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Surgical management of digital ulcers in systemic sclerosis: A systematic literature review

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ABSTRACT

Background: There is a strong rationale to develop locally-acting surgical treatments for digital ulcers (DUs) in patients with systemic sclerosis (SSc). Our aim was to examine the safety and efficacy of local surgical management for SSc-DU.

Methods: A systematic literature review was carried out until to August 2022 using 7 different databases. Original research studies concerning adult patients with SSc-DUs, and local surgical treatments were analysed using the PICO framework. We included randomized controlled trials, prospective/retrospective studies, and case series (minimum of 3 patients) References were independently screened by two reviewers including assessment of the risk of bias using validated tools.

Results: Out of 899, 13eligible articles were included. Autologous fat (adipose tissue AT) grafting was the surgical modality most identified (7 studies, 1 randomized controlled double blinded trial and 6 prospective open-label single arm studies). The healing rate (HR) with autologous fat grafting (4 studies) was 66–100 %. Three studies

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reported autologous adipose-derived stromal vascular fraction grafting: HR of 32–60 %. Bone marrow derived cell transplantation in a single study showed 100 % healing rate over 4–24 weeks. Surgical sympathectomy was examined in 3 studies, prospective without comparator with a median healing rate of 81 %. Two surgical studies (of direct microsurgical revascularisation and microsurgical arteriolysis) showed 100 % healing of ulcers, with no complications.

Conclusion: Several surgical approaches for SSc-DUs have demonstrated some degree of safety and effectiveness for DU healing. However, there are significant methodological issues. Future studies are warranted to rigorously investigate surgical interventions for SSc-DUs.

Introduction

Peripheral vasculopathy is a cardinal feature implicated in the complex aetiopathogenesis of SSc including microvascular damage which leads to progressive microvascular endothelial dysfunction, capillary dropout, and tissue ischemia [1]. In general, tissue ischemia drives the development of digital ulcers (DUs) in SSc, although other aetiopathogenic drivers may be important at different locations [2] DUs are often significantly painful and limit patients' ability to perform daily activities including occupation, and have broad-ranging psychological and emotional impacts. Ulcer complications including infection (e.g., osteomyelitis) and gangrene may result in significant tissue loss including through potential amputation.

Although there is a wide range of systemic (pharmacological) therapies available to prevent and/or heal ulcers, around one-third of patients with SSc may experience refractory DU disease [3–6] Furthermore, many systemic therapies are often poorly tolerated, which can limit successful dose escalation and/or requires drug discontinuation. Therefore, there is a strong therapeutic rationale to develop locally-targeted surgical approaches to SSc-DUs management. Such an approach would likely be better tolerated (e.g., through absence of major systemic side effects), and could provide novel approaches to modify the course of DU. Currently there is a limited evidence base, including the absence of randomized controlled trials, to confirm the safety and efficacy of surgical approaches for SSc-DU [7,8]. Furthermore, there are still many important practical issues that must be clarified to inform the utilization of surgical approaches (e.g., the optimal timing and combination with systemic pharmacological therapies) for DU.

Against this background, our aim was to conduct a systematic literature review (SLR) to evaluate the efficacy and safety of surgical management of SSc-DUs. The results will inform future planned DU treatment recommendations endorsed by the World Scleroderma Foundation (WSF).

Methods

This study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [9] (Fig. 1). A systematic literature search (SLR) of PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, Emcare (OVID) and Academic Search, each database was searched from inception to August 2022.

The research questions and search strategy are detailed in Supplementary Text S1 and S2. Based on the PICO framework, studies of any design (randomized controlled trial (RCT) and observational studies

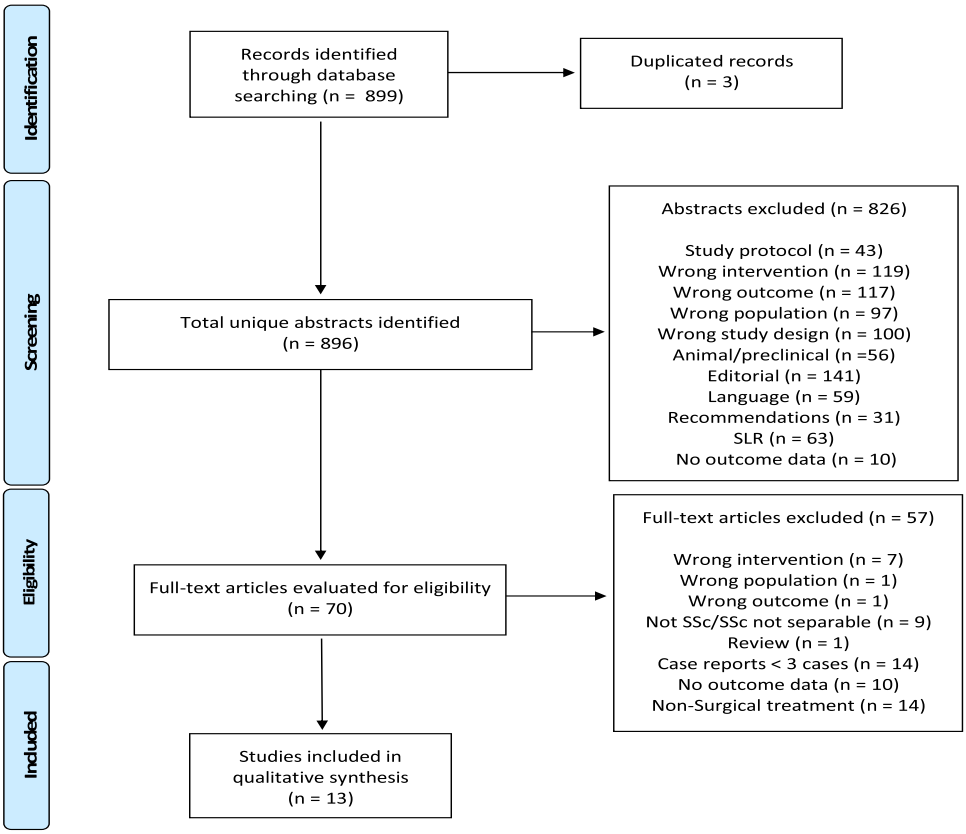

Fig. 1. PRISMA flow diagram detailing the study selection procedure.

(OBS)) enrolling adult (age ≥ 18 years) patients with definite SSc undergoing local treatment for DUs and reporting DU outcomes as either a primary or secondary endpoint were eligible for inclusion. Outcomes of interest were the number of DU before and after treatment and healing rates of DU, as well as the prevention of new DU and treatment safety data. Only manuscripts published in English were included in the final review (Table 1).

All abstracts were independently screened by two reviewers (YAS, CC). The full text of all eligible citations was then independently assessed by the same reviewers and relevant study data extracted. Any disagreement between reviewers was resolved by consensus. Owing to extensive interstudy heterogeneity, narrative summaries were used to present the data and meta-analysis of study results was not possible. The risk of bias of randomised controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool (ROB)-2 [10] and the ROBINS-I [11] was applied to observational studies. Risk of bias assessment was performed independently by two authors (YAS, CC). Disagreements were resolved by consensus.

Results

The SLR identified 899 references, and after deduplication, 896 titles and abstracts were screened (Fig. 1). Local treatment of SSc-DUs was mainly performed with either surgical or non-surgical procedures. Given the different indications, timing, and the overall differences across studies on surgical and non-surgical procedures, we deemed appropriate to describe the results separately and here are shown the results of surgical approaches are shown.

Thirteen articles on surgical treatment of SSc-DUs [7,12–23] were included in the final review. Due to the paucity of RCTs and prospective OBS, we also included retrospective OBS and case series with at least 3 patients.

Autologous fat (adipose tissue, AT) grafting was the most frequently used surgical modality (7 studies of which 1 RCT [13] and 6 prospective OBS [12,14–16,22,23] without a control group (total number of patients $N = 116$.).

Surgical sympathectomy was reported in 3 retrospective OBS [17,18,24], one case series of 8 patients reported bone marrow-derived cell transplantation (BMDC) [19]. Direct microsurgical revascularization was evaluated in a retrospective case series of 4 patients [20], and another retrospective case series reported microsurgical arteriolysis in 6 patients [21]. An overview of study characteristics is presented in Table 2.

Table 1
Research questions and PICO.

RESEARCH QUESTIONS		
What is the optimal local treatment approach for SSc-DUs?		
- Which is the role of DU assessment in the approach to local management?		
- *What is the efficacy of local treatment for SSc-DU?*		
- *What is the safety of local treatment for SSc-DU?*		
- *What local treatment protocols including debridement are being used?*		
- *What is the role for combining local with systemic (pharmacological) treatment for DU?*		
- *How many times per week should an ulcer be locally managed?*		
- *Should patient manage the DU by themselves?*		
- *What are the costs of DU in SSc?*		
- *Are there cost-savings associated with local treatment for DU?*		
P	Population	Patients with systemic sclerosis SSc ('scleroderma') and digital ulcers
I	Intervention	Local treatment of SSc DU
C	Comparator	No local wound treatment, or other local wound treatment or active systemic comparator or placebo or no comparator
O	Outcome	Efficacy: DU prevention, DU healing: overall number of DUs and/or number of new DUs; DU pain; DU complications, such as infection, gangrene, need for analgesia, need for hospitalisation, amputation Safety: Treatment-emergent adverse events

Patients, definition of DUs including healing

SSc classification criteria were specified according to 1980 American College of Rheumatology (ACR) criteria in 2 studies [15,22], the 2013 ACR/European League Against Rheumatism (EULAR) classification criteria for SSc in 4 studies [12–14,16] and the Leroy criteria in 3 studies [13,14,22] study. A definition of DU was available only in 3 (23 %) studies, they were defined as follows: "Painful area at least 6 mm in diameter with depth and loss of dermis located at the volar surface of the digit"; [14] "Painful area at >2 mm in diameter with depth and loss of dermis located at site of vascular etiology, volar surface of the digit distal to PIP" [13,14]; and "Lesion ≥*5* mm in diameter and visible skin defect" [16]. The DU healing was not defined in any of the included manuscripts.

Adipose tissue derived cells (ATDC) and adipose-derived stromal vascular fraction (SVF) grafting

Autologous adipose tissue grafting was the surgical modality investigated by the highest number of studies, [12–16,22,23] (7 studies of which 1 RCT, 4 cohort prospective studies and 2 case series). Risk of bias ranging from low to moderate.

Two main cell types were extracted after isolating adipose tissue: adipose tissue used as a whole (ATDC), and Stromal vascular fraction (SVF) separation and injection, and both were evaluated. Different techniques of adipose tissue handling, separation of centrifuged layers, site of injection and isolation of SVF are discussed below.

Coleman technique [25] was mainly used, for harvesting and purification of the isolated fat, the fat graft is harvested by a light negative pressure to reduce cellular trauma, to yield a greater number of viable cells. The graft is distributed in small aliquots by injections through multiple access sites. Such modality was implemented only in ATDC extraction [12–14,22], while different cellular separation methodology was utilized in SVF separation from retrieved adipose tissue [15,16,23].

Adipose tissue derived cells (ATDC)

The procedure of fat extraction and injection sites varied to some extent across the included studies. In the study by Bene et al. [22], Coleman technique was implemented, where the retrieved adipose tissue centrifuged and the middle layer, containing purified fat tissue, transferred to syringes and 2–3 mL of fat was injected into fingers with blunt cannula, either at the border of the larger ulcers with different depths, or at the finger base for the smaller digital ulcers. Del Papa et al. also reported AT grafting in 2 studies [13,14]. The intermediate layer was collected after centrifugation, [defined as AT derived cells (ATDC), containing both adipose stromal/stem cells and stromal vascular cell fraction (SVF) component], and used for injection, under local anesthesia. Moreover, in a study by Pignatti et al., aspirated fat was centrifuged and the infranatant fat was isolated and transferred to syringes [12], followed by creating a skin access and injection on both sides of proximal phalanx.

In the RCT by Del Papa et al. [13], adipose tissue (AT) group ($n = 25$) was compared to a age and sex matched group receiving a sham procedure (SP) which is a placebo surgery ($n = 13$). DU healing was reported in the majority (23/15) of patient of patients in the AT group compared to (1/13) in the SP group at 8 weeks of follow up ($p < 0.0001$). Twelve pts in the SP group, received rescue AT injection and all of them (100 %) healed after 8 weeks of observation. The AT treated patients showed a significant reduction of pain severity (measured by visual analogue scale) after 4 and 8 weeks ($p < 0.0001$ in all cases). Additionally, a significant increase of capillary numbers in the affected finger was recorded by nailfold videocapillaroscopy after 4 and 8 weeks ($p < 0.0001$). Likewise, the healing rate (HR) with autologous fat grafting assessed in the other 3 single-arm prospective studies, was 66 %, 88 % and 100 % [12,14,22]. Pain reduction was reported in the 3 studies. Background therapies were allowed in all studies except one study [14]

Table 2
Characteristics of the studies included in the SLR on surgical topical treatment for SSc-DU.

Study	Year	Intervention	Number of patients	Type of study	Primary outcome	comparator	Risk of bias
Adipose tissue Grafting							
Del Bene [22]	2014	Autologous fat graft	9	Case series	DU healing	none	N/A
Del Papa [14]	2015	Adipose tissue grafting	15	Case series	Time to DU healing	none	N/A
Granel [15]	2015	Adipose derived SVF	12	Cohort	Number and the severity of adverse events	none	Moderate
Daumas [23]	2017	Adipose derived SVF	12	Cohort	Hand function	none	Moderate
Del Papa [13]	2019	Adipose tissue grafting}	25	RCT	DU healing	13 SSc received Sham injections	Low
Pignatti [12]	2020	Adipose tissue grafting	12	Cohort	DU healing/ hand pain	none	Moderate
Park [16]	2020	Adipose derived SVF	18	Cohort	Not stated	none	Moderate
Surgical Sympathectomy							
Agarwal [17]	2004	Sympathectomy	6	Case series	Not stated	none	N/A
Hartzel [18]	2009	Sympathectomy	13	Case series	Du healing	none	N/A
Momeni [24]	2015	Sympathectomy, vascular bypass	17	Cohort	DU healing	none	serious
Bone marrow derived cells transplantation							
Ishigatsubo [19]	2010	Bone marrow derived cells transplantation	8	Case series	VAS pain	none	N/A
Other Microsurgical modalities							
Tham [21]	1997	Limited microsurgical arteriolysis (adventitial stripping)	6	Case series	Not stated	none	N/A
Kryger [20]	2007	Direct microsurgical revascularization (radial to digital artery bypass graft)	4	Case series	Healing of fingertip ulcers and avoiding amputation	none	N/A

DU = digital ulcers, VAS = visual analogue scale, SVF: stromal vascular fraction, N/A = not applicable

which was a prospective non-controlled study (Table 3), AT grafting examined in 15 patients with SSc-DU. As regards to safety of adipose tissue injection, finger edema and paresthesia were reported in 2 cases in one study [12], no other complications were reported within ATDC studies.

Stromal vascular fraction (SVF)

The method of isolation of SVF, also varied among the published studies, enzymatic digestion of adipose tissue was carried out differently in preparation SVF. Automated processing system and enzymatic digestion using GMP-grade reagents were utilized in 2 studies [15,23] while a different system kit was used in the study by Park et al. [16].

Separation and injection of stromal vascular fraction (SVF) from the whole ATDC, was reported in three prospective noncontrolled studies evaluating a total of 42 patients [15,16,23]. The same isolation technique to separate SVF from harvested adipose tissue, is utilized in two studies [15,23] The rates of healing were 60 %, 63 %, respectively within the two studies using the same technique, while it was 32 %, in the study by Park et al. Follow-up ranged between 6 months [15,16] up to 22 months [23]. Background therapies in the form of CCB and PG were permitted in all studies. Transient finger pallor and paresthesia were reported in 1 study [16], and no complications were reported in other studies.

Nevertheless, healing rates of DUs with adipose tissue were variable, ranging between 66–100 % in studies using whole ATDC (1 RCT, 3 prospective studies) [12–14,22], and 32 %–63 % in studies utilizing isolated SVF component (3 prospective trials) [15,16,23] (Table 4).

Bone marrow derived transplantation

One study by Ishigatsubu Y et al., evaluated effectiveness of bone marrow (BM) cell transplantation in SSc-DUs [19]. BM cells were retrieved from bilateral iliac crests using BM needles, followed by isolation of BM derived mononuclear cells, which were injected into the skeletal muscles of the ischemic limb. Complete healing was achieved in8 weeks in upper limb and in 24 weeks in lower limbs. In 1 case a new ulcer re-appeared on the injected side on follow up. Increased blood flow volume, and new capillaries by capillaroscopy in the nail bed were found after 2 weeks of injection [19]. BM derived transplantation was shown to be a relatively safe procedure, vertigo (case 1) and sore throat (case 3) were reported in the immediate postoperative period in two patients, respectively.

Surgical sympathectomy

Surgical sympathectomy was reported in 3 retrospective observational studies (total number of patients = 36) ([17,18,24]s). All 3 studies allowed background therapy (Table 3). The median healing rate was 81 %. Follow-up time ranged from 9 to 96 months.

Agarwal et al. [17] performed digital artery sympathectomy in 6 patients, with healing rates of 81 %. Digital plethysmography was performed before and after the sympathectomy to evaluate digital blood flow in 1 patient, which showed preoperative non-pulsatile wave forms that changed to pulsatile waveform postoperatively. Patients were followed up for 20 months. Mild wound separation was reported in two patients, but this healed in over 1–2 weeks with dressing [17].

Hartzel et al [18] showed that after digital artery sympathectomy 35 % of patients had complete healing while 25 % of patients reported reduction in ulcer size/pain. Followed up for an average of 96 months, 26 % of digits ultimately required amputation within treated non-healed ulcers. Flexion contracture in 1pt, delayed wound healing in 1 pt – digit amputation in 4 digits. Momeni et al. [24], reported that combined sympathectomy, vascular bypass, and vein graft in 17 patients, led to DU healing in 100 % of treated patients, mean follow-up time was 13 months (1–54 months). Wound infection in 3 pts, 2 stitch abscess and wound opening in 2 pts were reported [24].

Direct microsurgical revascularization and limited microsurgical arteriolysis (adventitial stripping)

A study by Kryger et al. [20]) retrospectively reported a surgical a radial-to-common digital artery bypass graft, in 4 patients with SSc-DU.

Table 3
Baseline characteristics and outcomes of studies included in the SLR on surgical topical.

	Baseline DU (n)	Background therapy (%) ETA	CCB	APA	PG	ARB	ACE-I	PDE-5i	IS	Follow-up (Month)	Healed ulcers (%)	Pain Reduction (VAS/10)	complications
Adipose tissue graft	.												
1. Autologous fat graft (Del-Bene) [22]	15	26 %	100 %	N	100 %	N	N	13 %	N	6–24	10 (66 %)	77 % reduced pain meds	Amputation in 2 long standing resistant ulcers
2. Adipose tissue implant (Del-*papa2015) [14]	15	no	no	no	no	no	no	no	no	2	15 (100 %)	Signifiant pain relief 0.001	NR
3. Adipose derived SVF (Granel) [15]	15	16 %	50 %	no	no	no	no	no	yes	6	8 (63 %)	Significant reduction pain at 1- and 6-month FU	NR
4 adipose derived SVF (Daumas) [23]	15	no	25 %	no	no	no	no	yes	no	22	9 (60 %)	Pain Vas reduced to 17 ±_15 from 59 ±17	NR
5. Adipose tissue grafting (Del-papa 2019) [13]	25 case 13- Ctr	no	100	no	100	no	no	no	no	2	23 (92 %)* in case 1 (7 %)-Ctr	50 % improvement in all cases	NR
64. Adipose tissue graft (Pignatti) [12]	9	yes	100	no	100	no	no	no	no	6	8 (88 %)	Pain reduction (NS)	Finger edema and paresthesia in 2 cases
6. Adipose derived SVF (park) [16]	19	5 %	50	no	27	no	no	no	yes	6	6 (32 %)	No effect on pain	Transient paresthesia in one pt. -Transient finger pallor in 3 pts Slight wound
Sympathectomy													
1- Sympathectomy (Agarwal) [17]	11	no	100	no	no	no	no	no	no	20	9 (81 %)	Improved in 81 % of SSc pts	separation in 2 pts
2- Sympathectomy (Hartzel) [18]	35	NR	NR	NR	NR	NR	NR	NR	NR	23	12 (35 %)	NR	-Flexion contracture in 1pt, delayed WH in 1 pt – digit amputation in 4 digits.
3- Sympathectomy, vascular bypass (Momeni) [24] ±vein graft	26	no	35	47	no	no	no	58	no	9	26 (100 %)	Pain resolved in 15 %, improved in 77 %	Infection in 3 pts, 2 stitch abscess. Wound opening in2
Bone marrow derived cells transplantation (Ishigatsubo) [19]	8	no	no	no	62	no	no	no	Yes	36	100 %	Reduction in vas related to reduction in ulcer size $r = 0.9$	1 pt Vertigo 1 pt Sore throat both resolved in 24 hrs
Limited microsurgical arteriolysis (adventitial stripping) Tham [21]	17	NR	NR	NR	NR	NR	NR	NR	NR	12	100 %	Pain improved significantly	NR
Direct microsurgical revascularization (radial to digital artery bypass graft) (Kryger) [20]	4	NR	NR	NR	NR								
NR	NR	NR	NR	4	100 %	Significant pain reduction in 100 % of pts	NR						

ARB = angiotensin receptor antagonist, ACEi = ACE inhibitors, APA = anti-platelet agents, CCB = calcium channel blockers, Ctr = control, ETA = endothelin antagonist, IS = immunosuppression, NR = not reported, PG = prostaglandins, PDE-5i = Phosphodiesterase type-5 inhibitors, Pt = patient, NR = not reported, VAS: visual analogue scale, FU: follow-up, SSc patients, WH = wound healing * = significant.

The proposed approach involved dissection and microsurgical technique and the authors suggested that this procedure revascularizes the hand without disrupting any existing collateral flow. DU healing was observed in all the 4 treated patients (4-month follow-up time), no side effects were highlighted.

A study by Tham et al, retrospectively evaluated 6 patients who failed medical treatment for DUs who underwent limited microsurgical arteriolysis (adventitial stripping) [21]). After the procedure all DUs had healed completely after an average of 27 days and severe digital ischemic pain was significantly improved in all the digits. Minimum follow-up time was 12 month (ranging from 12–36 months) and no recurrence of symptoms at follow-up was reported. Wound healing was

Table 4
Difference between (total) Adipose tissue derived cells (ATDCs) and Stromal Vascular Fraction (SVF).

	Total ATDC (4 studies)	SVF (3 studies)
Healing rates	- 66 % in 9 pts (10/15 ulcers)(22) - 92 % in treatment group (23/25 ulcers in treatment group vs. 7 % in placebo)(13) - 100 % (15/15)(14) - 88 % (8/9 DU)(12)	- 60 % (9/15 DUs)(23) - 63 % (8/15 DUs)(15) - 32 % (6/19 DU)(16)
Randomized trials	1	–
Background therapies	Given in all except 1 study (14), which also resulted in 100 % healing	Continued in all studies

ATDC: adipose tissue derived cell, SVF: stromal vascular fraction, SVF: stromal vascular fraction

delayed in two digits. Mild stiffness of the proximal interphalangeal joint occurred in two digits but did not affect the hand function.

Discussion

In our SLR we have evaluated the safety and efficacy of surgical modalities in the management of DUs in patients with SSc. Among the evaluated studies several surgical modalities were highlighted: the local implantation of adipose tissue derived cells, bone marrow derived cells, surgical sympathectomy and microvascular revascularization surgeries.

The larger bulk of evidence pertained to autologous AT injection that despite being well-tolerated, it was also associated with variable effectiveness rates among the 7 included studies. AT grafting in general has potential tissue regenerative properties, and in vitro cellular studies have shown, that adipose tissue (as a whole and isolated SVF) is a valuable source of cells expressing multipotent, angiogenic, antifibrotic, and immunomodulatory properties, which are fundamental for tissue repair [25,26].

Amongst the different cellular components extracted from adipose tissue: Adipose tissue used as a whole (ATDC), and SVF (separation and injection), were both evaluated. With regard to autologous fat grafting protocols, there are no validated procedures and great variations exist for almost all technical features. A number of bench approaches have been proposed and display promising results. To this day the Coleman technique is one of the most common approaches to fat harvesting and placement and is considered the standardized technique for fat grafting [27]. However, critical need remains for assessment of the percentage of different types of cells in fat samples [28]. Taking into account the aforementioned bias, the result of our SLR suggested that the whole ATDC might have better healing rates versus SVF separation. Due to the lack of a control group and the allowance of background systemic therapy in the majority of studies, results should be interpreted with caution [12–14,22,15,16,23]. To note, however the prospective OBS by Del Papa et al. [14], the only study not confounded by any background medications, albeit lacking a control group (all background medications were stopped 3 weeks before the procedure) reported a 100 % HR and may suggest that improvement may have been solely due to the effect of the ATDC.

Hand Function as the primary outcome (not DU healing) was evaluated, in a recent study, by Khanna et al 2022 [29], they evaluated adipose tissue injection after enzymatic degradation and isolation of stem cell from human adipose tissue, to purify adipose derived regenerative cell (ADRC). Their primary outcome was improvement of hand function, which was not achieved, although ADRC treatment had no evident effect on the healing of existing ulcers, but it was associated with reduction in the development of new ulcers in patients with lcSSc: 18.8 % (3 of 16) of ADRC-treated patients with lcSSc developed new ulcers during the study compared to 52.4 % (11 of 21) of placebo-treated patients with lcSSc. Another study by Daumas et al [30] also published a RCT on the efficacy of SVF for hand function in SSc, SVF was not shown to be superior to placebo in improving hand function. Regarding SSc-DU the mean number of healed DUs in SVF treated group was not significantly different from the placebo group.

Despite the fact that fat grafting in general has potential tissue regenerative properties, and in vitro cellular studies have shown, that adipose tissue (as a whole and isolated SVF) is a valuable source of cells expressing multipotent, angiogenic, antifibrotic, and immunomodulatory properties, which are fundamental for tissue repair(26,27). Variable HRs of AT grafting as a treatment modality in resistant SSc-DU needs to be explained (e.g., study design, case selection epitome measures, different treatment protocols). A more specific possible explanation for the lower DU HR with SVF may be the effect of enzymatic degradation of components within the AT used to isolate SVF. In addition, the ischemic local environment around the injected AT, may compromise their regenerative capacity, Finally, the possible induction of fibroblastic lineage differentiation according to invitro studies as SVF is injected into the fibrotic medium within SSc prone tissue, as suggested by previous invitro studies [31,32]. Therefore, additional studies are warranted to better identify the optimal AT preparation technique for regenerative function in SSc-DU, site of injection, timing and need for reinjection.

BMDC grafting is a novel and promising modality to treat SSC-DUs not only because of the high HRs but also for its capability to modulate the microcirculation by increasing blood flow volume and number of nail bed capillaries over a fairly short period of time. However available evidence is too scarce to draw definitive conclusions.

Likewise, periarterial sympathectomy, microsurgical revascularization and limited microsurgical arteriolysis may be promising approaches but due to the small number of treated patients and the lack of control groups in the available studies, their results need to be confirmed.

Safety of surgical modalities, was reported in all of our included studies. Adipose tissue injections and BM transplantations were shown to be relatively safe, with minimal side effects. However, sympathectomy procedures have higher rates of side effects (ie, infections delayed wound healing and digit amputation), such a rates may be due to the delayed referral to surgeon with poor blood supply in advance cases.

Effectiveness of sympathectomy were also reported in multiple studies of SSc pts with severe Raynaud's, however, in our SLR we had digital ulcers as our primary outcome, but keeping in mind that Raynaud's has impact on vascular perfusion and eventually DU development. Unfortunately, a huge disparity in surgical technique and indications exists, Nonetheless, the consensus among most hand surgeons is that substantial early benefits are observable with sympathectomy. This is evident by the healing of amputation stumps and ulcers in cases that were previously unresponsive to medical interventions. Divergent opinions exist among surgeons regarding whether this procedure serves as a palliative measure or a definitive solution for long-term enhancement, leading to varying approaches. More specifically, surgeons who believe in the protective effect tend to perform a more extensive procedure. reducing the frequency and severity of Raynaud's attacks, there could be a subsequent reduction in vasculopathy, which might arise due to arterial reperfusion injury [33,34].

Another significant consideration pertains to ulnar artery patency, which frequently becomes occluded in cases of severe chronic symptoms. Indeed, this phenomenon is observed in approximately 50 % of scleroderma autopsies. In a substantial study involving intractable Raynaud's sympathectomy patients, over 50 % required ulnar artery reconstruction alongside with extensive periarterial sympathectomy. The assessment of ulnar artery patency can be conveniently carried out using an economical handheld Doppler device within a clinical setting. When observed in conjunction with digital ulceration, it is likely that reconstruction would yield benefits [35]. Rheumatologists should be informed about the potential options available for those who do not respond to conservative management, including fat injection, and how to identify hand surgeons who are more inclined to provide a lasting

solution. There is a compelling argument for referring patients with persistent ischemic pain for evaluation earlier, before the development of ulcerations.

Initiatives aimed at fostering collaboration between rheumatologists and hand surgeons/vascular surgeons can enhance understanding of the potential benefits of surgical interventions and establish a stronger system for patient referrals. This would guarantee that individuals who could potentially gain from sympathectomy receive thorough evaluations. As sympathectomy can typically be conducted only once per hand, it is crucial to ascertain the optimal timing based on clinical and angiographic assessments. Timely referral of these patients may alleviate years of digital pain and persistent ulcers that do not respond well to medical treatments. Consequently, this may lead to improved surgical outcomes owing to less progressed disease.

Nevertheless, for all the above techniques, their indications in the management of DUs in SSc may need to precisely define their place in the conventional therapy plan, including whether they are best used alone or in combination with conventional treatments, and regarding possible complications and/or contraindications.

This study had some limitations. First, there is considerable disparities across studies in terms of outcomes, evaluation criteria, procedures, and protocols, which didn't allow combining the studies into a meta-analysis. Secondly, only 1 RCT was identified, with other studies being of moderate- and high-risk of bias, with their limitations included a lack of blinding, the use of non-standardized outcome measures, small sample sizes, case series, and short follow-up times. In addition, There was an inconsistency in defining DU, in the included studies which may have biased our findings, thus, we recommend the utilization of a unified DU definition, which is based on a consensus of SSc experts as a "Loss of epidermal covering with a break in the basement membrane which separates dermis from epidermis, it appears clinically as fibrin blood vessels and granulation tissue and/or underlying deeper structures with exclusion of scars, fissures and infection" [36]. Some studies included in the current review were case reports that only suggested possible treatments. While they may influence future research, they cannot establish effectiveness.

In conclusion, our SLR highlighted that there is still a knowledge gap preventing a successful and timely application of all the above-mentioned techniques in daily practice for the management of DUs in SSc. Findings from the available studies need to be interpreted with caution and therefore likely cannot be generalized for the treatment of all DU in SSc patients. A standard of care for SSc DU is yet to be established and particularly in the case of observational data, interpreting true treatment effect of the studied agent, as compared to the effects of background therapy or the natural history of DU, is challenging. In particular, not only the standardised protocols for cell extraction and grafting is required but we still need to fully understand the most suitable timing for these procedures in the conventional therapy plan with relevant primary endpoints for better comparability to provide a more robust evidence base for additional surgical treatment of DU in refractory cases. In addition, we need to clarify whether they are best used alone or in combination with conventional systemic treatments, and which is the real burden of complications and/or contraindications. Future studies thoroughly investigating surgical treatment of DU are needed, selecting well-defined DUs (size, location, etc.). Until evidence-based data on surgical treatment modalities exist, these cases should be discussed and decided interdisciplinary in experienced SSc centers.

Declaration of Competing Interest

YAS: No conflict of interest to declare

CC: No conflict of interest to declare

MH: Speaking fees from Actelion Pharmaceuticals, Eli Lilly, and Pfizer, outside of the submitted work. Member of a Data and Safety Monitoring Board for Certa Therapeutics.

JWS: No conflict of interest to declare

DG: No conflict of interest to declare

PM: Speaking fees from Actelion Pharmaceuticals and Boehringer Ingelheim.

MB: No conflict of interest to declare

LC: Has served as an Advisor and Steering Committee member for Eicos Sciences. Has received consulting fees from Mitsubishi Tanabe, Genentech, Kyverna, and Jasper.

LR: No conflict of interest to declare

NM: No conflict of interest to declare

YA: Consulting fees from Boehringer Ingelheim and Sanofi, payment, or honoraria from

Boehringer Ingelheim and participation in Data Safety or Advisory Board for Boehringer

Ingelheim, Menarini, Chemomab, Curzion, Medseni, Sanofi.

CPD: Received grants from GlaxoSmithKline, Inventiva, CSL Behring, Servier, Arxx

Therapeutics. Consulting fees from GlaxoSmithKline, Janssen, Bayer, Sanofi, Inventiva,

Boehringer Ingelheim, Roche, CSL Behring, Corbus, Acceleron.

OD: Consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: Abbvie, Acceleron, Alcimed, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL, Behring, Galapagos, Glenmark, Horizon, Inventiva, Kymera, Lupin, Medscape, Miltenyi Biotec, Mitsubishi Tanabe, MSD, Novartis, Prometheus, Roivant, Sanofi and Topadur. Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143).

TF: Held a paid leadership role with the Scleroderma Clinical Trials Consortium.

DEF: Grants or contracts from Amgen, Corbus, CSL Behring, Galapagos, Gilead, GSK,

Horizon, Kadmon, Novartis, Pfizer, Roche / Genentech, Talaris. Consulting fees from Amgen,

Corbus, Galapagos, Horizon, Kadmon, Pfizer, Talaris. Payment or honoraria from CME.

DK: Consulting fees from Actelion Pharmaceuticals, Acceleron, Amgen, Bayer, Boehringer

Ingelheim, Chemomab, CSL Behring, Genentech / Roche, Horizon, Paracrine Cell Therapy,

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TK: World Scleroderma Foundation Board Member, Edith Busch Foundation Advisory Board

Member, German Scleroderma Foundation Board Member.

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JP: No conflict of interest to declare

AA: No conflict of interest to declare

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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.2023.152266.

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