSc.[62,63] LDI and other laser Doppler-based techniques utilise the Doppler phenomenon, in which the wavelength of light changes from interaction with a

moving object, which can be measured. Unlike laser Doppler flowmetry which measures perfusion at a single point, LDI measures blood flow over an area to build a global map of perfusion. LDI has also been used in a number of therapeutic trials to assess treatment response in a laboratory-based setting.[64,65] Laser speckle contrast imaging is an emerging imaging technique which allows constant measurement of perfusion over a large area, with higher spatial and temporal resolution than laser Doppler-based techniques.[66] Recent evidence suggests that laser speckle contrast imaging is a highly reliable method to assess peripheral blood perfusion in patients with SSc and healthy controls.[66,67] Laser speckle flowmetry measures perfusion at a single point and requires further research including to examine the discriminatory capacity (e.g. between primary and secondary RP) of the technique.[68]

Infrared thermography

Infrared thermography uses a camera to measure skin surface temperature which is an indirect measure of tissue perfusion (from small and large blood vessels) (Figure 4).[69] Thermographic assessment has been reported to enable the successful distinction between primary and secondary RP.[69] Patients with RP (compared to healthy controls) often have cooler fingertips than the dorsal aspect of the hands. As below, some thermography protocols include a dynamic assessment including through a 'cold challenge' (Figure 4). The use of infrared thermography has been traditionally limited to specialist centres due to the historical high-cost of thermographic cameras and use of a temperature-controlled laboratory to perform provocation tests. However, the availability of relatively low-cost mobile phone-based thermographic imaging devices may facilitate wider access to infrared thermography used under ambient conditions.[67] In addition, there are significant differences in thermography imaging protocols between centres and internationally agreed protocols/consensus would help facilitate larger multi-centre studies of SSc-vasculopathy and potential future incorporation into routine clinical practice.

Dynamic assessment of microvascular function

A number of previous studies have incorporated some form of local provocation (e.g. local cold exposure or iontophoresis of vasoactive substances), to distinguish between primary and secondary RP.[6170] A subsequent 'rewarming' challenge during thermographic assessment has

also been advocated. For example, Anderson et al[71] reported that a 'distal-dorsal difference' of >1°C at 30°C between the fingertips and the dorsum of the hand differentiated between primary and secondary RP.

Doppler ultrasound

Doppler ultrasound is a useful tool which can identify significant macrovascular disease of the upper and lower limbs.[72] Doppler ultrasound is a relatively simple, non-invasive and reproducible test; however, it does require specialist training to make the necessary measurements.[38,72] The ankle brachial pressure index is an example of Doppler ultrasound and is calculated by the ratio of the systolic blood pressure in the upper and lower limbs, which can indicate the presence of significant lower limb ischaemia.[72] Abnormal colour and power Doppler sonography of the hand have been reported to be associated with past and new DUs in patients with SSc.[73,74]

Angiography

Formal angiography is indicated in the presence of confirmed large vessel pathology including by Doppler ultrasound in order to define the anatomy of the causative vascular lesion/s.[75] Imaging techniques include digital subtraction angiography (DSA), computerised tomography (CT) angiography and magnetic resonance imaging (MRI) angiography. An advantage of CT and MRI angiography is that intra-arterial access is not required; however, endovascular procedures can be performed at the time of DSA.[75] Furthermore, a disadvantage of both CT and MRI angiography is poor visualisation of the distal limb vessels.[75]

Definition and classification of digital ulcers

This is hugely challenging and there is a key need to accurately define and classify SSc-DUs, not only for clinical practice to inform therapeutic decision making, but also to develop new treatments.[676] A number of previous studies have reported that the inter-rater reliability of expert SSc clinicians is poor to moderate at best[77–79], In particular, the inter (between) rater reliability has been very low.[77–79] This is a major concern in the design of multi-centre clinical trials and highlights the need for multiple ulcer assessments to be performed by the same rater. Furthermore, the agreement between individual patients and clinicians is very low, irrespective of the addition of 'real world' clinical contextual information (e.g. the severity of

associated pain and the presence of discharge).[78] Different ulcer definitions have been used in recent multi-centre clinical trials of drug therapies for SSc-DU disease.[80–84] Recent initiatives to develop DU definitions have been undertaken by the auspices of the World Scleroderma Foundation (WSF) and the United Kingdom Scleroderma Study Group.[79,85] Both sets of definitions have included a 'loss of epithelium' and that if ulcer debridement was likely to confirm the presence of a DU, then it should be deemed an ulcer.[79,85] Although both definitions had high levels of intra-rater reliability (0.90 and 0.71, respectively), the inter-rater reliability was significantly higher for the WSF definitions (0.51 and 0.15, respectively)[79,85], although no studies have compared reliability of different methods using the same image bank.

In general, the assessment of DUs in clinical practice and research relies upon the distinction between healed/non healed ulcers and clinician experience-based judgement.[86] The Digital Ulcer Clinical Assessment Score in Systemic Sclerosis (DUCAS) is a proposed clinical score which includes the number of DUs, new digital ulceration, the presence of gangrene, need for surgical approach (above standard of care), infection of the DU, unscheduled hospitalisation for DU, and analgesics needed to control DU pain.[86] Early data supports that the DUCAS has good levels of face, content validity and construct validity, and warrants further investigation for use in clinical practice.[86] In a recent DeSScipher/European Scleroderma Trials and Research group (EUSTAR) survey which included complete responses from 84 centres, three items were considered essential for DU evaluation.[87] These were the number of DU (which were defined as loss of tissue), recurrent DU, and the number of new DU.[87] Furthermore, similar to the previously described study from the DUO registry, 80% of the centres also favoured categorisation of DU into 'episodic', 'recurrent' and 'chronic'.[87]

Another potential approach to assessment could involve the use of ulcer photographs. A recent pilot study demonstrated that it was feasible for patients with SSc to 'monitor' their own lesions by taking photographs with a smartphone camera over an extended period of weeks.[88] Furthermore, computer-assisted digital planimetry has been applied to SSc-DUs with excellent intra- and inter-rater reliability, either by fitting an eclipse to the shape of the ulcer, or by tracing the ulcer exterior by freehand.[89] Whereas, such an approach only measures ulcer surface dimensions, ultrasound also allows deeper measurement (e.g. of depth). Ultrasound

has been used to assess SSc-skin ulcers, including objective measurement of ulcer morphology and extent, and could also provide novel insights into pathogenesis.[90–92] In a pilot study which examined high-frequency ultrasound to assess a range of (fingertip, extensor, and calcinosis-related) DUs, the average width and depth was 6mm and 1mm, respectively, which highlights the potential challenge of assessing ulcers by means of visual inspection alone.[90]

Management

General approach

Patient education is central to management of SSc-RP and DUs and should be delivered as part of a dedicated multi-disciplinary team, including specialist rheumatology nursing. Care should be taken by patients to avoid unnecessary trauma to the digits to prevent potential tissue ulceration, protection against the cold, and avoiding emotional stress. Patients should be counselled, and supported in their efforts, about the importance of smoking cessation because smoking promotes vasoconstriction.[93,94] Smoking has been reported to be associated with more severe digital vascular disease[93] including in relation to the intensity of smoking.[93,94] Patients should seek early medical advice about new and/or worsening ulcers, including potential signs of infection. The development of persistent digital ischaemia should prompt the patient to seek emergency medical advice. As previously described, DUs can be infected (Figure 2) and there should be a low threshold for prescribing appropriate antibiotic therapy. DUs can also be exceptionally painful and therefore sufficient analgesia is required and often requires the introduction of opioid-based analgesia.

Differential diagnosis of critical digital ischaemia

Critical digital ischaemia/gangrene (Figure 2) is a medical emergency which requires prompt assessment and introduction of treatment.[95] This can occur as a result of both SSc-related (e.g. non-inflammatory angiopathy) and non-SSc related causes (e.g. smoking) [96]. Thorough investigation is required because some of these causes are potentially modifiable (e.g. large vessel disease and embolic disease).

Non-pharmacological interventions

Patients should be managed by an expert multi-disciplinary team including (but not limited to) rheumatology specialist nursing, physiotherapy and occupational therapy including education on lifestyle modification and functional adaptions (e.g. keeping warm and protecting the fingers to avoid traumatic ulcers).[97,98] Furthermore, meticulous wound care is mandatory for all ulcers to prevent infection and to minimise further tissue damage/loss.[99] The ulcer wound bed should be closely examined for signs of inflammation/infection, hyper-proliferation around the wound edges, evidence of exposure of the deeper structures (e.g. bone and tendon) and hydration status. For example, if the ulcer is 'wet' then appropriate dressings (e.g. with hydrogel and hydrocolloids) should be selected with an aim to reduce moisture/dry the wound, and vice versa for 'dry' wounds (with alginates and antimicrobials).[41] As previously described, clinicians should actively exclude proximal (large) vessel involvement early in the setting of digital ischaemia including ulcers, as this could potentially be amenable to therapeutic intervention. Non-surgical DU debridement is being performed by some clinicians in rheumatology and can be performed physically ('mechanical') with a scalpel or chemically (e.g. by using autolytic dressings). DU debridement removes non-viable (e.g. necrotic material) and can release pus, both of which can promote ulcer healing. Appropriate local analgesia is essential for successful DU debridement.[100] However, at present there is not strong evidence-base to support debridement in SSc at present, and requires further research. Furthermore, there is significant geographical variation in DU debridement. For example, in a survey which included responses from 137 rheumatologists, the majority (80%) of North American and European responders reported that they never or rarely debrided DUs, compared to 37% of Europeans.[101] Work is currently underway to understand the barriers to DU debridement amongst clinicians in rheumatology. Other non-pharmacological interventions have been trialled include (but are not limited to) hyperbaric oxygen in patients with refractory DU disease.[102,103]

Pharmacological interventions

There a wide range of treatments to prevent and treat (heal) DUs; some of which are also used for RP (Figure 5). It is important to be aware how the pharmacological treatment of DU disease is potentially related to underlying RP. Primary RP usually requires no pharmacological treatment and is managed by general/lifestyle measures (e.g. cold avoidance and keeping warm).[41] Secondary RP is managed by relatively 'mild' oral

vasodilatory drug therapies. Whereas, secondary RP and DU is managed with several different combinations including specific vasoactive therapies (e.g. bosentan). Drug treatments for DU disease should be tailored to the individual as there may be significant overlap/treatment benefit for other vascular-based complications (e.g. pulmonary arterial hypertension). Although a number of drug therapies have been explored (including but not limited to) statins, antioxidants, and anti-platelets/anticoagulation[104–108], in this review we shall focus on the most commonly used drug therapies for SSc-DU disease (and RP).

Vasoactive therapies

Vasoactive therapies attempt to address the underlying factors implicated in the pathogenesis of SSc-DUs (and SSc-RP). Calcium channel blockers are often used first line; however, clinicians are increasingly using phosphodiesterase type-5 inhibitors earlier in the treatment of SSc-associated digital vasculopathy. Vasodilatory side effects are not uncommon with vasoactive therapies (e.g. headaches and lower limb oedema) and are more common in patients in higher doses and potentially drug therapies in combination. Treatment with vasodilator therapy has been reported to be associated with a reduction in the development of DU.[7] In particular, there is some evidence that treatment with vasodilatory therapies (e.g. calcium channel blockers and phosphodiesterase type-5 inhibitors) is associated with approximately 30% reduction in DU development.[82,109] There is also some evidence that PDE5 inhibitors can improve the healing of ulcers[110]; however, for example no difference was observed in a recent placebo-controlled trial of sildenafil (discussed later). Despite a strong therapeutic rationale (including vascular remodelling) for therapies which target the renin angiotensin system (e.g. ACE inhibitors and angiotensin receptor blockers)[111], there is no convincing evidence for SSc-RP or SSc-DU disease. For example, in a multi-centre, randomised, placebo-controlled trial of quinapril which included 210 patients with limited cutaneous SSc or autoimmune RP (RP and a SSc-associated autoantibody), after 2 to 3 years of treatment there was no difference in DU disease, or other vascular complications including RP and pulmonary artery pressure.[81] Bosentan, an endothelin-1 receptor antagonist which is licensed in Europe for DU disease, reduces the number of new DUs, but does not impact DU healing.[80,112] In a double-blind, placebo-controlled trial which included 188 patients with at least one DU, treatment with Bosentan for 20 weeks was associated with a 30% reduction in new DUs, but not DU healing.[80] In contrast, recent clinical trials of Macitentan did not reduce

new DUs over 16 weeks[83] (possibly owing to differences in study populations, prior intervention and study design).[113] Intravenous prostanoids (given over 3 to 5 days) reduce the number of new DUs and fosters ulcer healing.[114–116] Prostanoids are also used in the context of critical digital ischaemia. There are no studies which have specifically assessed combination vasoactive therapies; however, the combination of PDE5 inhibition and endothelin receptor blockade has been reported to be a powerful treatment combination for digital vasculopathy.[117,118]

Other treatments

Surgical intervention is indicated for severe RP and DU disease refractory to medical management.[119] Indications for surgery include (but are not limited to) severe pain (which suggests tissue necrosis), secondarily infected ulcers, and to remove underlying calcinotic material.[119] There is increasing worldwide experience in performing digital (periarterial) sympathectomy and earlier intervention may be beneficial in patients with severe Raynaud's and early digital ischaemia.[120–123] There is also increasing interest in botulinum toxin injection, which promote local arterial vasodilation.[124,125] However, at the present time, the evidence base is limited and further research is needed in this area. For example, in a recent double-blind, placebo-controlled, laboratory-based clinical trial, local injections of botulinum toxin did not significantly improve blood flow to the hands in patients with SSc-RP.[126] Furthermore, although there were improvements in a number of secondary clinical outcomes (e.g. Raynaud's Condition Score), these were of questionable clinical benefit. Autologous fat grafting and stem cell transplant is a novel treatment approach which has also been shown to benefit DU healing.[127–130]

Unmet needs

There are a number of important unmet clinical needs and research priorities. Better approaches to the assessment and treatment of RP and DUs are urgently needed. Treatment of Raynaud's is seldom fully effective[131] and approximately one third of patients with SSc have refractory DU disease, despite advanced vascular therapies. Treatments for RP and DUs can be poorly tolerated due to vasoactive side-effects, and well-tolerated, effective treatments are urgently needed. One approach could be to develop locally-acting vascular approaches to

509 treatment which would likely be well tolerated from the lack of significant/absence of
510 systemic vasodilation.
511
512 A major barrier to drug development programs relates to the suitability of existing outcome
513 measures of efficacy. Significant concerns have been raised about our current methods to
514 assess treatment efficacy in RP, including the Raynaud's Condition Score diary .[132] A key issue
515 is that current outcome measures do not fully capture the complex, multi-faceted patient
516 experience of either RP or DUs [133,134]. A recent multinational qualitative research study
517 identified 7 inter-related themes (and subthemes) of the patient experience of SSc-RP that
518 comprised physical symptoms, emotional impact, triggers and exacerbating factors, constant
519 vigilance and self-management, impact on daily life, uncertainty, and adaptation.[135]
520 International collaborative research is ongoing to develop novel patient reported outcome
521 instruments for both RP and DUs.
522
523 It has been suggested that all DUs could have a potentially treatable ischaemic component
524 and should all be included in DU clinical trials. .[136] Recent clinical trials[80,82,112,137] of drug
525 therapies for SSc-DUs have generally focussed on fingertip DUs, on the premise that such DUs
526 are primarily driven by tissue ischaemia and more likely to benefit from vascular therapies.
527 Recent studies have shown that both fingertip and extensor DUs have a relatively (compared
528 to surrounding non-ulcerated skin) ischaemic core (as assessed by LDI) and with a reduction
529 in ischaemia with ulcer healing.[138,139] In a double-blind, randomised, crossover, placebo-
530 controlled study, the microvessels in the ischaemic DU centre were responsive to topical
531 glyceryl trinitrate with an increase in perfusion, and with a similar effect observed for both
532 fingertip and extensor DUs.[140] In addition, microangiopathic SSc-type capillary abnormalities
533 (e.g. enlargement and neoangiogenesis) have been reported immediately adjacent to the skin
534 surrounding both fingertip and extensor DUs, which could suggest that microangiopathy
535 contributes to the pathogenesis of both.[141] Macrovascular involvement also likely reduces
536 hand perfusion globally and could also promote the development of all types of SSc-DUs.[48]
537
538 Three major challenges complicating the design of RP clinical trials (and practice) are 1) the
539 impact of the weather; 2) the lack of a robust 'target' akin to a 'treat to target' approach in
540 inflammatory arthritis; and 3) the heterogeneity in the natural history of DU healing. In a

recent randomised, placebo-controlled study, the time to DU healing which was the primary end point of the study (hazard ratio of 1.33 and 1.27, respectively) was not reached. The authors speculated that this could potentially be due to the unexpected high healing rate in the placebo group.[82] Furthermore, the contrasting findings of the within-class clinical trials of Bosentan and Macitentan[113], and recent trials of promising treatments such as Selexipag (a non-prostanoid prostacyclin receptor agonist)[142] were disappointing.

Generalised vascular disease is a cardinal feature of SSc and likely to be responsible for the development of many of the organ-based complications associated with the disease. Biomarker studies support the presence of systemic vasculopathy, and autopsy studies have revealed silent lung and kidney vascular involvement.[143] For example, similar nailfold and pulmonary abnormalities, as well as progression of interstitial lung disease, have been reported in SSc.[144,145] DUs have also been reported to be associated with a worse disease course and prognosis including in patients with early disease.[146] In a study from the EUSTAR database, the use of CCBs was associated with a significant decrease in the prevalence (odds ratio of 0.41) of left ventricular ejection fraction <55%.[147] Therefore, confirmation of a unified (generalised) vascular phenotype in SSc could herald the use of vascular acting therapies as disease-modifying agents, in particular in patients with early SSc before the onset of significant skin fibrosis and organ dysfunction. A necessity to such an approach would be the successful case identification of patients with the earliest forms of SSc, likely using RP as the key entry symptom. Patients, including those with RP, are increasingly using mobile health technology to monitor their symptoms, and this can be a powerful method to encourage timely engagement with health care professionals.[148,149]

Conclusions

In conclusion, RP is a cardinal feature of SSc and is usually the first manifestation of the disease, thereby potentially allowing early diagnosis of SSc. Key investigations include the detection of autoantibodies and performing capillaroscopy. Structural and vascular imaging plays a major role in both the diagnosis of disease and managing the peripheral vascular disease complications. DUs are a visible ischaemic manifestation of the SSc-disease process and represents secondary Raynaud's with digital vascular compromise. Digital ischaemia resulting in DUs and gangrene are serious complications which require prompt assessment

and initiation of treatment. Patients should be managed by an expert multi-disciplinary team and first line treatment is non-pharmacological interventions including patient education. Although there are a range of vasodilator treatments to both prevent and treat DUs/RP, a number of patients experience refractory digital vascular disease. There are a number of unmet clinical and research needs relating to RP and DUs including establishing treatment efficacy in clinical trials. However, good progress is being made through international collaborative research. The concept of a unified vascular phenotype coupled with the early diagnosis of SSc, could potentially allow a paradigm shift in which vascular-acting therapies could be judiciously deployed as a means of disease-modification.

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Figure 1: Raynaud's phenomenon. Mobile phone photographs taken of attacks of Raynaud's in a patient with primary Raynaud's phenomenon and established peripheral nerve damage from entrapment neuropathies. There is pallor (index, middle and little fingers) and cyanosis (ring finger) with sparing of the thumb which is suggestive of primary Raynaud's phenomenon.[150]

Figure 2: Digital ulcers and complications in systemic sclerosis. Ischaemic digital ulcers on the fingertip (A) and volar aspect (B) of the digits. Digital ulcers on the extensor aspect (C) of the hands overlying the small joints and calcinosis-related (D) digital ulceration. Infected digital ulcer (E) and critical digital ischaemia (F).

Figure 3: The pathogenesis of systemic sclerosis-related digital ulcers. Proposed schematic illustrating how the major factors could be potentially involved in both ulcer development and healing. Focal ischaemia or trauma promotes loss of tissue integrity and ulceration. As the digital ulcer develops the central core of tissue ischaemia progresses. There is often inflammation/erythema of the surrounding the non-ulcerated skin and the mechanism/implications of this is currently unknown. It could be postulated that this represents increased blood flow from neoangiogenesis and promotes ulcer healing. However, excessive blood flow could also result in a form of reperfusion injury which causes further tissue injury. In addition, Infection is also associated with peri-ulcer inflammation. Over time with ulcer healing the tissue is either restored to normal or there is evidence of persistent digital ischaemic tissue loss. Digital pitting scars can also occur without prior ulceration.

Figure 4: The utility of non-invasive digital microvascular structural and functional imaging in the assessment of CTD-related digital vasculopathy. A, Low-powered (50x) magnification of the nailfold in primary Raynaud's; B, High-magnification (x200) of the same nailfold in A revealed normal-appearance uniformly spaced and sized hairpin capillary loops; C, Low-magnification appearance of nailfold in limited cutaneous systemic sclerosis with visible giant

capillaries; D, Corresponding high-magnification image of the same nailfold in C revealing giant capillaries and capillary drop-out; E & F, Low and high-magnification nailfold capillaroscopic images in dermatomyositis revealing characteristic ramified ('bushy') capillaries; G, Thermal image of the hands of a patient with eosinophilic fasciitis 5 minutes following local cold challenge revealing a healthy-looking preserved positive longitudinal gradient in the early stages of re-warming not consistent with Raynaud's phenomenon; H, Thermal image of the hands 5 minutes following local cold challenge in Raynaud's phenomenon with a negative longitudinal gradient consistent with delayed re-perfusion

Figure 5: Treatment of Raynaud's phenomenon and digital ulcers in systemic sclerosis. Adapted from the Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis.[41] A number of drug therapies are used for the treatment of both RP and digital ulcers in SSc. The potential benefits vs. the risks of adjunctive therapies must be considered on an individual patient basis. For example, anti-platelet therapies and anticoagulation may be potentially hazardous in patients with SSc due to potential gastrointestinal bleeding from gastric antral vascular ectasia, and statins can have adverse muscle effects in patients with SSc-myopathy.

Box 1: Red flags in the setting of Raynaud's phenomenon which suggest the presence of systemic sclerosis.

Cutaneous	Puffy fingers*
	Sclerodactyly and/or proximal skin thickening
	Digital ulcers
	Digital pitting scars
	Telangiectasia
Gastrointestinal	Gastro-oesophageal reflux disease*
	Abnormal oesophageal manometry
	Imaging evidence of gastrointestinal motility abnormalities
Immunological	Positive antinuclear antibody*
	SSc-specific autoantibodies

Vascular	Abnormal capillary morphology

*These suggest the 'very early diagnosis of systemic sclerosis' and is confirmed by either the presence of systemic sclerosis-specific autoantibodies and/or the scleroderma pattern on nailfold capillaroscopy.[39]

Key points

- Vascular injury and Raynaud's phenomenon are the earliest manifestations of systemic sclerosis.
- Patients with Raynaud's phenomenon need careful assessment to identify secondary causes including systemic sclerosis and key investigations include performing capillaroscopy and the detection of autoantibodies.
- Raynaud's and ischaemic complications including digital ulcers are a major cause of disease-related morbidity in systemic sclerosis.
- The definition and assessment of digital ulcers can be very challenging and recent efforts have made progress in this field.
- There are a number of available treatments to both prevent and heal digital ulcers.
- The concept of a unified vascular diagnosis could herald the onset of a potential disease-modifying effect for vascular acting therapies in systemic sclerosis.

Figure 1

Figure 2

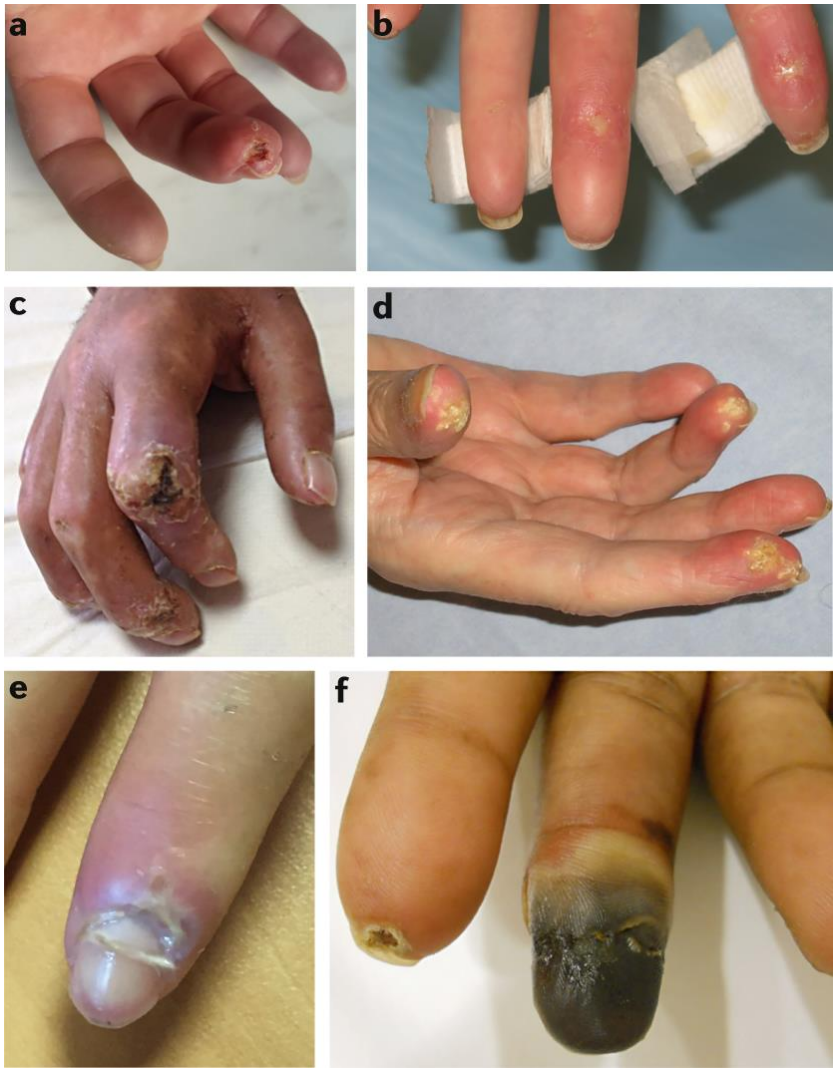

Figure 3

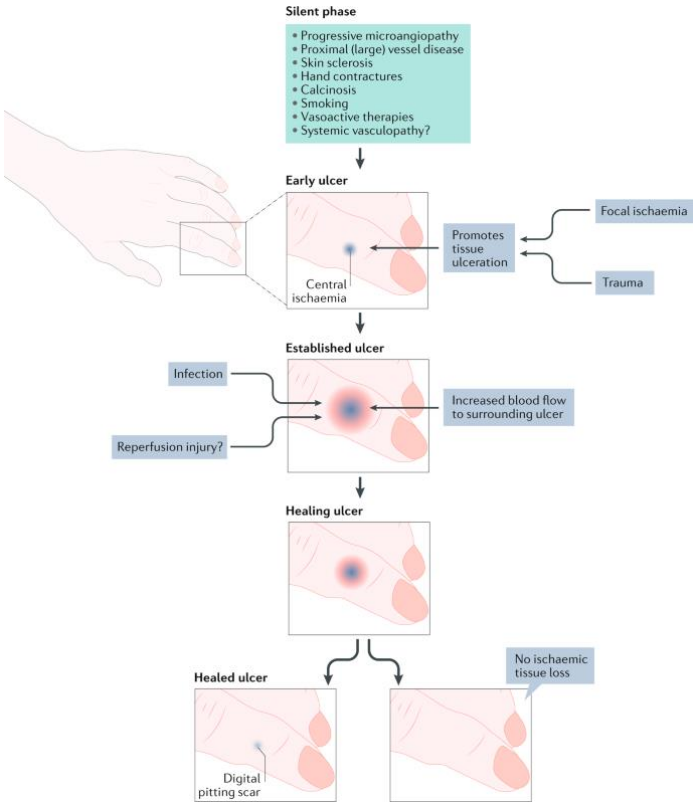

Figure 4