



Citation for published version:

Hughes, M, Allamore, Y, Chung, L, Pauling, JD, Denton, CP & Matucci-Cerinic, M 2020, 'Raynaud phenomenon and digital ulcers in systemic sclerosis', *Nature Reviews Rheumatology*, vol. 16, no. 4, pp. 208-221.
<https://doi.org/10.1038/s41584-020-0386-4>

DOI:

[10.1038/s41584-020-0386-4](https://doi.org/10.1038/s41584-020-0386-4)

Publication date:

2020

Document Version

Peer reviewed version

[Link to publication](#)

University of Bath

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1 Raynaud's Phenomenon and Digital Ulcers in Systemic Sclerosis

2
3 Michael Hughes^{1,2}, Yannick Allanore³, Lorinda Chung⁴, John D Pauling^{5,6}, Christopher P
4 Denton⁷, Marco Matucci-Cerinic⁸

5
6 Author affiliations

- 7 1. Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching
8 Hospitals NHS Foundation Trust, Sheffield, UK.
- 9 2. Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, The
10 University of Manchester, UK.
- 11 3. Department of rheumatology, Cochin Hospital, AP-HP, Paris Descartes University,
12 Paris, France.
- 13 4. Division of Immunology and Rheumatology, Department of Medicine, Stanford
14 University School of Medicine and Palo Alto VA Health Care System, Palo Alto, CA
- 15 5. Department of Pharmacy and Pharmacology, University of Bath, Bath, UK.
- 16 6. Royal National Hospital for Rheumatic Diseases (part of Royal United Hospitals Bath
17 NHS Foundation Trust), Bath, UK
- 18 7. Department of Rheumatology, Royal Free Hospital, University College London,
19 London, UK.
- 20 8. Division of Rheumatology, University of Florence, Florence, Italy.

21
22 Corresponding Author:

23 Dr Michael Hughes BSc (Hons) MBBS MSc MRCP (UK) (Rheumatology) PhD

24 Consultant Rheumatologist

25 Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS
26 Foundation Trust, Sheffield, S10 2JF, UK.

27 Michael.hughes-6@postgrad.manchester.ac.uk

28 ORCID ID: 0000-0003-3361-4909

29 Telephone: +44 (0)114 271 1900

30
31 Word count = 5818

32

33 Competing interests

- 34 • Michael Hughes – has received speaker honoraria from Actelion pharmaceuticals.
- 35 • Yannick Allanore – Yannick Allanore has/had consultancy relationship and/or has
36 received grants from Actelion, Bayer, BMS, Boehringer-Ingelheim, Inventiva, Roche,
37 Sanofi-Aventis, Servier, in the area of systemic sclerosis.
- 38 • Lorinda Chung– Reata—Data Safety Monitoring Board Eicos—Steering Committee
39 BMS—Advisory Board BI—Advisory Board Mitsubishi Tanabe—Consultant.
- 40 • John Pauling – has received speaker’s honoraria and research grant support from
41 Actelion pharmaceuticals. Dr Pauling has undertaken consultancy work for Actelion
42 pharmaceuticals and Boehringer Ingelheim.
- 43 • Christopher Denton – has received research grants from GlaxoSmithKline, CSL
44 Behring, and Inventiva and consulting fees from Roche, Actelion, GlaxoSmithKline,
45 Sanofi, Inventiva, CSL Behring, Boehringer Ingelheim, Leadiant, Galapagos and Bayer.
- 46 • Marco Matucci-Cerinic – speaking honoraria from Actelion and Biogen.

47

48 Abstract

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

64 **Introduction**

65 Systemic sclerosis (SSc) is a complex connective tissue disease which is characterised by
66 autoimmunity, progressive generalised obliterative vasculopathy and widespread aberrant
67 tissue fibrosis.^{1,2} Digital vascular disease (vasculopathy) occurs in virtually all patients with
68 SSc, ranging from symptoms of Raynaud's phenomenon (RP) (Figure 1) to irreversible
69 ischaemic tissue injury causing digital ulcers (DUs) (Figure 2) and sometimes gangrene.
70 Although SSc is a very heterogenous disease, RP is experienced by the majority (>95%) of
71 patients, and is the most common symptom and clinical sign of the disease.^{2,3} Whereas, in
72 primary RP tissue ischaemia is transient/reversible, in secondary RP (in particular SSc-RP)
73 persistent tissue ischaemia can occur resulting in digital ulceration and/or gangrene.
74 However, there are only limited to data to suggest an association between the severity of RP
75 and DUs⁴, which likely reflects the complexity of vascular (and skin involvement) in SSc.

76
77 The purpose of this review is to highlight 1) when to suspect SSc in the setting of RP, including
78 how to assess the patient with Raynaud's to identify 'red flags' indicating potential SSc; 2) the
79 spectrum of RP and DU disease in SSc encompassing relevant pathophysiology, diagnosis and
80 classification, and management. We will also highlight current unmet needs and research
81 priorities in RP and DU disease and discuss the concept of a unified vascular phenotype in
82 which vascular therapy could be a disease modifying strategy.

83 84 **Epidemiology**

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

92
93 DUs are common in patients with SSc and are a major cause of disease-related pain and
94 morbidity.⁶ Approximately half of patients with SSc experience DU with a point prevalence of
95 5 to 10%.⁷⁻¹¹ In a study from the European Scleroderma Trials and Research cohort database,

96 the probability of developing DUs was 70% by the end of the 10-year observation period.¹²
97 Several studies have reported that fingertip DUs have a higher prevalence than extensor
98 ulcers.^{13–15} In contrast, Ennis et al, reported that extensor ulcers had a similar prevalence (of
99 6%) and were as similarly disabling as fingertip DUs.¹¹ Patients often develop ulcers affecting
100 multiple digits simultaneously, including both fingertip and extensor-aspect DUs.¹⁵ Despite
101 the availability of a number of advanced therapies to prevent and treat DUs, around one third
102 of patients with SSc may develop recurrent ulceration.¹⁶

103 104 **Clinical presentation**

105 RP is a highly variable symptom complex which results from aberrant digital perfusion. Digital
106 colour changes (Figure 1) are the cardinal symptom of RP, although other body sites/vascular
107 beds can be affected including the toes, lips, ears, nose and nipples¹⁷ The stereotypical series
108 of colour changes (physiological basis in parentheses) from attacks of RP consists of initial
109 white/pallor (vasoconstriction/occlusion of pre-capillary arterioles), then blue/purple
110 (cyanosis from deoxygenation of sequestered blood), and finally red (post-ischaemic
111 hyperaemia).¹⁷ Digital ischaemia results in significant pain and paraesthesias. In general, the
112 majority of patients with primary RP will develop symptoms by 30 years of age, whereas, after
113 40 it is almost always secondary. SSc patients can identify with distinct patterns of RP over
114 time (that may reflect progression of vasculopathy) with established disease being associated
115 with fewer 'stereotypical' attacks of RP, and more persistent features of tissue ischaemia.¹⁸
116 Cold exposure is an important trigger for attacks of RP. However, most patients with SSc
117 experience symptoms throughout the year, given a lower threshold for cold sensitivity in SSc
118 patients.¹⁹ Another important trigger of attacks is emotional stress, both in primary and
119 secondary RP. A number of classification and diagnostic criteria for RP have been proposed.^{20–}
120 ²⁴ In general, these are based on patient reported episodic digital colour changes in response
121 to cold exposure, most of which have required at least two-colour changes in order to
122 diagnose or classify RP.

123
124 Approximately, 75% of patients with SSc will develop their first DU episode within 5 years of
125 their first non-RP symptom⁷. Moreover, progressive vasculopathy in patients with SSc can
126 progress to critical ischemia and gangrene, which may necessitate digital amputation, and can
127 affect approximately 1.5% of patients per year.²⁵ SSc-DUs are associated with significant

128 pain^{11,26} with higher analgesia requirements²⁷, reduced health related quality of life²⁸ and
129 hand-related disability including negative impact on occupation.^{8,26,29,30} Data from the Digital
130 Ulcers Outcome (DUO) registry identified that patients with ‘chronic’ and ‘recurrent’ DUs had
131 greater rates of impairment in activity including occupation, and need for both paid and
132 unpaid help.¹⁶ In addition, these patients also had the greatest need for interventions
133 including hospitalisation and analgesia.¹⁶ The mean annual cost per patient in the European
134 Union of SSc-DU has been estimated to be €23,619, was higher with complications (€27,309),
135 and approximately 10% as a result of lost work productivity from patients and/or their care
136 givers.³¹ The availability of non-proprietary medications should see this cost fall in the future.
137 SSc-DUs are typically very slow to heal. In an observational study which included 1,614 digital
138 lesions, the mean (minimum and maximum) time to healing for ‘pure’ (ischaemic) DUs was
139 76.2 (7 and 810) days, and for DU derived from calcinosis was 93.6 (30 and 388 days).¹⁴ The
140 DU characteristics associated with a significant delay in ulcer healing included the presence
141 of fibrin, wet or dry necrosis, eschar, exposure of bone and tendon, and gangrene.

142

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

150

151 **Pathophysiology**

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

158

159 In general, DUs which occur on the fingertips are considered to be ischaemic (Figure 3).
160 Whereas, those which occur over the extensor aspects, in particular over the small joints of
161 the hands, are also related to recurrent trauma at exposed sites, and potentially due to
162 increased skin tension (Figure 3). Patients can also develop digital ulceration in relation to
163 underlying subcutaneous calcinosis (Figure 3). The pathogenesis of calcinosis-associated
164 ulceration may differ significantly (e.g. to ischaemic ulcers) and local mechanical and
165 inflammatory phenomena may play a significant role.⁷ Whether SSc-DU can be considered
166 the consequence of 'severe Raynaud's' is debateable but DU are generally considered a
167 manifestation of more advanced vasculopathy. Patient-reported RP severity has been noted
168 to be higher in patients with active DU.⁴ SSc-associated microangiopathy as assessed by
169 capillaroscopy (namely capillary drop-out) is strongly associated with a number of clinical
170 outcomes in SSc including the occurrence of new DU disease.³⁶⁻³⁹ However, relatively little (if
171 anything) is known about the pathophysiology of ulcers which occur at other sites of the
172 hands which are less frequent including at the base of the nail and lateral aspect of the digits.
173 Irrespective of the underlying cause, skin ulcers can result in significant irreversible tissue loss
174 (Figure 3). Lower limb macrovascular involvement is well-recognised, in particular in patients
175 with limited cutaneous SSc and positive anticentromere antibody.^{40,41} Cutaneous ulceration
176 of the lower limbs, in general, has not been as comprehensively studied as the fingers with
177 respect to SSc-DU. The clinical appearances (Figure 4) and aetiopathogenic drivers of lower
178 limb ulceration (e.g. arterial and venous macrovascular disease, lymphatic abnormalities) can
179 be diverse and this is an area that warrants further study.^{42,43}

180

181 **Assessment**

182 Early recognition of SSc-related RP is important to facilitate earlier diagnosis and
183 management of SSc disease-related manifestations. Clinicians should be aware of a number
184 of 'red flags' (Box 1) which are strongly suggestive of secondary causes such as SSc. Important
185 red flags are included in the proposed 'very early diagnosis of SSc' [VEDOSS] criteria that
186 includes RP, puffy fingers and positive antinuclear antibody⁴⁴ and further validation is
187 ongoing. The identification of SSc-specific autoantibodies and/or the SSc pattern on nailfold
188 capillaroscopy strengthens the likelihood of future SSc.⁴⁴ The second objective of assessment
189 is to determine the impact of RP including the development of persistent tissue ischaemia
190 (e.g. DUs).

191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222

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.⁴⁵ In a large prospective study of 586 RP patients who were followed up over 3,197 patient years, 12.6% developed definitive SSc.⁴⁵ 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.⁴⁵

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.⁴⁶ Routine biochemistry (e.g. renal and liver function) and thyroid function can suggest alternative secondary causes of RP.⁴⁶ 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.⁴⁶

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

223 antigenic targets include anticentromere, anti-Scl-70 (which are commonly available), anti-
224 RNA polymerase (I-III), U3-RNP, Th/To and EIF-2B (which are less frequently available
225 specialist-/research-antibodies). Scleroderma overlap syndromes can occur with anti-
226 RUVBL1/2, U1-RNP, anti-SS-A/Ro60, anti-Ro52, and anti-Ku and anti-PM/Scl.⁴⁷ SSc sometimes
227 occurs in the presence of anti-synthetase antibodies such as anti-Jo-1, anti-PL7 and anti-
228 PL12.⁴⁸ Commercially available solid phase assays to detect SSc-associated antibodies (e.g.
229 line blots) can sometimes yield a false positive result and therefore a high index of suspicion
230 should be maintained, and correlation with IIF staining patterns made where applicable (e.g.
231 nucleolar staining for anti-U3 ribonucleoprotein and cytoplasmic staining for anti-synthetase
232 antibodies) and further confirmatory testing requested (e.g. with protein
233 immunoprecipitation) should be considered in patients with possible SSc.⁴⁹

234

235 **Assessment of digital vascular structure and function**

236 A range of non-invasive methods can be used to assess digital vascular structure and function.
237 Microvascular alterations are central to the early pathogenesis of SSc and many of the later
238 disease complications, including DUs. There is also a strong need to assess the macrovascular
239 system in patients with SSc. Some patients develop a disease-related SSc macroangiopathy,
240 whereas, others develop macroangiopathy related to atherosclerosis^{50,51} particularly when
241 classical cardiovascular risk factors coexist. Furthermore, involvement of the ulnar artery has
242 been reported to be strongly predictive of future DUs.^{52,53}

243

244 ***Nailfold capillaroscopy***

245 Nailfold capillaroscopy is a non-invasive imaging technique which allows the microcirculation
246 to be visualised *in situ* including examination of capillary morphology and architecture. The
247 key importance of performing nailfold capillaroscopy is reflected by the inclusion of
248 capillaroscopy in the 2013 American College of Rheumatology/European League Against
249 Rheumatism classification criteria for SSc.⁵⁴ Nailfold capillary abnormalities have also been
250 reported to be predictive of future DUs and other manifestations of SSc.^{36-38,55}

251

252 Capillaroscopy is performed at the nailfold where the capillaries of the distal row lie parallel
253 (compared to perpendicular) to the surface of the skin, and therefore allows them to be
254 visualised in their entirety. Nailfold capillaroscopy can be performed using a wide range of

255 low- and high-magnification devices. Low-magnification devices^{56,57} including the
256 dermatoscope, stereomicroscope and ophthalmoscope allow for a global (wide-field)
257 assessment of the nailfold area. Assessment at low-magnification allows the user to assess
258 whether the nailfold capillaries and architecture are broadly normal or abnormal. In the
259 future, the availability of low-cost, low-magnification USB-microscopes may broaden access
260 to capillaroscopy. High-magnification (x200-600) videocapillaroscopy is considered the 'gold
261 standard' and allows detailed examination of individual capillaries. Semi-quantitative
262 assessment (e.g. measurement of capillary diameter and numbers) can also be performed
263 and has been proposed as a promising future tool/biomarker to assess disease activity, and
264 possibly as an outcome measure for therapeutic trials of SSc-vasculopathy.⁵⁸

265
266 Normal nailfold capillaries (Figure 5) have a homogeneous, 'hair-pin' like appearance with a
267 regular distribution. In SSc-spectrum disorders the 'scleroderma' capillaroscopic pattern
268 (Figure 5) includes enlarged (including 'giant' capillaries), capillary loss ('loop dropout') and
269 microhaemorrhages. Characteristic microvascular alterations can also be identified in other
270 connective tissue diseases, in particular, dermatomyositis (Figure 5). Cutolo proposed
271 classification into the 'early', 'active' and 'late' scleroderma patterns.⁵⁹ Initially there are a
272 few giant capillaries and microhaemorrhages ('early'), which subsequently increase in
273 number, with moderate loss and mild disorganisation of capillaries ('active'). Finally, there is
274 severe loss of capillaries with gross disorganisation of the capillary architecture with extensive
275 avascular areas and marked evidence of aberrant neovascularization ('late' changes). The
276 recently externally validated 'fast track' decision algorithm allows individuals with a range of
277 prior capillaroscopic experience to successfully differentiate between abnormal (i.e.
278 scleroderma patterns) from non-scleroderma patterns, with excellent reported reliability.⁶⁰

279
280 Microvascular structural abnormalities (as assessed by capillaroscopy) have been reported to
281 be associated with functional microvascular disease (i.e. lower perfusion) in patients with
282 SSc.^{61,62} The agreement between objective non-invasive microvascular imaging and patient-
283 reported assessment of digital vascular function is poor and explanations for such findings
284 have not yet been fully elucidated.⁶³ Future research is indicated including to assess the
285 potential benefit of combining assessment of microvascular structure and function for use as
286 a combined outcome measure in future clinical trials of SSc-vasculopathy.

287

288 ***Laser-based techniques***

289 Laser Doppler imaging (LDI) has been widely used in research to investigate the
290 pathophysiology of RP and SSc.^{64,65} LDI and other laser Doppler-based techniques utilise the
291 Doppler phenomenon, in which the wavelength of light changes from interaction with a
292 moving object, which can be measured. Unlike laser Doppler flowmetry which measures
293 perfusion at a single point, LDI measures blood flow over an area to build a global map of
294 perfusion. LDI has also been used in a number of therapeutic trials to assess treatment
295 response in a laboratory-based setting.^{66,67} Laser speckle contrast imaging is an emerging
296 imaging technique which allows constant measurement of perfusion over a large area, with
297 higher spatial and temporal resolution than laser Doppler-based techniques.⁶⁸ Recent
298 evidence suggests that laser speckle contrast imaging is a highly reliable method to assess
299 peripheral blood perfusion in patients with SSc and healthy controls.^{68,69} Laser speckle
300 flowmetry measures perfusion at a single point and requires further research including to
301 examine the discriminatory capacity (e.g. between primary and secondary RP) of the
302 technique.⁷⁰

303

304 ***Infrared thermography***

305 Infrared thermography uses a camera to measure skin surface temperature which is an
306 indirect measure of tissue perfusion (from small and large blood vessels) (Figure 5).⁷¹
307 Thermographic assessment has been reported to enable the successful distinction between
308 primary and secondary RP.⁷¹ Patients with RP (compared to healthy controls) often have
309 cooler fingertips than the dorsal aspect of the hands. As below, some thermography protocols
310 include a dynamic assessment including through a 'cold challenge' (Figure 5). The use of
311 infrared thermography has been traditionally limited to specialist centres due to the historical
312 high-cost of thermographic cameras and use of a temperature-controlled laboratory to
313 perform provocation tests. However, the availability of relatively low-cost mobile phone-
314 based thermographic imaging devices may facilitate wider access to infrared thermography
315 used under ambient conditions.⁶⁹ In addition, there are significant differences in
316 thermography imaging protocols between centres and internationally agreed
317 protocols/consensus would help facilitate larger multi-centre studies of SSc-vasculopathy and
318 potential future incorporation into routine clinical practice.

319

320 ***Dynamic assessment of microvascular function***

321 A number of previous studies have incorporated some form of local provocation (e.g. local
322 cold exposure or iontophoresis of vasoactive substances), to distinguish between primary and
323 secondary RP.^{63,72} A subsequent 'rewarming' challenge during thermographic assessment has
324 also been advocated. For example, Anderson et al⁷³ reported that a 'distal-dorsal difference'
325 of >1°C at 30°C between the fingertips and the dorsum of the hand differentiated between
326 primary and secondary RP.

327

328 ***Doppler ultrasound***

329 Doppler ultrasound is a useful tool which can identify significant macrovascular disease of the
330 upper and lower limbs.⁷⁴ Doppler ultrasound is a relatively simple, non-invasive and
331 reproducible test; however, it does require specialist training to make the necessary
332 measurements.^{41,74} The ankle brachial pressure index is an example of Doppler ultrasound
333 and is calculated by the ratio of the systolic blood pressure in the upper and lower limbs,
334 which can indicate the presence of significant lower limb ischaemia.⁷⁴ Abnormal colour and
335 power Doppler sonography of the hand have been reported to be associated with past and
336 new DUs in patients with SSc.^{75,76}

337

338 ***Angiography***

339 Formal angiography is indicated in the presence of confirmed large vessel pathology including
340 by Doppler ultrasound in order to define the anatomy of the causative vascular lesion/s.⁷⁷
341 Imaging techniques include digital subtraction angiography (DSA), computerised tomography
342 (CT) angiography and magnetic resonance imaging (MRI) angiography. An advantage of CT
343 and MRI angiography is that intra-arterial access is not required; however, endovascular
344 procedures can be performed at the time of DSA.⁷⁷ Furthermore, a disadvantage of both CT
345 and MRI angiography is poor visualisation of the distal limb vessels.⁷⁷

346

347 **Definition and classification of digital ulcers**

348 This is hugely challenging and there is a key need to accurately define and classify SSc-DUs,
349 not only for clinical practice to inform therapeutic decision making, but also to develop new
350 treatments.^{67,8} A number of previous studies have reported that the inter-rater reliability of

351 expert SSc clinicians is poor to moderate at best⁷⁹⁻⁸¹, In particular, the inter (between) rater
352 reliability has been very low.⁷⁹⁻⁸¹ This is a major concern in the design of multi-centre clinical
353 trials and highlights the need for multiple ulcer assessments to be performed by the same
354 rater. Furthermore, the agreement between individual patients and clinicians is very low,
355 irrespective of the addition of 'real world' clinical contextual information (e.g. the severity of
356 associated pain and the presence of discharge).⁸⁰ Different ulcer definitions have been used
357 in recent multi-centre clinical trials of drug therapies for SSc-DU disease.⁸²⁻⁸⁶ Recent initiatives
358 to develop DU definitions have been undertaken by the auspices of the World Scleroderma
359 Foundation (WSF) and the United Kingdom Scleroderma Study Group.^{81,87} Both sets of
360 definitions have included a 'loss of epithelium' and that if ulcer debridement was likely to
361 confirm the presence of a DU, then it should be deemed an ulcer.^{81,87} Although both
362 definitions had high levels of intra-rater reliability (0.90 and 0.71, respectively), the inter-rater
363 reliability was significantly higher for the WSF definitions (0.51 and 0.15, respectively)^{81,87},
364 although no studies have compared reliability of different methods using the same image
365 bank.

366

367 In general, the assessment of DUs in clinical practice and research relies upon the distinction
368 between healed/non healed ulcers and clinician experience-based judgement.⁸⁸ The Digital
369 Ulcer Clinical Assessment Score in Systemic Sclerosis (DUCAS) is a proposed clinical score
370 which includes the number of DUs, new digital ulceration, the presence of gangrene, need for
371 surgical approach (above standard of care), infection of the DU, unscheduled hospitalisation
372 for DU, and analgesics needed to control DU pain.⁸⁸ Early data supports that the DUCAS has
373 good levels of face, content validity and construct validity, and warrants further investigation
374 for use in clinical practice.⁸⁸ In a recent DeSSciper/European Scleroderma Trials and
375 Research group (EUSTAR) survey which included complete responses from 84 centres, three
376 items were considered essential for DU evaluation.⁸⁹ These were the number of DU (which
377 were defined as loss of tissue), recurrent DU, and the number of new DU.⁸⁹ Furthermore,
378 similar to the previously described study from the DUO registry, 80% of the centres also
379 favoured categorisation of DU into 'episodic', 'recurrent' and 'chronic'.⁸⁹

380

381 Another potential approach to assessment could involve the use of ulcer photographs. A
382 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.⁹⁰ 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.⁹¹ 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.^{92–94} 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.⁹²

394

395 **Management**

396 **General approach**

397 Patient education is central to management of SSc-RP and DUs and should be delivered as
398 part of a dedicated multi-disciplinary team, including specialist rheumatology nursing. Care
399 should be taken by patients to avoid unnecessary trauma to the digits to prevent potential
400 tissue ulceration, protection against the cold, and avoiding emotional stress. Patients should
401 be counselled, and supported in their efforts, about the importance of smoking cessation
402 because smoking promotes vasoconstriction.^{95,96} Smoking has been reported to be associated
403 with more severe digital vascular disease⁹⁵ including in relation to the intensity of
404 smoking.^{95,96} Patients should seek early medical advice about new and/or worsening ulcers,
405 including potential signs of infection. The development of persistent digital ischaemia should
406 prompt the patient to seek emergency medical advice. As previously described, DUs can be
407 infected (Figure 2) and there should be a low threshold for prescribing appropriate antibiotic
408 therapy. DUs can also be exceptionally painful and therefore sufficient analgesia is required
409 and often requires the introduction of opioid-based analgesia.

410

411 **Differential diagnosis of critical digital ischaemia**

412 Critical digital ischaemia/gangrene (Figure 2) is a medical emergency which requires prompt
413 assessment and introduction of treatment.⁹⁷ This can occur as a result of both SSc-related
414 (e.g. non-inflammatory angiopathy) and non-SSc related causes (e.g. smoking)⁹⁸. Thorough

415 investigation is required because some of these causes are potentially modifiable (e.g. large
416 vessel disease and embolic disease).

417

418 **Non-pharmacological interventions**

419 Patients should be managed by an expert multi-disciplinary team including (but not limited
420 to) rheumatology specialist nursing, physiotherapy and occupational therapy including
421 education on lifestyle modification and functional adaptations (e.g. keeping warm and
422 protecting the fingers to avoid traumatic ulcers).^{99,100} Furthermore, meticulous wound care is
423 mandatory for all ulcers to prevent infection and to minimise further tissue damage/loss.¹⁰¹
424 The ulcer wound bed should be closely examined for signs of inflammation/infection, hyper-
425 proliferation around the wound edges, evidence of exposure of the deeper structures (e.g.
426 bone and tendon) and hydration status. For example, if the ulcer is 'wet' then appropriate
427 dressings (e.g. with hydrogel and hydrocolloids) should be selected with an aim to reduce
428 moisture/dry the wound, and vice versa for 'dry' wounds (with alginates and
429 antimicrobials).⁴⁶ As previously described, clinicians should actively exclude proximal (large)
430 vessel involvement early in the setting of digital ischaemia including ulcers, as this could
431 potentially be amenable to therapeutic intervention. Non-surgical DU debridement is being
432 performed by some clinicians in rheumatology and can be performed physically
433 ('mechanical') with a scalpel or chemically (e.g. by using autolytic dressings). DU debridement
434 removes non-viable (e.g. necrotic material) and can release pus, both of which can promote
435 ulcer healing. Appropriate local analgesia is essential for successful DU debridement.¹⁰²
436 However, at present there is not strong evidence-base to support debridement in SSc at
437 present, and requires further research. Furthermore, there is significant geographical
438 variation in DU debridement. For example, in a survey which included responses from 137
439 rheumatologists, the majority (80%) of North American and European responders reported
440 that they never or rarely debrided DUs, compared to 37% of Europeans.¹⁰³ Work is currently
441 underway to understand the barriers to DU debridement amongst clinicians in rheumatology.
442 Other non-pharmacological interventions have been trialled include (but are not limited to)
443 hyperbaric oxygen in patients with refractory DU disease.^{104,105}

444

445 **Pharmacological interventions**

446 There a wide range of treatments to prevent and treat (heal) DUs; some of which are also
447 used for RP (Figure 6). It is important to be aware how the pharmacological treatment of DU
448 disease is potentially related to underlying RP. Primary RP usually requires no
449 pharmacological treatment and is managed by general/lifestyle measures (e.g. cold
450 avoidance and keeping warm).⁴⁶ Secondary RP is managed by relatively 'mild' oral
451 vasodilatory drug therapies. Whereas, secondary RP and DU is managed with several different
452 combinations including specific vasoactive therapies (e.g. bosentan). Drug treatments for DU
453 disease should be tailored to the individual as there may be significant overlap/treatment
454 benefit for other vascular-based complications (e.g. pulmonary arterial hypertension).
455 Although a number of drug therapies have been explored (including but not limited to)
456 statins, antioxidants, and anti-platelets/anticoagulation¹⁰⁶⁻¹¹⁰, in this review we shall focus on
457 the most commonly used drug therapies for SSc-DU disease (and RP).

458

459 ***Vasoactive therapies***

460 Vasoactive therapies attempt to address the underlying factors implicated in the
461 pathogenesis of SSc-DUs (and SSc-RP). Calcium channel blockers (CCBs) are often used first
462 line although, although clinicians are increasingly using phosphodiesterase type-5 (PDE5)
463 inhibitors earlier in the treatment of SSc-associated digital vasculopathy, commonly in
464 combination with CCBs. Vasodilatory side effects are not uncommon with vasoactive
465 therapies (e.g. headaches and lower limb oedema) and are more common in patients in
466 higher doses and potentially drug therapies in combination. Treatment with vasodilator
467 therapy has been reported to be associated with a reduction in the development of DU.⁷ In
468 particular, there is some evidence that treatment with vasodilatory therapies (e.g. CCBs and
469 PDE5 inhibitors) is associated with approximately 30% reduction in DU development.^{84,111}
470 There is also some evidence that PDE5 inhibitors can improve the healing of ulcers¹¹²;
471 however, for example no difference was observed in a recent placebo-controlled trial of
472 sildenafil (discussed later). Despite a strong therapeutic rationale (including vascular
473 remodelling) for therapies which target the renin angiotensin system (e.g. ACE inhibitors and
474 angiotensin receptor blockers)¹¹³, there is no convincing evidence for SSc-RP or SSc-DU
475 disease. For example, in a multi-centre, randomised, placebo-controlled trial of quinapril
476 which included 210 patients with limited cutaneous SSc or autoimmune RP (RP and a SSc-
477 associated autoantibody), after 2 to 3 years of treatment there was no difference in DU

478 disease, or other vascular complications including RP and pulmonary artery pressure.⁸³
479 Bosentan, an endothelin-1 receptor antagonist which is licensed in Europe for DU disease,
480 reduces the number of new DUs, but does not impact DU healing.^{82,114} In a double-blind,
481 placebo-controlled trial which included 188 patients with at least one DU, treatment with
482 Bosentan for 20 weeks was associated with a 30% reduction in new DUs, but not DU healing.⁸²
483 In contrast, recent clinical trials of Macitentan did not reduce new DUs over 16 weeks⁸⁵
484 (possibly owing to differences in study populations, prior intervention and study design).¹¹⁵
485 Intravenous prostanoids (given over 3 to 5 days) reduce the number of new DUs and fosters
486 ulcer healing.^{116–118} Prostanoids are also used in the context of critical digital ischaemia. There
487 are no studies which have specifically assessed combination vasoactive therapies; however,
488 the combination of PDE5 inhibition and endothelin receptor blockade has been reported to
489 be a powerful treatment combination for digital vasculopathy.^{119,120}

490

491 **Other treatments**

492 Surgical intervention is indicated for severe RP and DU disease refractory to medical
493 management.¹²¹ Indications for surgery include (but are not limited to) severe pain (which
494 suggests tissue necrosis), secondarily infected ulcers, and to remove underlying calcinotic
495 material.¹²¹ There is increasing worldwide experience in performing digital (periarterial)
496 sympathectomy and earlier intervention may be beneficial in patients with severe Raynaud's
497 and early digital ischaemia.^{122–125} There is also increasing interest in botulinum toxin injection,
498 which promote local arterial vasodilation.^{126,127} However, at the present time, the evidence
499 base is limited and further research is needed in this area. For example, in a recent double-
500 blind, placebo-controlled, laboratory-based clinical trial, local injections of botulinum toxin
501 did not significantly improve blood flow to the hands in patients with SSc-RP.¹²⁸ Furthermore,
502 although there were improvements in a number of secondary clinical outcomes (e.g.
503 Raynaud's Condition Score), these were of questionable clinical benefit. Autologous fat
504 grafting and stem cell transplant is a novel treatment approach which has also been shown
505 to benefit DU healing.^{129–132}

506

507 **Unmet needs**

508 There are a number of important unmet clinical needs and research priorities. Better
509 approaches to the assessment and treatment of RP and DUs are urgently needed. Treatment

510 of Raynaud's is seldom fully effective¹³³ and approximately one third of patients with SSc have
511 refractory DU disease, despite advanced vascular therapies. Treatments for RP and DUs can
512 be poorly tolerated due to vasoactive side-effects, and well-tolerated, effective treatments
513 are urgently needed. One approach could be to develop locally-acting vascular approaches to
514 treatment which would likely be well tolerated from the lack of significant/absence of
515 systemic vasodilation.

516

517 A major barrier to drug development programs relates to the suitability of existing outcome
518 measures of efficacy. Significant concerns have been raised about our current methods to
519 assess treatment efficacy in RP, including the Raynaud's Condition Score diary.¹³⁴ A key issue
520 is that current outcome measures do not fully capture the complex, multi-faceted patient
521 experience of either RP or DUs^{135,136}. A recent multinational qualitative research study
522 identified 7 inter-related themes (and subthemes) of the patient experience of SSc-RP that
523 comprised physical symptoms, emotional impact, triggers and exacerbating factors, constant
524 vigilance and self-management, impact on daily life, uncertainty, and adaptation.¹³⁷
525 International collaborative research is ongoing to develop novel patient reported outcome
526 instruments for both RP and DUs.

527

528 It has been suggested that all DUs could have a potentially treatable ischaemic component
529 and should all be included in DU clinical trials.¹³⁸ Recent clinical trials^{82,84,114,139} of drug
530 therapies for SSc-DUs have generally focussed on fingertip DUs, on the premise that such DUs
531 are primarily driven by tissue ischaemia and more likely to benefit from vascular therapies.
532 Recent studies have shown that both fingertip and extensor DUs have a relatively (compared
533 to surrounding non-ulcerated skin) ischaemic core (as assessed by LDI) and with a reduction
534 in ischaemia with ulcer healing.^{140,141} In a double-blind, randomised, crossover, placebo-
535 controlled study, the microvessels in the ischaemic DU centre were responsive to topical
536 glyceryl trinitrate with an increase in perfusion, and with a similar effect observed for both
537 fingertip and extensor DUs.¹⁴² In addition, microangiopathic SSc-type capillary abnormalities
538 (e.g. enlargement and neoangiogenesis) have been reported immediately adjacent to the skin
539 surrounding both fingertip and extensor DUs, which could suggest that microangiopathy
540 contributes to the pathogenesis of both.¹⁴³ Macrovascular involvement also likely reduces
541 hand perfusion globally and could also promote the development of all types of SSc-DUs.⁵³

542

543 Three major challenges complicating the design of RP clinical trials (and practice) are 1) the
544 impact of the weather; 2) the lack of a robust 'target' akin to a 'treat to target' approach in
545 inflammatory arthritis; and 3) the heterogeneity in the natural history of DU healing. In a
546 recent randomised, placebo-controlled study, the time to DU healing which was the primary
547 end point of the study (hazard ratio of 1.33 and 1.27, respectively) was not reached. The
548 authors speculated that this could potentially be due to the unexpected high healing rate in
549 the placebo group.⁸⁴ Furthermore, the contrasting findings of the within-class clinical trials of
550 Bosentan and Macitentan¹¹⁵, and recent trials of promising treatments such as Selexipag (a
551 non-prostanoid prostacyclin receptor agonist)¹⁴⁴ were disappointing.

552

553 Generalised vascular disease is a cardinal feature of SSc and likely to be responsible for the
554 development of many of the organ-based complications associated with the disease.
555 Biomarker studies support the presence of systemic vasculopathy, and autopsy studies have
556 revealed silent lung and kidney vascular involvement.¹⁴⁵ For example, similar nailfold and
557 pulmonary abnormalities, as well as progression of interstitial lung disease, have been
558 reported in SSc.^{146,147} DUs have also been reported to be associated with a worse disease
559 course and prognosis including in patients with early disease.¹⁴⁸ In a study from the EUSTAR
560 database, the use of CCBs was associated with a significant decrease in the prevalence (odds
561 ratio of 0.41) of left ventricular ejection fraction <55%.¹⁴⁹ Therefore, confirmation of a unified
562 (generalised) vascular phenotype in SSc could herald the use of vascular acting therapies as
563 disease-modifying agents, in particular in patients with early SSc before the onset of
564 significant skin fibrosis and organ dysfunction. A necessity to such an approach would be the
565 successful case identification of patients with the earliest forms of SSc, likely using RP as the
566 key entry symptom. Patients, including those with RP, are increasingly using mobile health
567 technology to monitor their symptoms, and this can be a powerful method to encourage
568 timely engagement with health care professionals.^{150,151}

569

570 **Conclusions**

571 In conclusion, RP is a cardinal feature of SSc and is usually the first manifestation of the
572 disease, thereby potentially allowing early diagnosis of SSc. Key investigations include the
573 detection of autoantibodies and performing capillaroscopy. Structural and vascular imaging

574 plays a major role in both the diagnosis of disease and managing the peripheral vascular
575 disease complications. DUs are a visible ischaemic manifestation of the SSc-disease process
576 and represents secondary Raynaud's with digital vascular compromise. Digital ischaemia
577 resulting in DUs and gangrene are serious complications which require prompt assessment
578 and initiation of treatment. Patients should be managed by an expert multi-disciplinary team
579 and first line treatment is non-pharmacological interventions including patient education.
580 Although there are a range of vasodilator treatments to both prevent and treat DUs/RP, a
581 number of patients experience refractory digital vascular disease. There are a number of
582 unmet clinical and research needs relating to RP and DUs including establishing treatment
583 efficacy in clinical trials. However, good progress is being made through international
584 collaborative research. The concept of a unified vascular phenotype coupled with the early
585 diagnosis of SSc, could potentially allow a paradigm shift in which vascular-acting therapies
586 could be judiciously deployed as a means of disease-modification.

587

588 References

- 589 1. Katsumoto, T. R. & Whitfield, M. L. The pathogenesis of systemic sclerosis. *Annu. Rev.*
590 *Pathol.* **6**, 509–37 (2011).
- 591 2. Denton, C. P. & Khanna, D. K. Systemic sclerosis. *Lancet* **390**, 1685–1699 (2017).
- 592 3. Meier, F. M. P. *et al.* Update on the profile of the EUSTAR cohort: an analysis of the
593 EULAR Scleroderma Trials and Research group database. *Ann. Rheum. Dis.* **71**, 1355–
594 60 (2012).
- 595 4. Merkel, P. A. *et al.* Measuring disease activity and functional status in patients with
596 scleroderma and Raynaud's phenomenon. *Arthritis Rheum.* **46**, 2410–20 (2002).
- 597 5. LeRoy, E. C. *et al.* Scleroderma (systemic sclerosis): classification, subsets and
598 pathogenesis. *J. Rheumatol.* **15**, 202–5 (1988).
- 599 6. Hughes, M. & Herrick, A. L. Digital ulcers in systemic sclerosis. *Rheumatology* **56**, 14–
600 25 (2017).
- 601 7. Hachulla, E. *et al.* Natural history of ischemic digital ulcers in systemic sclerosis:
602 Single-center retrospective longitudinal study. *J. Rheumatol.* **34**, 2423–2430 (2007).
- 603 8. Steen, V., Denton, C. P., Pope, J. E. & Matucci-Cerinic, M. Digital ulcers: overt vascular
604 disease in systemic sclerosis. *Rheumatology (Oxford)*. **48 Suppl 3**, iii19–24 (2009).
- 605 9. Tiev, K. P. *et al.* Clinical features of scleroderma patients with or without prior or

- 606 current ischemic digital ulcers: Post-hoc analysis of a nationwide multicenter cohort
607 (ItinérAIR-Sclérodemie). *J. Rheumatol.* **36**, 1470–1476 (2009).
- 608 10. Khimdas, S. *et al.* Associations with digital ulcers in a large cohort of systemic
609 sclerosis: Results from the canadian scleroderma research group registry. *Arthritis*
610 *Care Res.* **63**, 142–149 (2011).
- 611 11. Ennis, H. *et al.* A prospective study of systemic sclerosis-related digital ulcers:
612 prevalence, location, and functional impact. *Scand. J. Rheumatol.* **42**, 483–6 (2013).
- 613 12. Wirz, E. G. *et al.* Incidence and predictors of cutaneous manifestations during the
614 early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR
615 database. *Ann. Rheum. Dis.* **75**, 1285–92 (2015).
- 616 13. Caramaschi, P. *et al.* A score of risk factors associated with ischemic digital ulcers in
617 patients affected by systemic sclerosis treated with iloprost. *Clin. Rheumatol.* **28**,
618 807–13 (2009).
- 619 14. Amanzi, L. *et al.* Digital ulcers in scleroderma: staging, characteristics and sub-setting
620 through observation of 1614 digital lesions. *Rheumatology* **49**, 1374–1382 (2010).
- 621 15. Lambova, S., Batalov, A., Sapundzhiev, L. & Müller-Ladner, U. Digital Ulcers in
622 Systemic Sclerosis - Frequency, Subtype Distribution and Clinical Outcome. *Curr.*
623 *Rheumatol. Rev.* **9**, 268–73 (2013).
- 624 16. Matucci-Cerinic, M. *et al.* Elucidating the burden of recurrent and chronic digital
625 ulcers in systemic sclerosis: long-term results from the DUO Registry. *Ann. Rheum.*
626 *Dis.* **75**, 1770 LP – 1776 (2016).
- 627 17. Pauling, J. D., Hughes, M. & Pope, J. E. Raynaud’s phenomenon - an update on
628 diagnosis, classification and management. *Clin. Rheumatol.* (2019).
- 629 18. Pauling, J. D., Reilly, E., Smith, T. & Frech, T. M. Evolving symptoms of Raynaud’s
630 phenomenon in systemic sclerosis are associated with physician and patient-reported
631 assessments of disease severity. *Arthritis Care Res. (Hoboken)*. (2018).
632 doi:10.1002/acr.23729
- 633 19. Pauling, J. D. J., Reilly, E. E., T, F., Smith, T. & Frech, T. M. Factors influencing
634 Raynaud’s condition score diary outcomes in systemic sclerosis. *J. Rheumatol.*
635 *jrheum.180818* (2019). doi:10.3899/jrheum.180818
- 636 20. LeRoy, E. C. & Medsger, T. A. Raynaud’s phenomenon: a proposal for classification.
637 *Clin. Exp. Rheumatol.* **10**, 485–8 (1992).

- 638 21. Brennan, P. *et al.* Validity and reliability of three methods used in the diagnosis of
639 Raynaud's phenomenon. The UK Scleroderma Study Group. *Br. J. Rheumatol.* **32**,
640 357–61 (1993).
- 641 22. Maricq, H. R. & Weinrich, M. C. Diagnosis of Raynaud's phenomenon assisted by color
642 charts. *J. Rheumatol.* **15**, 454–9 (1988).
- 643 23. Wigley, F. M. Raynaud's Phenomenon. *N. Engl. J. Med.* **347**, 1001–1008 (2002).
- 644 24. Maverakis, E. *et al.* International consensus criteria for the diagnosis of Raynaud's
645 phenomenon. *J. Autoimmun.* **48–49**, 60–5 (2014).
- 646 25. Nihtyanova, S. I., Brough, G. M., Black, C. M. & Denton, C. P. Clinical burden of digital
647 vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann. Rheum. Dis.* **67**,
648 120–3 (2008).
- 649 26. Mouthon, L. *et al.* Ischemic digital ulcers affect hand disability and pain in systemic
650 sclerosis. *J. Rheumatol.* **41**, 1317–23 (2014).
- 651 27. Guillevin, L. *et al.* Functional impairment of systemic scleroderma patients with digital
652 ulcerations: results from the DUO Registry. *Clin. Exp. Rheumatol.* **31**, 71–80 (2013).
- 653 28. Mouthon, L. *et al.* Impact of digital ulcers on disability and health-related quality of
654 life in systemic sclerosis. *Ann. Rheum. Dis.* **69**, 214–217 (2010).
- 655 29. Bérezné, A. *et al.* Impact of systemic sclerosis on occupational and professional
656 activity with attention to patients with digital ulcers. *Arthritis Care Res.* **63**, 277–285
657 (2011).
- 658 30. Brand, M. *et al.* An observational cohort study of patients with newly diagnosed
659 digital ulcer disease secondary to systemic sclerosis registered in the EUSTAR
660 database. *Clin. Exp. Rheumatol.* **33**, S47–54
- 661 31. Cozzi, F. *et al.* The social costs of digital ulcer management in scleroderma patients: an
662 observational Italian pilot study. *Joint. Bone. Spine* **77**, 83–4 (2010).
- 663 32. Giuggioli, D., Manfredi, A., Colaci, M., Lumetti, F. & Ferri, C. Scleroderma digital ulcers
664 complicated by infection with fecal pathogens. *Arthritis Care Res. (Hoboken)*. **64**, 295–
665 7 (2012).
- 666 33. Giuggioli, D., Manfredi, A., Colaci, M., Lumetti, F. & Ferri, C. Osteomyelitis
667 complicating scleroderma digital ulcers. *Clin. Rheumatol.* **32**, 623–7 (2013).
- 668 34. Barsotti, S. *et al.* Is there a role for laser speckle contrast analysis (LASCA) in
669 predicting the outcome of digital ulcers in patients with systemic sclerosis? *Clin.*

- 670 *Rheumatol.* (2019). doi:10.1007/s10067-019-04662-7
- 671 35. Herrick, A. L. The pathogenesis, diagnosis and treatment of Raynaud phenomenon.
672 *Nat. Rev. Rheumatol.* **8**, 469–479 (2012).
- 673 36. Sebastiani, M. *et al.* Capillaroscopic skin ulcer risk index: a new prognostic tool for
674 digital skin ulcer development in systemic sclerosis patients. *Arthritis Rheum.* **61**,
675 688–94 (2009).
- 676 37. Sebastiani, M. *et al.* Predictive role of capillaroscopic skin ulcer risk index in systemic
677 sclerosis: a multicentre validation study. *Ann. Rheum. Dis.* **71**, 67–70 (2012).
- 678 38. Smith, V. *et al.* Do worsening scleroderma capillaroscopic patterns predict future
679 severe organ involvement? a pilot study. *Ann. Rheum. Dis.* **71**, 1636–9 (2012).
- 680 39. Paxton, D. & Pauling, J. D. Does nailfold capillaroscopy help predict future outcomes
681 in systemic sclerosis? A systematic literature review. *Semin. Arthritis Rheum.* **48**, 482–
682 494 (2018).
- 683 40. Wan, M. C., Moore, T., Hollis, S. & Herrick, A. L. Ankle brachial pressure index in
684 systemic sclerosis: influence of disease subtype and antcentromere antibody.
685 *Rheumatology (Oxford)*. **40**, 1102–5 (2001).
- 686 41. Wig, S. *et al.* A longitudinal study of ankle brachial pressure indices in a cohort of
687 patients with systemic sclerosis. *Rheumatology (Oxford)*. **53**, 2009–13 (2014).
- 688 42. MANETTI, M. *et al.* Progressive Loss of Lymphatic Vessels in Skin of Patients with
689 Systemic Sclerosis. *J. Rheumatol.* **38**, 297 LP – 301 (2011).
- 690 43. Blagojevic, J. *et al.* Assessment, Definition, and Classification of Lower Limb Ulcers in
691 Systemic Sclerosis: A Challenge for the Rheumatologist. *J. Rheumatol.* **43**, 592 LP –
692 598 (2016).
- 693 44. Avouac, J. *et al.* Preliminary criteria for the very early diagnosis of systemic sclerosis:
694 results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research
695 Group. *Ann. Rheum. Dis.* **70**, 476–81 (2011).
- 696 45. Koenig, M. *et al.* Autoantibodies and microvascular damage are independent
697 predictive factors for the progression of Raynaud’s phenomenon to systemic
698 sclerosis: A twenty-year prospective study of 586 patients, with validation of
699 proposed criteria for early systemic sclerosis. *Arthritis Rheum.* **58**, 3902–3912 (2008).
- 700 46. Hughes, M. *et al.* Consensus best practice pathway of the UK Scleroderma Study
701 Group: Digital vasculopathy in systemic sclerosis. *Rheumatol.* **54**, 2015–24 (2015).

- 702 47. Flower, V., Pauling, J. D. & Mchugh, N. Autoantibodies in Raynaud's phenomenon. in
703 *Raynaud's Phenomenon: A Guide to Pathogenesis and Treatment* (eds. Wigley, F. M.,
704 Herrick, A. L. & Flavahan, N. A.) 253–266 (Springer Science+Buisness Media, 2015).
- 705 48. Pauling, J. D. *et al.* Presence of anti-eukaryotic initiation factor-2B, anti-RuvBL1/2 and
706 anti-synthetase antibodies in patients with anti-nuclear antibody negative systemic
707 sclerosis. *Rheumatology* **57**, 712–717 (2017).
- 708 49. Ho, K. T. & Reveille, J. D. The clinical relevance of autoantibodies in scleroderma.
709 *Arthritis Res Ther* **5**, 80 (2003).
- 710 50. Ho, M., Veale, D., Eastmond, C., Nuki, G. & Belch, J. Macrovascular disease and
711 systemic sclerosis. *Ann. Rheum. Dis.* **59**, 39–43 (2000).
- 712 51. Au, K. *et al.* Atherosclerosis in systemic sclerosis: a systematic review and meta-
713 analysis. *Arthritis Rheum.* **63**, 2078–90 (2011).
- 714 52. Park, J. H. *et al.* Ulnar artery vasculopathy in systemic sclerosis. *Rheumatol. Int.* **29**,
715 1081–1086 (2009).
- 716 53. Frerix, M., Stegbauer, J., Dragun, D., Kreuter, A. & Weiner, S. M. Ulnar artery
717 occlusion is predictive of digital ulcers in SSc: a duplex sonography study.
718 *Rheumatology (Oxford)*. **51**, 735–42 (2012).
- 719 54. van den Hoogen, F. *et al.* 2013 classification criteria for systemic sclerosis: an
720 American college of rheumatology/European league against rheumatism
721 collaborative initiative. *Ann. Rheum. Dis.* **72**, 1747–55 (2013).
- 722 55. Cutolo, M. *et al.* Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors
723 for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study.
724 *Arthritis Rheumatol. (Hoboken, N.J.)* **68**, 2527–39 (2016).
- 725 56. Baron, M. *et al.* Office capillaroscopy in systemic sclerosis. *Clin. Rheumatol.* **26**, 1268–
726 74 (2007).
- 727 57. Hughes, M. *et al.* A study comparing videocapillaroscopy and dermoscopy in the
728 assessment of nailfold capillaries in patients with systemic sclerosis-spectrum
729 disorders. *Rheumatol.* **54**, 1435–42 (2015).
- 730 58. Mihai, C. *et al.* The emerging application of semi-quantitative and quantitative
731 capillaroscopy in systemic sclerosis. *Microvasc. Res.* **118**, 113–120 (2018).
- 732 59. Cutolo, M., Sulli, A., Pizzorni, C. & Accardo, S. Nailfold videocapillaroscopy assessment
733 of microvascular damage in systemic sclerosis. *J. Rheumatol.* **27**, 155–60 (2000).

- 734 60. Smith, V. *et al.* Fast track algorithm: How to differentiate a “scleroderma pattern”
735 from a “non-scleroderma pattern”. *Autoimmun. Rev.* **18**, 102394 (2019).
- 736 61. Cutolo, M. *et al.* Peripheral blood perfusion correlates with microvascular
737 abnormalities in systemic sclerosis: a laser-Doppler and nailfold videocapillaroscopy
738 study. *J. Rheumatol.* **37**, 1174–80 (2010).
- 739 62. Ruaro, B. *et al.* Correlations between skin blood perfusion values and nailfold
740 capillaroscopy scores in systemic sclerosis patients. *Microvasc. Res.* **105**, 119–24
741 (2016).
- 742 63. Pauling, J. D., Shipley, J. A., Hart, D. J., McGrogan, A. & McHugh, N. J. Use of Laser
743 Speckle Contrast Imaging to Assess Digital Microvascular Function in Primary Raynaud
744 Phenomenon and Systemic Sclerosis: A Comparison Using the Raynaud Condition
745 Score Diary. *J. Rheumatol.* **42**, 1163–8 (2015).
- 746 64. Anderson, M. E., Moore, T. L., Lunt, M. & Herrick, A. L. Digital iontophoresis of
747 vasoactive substances as measured by laser Doppler imaging--a non-invasive
748 technique by which to measure microvascular dysfunction in Raynaud’s
749 phenomenon. *Rheumatology (Oxford)*. **43**, 986–91 (2004).
- 750 65. Gunawardena, H., Harris, N. D., Carmichael, C. & McHugh, N. J. Maximum blood flow
751 and microvascular regulatory responses in systemic sclerosis. *Rheumatology* **46**,
752 1079–1082 (2007).
- 753 66. Herrick, A. L. *et al.* A double-blind, randomized, placebo-controlled crossover trial of
754 the α 2C-adrenoceptor antagonist ORM-12741 for prevention of cold-induced
755 vasospasm in patients with systemic sclerosis. *Rheumatology (Oxford)*. **53**, 948–52
756 (2014).
- 757 67. Hummers, L. K. *et al.* A multi-centre, blinded, randomised, placebo-controlled,
758 laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine,
759 in patients with Raynaud phenomenon. *Ann. Rheum. Dis.* **72**, 1962–7 (2013).
- 760 68. Cutolo, M. *et al.* Is laser speckle contrast analysis (LASCA) the new kid on the block in
761 systemic sclerosis? A systematic literature review and pilot study to evaluate
762 reliability of LASCA to measure peripheral blood perfusion in scleroderma patients.
763 *Autoimmun. Rev.* **17**, 775–780 (2018).
- 764 69. Wilkinson, J. D. *et al.* A Multicenter Study of the Validity and Reliability of Responses
765 to Hand Cold Challenge as Measured by Laser Speckle Contrast Imaging and

- 766 Thermography: Outcome Measures for Systemic Sclerosis-Related Raynaud's
767 Phenomenon. *Arthritis Rheumatol. (Hoboken, N.J.)* **70**, 903–911 (2018).
- 768 70. Melsens, K. *et al.* The preliminary validation of laser Doppler flowmetry in systemic
769 sclerosis in accordance with the OMERACT filter: A systematic review. *Semin. Arthritis*
770 *Rheum.* (2019). doi:<https://doi.org/10.1016/j.semarthrit.2019.08.007>
- 771 71. Dinsdale, G. & Herrick, A. L. Vascular diagnostics for Raynaud's phenomenon. *J. Vasc.*
772 *Diagnostics* **2**, 127–139 (2014).
- 773 72. Pauling, J. D., Flower, V., Shipley, J. A., Harris, N. D. & McHugh, N. J. Influence of the
774 cold challenge on the discriminatory capacity of the digital distal-dorsal difference in
775 the thermographic assessment of Raynaud's phenomenon. *Microvasc. Res.* **82**, 364–8
776 (2011).
- 777 73. Anderson, M. E., Moore, T. L., Lunt, M. & Herrick, A. L. The 'distal-dorsal difference': a
778 thermographic parameter by which to differentiate between primary and secondary
779 Raynaud's phenomenon. *Rheumatology (Oxford)*. **46**, 533–8 (2007).
- 780 74. Pauling, J. & Murray, A. Non-invasive methods of assessing Raynaud's phenomenon.
781 in *Raynaud's Phenomenon* (eds. Wigley, F. M., Herrick, A. L. & Flavahan, N. A.) 199–
782 242 (Springer Science+Buisness Media, 2015).
- 783 75. Lüders, S. *et al.* Detection of severe digital vasculopathy in systemic sclerosis by
784 colour Doppler sonography is associated with digital ulcers. *Rheumatology* **56**, 1865–
785 1873 (2017).
- 786 76. Lescoat, A. *et al.* Vascular Evaluation of the Hand by Power Doppler Ultrasonography
787 and New Predictive Markers of Ischemic Digital Ulcers in Systemic Sclerosis: Results of
788 a Prospective Pilot Study. *Arthritis Care Res. (Hoboken)*. **69**, 543–551 (2017).
- 789 77. Allanore, Y., Drappe, J.-L. & Reifsnyder, T. Angiography. in *Raynaud's Phenomenon: A*
790 *Guide to Pathogenesis and Treatment* (eds. Wigley, F. M., Herrick, A. L. & Flavahan, N.
791 A.) 243–252 (Springer Science+Buisness Media, 2015).
- 792 78. Li, W. & Frech, T. M. The Critical Need for Accurately Defining Digital Ulcers in
793 Scleroderma. *J. Scleroderma Relat. Disord.* **2**, 69–71 (2017).
- 794 79. Herrick, A. L. *et al.* Lack of agreement between rheumatologists in defining digital
795 ulceration in systemic sclerosis. *Arthritis Rheum.* **60**, 878–82 (2009).
- 796 80. Hughes, M. *et al.* Does the Clinical Context Improve the Reliability of Rheumatologists
797 Grading Digital Ulcers in Systemic Sclerosis? *Arthritis Care Res. (Hoboken)*. **68**, 1340–5

- 798 (2016).
- 799 81. Hughes, M. *et al.* Reliability of digital ulcer definitions as proposed by the UK
800 Scleroderma Study Group: A challenge for clinical trial design. *J. Scleroderma Relat.*
801 *Disord.* (2018). doi:10.1177/2397198318764796
- 802 82. Matucci-Cerinic, M. *et al.* Bosentan treatment of digital ulcers related to systemic
803 sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled
804 trial. *Ann. Rheum. Dis.* **70**, 32–8 (2011).
- 805 83. Gliddon, A. E. *et al.* Prevention of vascular damage in scleroderma and autoimmune
806 Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-
807 controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis*
808 *Rheum.* **56**, 3837–46 (2007).
- 809 84. Hachulla, E. *et al.* Efficacy of sildenafil on ischaemic digital ulcer healing in systemic
810 sclerosis: the placebo-controlled SEDUCE study. *Ann. Rheum. Dis.* **75**, 1009–15 (2016).
- 811 85. Khanna, D. *et al.* Effect of Macitentan on the Development of New Ischemic Digital
812 Ulcers in Patients With Systemic Sclerosis: DUAL-1 and DUAL-2 Randomized Clinical
813 Trials. *JAMA* **315**, 1975–88 (2016).
- 814 86. Seibold, J. R. *et al.* Digital ulcers in SSc treated with oral treprostinil: a randomized,
815 double-blind, placebo-controlled study with open-label follow-up. *J. Scleroderma*
816 *Relat. Disord.* **2**, 42–49 (2017).
- 817 87. Suliman, Y. A. *et al.* Defining Skin Ulcers in Systemic Sclerosis: Systematic Literature
818 Review and Proposed World Scleroderma Foundation (WSF) Definition. *J.*
819 *Scleroderma Relat. Disord.* **2**, 115–120 (2017).
- 820 88. Bruni, C. *et al.* Preliminary Validation of the Digital Ulcer Clinical Assessment Score in
821 Systemic Sclerosis. *J. Rheumatol.* **46**, 603 LP – 608 (2019).
- 822 89. Blagojevic, J. *et al.* Classification, categorization and essential items for digital ulcer
823 evaluation in systemic sclerosis: a DeSScipher/European Scleroderma Trials and
824 Research group (EUSTAR) survey. *Arthritis Res. Ther.* **21**, 35 (2019).
- 825 90. Dinsdale, G. *et al.* Tracking digital ulcers in systemic sclerosis: a feasibility study
826 assessing lesion area in patient-recorded smartphone photographs. *Ann. Rheum. Dis.*
827 **77**, 1382 LP – 1384 (2018).
- 828 91. Simpson, V., Hughes, M., Wilkinson, J., Herrick, A. L. & Dinsdale, G. Quantifying digital
829 ulcers in systemic sclerosis: Reliability of digital planimetry in measuring lesion size.

- 830 *Arthritis Care Res. (Hoboken)*. (2017). doi:10.1002/acr.23300
- 831 92. Hughes, M. *et al.* A pilot study using high-frequency ultrasound to measure digital
832 ulcers: a possible outcome measure in systemic sclerosis clinical trials? *Clin. Exp.*
833 *Rheumatol.* **35 Suppl 1**, 218–219 (2017).
- 834 93. Suliman, Y. A. *et al.* Ultrasound characterization of cutaneous ulcers in systemic
835 sclerosis. *Clin. Rheumatol.* (2018). doi:10.1007/s10067-018-3986-5
- 836 94. Hughes, M. Response to ‘Ultrasound characterization of cutaneous ulcers in systemic
837 sclerosis’. *Clin. Rheumatol.* (2018). doi:10.1007/s10067-018-4099-x
- 838 95. Harrison, B. J., Silman, A. J., Hider, S. L. & Herrick, A. L. Cigarette smoking as a
839 significant risk factor for digital vascular disease in patients with systemic sclerosis.
840 *Arthritis Rheum.* **46**, 3312–6 (2002).
- 841 96. Jaeger, V. K. *et al.* Brief Report: Smoking in Systemic Sclerosis: A Longitudinal
842 European Scleroderma Trials and Research Group Study. *Arthritis Rheumatol.* **70**,
843 1829–1834 (2018).
- 844 97. Sharp, C. A., Akram, Q., Hughes, M., Muir, L. & Herrick, A. L. Differential diagnosis of
845 critical digital ischemia in systemic sclerosis: Report of five cases and review of the
846 literature. *Semin. Arthritis Rheum.* **46**, 209–16 (2016).
- 847 98. Allanore, Y. *et al.* Clinical characteristics and predictors of gangrene in patients with
848 systemic sclerosis and digital ulcers in the Digital Ulcer Outcome Registry: a
849 prospective, observational cohort. *Ann. Rheum. Dis.* **75**, 1736 LP – 1740 (2016).
- 850 99. Murphy, S. L. *et al.* Occupational Therapy Treatment to Improve Upper Extremity
851 Function in Individuals with Early Systemic Sclerosis: A Pilot Study. *Arthritis Care Res.*
852 *(Hoboken)*. **70**, 1653–1660 (2018).
- 853 100. Becetti, K. *et al.* *J. Rheumatol.* jrheum.181130 (2019). doi:10.3899/jrheum.181130
- 854 101. Lebedoff, N. *et al.* Review of local wound management for scleroderma-associated
855 digital ulcers. *J. Scleroderma Relat. Disord.* **3**, 66–70 (2017).
- 856 102. Ozgocmen, S., Kaya, A. & Coskun, B. K. Topical lidocaine helps reduce pain of digital
857 ulcers in systemic sclerosis (scleroderma). *Clin. Rheumatol.* **25**, 378–9 (2006).
- 858 103. Baron, M., Chung, L., Gyger, G., Hummers, L. & Khanna, D. Consensus opinion of a
859 North American Working Group regarding the classification of digital ulcers in
860 systemic sclerosis. *Clin. Rheumatol.* **33**, 207–214 (2014).
- 861 104. Markus, Y. M., Bell, M. J. & Evans, A. W. Ischemic scleroderma wounds successfully

- 862 treated with hyperbaric oxygen therapy. *J. Rheumatol.* **33**, 1694–6 (2006).
- 863 105. Mirasoglu, B., Bagli, B. S. & Aktas, S. Hyperbaric oxygen therapy for chronic ulcers in
864 systemic sclerosis – case series. *Int. J. Dermatol.* **56**, 636–640 (2017).
- 865 106. Beckett, V. L. *et al.* Trial of platelet-inhibiting drug in scleroderma. Double-blind study
866 with dipyridamole and aspirin. *Arthritis Rheum.* **27**, 1137–43 (1984).
- 867 107. Denton, C. P., Howell, K., Stratton, R. J. & Black, C. M. Long-term low molecular
868 weight heparin therapy for severe Raynaud’s phenomenon: a pilot study. *Clin. Exp.*
869 *Rheumatol.* **18**, 499–502 (2000).
- 870 108. Abou-Raya, A., Abou-Raya, S. & Helmii, M. Statins: potentially useful in therapy of
871 systemic sclerosis-related Raynaud’s phenomenon and digital ulcers. *J. Rheumatol.*
872 **35**, 1801–8 (2008).
- 873 109. Rosato, E., Borghese, F., Pisarri, S. & Salsano, F. The treatment with N-acetylcysteine
874 of Raynaud’s phenomenon and ischemic ulcers therapy in sclerodermic patients: a
875 prospective observational study of 50 patients. *Clin. Rheumatol.* **28**, 1379–1384
876 (2009).
- 877 110. Ladak, K. & Pope, J. E. A review of the effects of statins in systemic sclerosis. *Semin.*
878 *Arthritis Rheum.* **45**, 698–705 (2016).
- 879 111. Rademaker, M. *et al.* Comparison of intravenous infusions of iloprost and oral
880 nifedipine in treatment of Raynaud’s phenomenon in patients with systemic sclerosis:
881 a double blind randomised study. *BMJ* **298**, 561–4 (1989).
- 882 112. Tingey, T., Shu, J., Smuczek, J. & Pope, J. Meta-analysis of healing and prevention of
883 digital ulcers in systemic sclerosis. *Arthritis Care Res. (Hoboken).* **65**, 1460–71 (2013).
- 884 113. Hughes, M. & Herrick, A. *Prophylactic ACE inhibitor therapy in Raynaud’s*
885 *phenomenon: Helpful or harmful? Novel Insights into Systemic Sclerosis Management*
886 (2013). doi:10.2217/EBO.12.464
- 887 114. Korn, J. H. *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with
888 bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum.* **50**, 3985–93
889 (2004).
- 890 115. Pauling, J. D., Nagaraja, V. & Khanna, D. Insight into the Contrasting Findings of
891 Therapeutic Trials of Digital Ischaemic Manifestations of Systemic Sclerosis. *Curr.*
892 *Treat. Options Rheumatol.* (2019). doi:10.1007/s40674-019-00118-w
- 893 116. Wigley, F. M., Seibold, J. R., Wise, R. A., McCloskey, D. A. & Dole, W. P. Intravenous

- 894 iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to
895 systemic sclerosis. *J. Rheumatol.* **19**, 1407–14 (1992).
- 896 117. Wigley, F. M. *et al.* Intravenous iloprost infusion in patients with Raynaud
897 phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled,
898 double-blind study. *Ann. Intern. Med.* **120**, 199–206 (1994).
- 899 118. Badesch, D. B. *et al.* Continuous intravenous epoprostenol for pulmonary
900 hypertension due to the scleroderma spectrum of disease. A randomized, controlled
901 trial. *Ann. Intern. Med.* **132**, 425–34 (2000).
- 902 119. Ambach, A., Seo, W., Bonnekoh, B. & Gollnick, H. Low-dose combination therapy of
903 severe digital ulcers in diffuse progressive systemic sclerosis with the endothelin-1
904 receptor antagonist bosentan and the phosphodiesterase V inhibitor sildenafil. *J.*
905 *Dtsch. Dermatol. Ges.* **7**, 888–91 (2009).
- 906 120. Moinzadeh, P., Hunzelmann, N. & Krieg, T. Combination therapy with an endothelin-1
907 receptor antagonist (bosentan) and a phosphodiesterase V inhibitor (sildenafil) for
908 the management of severe digital ulcerations in systemic sclerosis. *J. Am. Acad.*
909 *Dermatol.* **65**, e102-4 (2011).
- 910 121. Muir, L. Surgical management. in *Raynaud's Phenomenon* (eds. Wigley, F. M., Herrick,
911 A. L. & Flavahan, N.) 361–372 (Springer Science+Buisness Media, 2015).
- 912 122. Momeni, A. *et al.* Surgical treatment of systemic sclerosis-is it justified to offer
913 peripheral sympathectomy earlier in the disease process? *Microsurgery* **35**, 441–6
914 (2015).
- 915 123. Chiou, G. *et al.* Digital Sympathectomy in Patients With Scleroderma: An Overview of
916 the Practice and Referral Patterns and Perceptions of Rheumatologists. *Ann. Plast.*
917 *Surg.* **75**, (2015).
- 918 124. Leyden, J. *et al.* Upper Extremity Angiographic Patterns in Systemic Sclerosis:
919 Implications for Surgical Treatment. *J. Hand Surg. Am.* (2019).
920 doi:10.1016/j.jhsa.2019.01.004
- 921 125. Satteson, E. S., Chung, M. P., Chung, L. S. & Chang, J. Microvascular hand surgery for
922 digital ischemia in scleroderma. *J. Scleroderma Relat. Disord.* 2397198319863565
923 (2019). doi:10.1177/2397198319863565
- 924 126. Iorio, M. L., Masden, D. L. & Higgins, J. P. Botulinum toxin A treatment of Raynaud's
925 phenomenon: a review. *Semin. Arthritis Rheum.* **41**, 599–603 (2012).

- 926 127. Żebryk, P. & Puszczewicz, M. J. Botulinum toxin A in the treatment of Raynaud's
927 phenomenon: a systematic review. *Arch. Med. Sci.* **12**, 864–870 (2016).
- 928 128. Bello, R. J. *et al.* The Therapeutic Efficacy of Botulinum Toxin in Treating Scleroderma-
929 Associated Raynaud's Phenomenon: A Randomized, Double-Blind, Placebo-Controlled
930 Clinical Trial. *Arthritis Rheumatol.* **69**, 1661–1669 (2017).
- 931 129. Bene, M. Del *et al.* Autologous fat grafting for scleroderma-induced digital ulcers. An
932 effective technique in patients with systemic sclerosis. *Handchir Mikrochir Plast Chir*
933 **46**, 242–7 (2014).
- 934 130. Bank, J., Fuller, S. M., Henry, G. I. & Zachary, L. S. Fat grafting to the hand in patients
935 with Raynaud phenomenon: a novel therapeutic modality. *Plast. Reconstr. Surg.* **133**,
936 1109–18 (2014).
- 937 131. Takagi, G. *et al.* Therapeutic vascular angiogenesis for intractable macroangiopathy-
938 related digital ulcer in patients with systemic sclerosis: a pilot study. *Rheumatology*
939 (*Oxford*). **53**, 854–9 (2014).
- 940 132. Del Papa, N. *et al.* Regional grafting of autologous adipose tissue is effective in
941 inducing prompt healing of indolent digital ulcers in patients with systemic sclerosis:
942 results of a monocentric randomized controlled study. *Arthritis Res. Ther.* **21**, 7
943 (2019).
- 944 133. Hughes, M. *et al.* Prediction and impact of attacks of Raynaud's phenomenon, as
945 judged by patient perception. *Rheumatol.* **54**, 1443–7 (2015).
- 946 134. Pauling, J. D. *et al.* Patient-reported outcome instruments for assessing Raynaud's
947 phenomenon in systemic sclerosis: A SCTC vascular working group report. *J.*
948 *Scleroderma Relat. Disord.* **0**, 2397198318774307 (2018).
- 949 135. Pauling, J. D., Saketkoo, L. A., Matucci-Cerinic, M., Ingegnoli, F. & Khanna, D. The
950 patient experience of Raynaud's phenomenon in systemic sclerosis. *Rheumatol.*
951 (2018). doi:10.1093/rheumatology/key026
- 952 136. Hughes, M. & Pauling, J. D. Exploring the patient experience of digital ulcers in
953 systemic sclerosis. *Semin. Arthritis Rheum.* **48**, 888–894 (2019).
- 954 137. Pauling, J. D. *et al.* Multinational Qualitative Research Study Exploring the Patient
955 Experience of Raynaud's Phenomenon in Systemic Sclerosis. *Arthritis Care Res.*
956 (*Hoboken*). **70**, 1373–1384 (2018).
- 957 138. Hughes, M., Murray, A., Denton, C. P. & Herrick, A. L. Should all digital ulcers be

- 958 included in future clinical trials of systemic sclerosis-related digital vasculopathy?
959 *Med. Hypotheses* **116**, (2018).
- 960 139. Khanna, D. *et al.* Effect of Macitentan on the Development of New Ischemic Digital
961 Ulcers in Patients With Systemic Sclerosis: DUAL-1 and DUAL-2 Randomized Clinical
962 Trials. *JAMA* **315**, 1975–88 (2016).
- 963 140. Ruaro, B. *et al.* Short-term follow-up of digital ulcers by laser speckle contrast analysis
964 in systemic sclerosis patients. *Microvasc. Res.* **101**, 82–85 (2015).
- 965 141. Murray, A. *et al.* Pilot study assessing pathophysiology and healing of digital ulcers in
966 patients with systemic sclerosis using laser Doppler imaging and thermography. *Clin.*
967 *Exp. Rheumatol.* (2016).
- 968 142. Hughes, M. *et al.* Reduced perfusion in systemic sclerosis digital ulcers (both fingertip
969 and extensor) can be increased by topical application of glyceryl trinitrate. *Microvasc.*
970 *Res.* **111**, 32–36 (2017).
- 971 143. Hughes, M. *et al.* Digital ulcers in systemic sclerosis are associated with
972 microangiopathic abnormalities of peri-lesional skin as assessed by capillaroscopy.
973 *Scand. J. Rheumatol.* (2016).
- 974 144. Denton, C. P. *et al.* Efficacy and Safety of Selexipag in Adults With Raynaud’s
975 Phenomenon Secondary to Systemic Sclerosis. *Arthritis Rheumatol.* **69**, 2370–2379
976 (2017).
- 977 145. Allanore, Y., Distler, O., Matucci-Cerinic, M. & Denton, C. P. Review: Defining a
978 Unified Vascular Phenotype in Systemic Sclerosis. *Arthritis Rheumatol.* (Hoboken, N.J.)
979 **70**, 162–170 (2018).
- 980 146. Beon, M., Harley, R., Wessels, A., Silver, R. & Ludwicka-Bradley, A. Myofibroblast
981 induction and microvascular alteration in scleroderma lung fibrosis. *Clin. Exp.*
982 *Rheumatol.* **22**, 733–42 (2004).
- 983 147. van Roon, A. M. *et al.* Abnormal Nailfold Capillaroscopy Is Common in Patients with
984 Connective Tissue Disease and Associated with Abnormal Pulmonary Function Tests.
985 *J. Rheumatol.* **46**, 1109 LP – 1116 (2019).
- 986 148. Mihai, C. *et al.* Digital ulcers predict a worse disease course in patients with systemic
987 sclerosis. *Ann. Rheum. Dis.* **75**, 681–6 (2016).
- 988 149. Allanore, Y. *et al.* Prevalence and factors associated with left ventricular dysfunction
989 in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients

- 990 with systemic sclerosis. *Ann. Rheum. Dis.* **69**, 218 LP – 221 (2010).
- 991 150. Hughes, M., Baker, A., Farrington, S. & Pauling, J. D. Patient organisation-led
992 initiatives can play an important role in raising awareness about Raynaud's
993 phenomenon and encourage earlier healthcare utilisation for high-risk groups. *Ann.*
994 *Rheum. Dis.* annrheumdis-2018-214161 (2018). doi:10.1136/annrheumdis-2018-
995 214161
- 996 151. Hughes, M. Effect of Season on Internet Searches for Information on Raynaud
997 Phenomenon. *J. Rheumatol.* jrheum.190463 (2019). doi:10.3899/jrheum.190463
- 998 152. Chikura, B., Moore, T., Manning, J., Vail, A. & Herrick, A. L. Thumb involvement in
999 Raynaud's phenomenon as an indicator of underlying connective tissue disease. *J.*
1000 *Rheumatol.* **37**, 783–786 (2010).

1001

1002

1003 **Figure 1: Raynaud's phenomenon.** Mobile phone photographs taken of attacks of Raynaud's
1004 in a patient with primary Raynaud's phenomenon and established peripheral nerve damage
1005 from entrapment neuropathies. There is pallor (index, middle and little fingers) and cyanosis
1006 (ring finger) with sparing of the thumb which is suggestive of primary Raynaud's
1007 phenomenon.¹⁵²

1008

1009 **Figure 2: Digital ulcers and complications in systemic sclerosis.** Ischaemic digital ulcers on
1010 the fingertip (A) and volar aspect (B) of the digits. Digital ulcers on the extensor aspect (C) of
1011 the hands overlying the small joints and calcinosis-related (D) digital ulceration. Infected
1012 digital ulcer (E) and critical digital ischaemia (F).

1013

1014 **Figure 3: The pathogenesis of systemic sclerosis-related digital ulcers.** Proposed schematic
1015 illustrating how the major factors could be potentially involved in both ulcer development
1016 and healing. Focal ischaemia or trauma promotes loss of tissue integrity and ulceration. As
1017 the digital ulcer develops the central core of tissue ischaemia progresses. There is often
1018 inflammation/erythema of the surrounding the non-ulcerated skin and the
1019 mechanism/implications of this is currently unknown. It could be postulated that this
1020 represents increased blood flow from neoangiogenesis and promotes ulcer healing. However,
1021 excessive blood flow could also result in a form of reperfusion injury and exacerbate further

1022 tissue injury. In addition, Infection is also associated with peri-ulcer inflammation. Over time
1023 with ulcer healing the tissue is either restored to normal or there is evidence of persistent
1024 digital ischaemic tissue loss. Digital pitting scars can also occur without prior ulceration.

1025

1026 Figure 4: The heterogeneity of lower limb cutaneous ulcer disease in SSc. A-D: significant
1027 variation in appearance in ulcer appearance reflecting differences in aetiopathogenesis
1028 including macrovascular arterial/venous involvement and other drivers (e.g. lymphatic
1029 abnormalities). E&F: Evolution of lower limb refractory ischaemia/ulceration in a patient with
1030 dcSSc (anti-Scl-70 antibody). E: cyanosis and small subungal ischaemic digital ulcer (2017). F:
1031 ischaemic paronychia ulceration right great toe despite combination therapy with sildenafil,
1032 bosentan and angiotensin II antagonist (2018).

1033

1034 **Figure 5: The utility of non-invasive digital microvascular structural and functional imaging**
1035 **in the assessment of CTD-related digital vasculopathy.** A, Low-powered (50x) magnification
1036 of the nailfold in primary Raynaud's; B, High-magnification (x200) of the same nailfold in A
1037 revealed normal-appearance uniformly spaced and sized hairpin capillary loops; C, Low-
1038 magnification appearance of nailfold in limited cutaneous systemic sclerosis with visible giant
1039 capillaries; D, Corresponding high-magnification image of the same nailfold in C revealing
1040 giant capillaries and capillary drop-out; E & F, Low and high-magnification nailfold
1041 capillaroscopic images in dermatomyositis revealing characteristic ramified ('bushy')
1042 capillaries; G, Thermal image of the hands of a patient with eosinophilic fasciitis 5 minutes
1043 following local cold challenge revealing a healthy-looking preserved positive longitudinal
1044 gradient in the early stages of re-warming not consistent with Raynaud's phenomenon; H,
1045 Thermal image of the hands 5 minutes following local cold challenge in Raynaud's
1046 phenomenon with a negative longitudinal gradient consistent with delayed re-perfusion

1047

1048 **Figure 6: Treatment of Raynaud's phenomenon and digital ulcers in systemic sclerosis.**
1049 Adapted from the Consensus best practice pathway of the UK Scleroderma Study Group:
1050 digital vasculopathy in systemic sclerosis.⁴⁶ A number of drug therapies are used for the
1051 treatment of both RP and digital ulcers in SSc. The potential benefits vs. the risks of adjunctive
1052 therapies must be considered on an individual patient basis. For example, anti-platelet
1053 therapies and anticoagulation may be potentially hazardous in patients with SSc due to

1054 potential gastrointestinal bleeding from gastric antral vascular ectasia, and statins can have
1055 adverse muscle effects in patients with SSc-myopathy.

1056

1057 **Box 1: Red flags in the setting of Raynaud’s phenomenon which suggest the presence of**
1058 **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

1059

1060 *These suggest the ‘very early diagnosis of systemic sclerosis’ and is confirmed by either the
1061 presence of systemic sclerosis-specific autoantibodies and/or the scleroderma pattern on
1062 nailfold capillaroscopy.⁴⁴

1063

1064 **Key points**

- 1065 • Vascular injury and Raynaud’s phenomenon are the earliest manifestations of
1066 systemic sclerosis.
- 1067 • Patients with Raynaud’s phenomenon need careful assessment to identify secondary
1068 causes including systemic sclerosis and key investigations include performing
1069 capillaroscopy and the detection of autoantibodies.
- 1070 • Raynaud’s and ischaemic complications including digital ulcers are a major cause of
1071 disease-related morbidity in systemic sclerosis.

- 1072 • The definition and assessment of digital ulcers can be very challenging and recent
1073 efforts have made progress in this field.
- 1074 • There are a number of available treatments to both prevent and heal digital ulcers.
- 1075 • The concept of a unified vascular diagnosis could herald the onset of a potential
1076 disease-modifying effect for vascular acting therapies in systemic sclerosis.
- 1077