

Patient experiences of digital ulcer development and evolution in systemic sclerosis

Michael Hughes^{1,2}, John D Pauling^{3,4}, Jennifer Jones⁵, Christopher P Denton⁶, Robyn T Domsic⁷, Tracy M Frech⁸, Ariane L Herrick^{1,9}, Dinesh Khanna¹⁰, Marco Matucci-Cerinic¹¹, Lorraine McKenzie¹², Lesley Ann Saketkoo¹³, Rachael Goberman-Hill^{5,14}, Andrew Moore⁵

1. Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, The University of Manchester, UK.
2. Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.
3. Royal National Hospital for Rheumatic Diseases (at Royal United Hospitals), Bath, UK.
4. Department of Pharmacy and Pharmacology, University of Bath, Bath, UK.
5. Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, Bristol, UK.
6. Department of Rheumatology, Royal Free Hospital, University College London, London, UK.
7. University of Pittsburgh Medical Center, Pittsburgh, PA.
8. University of Utah and Salt Lake Veterans Affairs Medical Center, Salt Lake City, USA.
9. Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester.
10. Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA.
11. Division of Rheumatology, University of Florence, Florence, Italy.
12. Patient representative. Contact via Professor Herrick, The University of Manchester.
13. Tulane University School of Medicine, New Orleans Scleroderma & Sarcoidosis Patient Care & Research Center, UMC Comprehensive Pulmonary Hypertension Center, New Orleans, LA, USA.
14. NIHR Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

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Rheumatology key message (n=15/15).

- SSc patients can predict new digital ulcers and symptoms change during ulcer evolution and healing.

SIR, painful digital ulcers (DUs) are common in patients with systemic sclerosis (SSc) and often refractory to treatment (1,2). DUs are generally considered to be the result of tissue ischaemia, in particular, those which occur on the fingertips (2). Other ~~anti~~pathogenic drivers have been proposed for extensor DUs and those related to calcinosis cutis, although all SSc-DUs are considered to share an important (and potentially treatable) ischaemic aetiology (3–5). Little is known about the earliest ‘pre-clinical’ stage of DU evolution prior to the development of overt tissue damage and/or how symptoms evolve during DU development and healing. The patient experience of SSc-DUs is highly complex and multi-faceted (6). We have recently reported a multicentre qualitative study that identified 5 major inter-related themes (and sub-themes) which characterise the patient experience of SSc-DUs: ‘physical symptoms and signs’, ‘psychological impact’, ‘functional impact’, ‘aggravating factors’ and ‘mitigating factors’ [AC&R]. The aim of the present analysis was to understand patients’ perceptions and beliefs about DU pathogenesis; to provide novel insights for both clinical practice, future clinical trial design, and to identify relevant domains for core outcome sets for SSc-DU assessment.

Our methodological approach has been described previously [AC&R]. In brief, 29 patients with a confirmed diagnosis of SSc participated in 4 focus groups across the United Kingdom (Bath, Manchester and London) [AC&R]. The study was approved by the East Midlands – Nottingham 1 research Ethics Committee (REC reference – 18/EM/0018) and all participants provided written, informed consent. Patients had a broad spectrum of prior DU experiences: 1 previous DU (n=3), 2-4 previous DUs (n=9) and ≥5 previous DUs (n=17). The mean (SD) age of patients was 59.9 (13.3) years and two thirds of patients were female (n=20) and the majority had limited cutaneous SSc (n=20). The mean (SD) disease duration (defined as time from first non-RP symptom) duration was 12.8 (9.7) years. The majority (n=27) of patients had ‘late’ disease which was defined as ≤3 years since their first non-RP symptom. The majority were receiving treatment with vasodilator medication for SSc-vasculopathy (including DU disease): calcium channel blockers (n=10), phosphodiesterase type-5 inhibitors (n=18) and endothelin receptor antagonists (n=9).

Focus groups were conducted using a bespoke topic guide and patients were recruited using a purposive sampling framework. Focus groups were audio recorded and anonymised transcripts were analysed using inductive thematic analysis (7). The present analysis reports patient perceptions and beliefs about DU pathogenesis and natural history.

Three major themes emerged which encompassed patients' perceptions and beliefs on DU pathogenesis.

Theme 1 – Underlying causes of SSc-DUs: Most participants believed that there was a reason for an ulcer to develop rather than their occurrence being haphazard. Reasons comprised of both 'external' and 'internal' precipitating factors. 'External' causes included trauma, exposure to water, chemicals or infection, cold or change in temperature, and from cuts or skin splitting (Q1-3). 'Internal' causes were Raynaud's phenomenon including from 'poor circulation', calcinosis, and due to the residual effects of previous ulcers rendering certain areas of the fingers susceptible to further ulceration (Q4-6).

Theme 2 – Symptoms prior to SSc-DU emergence: The majority of participants reported that they could recognise when an ulcer was about to emerge. The most common symptom was pain below the skin, often described as an internal pressure (Q7-8). Some participants also reported physical skin signs (e.g. a white patch with preserved overlying epithelialisation) which would subsequently breakdown/ulcerate (Q9-10).

Theme 3 – Patient experiences during DU evolution and healing: This was variable between participants. Surface characteristics ranged from being moist (including overt pus) to dry with a superficial crust, and occasionally with a central 'core' (Q11-14). Associated pain during ulcer healing also varied significantly between the participants.

Our data provides novel patient-perceived insights into the pathogenesis and natural history of SSc-DU. The emergence of SSc-DUs ~~are not haphazard~~ is not considered haphazard events and many patients have explanations for, and can ~~sometimes even predict~~ anticipate, the development of new ulcers. These observations could be used to develop behavioural approaches to help prevent DU such as severe cold avoidance, hand hygiene and avoidance of mechanical injury. The site of previous DU may represent ischaemic foci, vulnerable to further ulceration that may guide local therapies such as botulinum toxin or topical nitrates as secondary prevention. To our knowledge, we are the first to describe a 'pre-ulcer' stage which could provide a 'window of opportunity' to intervene before the onset of overt tissue damage and ulceration. Relevant to clinical trial design, DU symptoms differ significantly at the time of SSc-DU emergence, and during DU evolution and healing, which has important implications for the development of patient-reported outcome instruments for assessing SSc-DU.

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Table 1: Quotes supporting the themes which encompassed patients' development and evolution. Quotes (Q) are sequentially cited in the text and are identified by subject (participant) number and location: Bath (B), Manchester (M) and London (L) 1&2 focus groups.

Theme		Q	Subject	Quotation
Underlying causes of DUs	Trauma	1	P3 M1:	I just find it with a knock ... I've had a lot of minor ones but only really one big one, but it's always through trauma like touching something or, you know, if you just get your car keys and you catch it on a key or something
	Chemicals	2	P4 B1:	I also won't touch work surfaces at work because they use chemicals on them, and it's sticky, and that can really start my fingers off. So I don't use anything...Very careful about anything in the house, but I found when I go to work, if I put my finger down and think oh, they've polished it, they never clean it, they just polish it and those sorts of things can irritate the skin and start... Yeah, you know you go somewhere and you don't know if a chemical's been used to soak or clean the surfaces, actually it's something that starts them off
	Cuts or skin splitting	3	P1 M1:	it doesn't appear for no reason, there's usually a cut or a little where I've caught it somewhere, it usually turns into an ulcer. Yeah, it's never just appeared for no reason, it's always been a cut, you know
	Poor circulation	4	P8 L2:	For me it's lack of blood, lack of blood
	Calcinosis	5	P2 M1:	The calcium seems to come white, the calcium and then it gets infected and it turns into an ulcer
	Effect of previous ulcers	6	P4 B1:	the ulcers are only breaking open where I've had previous damage, obviously the fingers are compromised
Symptoms prior to DU emergence	Pain and pressure	7	P5 M2:	it just looks like a, it starts off with a very, very uncomfortable kind of hypersensitivity where again you think, oh it's going to come and you see like a little black dot and you think I've no idea what this is, but then it, it builds into what looks like an abscess maybe under your nail
		8	P6 B1:	I've definitely had sort of a feeling and with nothing there, that something's going to happen. And then it'll get really sore and it, with me, it just sort of broke into a yellow gungy mess
	Physical changes	9	P5 L1:	Yeah, for me I get that kind of, like, it kind of looks, looks like a whitish, but it's not a full on ulcer yet. ... I think they have their own life, once you've got one coming it's going to come and live out its life before it goes
		10	P7 L2:	it's almost like a weird infection, it starts off dry and I think it works its way in, in to the finger more and more, it feels like it's touching the nerve and it's like the...whole thing opens up
Patient experiences during DU evolution and healing	Ulcer characteristics	11	P4 B1:	It goes into like a white spot and then that will break down and then that will weep
		12	P7 B1:	Normally the skin of whichever finger's affected will harden. And that will almost turn into like a big kind of scab, or core if you like, and if that core is knocked out or removed in anyway shape, or form then it's properly painful and if you just touch it on anything it's agonising
		13	P5 L1:	I find, you know when that scab comes off underneath it is quite, it can be quite moist, like almost pus looking
		14	P1 L1	They kind of scab eventually don't they? They start off moist and then become a scab and dry up."