A prospective study of systemic sclerosis-related digital ulcers: prevalence, location, and functional impact

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Objectives: Although digital ulcers (DUs) are common in patients with systemic sclerosis (SSc), prevalence estimates vary, and functional impact and pathophysiology have been relatively little studied. We investigated the point prevalence of all DUs (both digital-tip and extensor) in a cohort of patients with SSc, testing the hypothesis that both digital-tip and extensor ulcers are associated with functional impairment.

Method: Over a 12-month period, patients attending an SSc clinic for annual review were assessed by specialist nurses: active DUs were documented and the Hand Mobility in Scleroderma (HAMIS) test performed. Patients also completed the Scleroderma Health Assessment Questionnaire (SHAQ), the Scleroderma Functional Index (SFI), and the Cochin Hand Function Scale (CHFS).

Results: A total of 25 active DUs (nine digital-tip and 16 extensor surface) were found in 15 of the 148 patients recruited, giving a prevalence for each ulcer type of 6% and an overall point prevalence of 10%. HAMIS scores were higher (indicating greater impairment) in those with active DUs than in those without: left hand difference 8.8 points [95% confidence interval (CI) 3.2–14.5], $p = 0.002$; difference significant for extensor as well as digital-tip ulcers. Active DUs were associated with higher visual analogue scale (VAS) scores for pain ($p = 0.04$), DUs ($p < 0.001$), and 'overall' assessment ($p = 0.03$).

Conclusions: Extensor surface ulcers have the same prevalence as digital-tip ulcers in patients with SSc, and are equally disabling. Clinical trials should therefore include both categories of DUs.

Digital ulcers (DUs) are a major source of pain and disability in patients with systemic sclerosis (SSc) (1), and are common in this patient group. An estimated 50% of all patients with SSc will experience a DU at some stage in their disease course (2–5). Prevalence rates have varied between studies (4–8), ranging from 8% to 31% (5, 7). Differences in reported DU frequencies reflect not only the difficulties in defining them (9) but also inconsistencies between studies as to which types are considered. Some studies have included ulcers only if they are on the tip of the finger or the terminal phalanx (4, 8), while others have included ulcers over the dorsal aspect. In one study dorsal DUs accounted for 30% of all finger ulcers (1). Ulcers overlying extruding calcinotic lesions are also often excluded (4–5, 10).

The aim of our prospective study was to document the point prevalence and location of all active finger ulcers in an unselected cohort of SSc patients attending a tertiary referral centre over a 12-month period, and to test the hypothesis that both digital-tip and extensor ulcers are associated with functional impairment.

Method

Patients attending specialist SSc clinics for annual review between January and December 2009 were invited to participate. Specialist nurses documented the presence or absence of active DUs (defined as a distinct lesion with loss of epidermis) and, when present, their location (digital-tip or extensor surface), site-specific calcinosis, or infection requiring antibiotic treatment. All patients (both with and without DUs) underwent the Hand Mobility in Scleroderma Test (HAMIS) (11). Clinical data, including gender, age, disease subtype, disease duration, smoking habit, and autoantibody status, were obtained for all patients.

All patients were also asked to complete the following self-administered measures of physical function: the

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Scleroderma Health Assessment Questionnaire (SHAQ) (12), incorporating six visual analogue scales (VAS), the Scleroderma Functional Index (SFI) (13), and the Cochin Hand Function Scale (CHFS) (14). The HAMIS, SHAQ, SFI, and CHFS were scored according to published instructions (11–14). Unifactorial logistic regression was applied to assess association with ulcer status of each demographic and clinical variable. Linear regression was applied to assess association with ulcer status of hand function and pain scores. Analyses were performed using Stata statistical software, version 10.

The study received ethical approval from the North West Greater Manchester National Research Ethics Service (NRES) Committee.

Results

Of the 199 patients approached, 148 (74%) agreed to participate. Digital ulcers were present in 15 of these 148 patients, giving an overall point prevalence of 10% [95% confidence interval (CI) 6–16]. Five of these 15 patients had more than one ulcer: two patients had two ulcers, one patient had three ulcers, and two patients had four ulcers. In total, there were 25 DUs (nine digital-tip, 16 extensor surface) between the 15 patients. Nine patients had digital-tip ulcers and nine had extensor surface ulcers (three had both), giving a similar point prevalence for each location of 6% (95% CI 3–11). Site-specific calcinosis was associated with four of nine (44%) digital-tip and five of 16 (31%) extensor surface ulcers. Infection requiring antibiotic treatment was associated with four of nine (44%) digital-tip and two of 16 (13%) extensor surface ulcers. Demographic and clinical characteristics are shown in Table 1 for the population as a whole, and for those with and without active DUs. No significant association was detected between patients with and without DUs and any of the demographic and clinical variables assessed.

Impact on hand function and pain

Nine patients had DUs on their left hand and 10 on their right, and four had ulcers on both hands. All 15 patients with ulcers were right-handed. The HAMIS was performed in 143 (97%) patients with mean scores of 9.3 (left hand) and 9.6 (right hand). In five patients the test was not possible because of severe hand contractures. On the left hand, HAMIS scores were higher, indicating greater impairment, in those with active DUs than those without: the difference was 8.8 (95% CI 3.2–14.5) points ($p = 0.002$). For patients with DUs on the right hand, this difference was less marked and did not reach statistical significance: the difference was 4.8 (95% CI –1.0 to 10.6) points ($p = 0.11$).

When the above analysis was repeated by ulcer location, there was a similar and statistically significant difference between those without and those with ulcers in either location for the left hand (mean scores of 17.8 and 18.8 for those with digital-tip and extensor surface ulcers, respectively: a difference for digital-tip ulcers of 8.9 points, 95% CI 2.0–15.8, $p = 0.01$ and for extensor surface ulcers of 9.7 points, 95% CI 1.3–18.1, $p = 0.02$). For the right hand there was a similar (mean 16.9 points) and significant difference in HAMIS score for those with extensor surface ulcers (difference of 7.4 points, 95% CI 0.3–14.4, $p = 0.04$) but no evidence of a difference in HAMIS score for those with digital-tip ulcers: mean 9.0 points, difference –0.6, 95% CI –10.6 to 9.4 points, $p = 0.90$ (Figure 1).

SHAQ, SFI, and CHFS scores assessing manual dexterity and physical function are shown in Table 2. DUs were associated with higher SHAQ, SFI, and CHFS median scores, indicating greater functional impairment, but this was statistically significant only for SHAQ VAS scores relating to DU/digital vasculopathy: pain, digital ulceration, and 'overall'. Completion rates for the SHAQ and SFI were good (97%) but completion of the CHFS (at 69%) was poorer, reflecting the fact that patients completed this measure at home.

Table 1. Demographics and clinical characteristics of participants.

Variable	Total (n = 148)	No DUs (n = 133)	DUs (n = 15)	p
Female	125 (84)	113 (85)	12 (80)	0.62
Age (years)	60 (21–88)	60 (21–83)	57 (36–88)	0.95
lcSSc	109 (74)	100 (75)	9 (60)	0.21
Disease duration (years) (n = 137)	11 (1–54)	11 (1–43)	13 (1–54)	0.44
Raynaud's duration (years) (n = 147)	16 (1–69)	16 (1–69)	17 (8–52)	0.13
Calcium channel blockers	70 (48)	60 (45)	10 (67)	0.11
Smoking status (n = 141)				0.15
Current	17 (12)	13 (10)	4 (27)	
Ex-smoker	52 (37)	49 (39)	3 (20)	
Never	72 (51)	64 (51)	8 (53)	
ACA positive	54 (36)	48 (36)	6 (40)	0.77
Anti-Scl-70 positive	17 (11)	16 (12)	1 (7)	0.54

DU, Digital ulcer; lcSSc, limited cutaneous systemic sclerosis; ACA, anti-centromere antibody. Values given as n (%) or median (range).

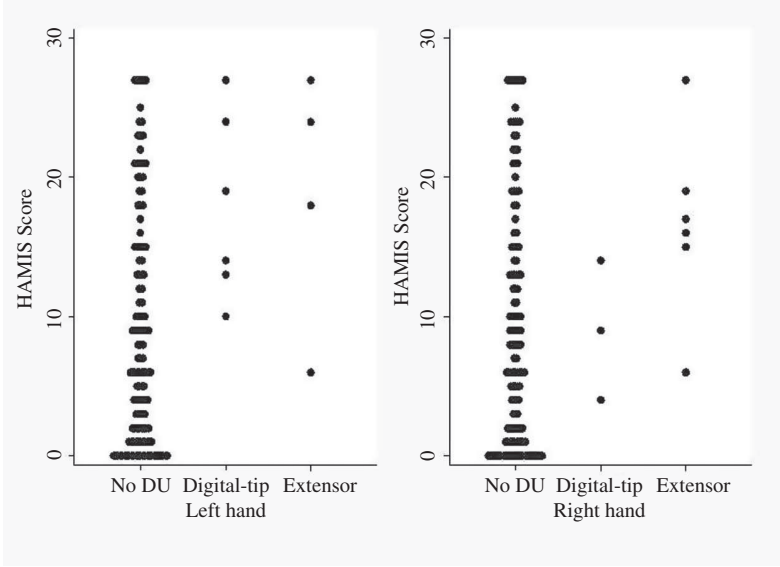

Figure 1. HAMIS scores for each hand by ulcer location. One patient with both digital-tip and extensor surface ulcers on the left hand is presented twice in the left-hand panel. One patient with an extensor surface ulcer on the right hand was unable to complete the HAMIS due to contracture and so is omitted from the right-hand panel.

Discussion

In an unselected cohort of patients with SSc, extensor surface DUs are at least as common and disabling as those on the finger-tip. This suggests that clinical trials of DUs should include extensor surface as well as digital-tip ulcers, otherwise a large proportion of the DU burden will not be taken into account, to the detriment of patient care.

Our reported prevalence of DUs (10%) is consistent with previous reports of 8% and 12% in Canadian (5) and French (4) cohorts, respectively, but lower than the 24% and 31% reported in a German registry (8) and a French cohort, respectively (7). An important limitation across existing studies of DUs continues to be the relative lack of agreement over what constitutes a DU (9) and the lack of clear criteria for the assessment of DUs within individual studies or registries.

We sought to minimize inter-rater variability throughout the study by employing the same specialist nurses to identify and assess active DUs, defined as a distinct lesion with loss of epidermis, and recording all finger ulcers distal to the metacarpophalangeal joints, including those overlying calcinosis. We recruited patients only from routine annual review appointments during a 12-month period; many of which feel during the summer months. Patients with severe digital ulceration admitted for care outside of their annual review appointments were not counted, nor were those who developed DUs before or after these appointments. We did not attempt to document the prevalence of previous ulcers, which in part relies on patient recall. We consider that this study represents a true prevalence of active DUs across a cohort of SSc patients in a standardized manner. By demonstrating that, at any one time, 10% of patients with SSc are likely to have an active (non-healed) ulcer, we have confirmed the enormity of the clinical problem posed by DUs.

The degree of functional impairment associated with DUs has been recognized relatively recently (5, 7, 15). Our HAMIS results provide further evidence that DUs adversely affect hand function. Separate analyses of right

Table 2. Physical function scores of participants.

Variable	No DUs Median (IQR)	DUs Median (IQR)	Difference (95% CI)	p
SHAQ overall	n = 129	n = 15		0.85
	1.4 (0.5–2.3)	1.8 (0.9–2.0)	0.1 (–0.5–0.6)	
VAS	n = 127	n = 15		
Pain	0.8 (0.1–1.5)	1.2 (0.8–2.1)	0.5 (0.0–0.9)	0.04
Raynaud's	0.7 (0.1–1.5)	1.0 (0.6–2.1)	0.4 (–0.1–0.8)	0.11
DU	0.1 (0.0–0.6)	1.1 (0.4–2.2)	0.9 (0.5–1.3)	< 0.001
Overall	0.8 (0.2–1.6)	1.3 (0.8–2.0)	0.4 (0.0–0.8)	0.03
SFI overall	n = 130	n = 14		0.36
	9 (3–15)	12 (6–18)	2.0 (–2.3–6.2)	
CHFS	n = 92	n = 10		0.11
	14 (4–29)	25 (18–47)	10.0 (–2.5–22.6)	

DU, Digital ulcer; SHAQ, Scleroderma Health Assessment Questionnaire; VAS, visual analogue scale; SFI, Scleroderma Functional Index; CHFS, Cochin Hand Function Scale; IQR, interquartile range; CI, confidence interval.

and left hands demonstrated the importance of both digital-tip and extensor surface DUs in causing pain and discomfort and we consider this a key finding as there has been a tendency in the past for studies of SSc-related DUs to focus attention on only digital-tip lesions.

We also confirmed the findings of Mouthon et al (7) that DUs are associated with higher SHAQ and CHFS scores, although in our study the differences in SHAQ (median 1.8 vs. 1.4) and CHFS scores (median 25 vs. 14) were not statistically significant between DU and non-DU groups, reflecting the small sample size. CHFS scores in the DU groups were comparable between studies [27.4 in Mouthon et al's study (7) and 27.8 in a later study by the same group (15) compared to 25 in the current study].

Our study was not adequately powered to look for associations between the presence of DUs and different demographic and clinical features. Within the present study, no significant differences between DU rates and limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subtypes were detected, although 40% of DUs were found in patients with dcSSc, who comprised only 26% of the overall cohort.

In conclusion, we have shown in a prospective study that the prevalence of active DUs in patients with SSc is of the order of 10%, and is fairly evenly split between finger-tip and extensor ulcers. DUs (of both the extensor surface and the finger-tip) were associated with impairment of hand function. When seeking to find effective treatments for SSc-related DUs, extensor surface as well as finger-tip lesions should be included.

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References

1. Amanzi L, Braschi F, Fiori G, Galluccio F, Miniati I, Guiducci S, et al. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions. Rheumatology (Oxford)2010;49:1374–82.
2. Della Rossa A, Valentini G, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, et al. European multicentre study to define disease activity criteria for systemic sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centres. Ann Rheum Dis 2001;60:585–91.
3. Mawdsley AH. Patient perception of UK scleroderma services – results of an anonymous questionnaire. Rheumatology (Oxford) 2006;45:1573.
4. Tiev KP, Diot E, Clerson P, Dupuis-Simeon F, Hachulla E, Hatron P, et al. Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinérAIR-Sclérodermie). J Rheumatol 2009;36:1470–6.
5. Khimdas S, Harding S, Bonner A, Zummer B, Baron M, Pope J; Canadian Scleroderma Research Group Registry. Associations with digital ulcers in a large cohort of systemic sclerosis: results from the Canadian Scleroderma Research Group Registry. Arthritis Care Res 2011:63;142–9.
6. Hachulla E, Clerson P, Launay D, Lambert M, Morell-Dubois S, Queyrel V, et al. Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. J Rheumatol 2007;34:2423–30.
7. Mouthon L, Mestre-Stanilas C, Berezne A, Rannou F, Guilpan P, Revel M, et al. Impact of digital ulcers on disability and health-related quality of life in SSc. Ann Rheum Dis 2010;69:214–17.
8. Sunderkotter C, Herrgott I, Bruckner C, Moinzadeh P, Pfeiffer C, Gerss J, Hunzelmann N, et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol 2009;160:835–43.
9. Herrick AL, Roberts C, Tracey T, Silman A, Anderson M, Goodfield M, et al. Lack of agreement between rheumatologists in defining digital ulceration in systemic sclerosis. Arthritis Rheum 2009;60:878–82.
10. Nihtyanova SI, Brough GM, Black CM, Denton CP. Clinical burden of severe digital vasculopathy in systemic sclerosis. Ann Rheum Dis 2008;67:120–3.
11. Sandqvist G, Eklund M. Validity of HAMIS: a test of hand mobility in scleroderma. Arthritis Care Res 2000;13:382–7.x
12. Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984–91.
13. Silman A, Akeeson A, Newman J, Henriksson H, Sandquist G, Nihill M, et al. Assessment of functional ability in patients with scleroderma: a proposed new disability assessment instrument. J Rheumatol 1998;25:79–83.
14. Brower LM, Poole JL. Reliability and validity of the Duruoz hand index in persons with systemic sclerosis (scleroderma). Arthritis Care Res 2004;51:805–9.
15. Berezne A, Seror R, Morell-Dubois S, de Menthon M, Fois E, Dzeing-Ella A, et al. Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. Arthritis Care Res 2011;63:277–85.