



LAUDES Study: impact of digital ulcers on hand functional limitation, work productivity and daily activities, in systemic sclerosis patients

Ivan Castellví¹ · Saioa Eguiluz² · Alejandro Escudero-Contreras³ · Juan José Ríos⁴ · Jaime Calvo-Alén⁵ · José Luis Callejas-Rubio⁶ · Carlos De la Puente⁷ · Carmen Pilar Simeón⁸ · Francisco Javier Narváez⁹ · Gerard Espinosa¹⁰ · Patricia E. Carreira¹¹ · Manuel Rubio-Rivas¹² · Juan José Alegre¹³ · Alfredo Guillén-Del-Castillo⁸ · Jose Andrés Román-Ivorra¹⁴ · Vicent Fonollosa⁸ on behalf of LAUDES Study Group

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Abstract

The objective of this study was to evaluate the impact of digital ulcers (DUs) in daily life of systemic sclerosis (SSc) Spanish patients. We developed a multicenter observational study to compare functional disability in SSc patients with active DUs vs. those without DUs. An additional correlation between perception of patients and physicians on disability due to DUs was performed. A total of 199 patients were enrolled, 70 (35%) with DUs. Patients with DUs were younger (48 vs. 58 years; $p < 0.001$) and had more frequently the diffuse subtype of SSc (45 vs. 24%; $p = 0.004$) than patients without DUs. Patients with DUs showed significantly higher scores in the Cochin Hand Function Scale overall ($p < 0.002$) and for each of its five dimensions. They also showed higher scores in the Systemic Sclerosis Health Assessment Questionnaire items related to hand function such as, dress and self-care ($p < 0.013$), eat ($p < 0.013$) and grip ($p < 0.03$), and higher Visual Analogic Scale scores for pain ($p < 0.013$), trouble related with Raynaud's Phenomenon ($p < 0.001$) and sense of severity ($p < 0.004$). Impact on daily activities was significantly higher in patients with DUs ($p = 0.002$), with a non-significant trend to experience higher impact on work productivity ($p = 0.07$). A high correlation was found between DUs patients and physicians opinion on the impact of DUs (daily life: Pearson $R = 0.86$; work productivity: Pearson $R = 0.87$). Study findings show an impaired hand function and increased disability for daily life activities and work productivity in SSc patients with DUs compared with patients without DUs in Spanish population.

Keywords Scleroderma and related disorders · Hand · Disability evaluation · Human activities · Quality of life

✉ Ivan Castellví
icastellvi@santpau.cat

¹ Unitat de Reumatologia, Hospital de la Santa Creu i Sant Pau, Carrer de Sant Quintí, 89, 08026 Barcelona, Spain

² Servicio de Medicina Interna, Hospital Universitario de Cruces, Barakaldo, Spain

³ Unidad de Gestión Clínica de Reumatología, Hospital Universitario Reina Sofía, Córdoba, Spain

⁴ Servicio de Medicina Interna, Hospital Universitario La Paz, Madrid, Spain

⁵ Servicio de Reumatología, Hospital Universitario Araba, Vitoria, Spain

⁶ Unidad de Enfermedades Autoinmunes Sistémicas, Hospital Universitario San Cecilio, Granada, Spain

⁷ Servicio de Reumatología, Hospital Universitario Ramón y Cajal, Madrid, Spain

⁸ Unitat de Malalties Autoimmunes Sistèmiques, Servei de Medicina Interna, Hospital Universitari Vall d'Hebron, Barcelona, Spain

⁹ Servei de Reumatologia, Hospital Universitari de Bellvitge, Barcelona, Spain

¹⁰ Servei de Medicina Interna, Hospital Clínic de Barcelona, Barcelona, Spain

¹¹ Servicio de Reumatología, Hospital Universitario 12 de Octubre, Madrid, Spain

¹² Unitat de Malalties Autoimmunes, Servei de Medicina Interna, Hospital Universitari de Bellvitge, Barcelona, Spain

¹³ Servei de Reumatologia, Hospital Universitari Dr. Peset, València, Spain

¹⁴ Servei de Reumatologia, Hospital Universitari i Politènic la Fe, Universitat Catòlica de València, València, Spain

Introduction

Systemic sclerosis (SSc) is a rare chronic autoimmune disease, of unknown etiology due to a combination of endothelial damage, dysregulation of fibroblasts and immune system activation, which leads to vasculopathy, skin fibrosis and internal organ involvement. Severity of clinical manifestations can vary from mild skin and vascular damage to severe visceral involvement. Raynaud's Phenomenon (RP) is almost universal in SSc and their clinical course is usually more aggressive in SSc patients. RP is associated with intimal proliferation and vasculature occlusion [1]. This, in turn, leads to the occurrence of digital ulcers (DUs), the most frequent manifestations of systemic sclerosis-associated vasculopathy. The etiopathogenesis of DUs are multifactorial and includes vasculopathy, repetitive micro trauma, or skin changes. Digital ulcers represent a major clinical challenge [2, 3], and appear in approximately 30% of the patients with SSc [4]. Furthermore, DUs have been described as a cause of patient quality of life impairment [5–7] due to pain, disability and potential need of hospitalization [8]. In addition, chronic DUs may be further complicated with irreversible loss of tissues [4] or osteomyelitis [9] with a potential need of amputation in severe cases.

Management of DUs requires both pharmacologic and non-pharmacologic interventions [2]. Systemic sclerosis patients with active DUs suffer from a higher degree of work disability [10] and increased negative effects in daily life activities [6] compared to those without DUs. The degree of these limitations due to DUs in the Spanish population is unknown. This study was designed with the objective to compare the overall health status, hand-functionality and functional limitations for both work productivity and daily life activities, between patients with active DUs and patients who never had DUs. Patients were enrolled in a real-world clinical practice setting, which also allowed for a comparison between the perceptions of patients and physicians regarding these limitations.

Methods

Design

This was a cross-sectional study designed to analyze the impact of DUs on hand function, work productivity and daily life activities, in patients with systemic sclerosis. Between September 2012 to January 2013 Three consecutive patients with SSc, two without DUs and one with DUs were examined by each investigator at a time from

50 tertiary or secondary hospitals from Spain (population area from 50,000 to 400,000 people/each center). The study was approved by the Spanish Medicine Agency and by the Ethics Committees of the Hospital de la Santa Creu i Sant Pau (19th July 2012. Protocol number: ACT-NUL-2012-01) and was performed in accordance with the Good Clinical Practice guidelines and the last version of the Declaration of Helsinki [11]. All patients provided written informed consent before enrolment.

Patients

The study included SSc patients ≥ 18 year-old that were classified fulfilling the LeRoy classification criteria [12]. We considered two groups: patients without active or history of DUs (nonDU group), and patients with active ulcers or that had suffered from active DUs for more than 7 days. Active DUs were determined by the physician and defined as a loss of epithelization with a visible deepness in the palmar or dorsal surface of a finger, sited at or distal to proximal interphalangeal joint. Patients with DUs due to another etiology different than systemic sclerosis, and those with other disorders which may be confounding factors for assessing hand functionality (amputations, arthritis, other connective tissue diseases), were excluded from the study. These confounding factors were under investigators consideration.

Study procedures

Functional limitations of the hands were assessed using the Cochin Hand Function Scale (CHFS) and the overall physical disability was assessed with the Health Assessment Questionnaire for systemic sclerosis (SHAQ) questionnaire [13]. Both patients and physicians filled the visual analogic scales (VAS) of the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP) questionnaire [14]. The CHFS focuses on hand functionality and refers to five daily activities with items on personal hygiene, dressing, eating-cooking, office and other activities. There is an additional overall score. The six items have a total of 18 questions which are scored between 0 and 5. Therefore, results range from 0 (worst) to 90 (best) [13].

The SHAQ questionnaire measures 8 functional domains of physical capacity (dress/get up/eat/walk/hygiene/to reach objects/grip/activities). Patients chose among four answers (no difficulty; some difficulty; big difficulty; unable) scoring from 0 to 3. The sum was divided by 8, making a composite index which, if lower than 1, means no or mild functional limitation and if higher than 1 means moderate to severe functional limitation. The SHAQ questionnaire has also a pain VAS and VAS on five SSc symptoms and signs (RP, DUs, gastrointestinal problems, pulmonary problems, and global assessment of the severity of the disease) [15, 16].

The VAS score ranges from 0 (worst score, bigger problems) to 100 (best score, lower problems). WPAI-SHP is a questionnaire on work productivity limitation. Visual analogic scales referring to daily life activities and work productivity was filled separately for both SSc and DUs limitations. This questionnaire was filled by both patients and physicians, with a score ranging from 0 (best score, lower problem) to 100 (worst score, bigger problem).

Statistical analysis

Comparison between the degree of the limitations in patients with and without DUs was performed. Additionally, the perception of the patients with DUs was compared with that of the physician.

Comparisons of categorical variables between patients with and without DUs were performed with the Chi-Square Test or Fisher's Test. Quantitative variables were compared with the Student's *T* test or the Mann–Whitney's *U* test if a non-parametric test was more appropriated. Previous to the statistical analysis We used the test of Kolmogorov–Smirnov to evaluate the normality of continuous variables. Data were presented as mean (range) for continuous variables with normally distribution and median (range) if variables did not distribute normally; and numbers (percentages) for categorical variables. The Pearson's correlation coefficient was used to evaluate the correlation between the opinion of patients and physicians on the impact of DUs on work productivity and daily activities. A multivariate analysis on the risk factors for DUs was performed with a logistic regression model. For multivariate analysis we considered all the variables for which a *p* value < 0.2 was obtained in the univariate

analysis. All the statistical analyzes with *p* values ≤ 0.05 were considered statistically significant, adjusting the level of significance through the Bonferroni method in the case of multiple contrasts. SPSS Statistics© software version 19 (IBM, Armonk, NY) was used for statistical analysis.

Results

A total of 222 patients with SSc in 74 investigational centers were screened in 3 months period. Twenty-three patients were not included as they did not fulfill the study criteria. Therefore, a total of 199 evaluable patients were analyzed (Table 1). One hundred and sixty-four were women (82%), 70 (35%) patients were classified in DUs group and 129 (65%) in non DU group. The mean age was 54.5(± 14.7) years. Mean time from the diagnosis of SSc was 8.5 ± 7.6 years without significant differences between patients with and without active DUs (8 ± 7.6 vs. 9.4 ± 8.0 years; *p* = 0.24). Limited SSc was the most common type of SSc (64%) followed by the diffuse cutaneous form (31%). Only two patients failed to show RP, both in the group of never-DU. Sixty-two out of the 70 patients with active DUs (88%) had a history of previous active DUs with a median of 5 (range: 1–72) previous ulcers. Twenty-two patients (35%) in the active DUs group had DUs-related complications. Among patients with active DUs, 35 (50%) had DUs in both hands.

The mean time of evolution of the most current episode of active DUs was 77.1 ± 109.5 days. Patients with active DUs had a median of two (range: 1–10) DUs. Nine out of

Table 1 Baseline characteristics of Systemic Sclerosis patients

Characteristics	Total <i>N</i> = 199	Active DUs <i>N</i> = 70 (35%)	Never DUs <i>N</i> = 129 (65%)	<i>P</i>
Age, years, mean (range)	54 (21–90)	48 (52–80)	58 (21–90)	0.00001
Female, <i>n</i> (%)	164 (82)	54 (79)	110 (86)	0.31
Type of SSc, <i>n</i> (%)				
Limited	125 (64)	37 (54)	88 (70)	0.004
Diffuse	61 (31)	31 (45)	30 (24)	
SSc sine scleroderma	4 (2)	–	4 (3)	
Early SSc	5 (2)	–	5 (4)	
Smoking habit, <i>n</i> (%)				0.32
Smoker	19 (9)	7 (10)	12 (9)	
Former smoker	51 (26)	22 (31)	29 (68)	
Never smoked	129 (65)	41 (58)	88 (22)	
Raynaud phenomenon, <i>n</i> (%)	197 (99)	70 (100)	127 (98)	0.54
Time since diagnosis of SSc, years, median	8.5	9.4	8	0.24

Percentages are based on observed data

DU digital ulcer, SSc systemic sclerosis

Table 2 Features in patients with Systemic Sclerosis and active digital ulcers

Characteristics	Active DUs <i>N</i> = 70
Onset Raynaud's previous to DU, years (SD)	12.5 (8.8)
Onset first non-Raynaud's symptom, years (SD)	10.2 (8.5)
Organ involvement, (%) ^a	
Gastrointestinal	35 (67)
ILD	23 (44)
Joint contractures	30 (58)
PAH	10 (19)
Arthritis	14 (27)
SRC	2 (4)
Myositis	2 (4)
Heart	6 (12)
Number DUs per patient, mean (SD)	1.9 (1.5)
Current treatment for DUs, (%)	
CCB	42 (60)
Antiplatelet	43 (61)
Prostanoids	10 (14)
PDE 5i	12 (17)
ERA	50 (71)
NSAIDs	40 (57)
Both hands affected by DUs, <i>n</i> (%)	35 (50)
Complications of DUs, <i>n</i> (%)	
Infection	9 (13)
Osteomyelitis	0 (0)
Gangrene	0 (0)
Number of current DUs, median (range)	
Total DUs	2 (1–10)
Ischemic DUs	2 (0–7)
Mechanical DUs	0 (0–5)
Calcinosis DUs	0 (0–2)
Current DUs episode evolution time, days, median (range)	40 (8–710)
Previous history of DUs, <i>n</i> (%)	62 (88)

SRC scleroderma renal crisis, CCB calcium channel blockers, PDE 5i phosphodiesterase 5 inhibitors, ERA endothelin receptor antagonists, NSAID non-steroidal anti-inflammatory drugs

^a*N* = 52

70 patients (13%) presented DU infection history. Features of patients with active DUs are resumed in Table 2.

Sixty-nine patients (35%) were currently employed; 33 (47) and 36 (28) of the patients with and without active DUs, respectively ($p < 0.001$).

Degree of overall hand disability, as scored in the CHFS questionnaire, was higher in patients with active DUs (32.3 ± 22.1 vs. 20.4 ± 24.8 , respectively; $p < 0.002$). As shown in Fig. 1, these significant differences were also observed in the individual five components of the CHFS (for: personal hygiene 2.7 vs. 1.8; $p = 0.022$; dressing 4.2 vs. 2.3; $p < 0.001$; eating-cooking 14.2 vs. 9.6; $p = 0.008$; office 3.4 vs. 2.4 $p = 0.024$ and other activities 7.9 vs. 5.1; $p < 0.001$).

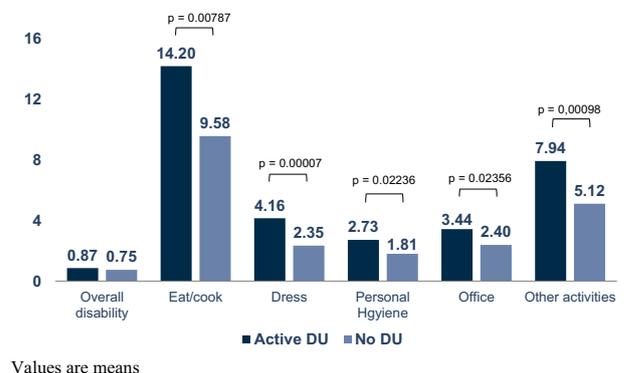
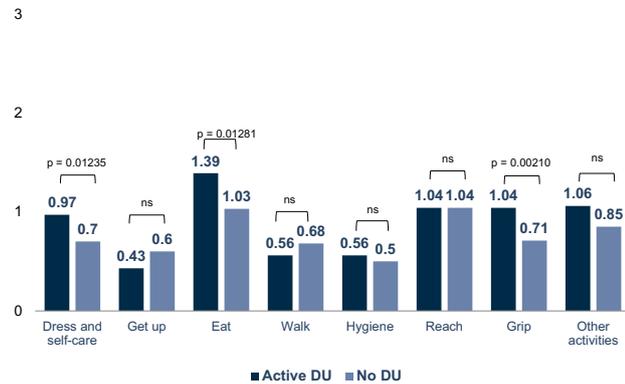
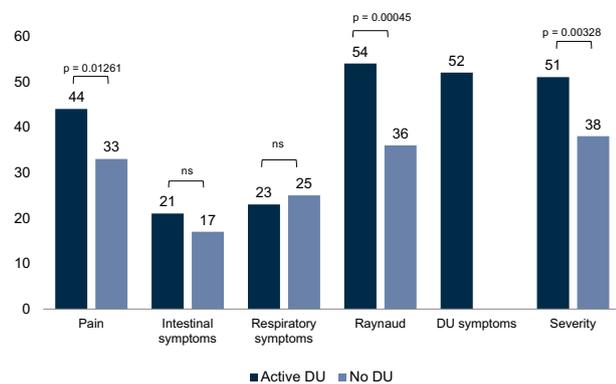


Fig. 1 Cochin Hand Function Scale (CHFS). Comparison active digital ulcers (DUs) versus never DUs. Values are means

DUs versus no DUs.



Values are means. Range 0-3



Values are means. Range 0-100

Fig. 2 Health Assessment Questionnaire for systemic sclerosis (SHAQ). Comparison active digital ulcers (DUs) versus no digital ulcers. **a** Values are means. Range 0–3. **b** Values are means. Range 0–100

The degree of disability due to SSc was measured with the SHAQ questionnaire (Fig. 2) whose overall result was not significantly different between patients with and without active DUs. On the contrary, significant differences were observed for individual results in three out of eight dimensions of the SHAQ with higher scores in patients with active DUs, meaning a bigger disability in this group of patients (dressing and self-care, mean 0.97 vs. 0.70; $p=0.012$; eating 1.39 vs. 1.03; $p=0.013$; hand grip 1.04 vs. 0.71; $p=0.002$) (Fig. 2a).

The VAS section of the SHAQ questionnaire on the impact of the symptoms in daily life activities, showed significant differences for three out of five items (pain VAS 44 vs. 33; $p=0.013$; RP 54 vs. 36; $p<0.001$; sense of severity 51 vs. 38; $p=0.003$) (Fig. 2b).

The degree of disability for daily-life activities and working productivity for both SSc and active DUs was assessed with the VAS of the WPAI-SHP questionnaire

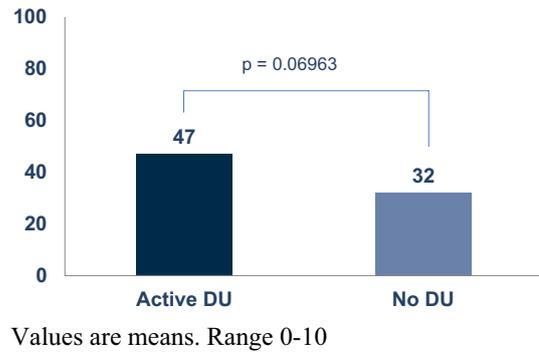


Fig. 3 Patient self-assessment on impact of digital ulcers on daily life activities and work productivity. Values are means. Range 0–100

completed both by patients and investigators. Results of the patient-assessment for the impact by SSc, in the whole group, showed that the degree of disability for daily-life activities was significantly higher in patients with active DUs (mean VAS 53 vs. 38; $p<0.002$). Although the impact on work productivity was bigger in patients with active DUs, no statistical significance was observed (Fig. 3).

Patients with active DUs were employed in 40% of the cases (28 out of 70) compared to 26% (32 out of 125) of the patients in the group of patients who never had DUs ($p=0.051$). Regarding the physicians assessment of these two questions, the impact of DUs in patients with active DUs at work and in their daily life activities were 54 and 55, respectively, as evaluated by VAS. These VAS-scores were 53 and 56, respectively, for this population when self-assessed by the patients. Physicians thought that 57% (40 out of 70) of the patients with active DUs were unemployed, the real figure was 60% (42/70) as answered by the patients. There was a good correlation between investigators and patients with active DUs in both, the opinion on the work productivity impact (Pearson $R=0.74$; $p<0.001$) and that of the impact on daily activities ($R=0.74$; $p<0.001$) due to active DUs.

Finally, we used a multivariate model to analyze the different risk factors associated with DUs. We found that patients with DUs were younger (48.4 ± 13.2 vs. 57.8 ± 14.4 years old; $p<0.0001$), had the diffuse cutaneous subtype frequently (45.6 vs. 23.6%; $p<0.01$), were more likely to have anti-topoisomerase antibodies (44.8 vs. 22.0%; $p<0.0001$), had more joint contractures in their hands (57.7 vs. 31.9%; $p<0.0001$), and had worse % DLCO predicted levels (59.2 ± 21.6 vs. 70.1 ± 20.5 ; $p<0.01$). Patients with DUs were more likely to have no sedentary work (53.03 vs. 35.9%; $p<0.03$). Except the relationship between DUs and CHFS, SHAQ and WPAI-SHP explained before we did not find more associations (data not shown).

Discussion

Digital ulcers have a significant impact on the quality of life of the patients due to impairment or disability on hand function, daily life activities and work productivity. One of the most important results is that patients with DUs felt a higher level of SSc severity compared to patients without DUs. Previous reports have shown that patients with DUs show more frequent psychological troubles such as aesthetic prejudice [6] or anxiety [17]. Furthermore, severe DUs with large or prominent scars may lead to social impairment or self-image problems. It should be pointed out that according to our results, there was a high degree of agreement between physicians and patients when evaluating the disability related to work and daily life activities. These data are in disagreement with a previous study in which the level of agreement between patients and physicians was low when assessing overall SSc disease severity [21]. The physicians gave more attention to the time of evolution and creatinine levels than patients [21]. As our study focuses on limitation due to DUs, a possible explanation of this discrepancy is that physicians in our study do not pay attention to these other systemic factors, allowing for a higher agreement.

Another surprising finding was the percentage of active workers in the SSc patients with DUs. A total of 40% of the patients with DUs were employed vs. 26% of employed patients without DUs. Previous studies have shown that DU does not have a direct effect on the employment status of SSc patients [17]. Bérezné et al. showed that although DUs decreased productivity at work, no significant difference was observed for work status between patients with or without DUs. Furthermore, a cross-sectional study of 476 SSc patients showed that no statistical significance was observed in the employment status (employed vs. unemployed) of patients with DUs [22]. One explanation about these findings could be that workers with SSc and DUs can have more injuries, more stress and less protection against cold. Another explanation could be the differences between laboral markets and accessibility to change jobs and social resources in different countries.

Our findings in Spanish patients are in concordance with other cohorts of SSc patients [4].

The Pittsburg database included more than 2000 patients with prospective follow-up. Among them, the patients who presented persistent DUs were more prone to suffer hand-disability and pain, as assessed with the SHAQ questionnaire, as compared with those patients who had SSc and never had DUs [4]. Furthermore, two French observational studies, which evaluated 213 and 189 patients members of the French SSc patient society also showed that active DUs leads to an increased disability,

with at least one DU (31.4% and 31.7% of patients, respectively) [6, 17]. Patients with DUs demonstrated a significantly higher global disability, as assessed with the SHAQ questionnaire, and worse functional hand disorders, as assessed by CHFS [6, 17]. Work productivity and daily life activities were significantly impaired compared with those patients without DUs [17, 18]. In our study, we did not find a significant overall disability in SHAQ between groups, but we find differences in hand domains of SHAQ. It probably means that other areas of SHAQ different of evaluation of hand involvement cannot detect a predominant hand dysfunction if the other domains were not affected.

Another source of data on these issues is the Digital Ulcers Outcomes (DUO) European Registry, whose data also show a decreased work productivity and decreased ability to perform daily life activities in patients with active DUs. Noteworthy, data from DUO registry suggest a functional impairment increase with the number of DUs [5].

Hand function seems to be the most important factor contributing to DUs-related disability because DUs are often multiple [8], involving multiple fingers and both hands [19]. The findings of the present study are in concordance with these observations. We demonstrated a significant difference for all the components of the CHFS. Furthermore, the components of the overall health questionnaire SHAQ were the most significantly different between both groups. In addition, our results also showed that patients with DUs had more frequent inconveniences related to pain and RP, suggesting that evolution of RP is worse in this group of patients. The large impact of pain on the quality of life in patients with SSc should be highlighted and its treatment should be given the highest priority [20].

Our study had some limitations. First, the observational, non-randomized design may be a source of bias in the allocation of patients to the two groups and may cause imbalance and selection bias. Second, some of the measuring tools used have been previously criticized. For example, the accuracy of VAS has been criticized due to the difficulty in establishing anchors, which properly delimitate the scores, and for the broadness of this measuring tool. Another limitation was that we did not exclude patients with finger joint contracture that can influence the punctuation in some values. Additionally, the observed differences between groups may be compromised due to the high percentage of patients with DU that were pharmacologically treated, especially with endothelin receptor antagonists. The strengths of the study are founded on the large sample size and the fact that some measuring tools have been extensively used (CHFS, SHAQ) and validated due to their ability to give significant percentages variations in quality of life of patients with SSc [13, 23].

In conclusion, in the comparison with patients with SSc who had never had DUs, patients with active DUs

experienced increased hand disability, more inconveniences related to pain and RP, and reported greater disease severity. In addition, patients with DUs had limited capacity for daily life activities and work productivity with a higher level of agreement between patients and physicians on these two issues. All these findings are the result of a study performed in a real-world setting in Spain, without the constraints of clinical trials and confirm similar results from other observational studies, regardless of geographic origin. Research on pharmacologic interventions and support measures for patients with DUs are critical to prevent and/or heal DUs that would, in turn, improve the quality of life of these patients.

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Author contribution IC contributed in desing, recruiting, statistical analysis, interpretation of results, discussion and final manuscript preparation. SE contributed to desing, recruiting, interpretation and final manuscript preparation. AE-C, JJR, JC-A, JLCR, CdIP, CPS, FJN, GE, PEC, MR-R, JJA, AG, JAR and VF contributed in recruiting, interpretation of results, discussion and final manuscript preparation. All co-authors take full responsibility for all parts of the final manuscript.

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Compliance with ethical standards

Conflict of interest IC have received speaker fees from Actelion, Roche, BMS and Pfizer. JJR and JJA have received educational grants from Actelion outside the submitted work. JJA has also received speaker fees from Actelion. SE has received a grant from Actelion for the work under consideration, and personal fees from Actelion and an educational grant from GlaxoSmithKline outside the submitted work. JAR has been board member for Roche, Actelion, Lilly, Gebro and MSD, and has received speaker fees from Roche, Abbvie, Lilly, BMS, UCB, Novartis, Pfizer, Celgene, FER and SVR, and travel grants from Janssen, Pfizer and Gebro. AE-C, JC-A, JLCR, CdIP, CPS, FJN, GE, PEC, MR-R, AGdC, and VF declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the national research committees of the participant institutions and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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