Preliminary Validation of the Digital Ulcer Clinical Assessment Score in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To date, "healed/non-healed" and clinical judgment are the only available assessment tools for digital ulcers (DU) in patients with systemic sclerosis (SSc). The aim of our study is to examine a preliminary composite DU clinical assessment score (DUCAS) for SSc for face, content, and construct validity.

Methods. Patients with SSc presenting at least 1 finger DU were enrolled and assessed with the Health Assessment Questionnaire–Disability Index, Cochin scale, visual analog scale (VAS) for DU-related pain, patient global DU status, and global assessment as patient-reported outcomes (PRO), and physician VAS for DU status (phyGDU) as an SSc-DU expert physician/nurse measure. The DUCAS included 7 DU-related variables selected by a committee of SSc DU experts and weighted on a clinical basis. Face validity was examined by consensus and partial construct validity was tested through convergent correlation with other measures of hand function, using Spearman's correlations. A range of patients with SSc was examined. A linear regression model with backward stepwise analysis was used to determine the relationship of individual variables with the primary clinical parameter, phyGDU.

Results. Forty-four patients with SSc (9 males, mean age 55 ± 15 yrs, mean disease duration 9.9 ± 5.8 yrs) were enrolled in the study. Overall DUCAS showed significant positive correlations with all abovementioned PRO ($r > 0.4$, $p < 0.01$). When all scores and scales were modeled, only DUCAS significantly predicted phyGDU ($r = 0.59$, $R^2 = 0.354$, Akaike information criterion = 385.4).

Conclusion. Preliminarily, we suggest that the DUCAS may be a new clinical score for SSc-related DU, having face and content validity and convergent/divergent correlations (construct validity). These early data suggest that this score deserves further evaluation. (J Rheumatol First Release November 15 2018; doi:10.3899/jrheum.171486)

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SYSTEMIC SCLEROSIS | DIGITAL ULCER | OUTCOME MEASURES
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Digital ulcers (DU) are a frequent and disabling clinical complication of systemic sclerosis (SSc), affecting 43–48% of patients[1]. DU occur most frequently on finger or toe tips and can be the consequence of endothelial damage, trauma, or calcinosis, damaging epidermis and underlying tissues. DU impair hand function and compromise patients' quality of life. They may result in complications such as infections, gangrene, or osteomyelitis, and may lead to amputation[1,2]. Tissue loss determines functional disability and associated social and self-image problems[2]. The mean time to healing of SSc-DU is about 10–12 weeks[3]. For these reasons, reliable, valid outcome measures need to be developed that can be used in randomized clinical trials (RCT) to improve the assessment of DU therapy in SSc, as well as in clinical practice.

Some tools are available. Many patient-reported outcomes (PRO) have previously been validated. Health Assessment Questionnaire–Disability Index is patient-oriented and well known, and assesses disease-related disability[4,5,6,7]. It reflects variations in DU status as shown in posthoc RAPIDS (RAndomized, double-blind, placebo-controlled study with bosentan on healing and Prevention of Ischemic Digital ulcers in patients with systemic Sclerosis)-1 and -2 study analyses[8]. Similarly, the Cochin scale (Duruoz Hand Index) assesses hand-focused functional disability[9] and is significantly higher in the SSc population with versus without DU[10].

Other tools that may be used in daily practice are visual analog scales (VAS) focused on pain (DU pain), patient's global assessment of the disease (PtGA), and global assessment of DU by the patient (PtGDU) or by the SSc-DU expert physician/nurse (PhyGDU)[7]. Although these measures could be used in SSc, there is no valid tool available to assess DU progression or healing. In RCT, only the "healed-not/healed" assessment of DU was considered, while a real composite evaluation tool to assess DU change is lacking. Thus, there is a need for a validated, simple method to objectively or semi-objectively evaluate a drug's efficacy in SSc-DU.

In our study, we examined the face, content, and construct validity of a composite DU Clinical Assessment Score (DUCAS) in SSc.

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MATERIALS AND METHODS

Patients enrolled in the study were classified as having SSc according to the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria[11], aged older than 18, presenting at least 1 finger DU and attending the Wound Care Clinic of the Department of Rheumatology of the University Hospital of Florence. Patients gave voluntary, informed consent for study participation and local ethical committee (*Comitato Etico Area Vasta Centro*) approval was obtained for the study (reference OSS15.109 – protocol number 2015/0032293).

Baseline background data were collected, including age, sex, disease-related autoantibodies (including antinuclear antibodies, anticentromere antibodies, antitopoisomerase I, anti-RNA polymerase III antibodies, etc.), skin involvement (limited or diffuse), modified Rodnan skin score (mRSS), history of previous digital ulcers[12], nailfold videocapillaroscopy pattern[13], internal organ involvement, and current treatment at the time of study enrollment (vasoactive, immunosuppressive). Internal organ involvement was defined as follows: gastrointestinal — dysphagia, or heartburn, or esophageal reflux, or small intestine bacterial overgrowth, or fecal leakage; by imaging endoscopy or clinical questioning of articular-inflammatory joint synovitis by examination; pulmonary arterial hypertension — mean pulmonary arterial pressure ≥ 25 mmHg and pulmonary wedge pressure ≤ 15 mmHg on right heart catheterization; interstitial lung disease — chest high-resolution computed tomography; kidney — history of scleroderma renal crisis or creatinine clearance below 30 ml/min/24 h; heart — the presence of ventricular arrhythmias on 24-h Holter electrocardiogram or left ventricle ejection fraction below 50% on echocardiography; muscle — inflammatory myopathy, as defined by creatine kinase above upper normal value, and/or proximal muscle weakness, and/or signs of inflammatory myopathy on electromyography or magnetic resonance imaging.

Development. DUCAS is a composite clinical score proposed by 8 SSc experts regarding DU (5 senior rheumatologists, 1 junior rheumatologist, and 2 rheumatology specialist nurses with expertise in DU care). In a face-to-face meeting, with open discussion, an initial list of all potential relevant domains was compiled. Among those, a 100% consensus was achieved for 6 clinical domains related to SSc-DU status: (1) number of DU, where DU was defined as a loss of epidermal covering with a break in the basement membrane (which separates the dermis from epidermis); appearing clinically as visible blood vessels, fibrin, granulation tissue and/or underlying deeper structures (e.g., muscle, ligament, fat) or as it would be appear on debridement[12]; (2) the appearance of a new DU as defined above since the previous assessment; (3) gangrene, as the death of tissues, with the involved tissue macroscopically presenting as dry, shrunken, and dark black tissue; (4) need for surgical procedures — a procedure that is beyond the usual standard of care, defined as surgical amputation, sympathectomy, inpatient surgical debridement or plastic surgery, onabotulinumtoxin A injections, revascularization or other vascular surgical intervention; (5) need for hospitalization, clinically as the need to be hospitalized for DU treatment, not performed electively; and (6) presence of infection as evidenced by perilesional erythema or swelling, together with abundant and/or purulent exudates, sometimes with pain and odor[3]. Based on this consensus-based clinical definition, 7 variables were selected to create the DUCAS score: number of DU, new DU since the last evaluation, gangrene, infection, need for hospitalization for DU related issues, need for surgical procedures beyond the usual standard of care, and need for new prescription or titration of analgesics to control DU-induced pain. Each variable was described as a dichotomous variable (new DU since last evaluation, presence of gangrene, need surgical approach to DU, unscheduled hospitalization for DU) or as a categorical variable (no. DU, infection, analgesics to control DU-induced pain; up to 5 categories each).

In a weighting exercise, absence of the variable was scored as 0. Presence of both types of variables was weighted and the weighting was based on the mean score given to the variables when individually scored on a 1–5 basis by the 8 experts. On a clinical basis the experts decided that the decreasing analgesics were equal to –0.5.

Dichotomous variables were scored as follows: –0.5/+0.5 (decreased or increased dosage of analgesics), 0/1 (new DU absence or presence), or 0/3 (absence or presence of gangrene, need for unscheduled hospitalization for DU and need for surgical approach).

Categorical variables were weighted as follows: the number of digital ulcers was categorized according to their number as 0, 1, 2 or ≥ 3 DU; infection of DU was categorized as 0 = none, 1 = present, requiring systemic antibiotics; 2 = present, complicated by osteomyelitis; 3 = present, complicated by septicemia. The analgesics to control DU pain were evaluated for their class [categorical: 0 = no drug as no pain, 1 = no drug although pain present, 2 = nonopioid analgesics, 3 = minor opioids (e.g., codeine and tramadol), 4 = major opioids (e.g., buprenorphine, fentanyl, methadone, morphine, oxycodone, hydromorphone)] and their dosage (dichotomous: increased or decreased from previous evaluation). The categorical variables were assumed to be equally spaced.

The sum of the scores of all variables determined the total DUCAS score, with a range from 0 to 19.5, as shown in Table 1.

Procedure. During a single visit, a DU rheumatology specialist nurse completed phyGDU and collected clinical data, a SSc expert physician (blinded to the phyGDU) filled the DUCAS score, and patients were administered HAQ–DI, Cochin, DU pain, ptGDU, and ptGA. Each assessor was blinded to the PRO and the other clinical evaluations. All data were entered into a database and analyzed using statistical software SPSS for Windows, version 19.0.

Face validity was based on the consensus agreement that items reflected the logic of the concept, with all experts being asked whether the score made sense for them.

Content validity was measured by examining the range of patients examined in the sample. The measure was tested by examining sex, age, disease duration, disease type, mRSS, and lung, gastrointestinal, musculoskeletal, and laboratory results.

Table 1. Items proposed for the DUCAS and their scoring (max = 19.5).

DUCAS		
No. DU	None	0
	1 DU	1
	2 DU	2
	≥ 3 DU	3
New DU since last evaluation	Present	1
	Absent	0
Gangrene	Present	3
	Absent	0
Need for surgical procedures beyond standard of care	Present	3
	Absent	0
Infection	None	0
	Present, requiring systemic antibiotics	1
	Present, complicated by osteomyelitis	2
	Present, complicated by septicemia	3
Need for hospitalization for DU-related issues	Present	3
	Absent	0
Analgesics to control DU-induced pain	No drug, no pain	0
	No drug, although pain present	1
	Nonopiod analgesics	2
	Minor opioids	3
	Major opioids	4
	Dosage increased from previous evaluation	+0.5
	Dosage decreased from previous evaluation	–0.5
Total		

DU: digital ulcers; DUCAS: DU Clinical Assessment Score.

Construct validity required convergent and divergent correlations among the DUCAS and other measures. Convergent correlations measured the same general concept (showed positive correlations with the DUCAS). Divergent correlations tested the relationship between the DUCAS and measures that did not examine the same concept; in the latter case, no correlations should be found.

Descriptive statistics included means, SD, median, ranges and percentages. Spearman's correlation tests were used for correlations.

A linear regression model with backward stepwise analysis was used to determine the relationship of individual variables within the DUCAS with the primary clinical measure, phyGDU; this was chosen as the reference standard. It is not a good gold standard but currently it is the best available measure. All statistical tests were 2-sided and results were considered statistically significant if $p < 0.05$. Statistical analysis was performed in the R Statistical Programming Language (R Core Team).

RESULTS

Face validity was determined by giving the DUCAS to 8 experts in the field (5 senior rheumatologists, 1 junior rheumatologist, and 2 rheumatology specialist DU-care nurses). At a face-to-face meeting, a survey of the question was made and there was 100% agreement that DUCAS was logical and appropriate for further testing.

Forty-four patients with SSc were enrolled, representing a large range of patients and satisfying the requirements for content validity (Table 2). For example, their mean age was 55 ± 15 years, 27% had diffuse cutaneous disease, 73% had limited cutaneous SSc, disease duration was 2–23 years, and 80% were female. These patients represented the type and range of disease severity and organ involvement usually found in clinical trials[14,15]. There was a high prevalence of previous DU and late SSc pattern on capillaroscopy, as well as a frequent use of vasodilating and vasoactive drugs as in DU trials (Table 2)[16].

DU pain was moderate, with mean DU pain VAS 48.2 ± 31.5 mm. The mean number of DU requiring treatment was 2.0 ± 1.4, and mean DUCAS score was 4.2 ± 2 (range 0–19.5).

The DUCAS showed significant positive correlations with all tested PRO ($R = 0.44$–0.63, all $p < 0.01$; Table 3), showing construct convergent validity with commonly used clinical scores testing hand disability and functionality. Conversely, divergent validity was satisfied by the lack of correlations with measures not reflecting the same concept. There was no statistically significant correlation between DUCAS and forced vital capacity ($r = 0.19$, $p = 0.215$), creatinine blood levels ($r = –0.14$, $p = 0.328$), height ($r = 0.02$, $p = 0.895$), and creatine kinase levels ($r = 0.14$, $p = 0.546$).

In a further analysis, when all the abovementioned clinician and patient's questionnaires/scales were modeled to find those variables that independently determined the physician global estimate of DU severity, only the overall DUCAS significantly predicted phyGDU, with $r = 0.59$, $R^2 = 0.354$, and Akaike information criterion = 385.4 (Table 4).

Table 2. Clinical, laboratory, and ongoing therapeutic characterization of the study population.

Age, yrs, median (range)	55 (22–77)
Male sex	9 (20)
Height, cm, median (range)	162 (150–187)
Years since diagnosis, median (range)	10 (2–23)
ANA	44 (100)
ACA	15 (34)
Scl-70	24 (54)
RNAP-3	1 (3)
Anti-RNP	4 (9)
NVC pattern early vs active vs late	2 vs 10 vs 32 (5 vs 22.5 vs 72.5)
Limited/diffuse cutaneous subset	32/12 (73–27)
Previous DU	40 (91)
No. current DU, median (range)	2 (1–7)
mRSS, median (range)	9 (2–35)
Lung involvement	27 (61)
FVC, median (range)	91.3 (54–180)
DLCO, median (range)	59.10 (38–102)
GI involvement	28 (64)
Creatinine, mg/dl, median (range)	0.80 (0.55–1.60)
Creatine kinase, mg/dl, median (range)	94 (34–505)
PAH	8 (18)
Scleroderma renal crisis	1 (2)
Cardiac involvement	11 (25)
Muscular involvement	8 (18)
Intravenous iloprost	26 (59)
Endothelin receptors antagonists	18 (41)
Phosphodiesterase 5 inhibitors	13 (31)
Calcium channel blockers	14 (32)
Losartan	16 (36)
Fluoxetine	8 (18)
Mycophenolate mofetil	9 (20)
Methotrexate	8 (18)
Azathioprine	1 (2)
Hydroxychloroquine	7 (16)
Steroids < 7.5 mg/day prednisone equivalent	19 (43)
Statins	9 (20)

Data are n (%) unless otherwise indicated. ACA: anticentromere antibodies; ANA: antinuclear antibodies; DU: digital ulcers; FVC: forced vital capacity; mRSS: modified Rodnan skin score; NVC: nailfold videocapillaroscopy; RNAP-3: anti-RNA polymerase III antibodies; Scl-70: antitopoisomerase I antibodies; GI: gastrointestinal; PAH: pulmonary arterial hypertension.

Table 3. Spearman correlations for DUCAS and other physician and patient outcome measures.

	Spearman's Correlation with DUCAS	p
PtGA	0.56	< 0.001
PtGDU	0.54	< 0.001
DU pain	0.44	0.003
HAQ-DI	0.44	0.003
Cochin	0.51	< 0.001
PhyGDU	0.63	< 0.001

DU pain: pain due to digital ulcer; DUCAS: DU Clinical Assessment Score; HAQ-DI: Health Assessment Questionnaire–Disability Index; PhyGDU: global assessment of DU by expert physician/nurse; PtGA: patient's global assessment; PtGDU: patient's global assessment of DU; Cochin: Duruoz Hand Index.

DISCUSSION

DU are a frequent SSc complication, requiring prompt medical intervention for treatment, or prevention. Their presence may determine disability and have an important effect on daily activities, function, and quality of life.

Table 4. Linear models to predict phyGDU for DUCAS and other physician and patient outcome measures.

	Estimate	SE	p
PtGA	0.011	0.199	0.955
PtGDU	0.171	0.233	0.467
DU pain	0.048	0.182	0.793
HAQ-DI	4.58	7.563	0.549
Cochin	0.035	0.252	0.891
DUCAS	4.636	1.617	0.007

Cochin: Duruoz Hand Index; DU pain: pain due to digital ulcer; DUCAS: DU Clinical Assessment Score; HAQ-DI: Health Assessment Questionnaire–Disability Index; NA: not applicable; phyGDU: global assessment of DU by expert physician/nurse; PtGA: patient's global assessment; PtGDU: patient's global assessment of DU.

Currently, the most frequently used measure to detect DU changes is the overall DU count or the presence/absence of new DU since the previous assessment. RCT such as the RAPIDS-2 used these variables as primary or secondary endpoints to test drug efficacy, together with time to healing and disability[16]. These difficulties and results point to a lack of a globally accepted DU definition and to the challenges and variability of grading DU, even when done by experts[16,17,18]. These observations suggest that a new, more objective score could be useful to measure DU in SSc. A recent publication by Ahrens, *et al* proposed a DU severity score based on depth and diameter of the lesions (both hyperkeratosis and ulcers), which was not correlated with the baseline hand functionality questionnaire but significantly reflected changes in time[17]. When compared to the Ahrens, *et al* score, DUCAS may be less time-consuming (especially when patients have multiple lesions) and is specific, limiting itself to DU. This anatomic limitation was specifically chosen because there now exists a specific DU definition (also recently revised after a systematic review analysis)[12] and because DU are felt to be pathogenetically microvascular and ischemic in nature, for which effective preventing/healing drugs are available. We are aware that other classifications for DU have been published, including the one proposed by Baron, *et al*[18]. Also, *ad hoc* definitions have been used in RCT. If one used those ulcer definitions, one might have arrived at different results. We feel that the definition used in our study is a relatively objective one and is, in fact, undergoing further validation in other contexts, thus allowing further evaluation of DUCAS using a fully validated definition of DU. Also, the other aspects of the DUCAS are relatively specific and straightforward, and therefore the definition/classification used is likely to be acceptable and credible.

The DUCAS was developed to test efficacy in clinical trials but might also be helpful in clinical practice. It expands the "usual" items used in efficacy evaluations because it includes reduction in DU-related complications (certainly a

beneficial drug effect), not only a decrease in the number of DU. Although patient input is important, DUCAS is an investigator/physician–defined measure and for this reason patients were not involved in the development process. The DUCAS score, once validated, could be a useful outcome measure in parallel with dedicated PRO.

Our study proposes a simple primarily objective composite tool to assess the general effects of peripheral SSc microvascular alterations, including not only the DU count but also new measures and DU-related complications, such as infection, pain, gangrene and hospitalization/surgery.

The DUCAS score has some strengths. It is developed in a reasonably formal manner, so it should be possible to use it in RCT to test drug efficacy. It is being developed in an appropriate population of patients with SSc and there were no missing data. The questions in the DUCAS make sense (face validity) and it applies across a relatively large range of patients (content validity). It correlates with other measures of the same construct and does not correlate with measures not measuring the same construct (construct validity). Although not specifically tested (this needs to be done formally), it is obviously feasible, requiring little time and requiring elements that are easily obtained during routine care. Finally, it was shown to be comparable to the phyGDU. While the phyGDU is inherently subjective, the DUCAS is made up of objective or semiobjective measures and thus should lead to more uniform outcomes and clearer, more credible, and more discriminating results.

Our present study has some limitations, although these are, in our view, reasonable, given the preliminary nature of the work to date. While including 44 patients of varying age, sex, disease duration, disease subsets, etc., an even larger group of patients would be desirable. A minimal clinically important difference should be derived. Other studies, done longitudinally, will be needed to test responsiveness and discrimination.

During such studies, one could consider using imaging tools such as ultrasound[19] to support counting DU as objectively as possible. Other microvascular imaging techniques such as nailfold videocapillaroscopy and laser techniques[20] could also be used to compare microvasculature and DU evolution with treatment.

The DUCAS is a consensus-derived composite score that is now partially validated. It includes DU activity, hand and overall function, and complications that may reflect a more comprehensive approach to DU than measuring the number of DU or whether they are healed.

Our study shows that DUCAS has preliminary validity with face, content, and construct validity, and good correlation with disability/functionality indices. It also has feasibility informally. Completion of full validation in SSc, using Outcome Measures in Rheumatology (OMERACT) criteria, and including responsiveness and discrimination, remains to be done.

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