THE DUCAS: A PRELIMINARY PROPOSAL FOR A DIGITAL ULCER CLINICAL ASSESSMENT SCORE IN SYSTEMIC SCLEROSIS

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ABSTRACT

OBJECTIVES: At present, "healed/non-healed" and clinical judgment are the only available assessment tools for digital ulcers(DU) in Systemic sclerosis(SSc) patients. 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: SSc patients presenting at least one finger DU were enrolled and assessed with Health assessment questionnaire disability index (HAQ-DI), Cochin scale, Visual analogic scale(VAS) for DU-related pain, global DU status(ptGDU) and patient global assessment as PROs and physician VAS for DU status(phyGDU) as a physician 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 though consensus and partial construct validity was tested through converting correlation with other measures of hand function, through Spearman's correlation test. A range of SSc patients was examined. A linear regression model with forward and backward stepwise analysis was used to determine the relationship of individual variables with the primary clinical parameter, phyGDU.

RESULTS: 44 SSc patients(9 males, mean age 54,3±15,6 years, mean disease duration 9,9±5,8 years) were enrolled in the study. Overall DUCAS showed significant positive correlations with all abovementioned PROs($r>0.4$, $p<0,01$). When all scores and scales were modeled, only DUCAS significantly predicted phyGDU($r=0.59$, $R^2=0.354$, AIC=385.4).

CONCLUSIONS: Preliminarily, we suggest that the DUCAS may be new clinical score for SSc related DU, having face validity, content validity and convergent/divergent correlations (construct validity). These early data need suggest that this score deserves further evaluation.

KEY WORDS: systemic sclerosis, digital ulcer, outcome measures, score

INTRODUCTION

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. In addition, they may result in complications such as infections, which in turn can lead to gangrene, osteomyelitis and 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 estimated to be approximately 10-12 weeks [3]. For these reasons, reliable, valid, outcome measures that can be used in randomized clinical trials (RCTs) to improve the assessment of DU therapy in SSc, as well as in clinical practice, need to be developed.

Some tools are available. Many patients reported outcomes (PROs) have previously been validated, with HAQ-DI being patient-oriented and well-known: it assesses disease-related disability [4-8], while the Cochin Scale is available to assess hand focused functional disability [9]. Visual Analogic Scales (VAS), focused on pain (DU_pain), patient's general assessment of the disease (PtGA) and global assessment of DU, both by the patient (PtGDU) or by the physician/nurse (PhyGDU) are other tools that may be used in daily practice [8]. Despite these measures can be employed in SSc, there is no valid tool available to assess DU progression or healing. Up to now in RCTs, only the "healed-not/healed" assessment of DU was considered, while a real composite evaluation tool to assess DU progression, in particular referring to either improvement or worsening, is lacking. Thus, there is a need for a validated method to objectively evaluate the drugs' efficacy on DU in SSc.

The aim of this study is to start the process of developing a preliminary composite DU clinical assessment score (DUCAS) by testing its face, content and construct validity.

METHODS

Patients classified as SSc according to the 2013 ACR/EULAR classification criteria [10], aged older than 18, presenting at least one finger DU and attending the Wound Care Clinic of the Departments of Rheumatology of the University Hospital of Florence and of the Royal Free Hospital in London, were enrolled in the study. Patients gave voluntary, informed consent for study participation and local Ethical Committee approval was obtained for the study.

Baseline disease background data were collected, including age, gender, disease related autoantibodies (including anti-nuclear antibodies, anti-centromere antibodies, anti-topoisomerase I, anti-RNA polymerase III antibodies, etc), skin involvement (limited or diffuse), modified Rodnan

skin score, history of previous digital ulcers, nailfold videocapillaroscopy pattern, internal organ involvement (i.e. gastrointestinal, articular, pulmonary arterial hypertension, interstitial lung disease, kidney, heart, muscle) and ongoing treatment (vasoactive and/or immunosuppressive).

The DUCAS is a composite clinical score proposed by 8 experts in the field of SSc related DUs (5 senior rheumatologists, 1 junior rheumatologist and 2 rheumatology specialist nurses with expertise in DU care). The committee, based on 100% consensus, selected 5 clinical domains related to SSc-DU status: 1. a *new DU* as the appearance of a new loss of skin epithelium involving the epidermis, the dermis, the subcutaneous tissue and, sometimes, the bone [3]; 2. *Gangrene*, the death of tissues, with the involved tissue macroscopically presenting as dry, shrunken and dark black tissue [3]; 3. *Need for hospitalization*, clinically as the need to be hospitalized for treatment, not performed electively; 4. *Need for surgical procedures* - the need to undergo an over the standard of care procedure, defined clinically, such as surgical amputation, sympathectomy, inpatient surgical debridement or plastic surgery, botox injections, revascularization or other vascular surgical intervention; 5. *Presence of infection* as evidence of peri-lesional erythema or swelling, together with abundant and/or purulent exudates, sometimes with pain and typical smell [3]. Based on this consensus-based clinical definitions, 7 variables were selected to create the DUCAS score: number of DU, appearance of new DU since the last visit, presence of gangrene, presence of infection, need for hospitalization for DU related issues, need for surgical procedures over standard of care, need for new prescription or titration of analgesics to control DU-induced pain. Presence/absence of some item, as well as different degrees or classes of others, were given a score from 0 to 5 representing the severity of the single item according to each committee member personal clinical experience. Mean scores for each parameter was then calculated and used to create the DUCAS score, with range from 0 to 19.5 (see Table 1 for details).

On the same visit, a DU rheumatology specialist nurse completed PhyGDU, a SSc expert filled the DUCAS score and patients were administered HAQ–DI, Cochin, DU_pain, ptGDU and ptGA. Each assessor was blinded to the PROs and the other clinical evaluation, which were all entered in a database and analyzed using statistical software SPSS for Windows, version 19.0. First, face validity was decided based on the consensus agreement that items reflected the logic of the concept.

Spearman's correlation tests for the overall DUCAS were calculated to examine construct validity, wherein other measures of the same construct were correlated with the DUCAS (convergent correlation). A linear regression model with forward and backward stepwise analysis was used to determine the relationship of individual variables within the DUCAS with the primary clinical parameter, phyGDU. Results were considered statistically significant if $p<0.05$.

RESULTS

Forty-four SSc patients were enrolled in the study and represented a large range of patients, with 27% diffuse and 73 % limited cutaneous SSc (disease duration of 2-23 years, 80 % female). These patients presented high prevalence of lung and gastrointestinal involvement (61% and 64% respectively) and 18% of them were also affected by pulmonary hypertension. There was a high prevalence of a history of previous DU and late NVC SSc pattern on capillaroscopy, as well as a frequent use of vasodilating and vasoactive drugs (see Table 2 for further study population characterization).

Face validity was determined by consensus among 8 experts in the field ranging from senior to junior rheumatology faculty and including SSc-DU expert nurses as well.

There was moderate functional disability, with mean HAQ-DI 1.1±0.8 and mean COCHIN 28.9±19.6. Overall, DU pain was also moderate, with mean value on 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. There was a statistically significant difference between physician and patient assessment, with mean phyGDU 44,3±23mm and mean ptGDU 54±30mm (Wilcoxon p=0.022, phyGDU versus ptGDU), although this difference was the bordered of the minimally clinical important difference for these measures and thus represents a very borderline difference [11]. Overall DUCAS showed significant positive correlations with all tested PROs (see Table 3), showing construct convergent validity with commonly used clinical scores testing hand disability and functionality. Conversely, no statistically significant correlation was seen between DUCAS and FVC (r=0.19, p=215), creatinine blood levels (r=-0.14, p=0,328), height (r=0.02, p=0,895) and creatinine kinase levels (r=0.14, p=0,546), thus showing construct divergent validity.

In a further analysis, when all the above-mentioned clinician and patient's questionnaires/scales were modeled, only the overall DUCAS significantly predicted PhyGDU, with r=0.59, R^2= 0.354 and AIC=385.4 (see figure 1). After backwards stepwise analysis overall DUCAS and ptGDU best predicted PhyGDU, with an adjusted r=0.66, R^2=0,437 and AIC=380,3 (see Table 3).

CONCLUSIONS

Our study shows that DUCAS has face, content and construct validity, with good correlation with disability/functionality indexes. It represents a preliminary step toward validation of this measure

both for clinical trials and clinical practice. A complete validation process in a larger study population involving multiple different rheumatology centers is needed to evaluate the remaining OMERACT criteria (further measurement for content validity, construct validity, reliability, responsiveness, discrimination, responsiveness, feasibility in SSc).

DU are a frequent complication requiring prompt medical intervention for treatment, or prevention. Their presence may determine disability with an important limitation in daily life activities, function and quality of life. The data on our study population shows a general low to moderate disability level measured by HAQ-DI, while hand functionality and pain were definitely more severe. This is supported by the recent results of Mouthon *et* al, showing the relevant difference of the impairment of hand functionality and pain perception in patients with and without DU [12]. The similarity of HAQ-DI levels might be influenced by the presence of activities beyond hand function among its items [12]. Patient-reported outcomes have also been previously used in RCTs assessing the response in the RAPIDS-1 & 2 studies showed that variations in HAQ-DI were significantly associated with DU status change [13].

Presently, the only available measure to detect DU changes is the overall DU count, or the presence/absence of new DU since the previous assessment. RCTs such as the RAPIDS-2 used these parameters as primary or secondary endpoint to test drug efficacy, together with time to healing and disability parameters [14]. The assessment of these endpoints may be influenced by the investigator experience in judging DU presence/absence, also taking into consideration the lack of a globally accepted definition of DU. All these observations suggest that a new score should be employed 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 baseline hand functionality questionnaire but significantly reflected changes in time [15]. When compared to it, DUCAS may be less time consuming (especially in case of patients with multiple lesions) and only included DU: this was specifically chosen due to the existence of a specific definition (also recently revised after a systematic review analysis) [16] and to the known microvascular ischemic nature, for which effective preventing/healing drugs are available. In this light, DUCAS could be helpful in clinical practice and in RCTs to test drug efficacy: in fact, not only the DU decrease in number but also the reduction in DU-related complications could be considered a beneficial drug effect.

For this purpose, our study proposes a new 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/surgical approach.

The present study has some limitations, although these are, in our view, reasonable, given the preliminary nature of the work thus far. While including 44 patients of varying age, gender, disease duration, disease subsets etc, an even larger group of patients would be desirable. The DUCAS scoring and questions will need testing for linearity, weighting and to show that they represent an appropriate interval scale. Other studies, done longitudinally will be needed to test responsiveness and discrimination and criterion validity will be very difficult to test. However, the DUCAS score has also some strengths. It is being developed in an appropriate population of SSc patients and the composite score shows face, content and significant construct validity. En face, the questions in the DUCAS make sense and it seems a useful in a large range of patients. 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.

In conclusion, the DUCAS is a consensus-derived composite score which is now partially validated. It includes DU activity, hand and overall function and complications that may reflect a more comprehensive approach on DU than the measure of a single DU or the fact that is healed or not healed. Moreover, DUCAS might be used in RCTs, testing the drug effect on DU.

KEY MESSAGES

− DUCAS is a simple composite scoring system which allows evaluation of digital ulcers in

systemic sclerosis

− DUCAS correlates well with clinician evaluation of the ulcer and of patient's evaluation of

disability and functionality of hands

− DUCAS may become, once validated, an objective tool to be used in randomized clinical

trials.

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Table 1. The items proposed for the DUCAS and items scoring (max=19,5)

DUCAS								
1	**Number of Digital Ulcers**						None	0
							1 DU	1
							2 DUs	2
							More than 3 Dus	3
2	**New Digital Ulcers**						YES	1
							NO	0
3	**Gangrene**						YES	3
							NO	0
4	**Surgical approch to DU (above standard care)**						YES	3
							NO	0
5	**Infection of DU**						None	0
							Requiring systemic antibiotics	1
							Osteomyelitis	2
							Septicemia	3
6	**Unscheduled hospitalisation for DU**						YES	3
							NO	0
7	**Analgesics to control DU pain**						No pain	0
							Non requiried analgesics	0,5
							Non-opioids analgesics	1
							Minor opioids	2
							Major opioids	3
							dose increased since last visit	*+0.5*
							dose decreased since last visit	*-0,5*
							TOTAL SCORE	

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

Age - median (range)	55 (22-77)
Male gender - n (%)	9 (20)
Height , cm – median (range)	162 (150-187)
Years since diagnosis - median (range)	10 (2-23)
ANA - n (%)	44 (100)
ACA - n (%)	15 (34)
Scl70 - n (%)	24 (54)
RNAPol3 - n (%)	1 (3)
antiRNP - n (%)	4 (9)
NCV patter early vs active vs late - n (%)	2 vs 10 vs 32 (5 vs 22,5 vs 72,5)
limited/diffuse - n (%)	32/12 (73-27)
Previous DU - n (%)	40 (91)
Number current DU - median (range)	2 (1-7)
mRSS- median (range)	9 (2-35)
Lung involvement - n (%)	27 (61)
FVC - median (range)	91,3 (54-180)
DLCO - median (range)	59,10 (38-102)
Gastrointestinal involvement - n (%)	28 (64)
Creatinine, mg/dl – median (range)	0.80 (0.55-1.60)
Creatinine-kinase, mg/dl – median (range)	94 (34-505)
Pulmonary hypertension - n (%)	8 (18)
Scleroderma renal crisis - n (%)	1 (2)
Cardiac Involvement - n (%)	11 (25)
Muscular involvement - n (%)	8 (18)
Intravenous Iloprost - n (%)	26 (59)
Endotelin Receptors Antagonists - n (%)	18 (41)
Phosphodiesterase 5 inhibitors - n (%)	13 (31)
Calcium Channel Blockers - n (%)	14 (32)
Losartan - n (%)	16 (36)
Fluoxetine - n (%)	8 (18)
Mycophenolate Mofetil - n (%)	9 (20)
Methotrexate - n (%)	8 (18)
Azatioprine - n (%)	1 (2)
Hydroxychloroquine - n (%)	7 (16)
Steroids < 7,5 mg/day prednisone equivalent - n (%)	19 (43)
Statins - n (%)	9 (20)

Table 3. Spearman correlations for DUCAS and linear models to predict PhyGDU

	Linear Regression for DUCAS		Linear Model to PhyGDU			Linear Model to PhyGDU after backwards stepwise		
	Spearman Correlation	p	Estimate	SE	p	Estimate	SE	p
PtGA	0,56	<0,001	0,011	0,199	0,955			
PtGDU	0,54	<0,001	0,171	0,233	0,467	0,272	0,101	0,01
DU_Pain	0,44	0,003	0,048	0,182	0,793			
HAQ-DI	0,44	0,003	4,58	7,563	0,549			
COCHIN	0,51	<0,001	0,035	0,252	0,891			
PhyGDU	0,63	<0,001	N.A.	N.A.	N.A.			
DUCAS	N.A.	N.A.	4,636	1,617	0,007	4,841	1,489	0,002

PtGA= patient global assessment; PtGDU: patient global assessment of digital ulcer; DU pain= pain due to digital ulcer; PhyGDU= Physician global assessment of digital ulcer; HAQ-DI= health assessment questionnaire disability index; N.A.= Not Applicable