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# Domain reporting in Systemic Sclerosis-Related Digital Ulcers: An OMERACT Scoping Review

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ABSTRACT

*Background:* Digital ulcers (DUs) are a major cause of pain and disability in patients with systemic sclerosis (SSc). The aim of this scoping review was to evaluate the outcome domains used in studies of SSc-associated DUs.
*Methods:* Electronic databases (EMBASE, MEDLINE and the Cochrane Library) were searched for articles written (1947 onwards) in English relating to SSc-DUs. A minimum of 15 participants for studies of imaging and 25 participants for questionnaire-based studies was required for inclusion. Information on all primary and secondary domains was extracted.
*Results:* 4869 manuscripts were identified, of which 40 met the eligibility criteria and were included in the synthesis. Most studies were randomized controlled trials (n=13), or prospective (n=12)/retrospective (n=8) observational studies. Interventions included oral or intravenous drugs (n=25), topical/local treatments (n=5), and surgical interventions (n=2). Approximately half the studies assessed either the count/number of DUs (n=23) and/or improvement in DUs (n=20). Functional impact of DUs was examined in 25% (n=10) of studies. Other domains were related to complications of DUs (n=7), pain (n=6), health-related quality of life (n=4), microvascular assessment/pathophysiology (n=4), global assessment of DUs (n=2), and histopathology (n=1).
*Conclusion:* This scoping review identified a broad range of disease-related domains used to study SSc-DUs. There is significant heterogeneity in these domains. These data will inform the ongoing work of the OMERACT Vascular Disease in Systemic Sclerosis Working Group to define a core set of disease broad domains to capture the burden of DUs in SSc.

## Introduction

Digital ulcers (DUs) occur in over half of patients with systemic sclerosis (SSc) and are associated with significant pain and disability [1–3]. DUs are often defined as lesions with a loss of surface epithelization and discernible depth with a break in the basement membrane [4,5]. DUs in SSc often occur early (within the first 5 years) in the course of the disease [1,6,7]. The pathogenesis of DUs is incompletely understood,

*Abbreviations:* DUs, Digital ulcers; SSc , Systemic sclerosis.

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although ischemia is believed to play a central role, particularly in fingertip ulcers [3,6,8]. Mechanical factors also likely drive ulceration on the dorsal aspects of the hands (e.g., overlying the small joints), an area vulnerable to recurrent microtrauma [8,9]. DUs can also develop in relation to underlying subcutaneous calcinosis [10,11]. Complications of ulcers, including infection and gangrene, can significantly delay healing and may require surgical intervention [2,12–14].

DUs are also associated with a severe disease course of SSc, including internal organ involvement [15,16]. Despite current treatment approaches, including drug therapies, DUs are often slow to heal, and many patients experience recurrent digital ulceration [9,17]. Pain is a cardinal feature of DUs, and patients also often experience other intrusive physical symptoms (e.g., sensitivity) [18–20]. DUs are associated with significant emotional impact, including effects on personal relationships, and impairment of physical, social, and occupational activities [19]. Furthermore, there is a significant societal burden from SSc-DUs, including the costs of healthcare utilization [21].

Assessment of DU burden (impact and severity) is challenging in both clinical practice and clinical trials, posing a major barrier to the development of new and optimized treatment approaches for DUs, including non-pharmacological interventions. Agreement among experts in SSc assessing DUs is poor to moderate [5,22–24]. Furthermore, agreement between patients' and rheumatologists' assessments is also poor, even when clinicians are aware of 'real-world' clinical contextual information, such as the presence of discharge [24]. Much of the current understanding of the impact of SSc-DUs is derived from cross-sectional studies utilizing patient-reported outcome instruments to assess broader aspects of SSc disease severity [18].

Against this background, this scoping review of the literature aimed to evaluate the broad domains of illness, and the range of instruments and outcome domains, used in clinical studies of DUs in patients with SSc.

## Methods

### *Working group*

This scoping review [25], was conducted by the Outcome Measures in Rheumatology (OMERACT) Vascular Disease in Systemic Sclerosis Working Group which consists of six clinicians with an interest in SSc-DUs, a methodologist, and two patient research partners [26]. This project followed the OMERACT domain selection process [27].

### *Search strategy*

A literature search strategy (**Supplementary Material**) was developed for use in EMBASE (OVID interface, 1947 onwards), MEDLINE (OVID interface, 1947 onwards), and Cochrane Central Register of Controlled Trials (OVID interface, 1947 onwards). These databases were searched for studies pertaining to participants with SSc-DUs. The databases were searched for studies pertaining to participants with a clinical diagnosis of SSc-associated DU with no limitation by classification criteria used, (given the various iterations in classification criteria for SSc utilized over the study period). Furthermore, patients were not limited to having a DU at baseline, but were required to have undergone an assessment for DUs.

### *Eligibility criteria*

There was no limitation by intervention, comparator, or study setting. Randomized control trials (RCTs), quasi-randomized studies, case-control studies, prospective and retrospective cohort studies, case series, and cross-sectional studies written in English were eligible. Due to the large number of studies examining SSc-DU, this analysis was limited to studies with a minimum of 15 participants for studies of imaging modalities and 25 participants for questionnaire-based studies were required for inclusion. Basic laboratory, genetic, or pre-clinical studies, and articles that were only available in abstract form were excluded.

### *Data extraction*

Scoping review sources were uploaded to a citation management software (Covidence) and duplicate files were deleted. Two authors (MH, NM) independently completed screening of the title/abstract body and full text according to the inclusion criteria outlined above. Disagreements were resolved through consensus between the screening authors. A standardized data extraction form was developed and approved by all the study authors. Data extraction was independently piloted by two review authors (MH, NM) by extracting pertinent data for the first ten studies deemed eligible for inclusion. Thereafter, the remainder of the data extraction was performed by a single author (MH).

### *Data analysis and interpretation*

Study characteristics including design, sample size, participant demographics, and intervention characteristics were extracted. The data are presented as descriptive statistics. Primary and secondary broad domains measured, and associated instruments used in the included studies, relevant to SSc-DUs were recorded. All the authors participated in identifying the overarching disease-related domains.

## Results

### *Study selection*

The study selection process is depicted in Fig. 1. 4869 records were identified before duplicates (n=1126) were removed. Of the remaining 3743 records, 123 were eligible for full-text screening and 40 were included in the final analysis. The three most common reasons for exclusion of full texts were wrong study design as specified in the eligibility criteria (n=36), abstract only (n=17), and insufficient sample size (n=14).

### *Study characteristics*

Study characteristics are presented in Table 1, including study design, intervention, comparator (where applicable), and sample sizes. The studies were published between 1985 and 2020, with the majority (n=30) published after 2010. Sample sizes varied widely in both the intervention (8 to 1439) and comparator (6 to 186) groups. Most studies were randomized controlled trials (n=13), or prospective (n=12)/retrospective (n=8) observational studies. Active interventions included oral/intravenous drug therapies (n=25), topical/local treatments (n=4), and surgical intervention (n=2).

The broad domains used to assess SSc-DUs are presented in Table 2. These broad domains can be grouped under three main themes: 'DU burden', 'DU impact', and 'Special tests' [28,29]. The broad domains and instruments used to assess these are presented as **Supplementary Table 1**.

### *Digital ulcer burden*

DU burden encompasses the number (count), healing (i.e., ulcers which take longer to heal are more burdensome), and global burden and impact of DUs. DU burden was assessed in approximately half the studies, as assessed by DU count/number (n=23) or DU improvement (n=20). DU complications such as infection or need for surgical debridement were assessed in approximately one-sixth of studies (n=7). Two studies utilised a global assessment of DUs.

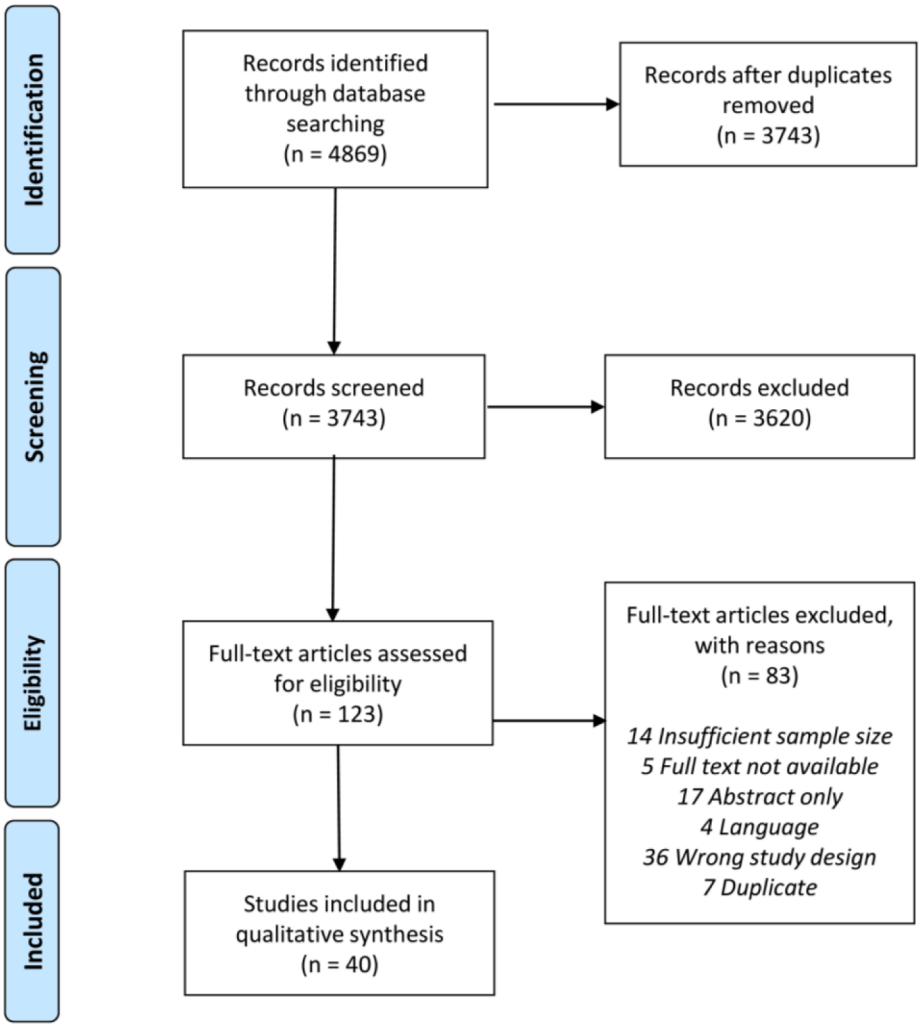


**Fig. 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing the search and study selection process.

*Impact of digital ulcers*

Function was assessed in one-quarter (n=10) of studies. Pain directly attributed to ulcers was examined in several studies (n=6). Health-related quality of life was assessed in four studies.

*Special tests*

Specialized testing including objective assessment of the microvasculature of tissues adjacent to digital ulcers using laser-based techniques was included in four studies. One study examined DU histopathology, utilizing ulcer biomarkers (i.e., ulcer wound biopsy and assessment of vascular biomarkers).

## Discussion

This scoping review identified three broad-ranging themes comprising the broad domains considered important by investigators when studying SSc-DUs: 'DU Burden', 'DU function', and 'Special tests'. However, there is currently significant heterogeneity and a lack of consensus regarding the broad domains that have been used to study SSc-DUs.

DU burden was the domain most commonly reported, and predominantly related to assessment of DU count/number (n=23) or DU improvement (n=20). Although DU complications can significantly impact on healing and may require surgical intervention [9,30], these important aspects were only reported in seven studies. The overall (global) impact of DUs in patients with SSc has been little studied, with only two studies incorporating clinician global assessment, and only one which incorporated patient global assessment (**Supplementary Table 1**).

The functional impact of DUs was assessed in one-quarter of studies (n=10). SSc-DUs, especially when severe, have a major impact on the lives of those affected, including impairment of physical and social activity, emotional impact, and effects on personal relationships [19]. Although pain is a cardinal feature of SSc-DUs and patients use a broad range of narrative devices to describe this symptom [19,20], only six studies assessed ulcer-related pain. Furthermore, the lived patient experience of DU pain is complex [18–20]. For example, our previous qualitative research identified five narrative devices: 'Words to express DU-associated pain', 'Descriptions of physical and psychological reactions to pain', 'Comparisons with other painful events', 'Descriptions of factors that exacerbate pain', and 'Descriptions of strategies for coping with the pain' [20]. Patients with SSc-DUs also live with significant anxiety and uncertainty and make many adaptations to try and prevent and/or mitigate future DU episodes [19]; however, this has not been specifically captured in ulcer-related studies to date.

Investigators have utilized specialized tests, including non-invasive imaging to study the pathogenesis of SSc-DU and assess response to intervention; however, there is currently significant heterogeneity in approaches to these issues and no standardized approach for utilizing such tools has emerged to date [31]. Although the pathobiology of DUs

**Table 1**
Characteristics of studies of digital ulcers in systemic sclerosis included in the scoping review.

| First author | Year | Study design | Intervention | Comparator | Sample size * Intervention | Comparator |
|---|---|---|---|---|---|---|
| Mohrland [32] | 1985 | Randomized controlled trial | Prostaglandin E1 | Placebo | 16 | 15 |
| Williams [33] | 1985 | Randomized controlled trial | Topical dimethyl sulfoxide | Topical normal saline | 53 | 31 |
| Wigley [34] | 1992 | Randomized controlled trial | Iloprost | Placebo | 18 | 17 |
| Vayssairat [35] | 1999 | Randomized controlled trial | Beraprost sodium | Placebo | 55 | 52 |
| Bettoni [36] | 2002 | Prospective cohort | Iloprost | | 30 | |
| Korn [37] | 2004 | Randomized controlled trial | Bosentan | Placebo | 79 | 43 |
| Gore [38] | 2005 | Retrospective cohort | Sildenafil | | 10 | |
| Abou-Raya [39] | 2008 | Randomized controlled trial | Atorvastatin | Placebo + healthy volunteers | 56 | 28 |
| Rosato [40] | 2009 | Prospective cohort | N-acetylcysteine | | 50 | |
| Tsifetaki [41] | 2009 | Prospective cohort | Bosentan | | 30 | |
| Giuggioli [42] | 2010 | Uncontrolled trial | Oxycodone | | 29 | |
| Mouthon [43] | 2010 | Prospective cohort | None | | 213 | |
| Zelenietz [44] | 2010 | Retrospective analysis of Randomized control trial | Bosentan | Placebo | 176 | 133 |
| Bérezné [45] | 2011 | Prospective cohort | | | 189 | |
| Matucci-Cerinic [46] | 2011 | Randomized controlled trial | Bosentan | Placebo | 98 | 90 |
| Roman Ivorra [47] | 2011 | Retrospective cohort | Bosentan | | 67 | |
| Cozzi [48] | 2013 | Retrospective cohort | Bosentan | Matched control group | 30 | 30 |
| Ennis [49] | 2013 | Prospective cohort | | | 148 | |
| Agard [50] | 2014 | Retrospective cohort | Bosentan | | 89 | |
| Chung [51] | 2014 | Prospective, open-label | Ambrisentan | | 20 | |
| Mouthon [52] | 2014 | Prospective cohort | None | | 190 | |
| Barsotti [53] | 2015 | Retrospective cohort | Allogenic skin grafting | | 43 | |
| Meijs [54] | 2015 | Prospective cohort | Bosentan | Healthy controls | 52 | 51 |
| Ruaro [55] | 2015 | Imaging study | None | | 20 | |
| Shah [56] | 2016 | Retrospective cohort | Treprostinil | | 51 | |
| De Cata [57] | 2016 | Retrospective cohort | Iloprost and bosentan | | 34 | |
| Hachulla [58] | 2016 | Randomized controlled trial | Sildenafil | Placebo | 42 | 42 |
| Khanna [59] | 2016 | Randomized controlled trial | Macitentan | Placebo | 368 | 186 |
| Küçükşahin [60] | 2016 | Prospective study | Bosentan | | 30 | |
| Matucci-Cerinic [17] | 2016 | Prospective cohort | None | | 1459 | |
| Hamaguchi [61] | 2017 | Prospective cohort | Bosentan | | 28 | |
| Hughes [62] | 2017 | Crossover study | Topical glyceryl trinitrate | Topical placebo ointment | 16 | |
| Motegi [63] | 2017 | Prospective single-blind controlled trial ** | Botulinum toxin B injection | No treatment | 37 | 8 |
| Seibold [64] | 2017 | Randomized controlled trial | Treprostinil | Placebo | 72 | 76 |
| Hassanien [65] | 2018 | Randomized controlled trial | Topical oxygen-ozone + calcium channel blocker | Calcium channel blocker | 25 | 25 |
| Simpson [66] | 2018 | Cross-sectional study | | | 36 | |
| Del Papa [67] | 2019 | Randomized controlled trial | Regional grafting of autologous adipose tissue | Sham procedure | 25 | 13 |
| Gualdi [68] | 2019 | Retrospective cohort | Hyaluronic acid-based wound dressing | | 79 | |
| Nagaraja [69] | 2019 | Randomized controlled trial | Riociguat | Placebo | 9 | 8 |
| Barsotti [70] | 2020 | Cross-sectional study | | | 31 | |

* Number of patients with SSc included in the study.
** Single-blinded study – patients.

**Table 2**
Domains used in clinical research studying digital ulcers in systemic sclerosis.

| Broad domain | Target domain (number of studies) |
|---|---|
| Burden of Digital Ulcers | Digital ulcer count/number [23] |
| | Digital ulcer improvement [20] |
| | Digital ulcer complications [7] |
| | Global digital ulcer assessment [2] |
| Impact of Digital Ulcers | Function [10] |
| | Pain [6] |
| | Health-related quality of life [4] |
| Special Tests | Microvascular assessment [4] |
| | Histopathology [1] |

in SSc is complex, ischemia is believed to drive pathogenesis and significantly delay or impair ulcer healing. Objective microvascular assessment was performed in four studies. Laser-derived imaging methods are considered promising potential surrogates for clinical trials of SSc-DUs, and could support early-phase proof of concept studies before larger confirmatory trials are undertaken [31]. One study utilized DU histopathology; however, this required repeated invasive ulcer biopsies. The potential role of circulating vascular biomarkers should also be examined.

Although this review benefited from a comprehensive study design, there are some limitations to consider. This review incorporated broad inclusion criteria and used multiple databases. However, because only articles written in English, and those with a minimum number of participants were considered for inclusion, it is possible that other relevant domains could have been missed. A specific definition for DUs was not required to be adhered to, which could be important considering the poor reliability for identifying DUS reported between rheumatologists with an interest in SSc and patients themselves [5,22,24]. There was no restriction to specific ulcer locations, and some studies were confined to study of fingertip and 'non-extensor aspect' ulcers. Most studies related to oral or intravenous drug therapies, with only a limited number of studies on topical/local treatments and surgical interventions, reflecting the lack of reports of these treatment modalities.

This scoping review identified the spectrum of relevant outcome broad domains in the study of SSc-DU. Next steps in the project include

achieving further consensus among stakeholders and voting on a core disease domain set per the OMERACT framework.

In conclusion, this scoping review identified a broad range of disease-related domains for studying SSc-DUs, including in RCTs. These results will inform the OMERACT Vascular Disease in Systemic Sclerosis Working Group in the development of a core set of disease domains to assess the impact of SSc-DUs.

## Declaration of Competing Interest

Dr Hughes reports speaking fees from Actelion Pharmaceuticals, Eli Lilly, Janssen, and Pfizer. Research funding from Janssen. Member of a Data and Safety Monitoring Board for Certa Therapeutics.

Dr. Pauling reports grants and personal fees from Janssen, outside the submitted work; Dr Pauling reports personal fees from Astra Zenaca, Boehringer Ingelheim, Sojournix Pharma and Permeatus, Inc.

Dr Proudman reports receiving funds for the following activities: advisory board: Boehringer-Ingelheim, Janssen, Gossamer. Research Support: Janssen.

Dr. Merkel reports receiving funds for the following activities in the past 2 years: Consulting: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, Cabaletta, ChemoCentryx, CSL Behring, Dynacure, EMDSerono, Forbius, Genentech/Roche, GlaxoSmithKline, InflaRx, Jannsen, Jubilant, Kiniksa, Kyverna, Magenta, MiroBio, Mitsubishi, Neutrolis, Novartis, NS Pharma, Pfizer, Q32, Regeneron, Sparrow, Takeda, Vistera. Research Support: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Eicos, Electra, Forbius, Genentech/Roche, GlaxoSmithKline, InflaRx, Sanofi, Star, Takeda. Stock options: Kyverna. Royalties: UpToDate.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152220.

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