Digital ulcers score: a scoring system to assess digital ulcers in patients suffering from systemic sclerosis

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ABSTRACT

Objective. *To develop a standardised scoring system to assess the severity of DUs in SSc patients and correlate it with functional outcomes.*

Methods. *In this cross-sectional, longitudinal study in SSc patients with DUs (n=65) we developed a Digital Ulcers score (DUS) for the assessment of DUs. DUS and the ABILHAND score were measured at each visit and differences were analysed using Tamhane's T2 test. Spearman's Rho test was applied for correlational analysis of DUS and functional outcomes. We calculated a linear regression model using clustered standard errors for correlation analysis between DUS and ABILHAND over time.*

Results. *117 assessments of DUS were performed in 65 SSc patients. Mean DUS was 11.6±1.9 (range: 0-68). Subgroup analyses showed a higher DUS in patients suffering from diffuse cutaneous SSc when compared to patients with limited cutaneous SSc (12.8±3.0 vs. 9.7±2.2 p=0.18). There was no correlation between the DUS and manual ability using the ABILHAND score (overall: n=106 r=-0.138, p=0.22). We observed a small but significant linear correlation between the DUS and the ABILHAND-score for a single patient over time (n=14, R2=0.31, r=0.06, p=0.02).*

Conclusion. *The DUS is a feasible scoring instrument to assess severity of DUs in SSc patients. In accordance with the literature the severity of DUs correlates with clinical parameters but also severity of the disease. Further study is needed to establish the DUS as a standardised tool for the assessment of DUs.*

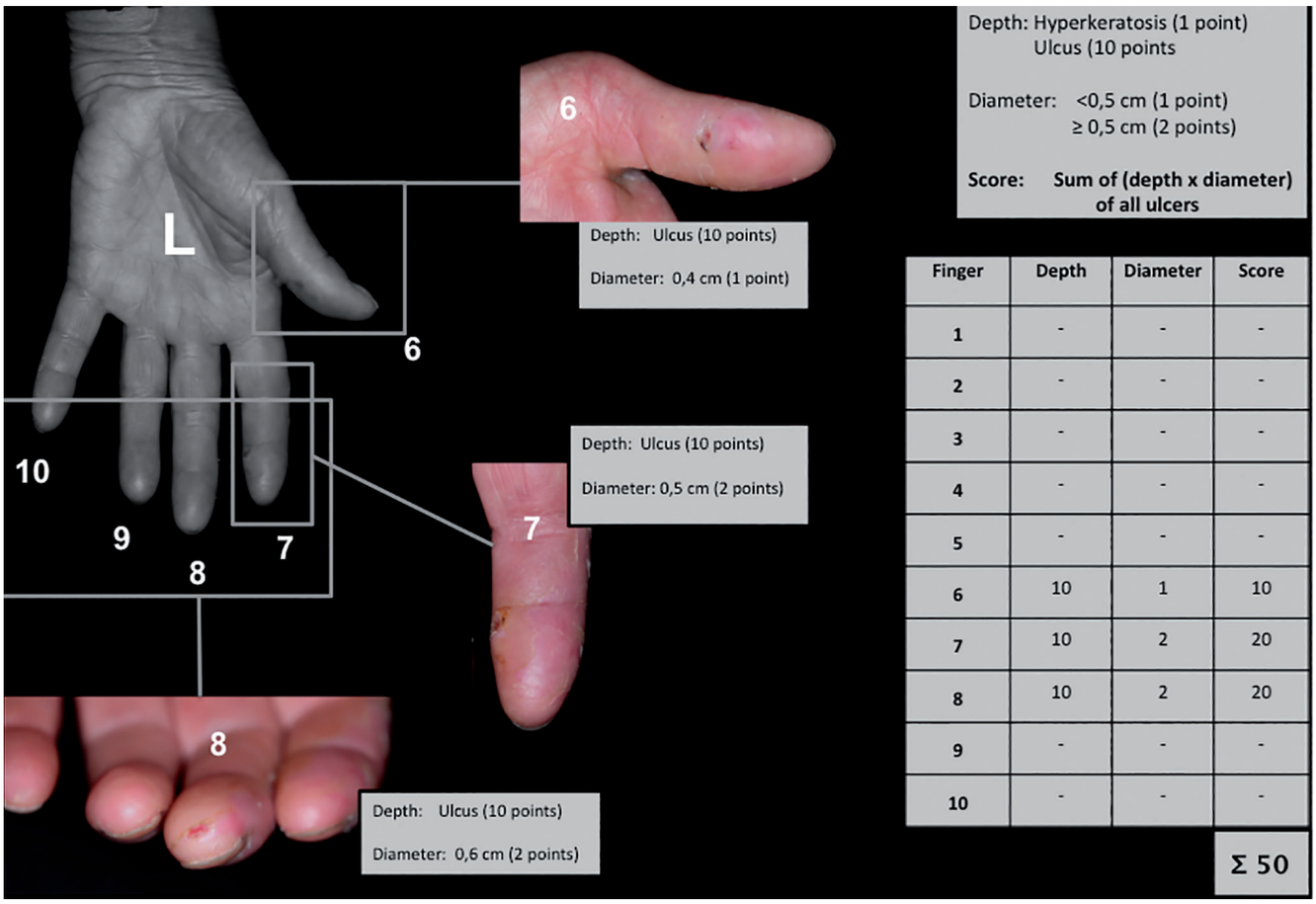
Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease that is characterised by vascular dysfunction, inflammation and fibrosis, both of the skin and of internal organs. One of the most painful complications of the underlying vasculopathy in SSc are digital ulcers (DUs) which are epithelial lesions with tissue loss occurring at the fingers or the feet (1). Digital lesions can be classified into three groups: DUs that developed on digital pitting scars, primary DUs and DUs that develop on calcinosis (2). While the precise pathological sequence of events leading to DUs is still unknown, histopathological studies have shown obliterative vasculopathy in the dysfunctional vessels (3).

Up to 50% of the patients suffering from SSc will develop a DU at least once during the course of their disease (2, 4). In one third of those patients DUs become a persistent problem with slow healing and frequent reoccurrence; around 12% of patients with DUs requiring hospitalisation either for vasoactive treatment to support the healing process or antibiotics to treat infection (5, 6). Some patients also require surgical treatment, although medical therapy of DUs remains the primary aim. However, despite modern treatment options it is not possible to prevent the occurrence of new DUs nor is always it possible to prevent progression of active DU to gangrene or autoamputation.

There is a need for an accurate, reproducible and feasible method of assessing the severity of DUs for both clinical decision-making and for medical studies. While some authors characterised DUs by measuring diameter and area of DUs (7-9), others tried to measure DUs using photography (10, 11). The number of DUs and the number of healed DUs still remain the most frequent used outcome parameters in clinical studies evaluating the therapeutic effects in patients suffering from DUs. Up to now there is no established standardised method to quantify the severity of DUs.

The aim of this study was to develop a standardised scoring system for DUs



Finger	Depth	Diameter	Score
1	-	-	-
2	-	-	-
3	-	-	-
4	-	-	-
5	-	-	-
6	10	1	10
7	10	2	20
8	10	2	20
9	-	-	-
10	-	-	-

Fig. 1. Exemplary presentation of the assessment of DUs with the DUS. DUs: Digital ulcers; DUS: Digital Ulcers score.

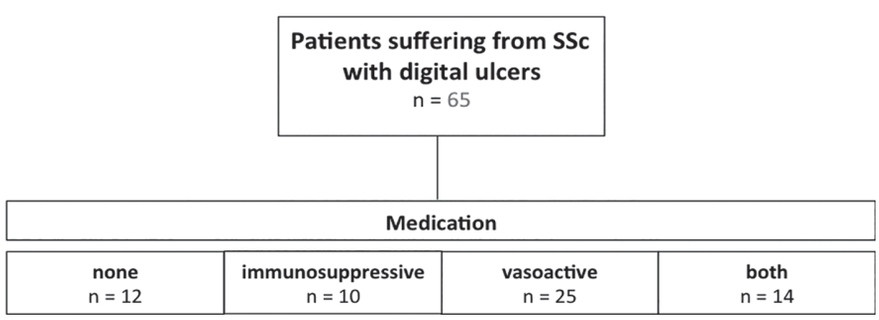


Fig. 2. Study cohort.
Overal, 65 patients suffering from SScl were included in the study. 117 assessment of Digital Ulcer score (DUS) was performed. 19.7% of the patients rwceived no medication, 16.4% received immunossuppressants, 41% received isoactive medication and 21.9% of the patients received both, vasoactive and immunossuppressive medication. n: number; SSc: systemic sclerosis.

and to correlate the score with established functional data on manual ability in a cross-sectional and a longitudinal approach.

Materials and methods

Patients and study design

Between 2013 and 2015 patients suffering from SSc with DUs and presented at our interdisciplinary outpatient clinic at the Department of Rheumatology and Dermatology, Charité University Hospital Berlin, Germany were enrolled in the study. By using a cross-sectional and longitudinal approach we aimed to develop a scoring system to assess the severity of DUs in SSc patients.

Ethics statement

The observational and anonymous nature of the analysis in this study did not require additional formal ethical review and individual patient written consent according to the Charité University Hospital ethics committee.

Assessments

Each time when patients were seen at our special consultations, number, localisation and extent of DUs were assessed. In order to avoid an inter-rater variability the same specialist physician evaluated DUs and calculated the DUS. Manual ability as functional outcome was assessed with the ABILHAND questionnaire. It evaluates the difficulties a patient may experience in performing manual activities of daily living (13).

At the time of inclusion the modified Rodnan Skin Score (mRSS) and the presence of joint contractures were recorded. Joint contractures were defined as stiffness of the finger joints due to fibrosis of tendons and ligaments or the muscles themselves.

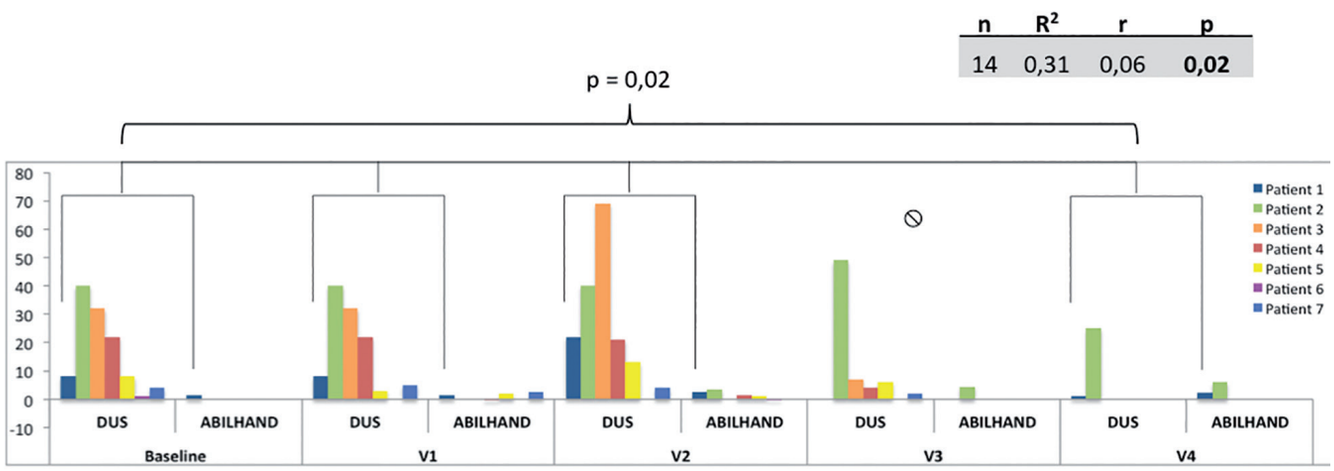
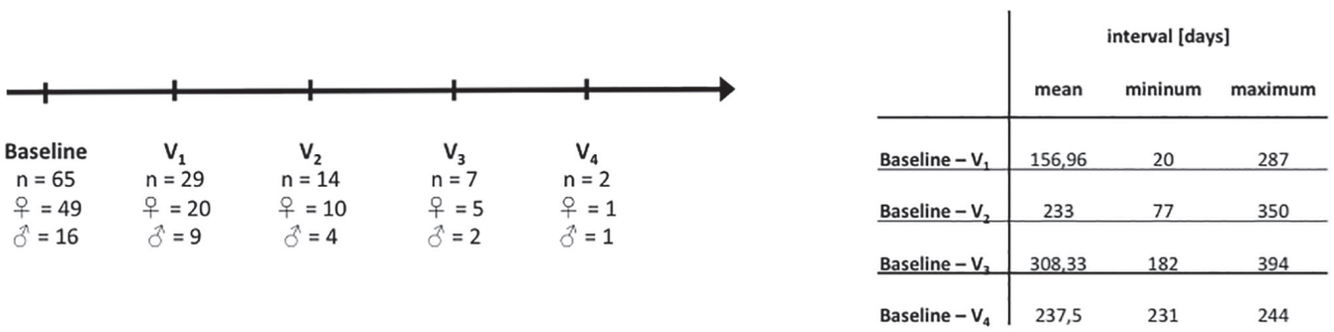


Fig. 3. Correlation between Digital Ulcer score (DUS) and manual ability over time.
Manual ability was measured using the ABILHAND score. On the x-axis baseline visit and follow up visits are depicted. Each patient was assigned to a different colour. At each visit assessment of DUS and ABILHAND score was performed. The ratio of DUS and ABILHAND Score was analysed for each accepted for patient over time using a linear regression model with standard clustered errors. Significance was $p<0.05$.



	interval [days]		
	mean	mininum	maximum
Baseline – V_1	156,96	20	287
Baseline – V_2	233	77	350
Baseline – V_3	308,33	182	394
Baseline – V_4	237,5	231	244

Fig. 4. Study design.
Within our interdisciplinary outpatient clinic patients suffering from systemic sclerosis were assessed every time they visited our special consultation. Overall, n=19 patients were followed up once. Up to 4 follow-up visits were recorded. n. number; V1-V4: Follow-up visits.

Data regarding the course of the disease *i.e.* disease duration, age of disease onset, presence of autoantibodies, cutaneous classification of disease, medical history, presence of contractures and current medication were collected.

Development of the Digital Ulcers score (DUS)

In a first step we developed a scoring system to assess the severity of DUs in a standardised manner (appendix). In order to assess the extent of DUs the localisation, size, depth and nature of DUs were recorded at each visit. Keratotic and ulcerative lesions were included for development and verification of the score. Consequently, the DUS results from assessing each single ulcer by multiplying the depth of the ulcer (1 point for hyperkeratosis, 10 points for ulcus) by the diameter (1 points if <0.5 cm, 2 pints for 0.5cm). The score is then calculated as the sum score of all ulcers. An example of the assessment of DUs with the DUS is shown in Figure 1.

Analyses

In a second step patients' characteristics at baseline and at each follow-up visit were evaluated. Correlation analysis of the DUS and the functional outcome at each visit was performed using Spearman's Rho test. In order to analyse the correlation between the DUS and the functional outcome *i.e.* ABILHAND for each single patient over time a linear regression model using standard clustered errors was calculated.

For all tests, statistical significance was set at $p<0.05$. Analyses were performed using SPSS 20 statistical software (SPSS Inc., Chicago, USA) statistical software and STATA 13 data analysis and statistical software (StataCorp LP, College Statopm. USA). Data is presented as mean ± SEM for parametric variables and mean ± SE for non-parametric variables.

Results

Characterisation of the study cohort

65 patients suffering from SSc with DUs, 52 female and 13 male patients, were included in the study (Fig. 2). 29 patients were seen for at least two visits with a maximum interval of 287 days (Fig. 4). Seven patients were followed up for three follow-up visits and were included into the longitudinal analyses. A total of five follow-up visits were assessed (Fig. 4).

Mean age at baseline was 52±15 years, with a mean duration of disease of 11.3±10.1 years and a mean age of onset of 42.0±17.9 years (Table I). The

Table I. Characterisation of the study population at baseline visit. All collected parameters were analysed. mRSS: modified Rodnan Skin Score.

Characteristics	Overal n=65 mean + SEM		Overal n=65 n	%
		Medication		
Age (yrs)	52 ± 15	none	12	18.8
Duration of disease (yrs)	11.29 ± 10.1	immunosuppressive	10	15.6
Age of onset (yrs)	42.0 ± 17.9	vasoactive	25	39.1
Ulcer (n)	3.59 ± 3.1	both	14	21.9
mRSS	9.12 ± 6.4	*Type of diseases*		
		limitd cutaneous	34	54.8
		diffuse cutaneous	28	45.2

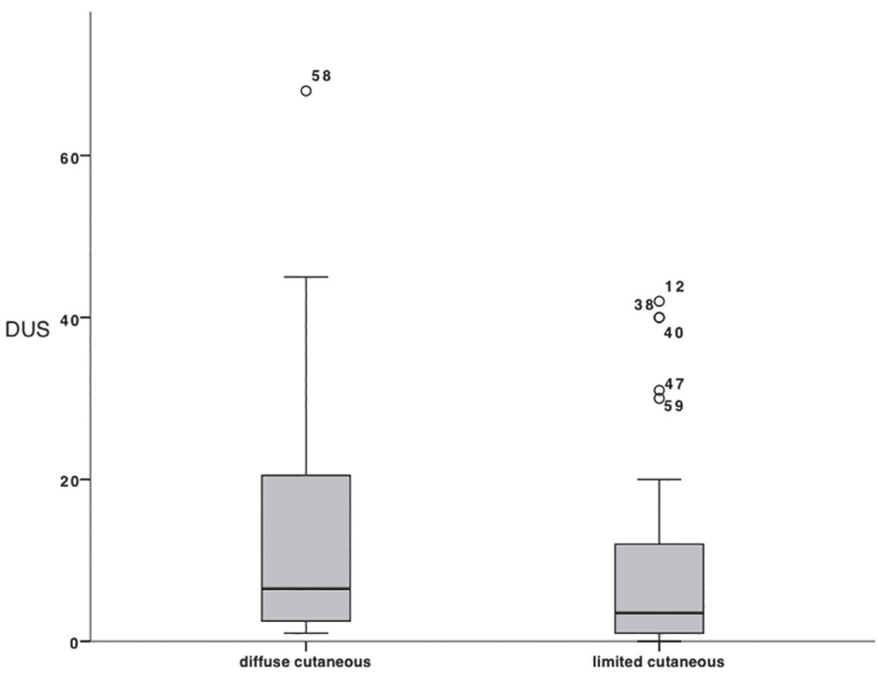


Fig. 5. Digital Ulcers score (DUS) in patients suffering from systemic sclerosis with regard to the type of disease.
Mean DUS was 12.82±3.0 (SE) in patients suffering from diffuse cutaneous SSc. Patients with limited cutaneous SScl had a mean DUS of 9.74±2.2 (SE). Mann-Whitney U-Test was performed, significance was accepted for $p<0.05$. DUS: Digital Ulcers score; SSc: systemic sclerosis.

patients enrolled showed a mean of 4±3 DUs, mean mRSS was 9.1±6.4 (Table I).

Overall, 18.6% (n=12) of the patients enrolled did not receive any medication (group 1), while 15.6% (n=10) of the patients received immunosuppressants, 39.1% (n=25) of the patients received vasoactive and 21.9% (n=14) of the patients received both, immunosuppressive and vasoactive medication (Fig. 2). 54.8% (n=34) of the patients in our study were suffering from limited cutaneous (lc) SSc, 45.2% (n=28) of the patients were suffering from diffuse cutaneous (dc) SSc (Table I).

DUS and correlation to hand function

Altogether 117 assessments in SSc patients suffering from DUs using the DUS were performed. Overall, the mean DUS was 11.6±1.9 (range: 0–68; Fig. 5). Further subgroup analyses showed a higher DUS in patients suffering from dcSSc when compared to patients with lcSSc (12.8±3.0 *vs.* 9.7±2.2 $p=0.18$).

We observed higher mean DUS in patients receiving immunosuppressive and vasocactive medication than in patients with immunosuppressive, vasoactive or no medication. However, this difference did not reach statistical significance due to the limited number of patients observed (Fig. 6).

A correlation analysis between the DUS and manual ability measured by the ABILHAND questionnaire did not show a significant correlation (overall: n=106 r=-0.138, $p=0.22$; Fig. 3). Looking at the correlation between the DUS and the hand function over time, we applied a linear regression model using clustered standard errors. Here we found a small, albeit significant linear correlation between the DUS and the ABILHAND score (n=14, $R^2=0.31$, r=0.06, $p=0.02$; Fig. 7).

Accounting for the fact that finger contractures might be a confounder of hand function we assessed whether there was a significant difference in hand function between patients with ≥ 5 finger joint contractures and patients with <5 contractures. We did not find any differences between the groups suggesting that in the present study contractures are not a confounding variable of hand function.

Discussion

Although there is a recent increase in the number of studies describing patients suffering from DUs, a standardised tool to evaluate the severity of DUs is still missing. It is important to have such a tool in clinical practice, in particular if therapeutic effects of interventional therapies have to be monitored over time.

In this study we were not able to delineate a significant correlation between the DUS and hand function. This might be due to one of the shortcomings of the present study. For the assessment of hand function the ABILHAND score was the only parameter assessed. One might argue that additional scoring, such as the Scleroderma Health Assessment Questionnaire (SHAQ) Visual Analogue Scale (VAS) and the Cochin Hand Function Scale (CHFS), is required to better evaluate hand function. It might also be appropriate to consider more confounding parameters. For example, a standardised recording of pain might deliver valuable information to account for pain-related impairment in hand function without presence of DUs. Furthermore, not only digital ul-

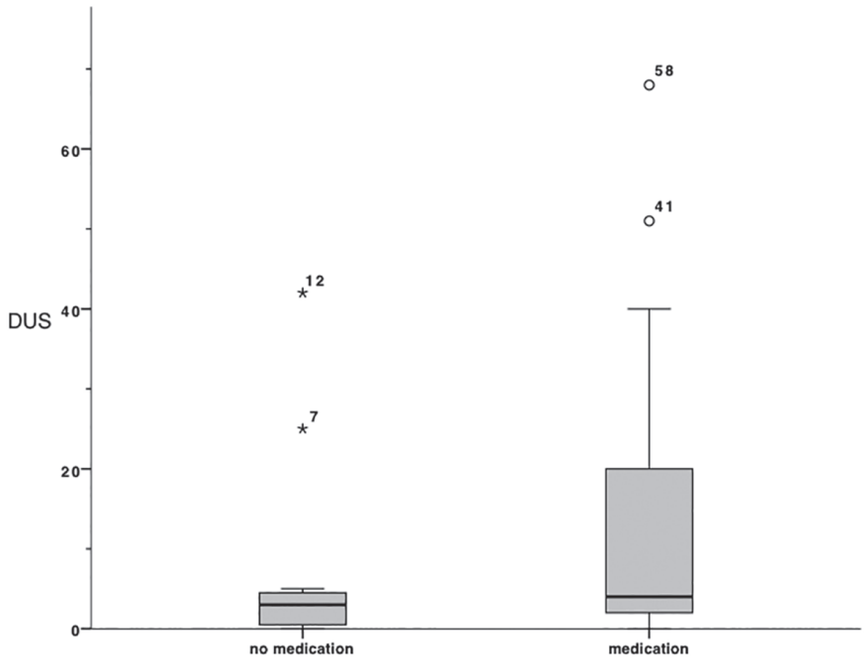


Fig. 6. Digital Ulcers score (DUS) in patients suffering from systemic sclerosis with regard to their current therapeutic regime.
Mean DUS was 7.33±3.7 (SE) in patients who did not receive any medication. Patients who were under medication(immunosuppressivevasoactive/both) had a mean DUS 11.82+2.1 (SE). Mann-Whitney U-Test was performed, significance was accepted for $p<0.05$. DUS: Digital Ulcers score.

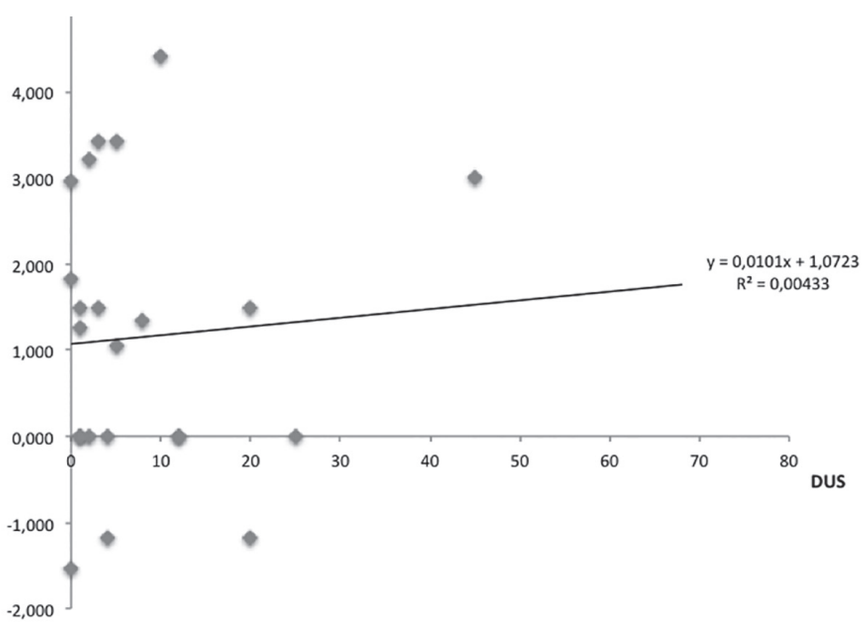


Fig. 7. Correlation between DUS and hand function at baseline visit.
Hand function was assessed with the ABILHAND score. Correlation analysis was performed using the Spearman significance was accepted for $p<0.05$. DUS: Digital Ulcers score.

cers as a consequence of vasculopathy, but also skin thickening of the fingers and contractures might be responsible for a decrease in hand function.

As our data are based on secondary data accumulation we acknowledge a possible selection bias and data collection bias contributing to the limitations of any retrospective analysis.

Nevertheless, we were able to demonstrate a significant correlation between DUS and hand function over time (Fig. 7), suggesting that the DUS might be a suitable tool to assess the severity of DUs but also as therapeutic effects for a single patient over time.

Interestingly, while in the literature dcSSc is a known risk factor for the presence of DUs (4, 12, 13), in our cohort the percentage of patients with DUs suffering from lcSSc was greater than the percentage of patients suffering from dcSSc (45.2% *vs*. 54.8; $p>0.05$; Table I). This might be explained by the fact that lcSSC is more frequent than dcSSc. It also corresponds with the frequencies reported in the literature (14, 15). However, patients with dcSSc showed significantly higher DUS values than patients with lcSSc thus confirming the more severe course of disease in dcSSc (12.1±8.1 *vs*. 6.6±3.0; $p=0.04$).

Besides looking at hand function and pain, it might be interesting to evaluate the overall burden of comorbidities that develops secondary to DUs in SSc patients. A quantitative link between the DUS and potential comorbidities could be analysed to assess a correlation. Potential comorbidities might include depression due to pain, visible tissue defect and inflammatory activity. Also, cardiovascular risk might be increased in those patients due to SSc-related microvascular damage and inflammation. This might offer a fruitful field for further studies.

Taken together, we developed a novel scoring system to assess DUs. It considers clinical patient data thus facilitating to depict the course of the disease over time and supports both clinical care and bedside decision-making. In the future we will validate the score in order to establish the DUS as a new standardised tool for the assessment of DUs, which is required in clinical care, but also clinical studies evaluating the effectiveness of novel vasoactive approaches.

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