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

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Disclosures

Same as Systemic (pharmacological) DU SLR

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Abstract (n=244/250)

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 performed up to August 2022 using 7 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

Thirteen (out of 899) eligible 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, total n=116). The healing rate (HR) with autologous fat grafting (4 studies) was 66-100%. Three studies reported autologous adipose-derived stromal vascular fraction grafting: HR of 32-60%. Bone marrow derived cell transplantation in a single study of 8 patients showed 100% healing rate over 4-24 weeks. Surgical sympathectomy was examined in 3 prospective studies (n=36) without a comparator group with a median healing rate of 81%. Two surgical studies (of direct microsurgical revascularisation (n=4) and microsurgical arteriolysis (n=6)) showed 100% healing of ulcers, with no complications

Conclusion

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

Key words:

Systemic sclerosis; Scleroderma; Digital ulcers, Management, Surgery; Surgical intervention

Introduction

Peripheral vasculopathy is a cardinal feature implicated in the complex aetiopathogenesis of SSc including microvascular damage which leads to progressive peripheral endothelial dysfunction, capillary dropout, and tissue ischemia (1). In general, tissue ischaemia is believed to drive 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 potential amputation.

Although there 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)(4)(5)(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-DU management. Such an approach would likely be better tolerated (e.g., through absence of major systemic side effects), and could provide novel mechanistic approaches to modify the course of DU. However, currently there is a limited evidence base, including the absence of randomised controlled trials, to confirm the safety and efficacy of surgical approaches for SSc-DU (7)(8). Furthermore, there are 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 with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (9). A systematic literature search (SLR) of

PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, Emcare (OVID) and Academic Search Premier databases was performed in 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 (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.

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 and the ROBINS-I 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. After deduplication, 896 titles and abstracts were screened (supplementary figure 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 only the results on surgical approaches are shown.

Thirteen articles on surgical treatment of SSc-DUs (7,10–21)were included in the final review. Due to the paucity of RCTs and OBS, we also included retrospective studies and case series with at least 3 patients.

Autologous fat (adipose tissue, AT) grafting was the surgical modality mostly identified (7 studies of which 1 RCT (11) and 6 prospective OBS (10,12–14,20,21) without a control group (total number of patients=116.)).

Surgical sympathectomy was reported in 3 retrospective OBS (15,16,22), one case series reported bone marrow-derived cell transplantation in 8 pts (17). Direct microsurgical revascularization was evaluated in a retrospective case series of 4 patients (18), and another retrospective case series reported microsurgical arteriolysis in 6 patients (19). An overview of study characteristics is presented in Table 1.

Patients, definition of DUs including healing

SSc classification criteria were specified according to 1980 American College of Rheumatology (ACR) criteria in 2 studies (13,20), the 2013 ACR/European League Against Rheumatism (EULAR) classification criteria for SSc in 4 studies ((10–12,14) and the Leroy criteria in 3 studies (11,12,20). A definition of DU was available only in 3 (23%) studies as follows: “Painful area at least 6 mm in diameter with depth and loss of dermis located at the volar surface of the digit”; (12) “Painful area at least >2mm in diameter with depth and loss of dermis located at site of vascular etiology, volar surface of the digit distal to PIP” (11,12); and “Lesion >= 5 mm in diameter and visible skin defect “(14). Ulcer healing was not defined in any of the included manuscripts.

Adipose tissue and adipose-derived stromal vascular fraction grafting

Autologous fat (adipose tissue AT) grafting was the surgical modality investigated by the largest number of studies, (10–14,20,21) (7 studies of which 1 RCT, 4 cohort prospective studies and 2 case series). Risk of bias ranged from low to moderate.

The procedure of fat extraction and injection sites varied across the included studies. In the study by Bene et al.(20), a 3-mm cannula was used to retrieve the AT which was then centrifuged. Only the middle layer, containing purified fat tissue was transferred to 1-mL syringes and 2–3 mL of fat was injected into fingers with a 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. reported AT grafting in 2 studies (11,12), the intermediate layer was collected after centrifugation, [defined as AT derived cells (ATDC), containing both adipose stromal/stem cells (ASCs) and stromal vascular cell fraction (SVF) component], and used for injection. A total amount of 0.5–1 ml of the autologous ATDC were injected at the base of the affected finger, by sequential introduction of small aliquots in different directions from the injection site, under local anesthesia.

In another study by Pignatti et al., aspirated fat was centrifuged and the infranatant fat was isolated and transferred to syringes. After creating skin access with a 19-gauge needle at the medial and lateral dorsal side of each proximal phalanx, an injection cannula was introduced.

The method of isolation also varied amongst 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 (13,21) while a different system kit was used in the study by Park et al(14). DU improvement ranged between 66%-100% in studies using ATDC (1 RCT, 3 prospective studies) (10–12,20), and 32%-63% in studies utilizing isolated SVF component (3 prospective trials)(13,14,21). Thus, adipose tissue derived cells (ATDC) and isolated SVF were both utilized in SSc DU with variable healing rates, (table 3).

Adipose Tissue Derived Cells (ATDC):

In the RCT(11), adipose tissue (AT) group (n=25) was compared to an age and sex matched group receiving a sham procedure (SP) which is a placebo surgery (n=13). DU healing was reported in the majority (23/25) of patients in AT group compared to (1/13) in the SP group at 8 weeks of follow up ($p<0.0001$). Twelve patients 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 % (10,12,20). Pain reduction was reported in the 3 studies. Background therapies were allowed in all studies except one study (12) which was a prospective non-controlled (table 2) study of AT grafting in 15 patients with SSc-DU. Finger edema and paresthesia were reported in 2 cases in 1 study(10). No other complications were reported within ATDC studies.

Stromal vascular fraction (SVF)

Separation and injection of stromal vascular fraction (SVF) from the total ATDC, was reported in three prospective noncontrolled studies evaluating a total of 42 patients(13,14,21). The same isolation technique to separate SVF from harvested adipose tissue was utilized in two studies ((13,21) The rates of healing were 60% and 63% in the two studies using the same technique, while it was 32 %, in the study by Park et al. Follow-up was between 6 months (13,14) or up to 22 months (21). Background therapies in the form of CCB and PG were permitted in all studies. Transient finger pallor and paresthesia were reported in 1 study (14), and no complications were reported in other studies

Bone Marrow Derived Transplantation

One study by Ishigatsubu Y et al., evaluated efficacy of bone marrow (BM) cells transplantation in SSc-DUs. BM cells retrieved from bilateral iliac crests using BM needles, followed by isolation of BM derived mononuclear cells were injected in the skeletal muscles of the ischemic limb. Complete healing was obtained by 8 weeks in upper limbs and by 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 (17).

Surgical Sympathectomy

Surgical sympathectomy was reported in 3 retrospective observational studies (total number of patients=36). All 3 studies allowed background therapy (Table 2). The median healing rate was 81%. Follow-up time ranged from 9 to 96 months.

Agarwal et al (15) 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 wave forms postoperatively. Patients were followed up for 20 months. Mild wound separation was reported in two patients, that healed in 1-2 weeks with dressing.

Hartzel et al (15) 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 with non-healed ulcers ultimately required amputation. Momeni et al.(22), reported that combined sympathectomy, vascular bypass, and vein graft in 17 patients, led to DU healing in 100% of treated patients over a mean follow-up time of 13 months (1-54 months). Wound infection occurred in 3 patients, while 2 patients had stitch abscesses and 2 patients experienced wound opening.

Direct Microsurgical Revascularization and limited microsurgical arteriolysis (adventitial stripping)

A study by Kryger et al.,) reported a surgical technique using a radial-to-common digital artery bypass graft in 4 patients with SSc-DU. 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 4 treated patients (4-month follow-up time) with no side effects reported.

Tham et al retrospectively evaluated 6 patients recalcitrant to medical treatment for DUs, who underwent limited microsurgical arteriolysis (adventitial stripping). After the procedure, all DUs had healed completely over an average of 27 days, and severe digital ischaemic pain was significantly improved in all the digits. After a minimum follow-up time of 12 months (ranging from 12-36 months), no recurrence of symptoms was reported. Wound healing was delayed in two digits. Mild stiffness of the proximal interphalangeal joint occurred in two digits but did not affect 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.

Autologous adipose tissue injection was the most studied modality (7 studies, 1 RCT and 6 prospective single arm studies). Adipose tissue injection, was found to be well-tolerated, however, associated with variable efficacy rates among the 7 included studies.

Amongst the different cellular components extracted from adipose tissue: Adipose tissue used as a whole (ATDC), and SVF (separation and injection), were both evaluated. Results suggested that the whole ATDC might have better healing rates versus SVF separation. DU improvement ranged between 66%-100% in studies using whole ATDC (1 RCT, 3 prospective studies) (10–12,20), versus 32%-63% in studies utilizing isolated SVF component (3 prospective noncontrolled studies)(13,14,21). In 1 RCT using whole ATDC (11), thehealing rate was 92% in cases vs. 7% in controls. A prospective non-controlled study by Del Papa et al (12) reported a 100% healing rate for 15 DUs. This study was not confounded by any background medications (all background medications were stopped 3 weeks before the procedure) while all other studies continued background therapies,suggesting that improvement may have been solely due to the effect of the ATDC.

Fat grafting in general has potential tissue regenerative properties. In addition, *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(23,24).

A recent study, by Khanna et al 2022 (25), also evaluated adipose tissue injection after enzymatic degradation and isolation of stem cells from human adipose tissue, to purify adipose derived regenerative cells (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, 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 (26), also published a RCT on the effect 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.

The variable healing rates of adipose tissue injections hinders its use as a standard of care treatment modality in resistant SSc-DU. A possible explanation of the lower DU healing rate with SVF, may be due to the effect of enzymatic degradation of components within the adipose tissue, in order to isolate SVF. Additional explanations include the ischemic local environment around the injected AT, which may compromise their regenerative capacity, as well as the possible induction

of fibroblastic lineage differentiation as SVF is injected into the fibrotic medium within SSc prone tissue, as suggested by previous *in vitro* studies (27,28). More research is warranted to better identify the optimal adipose tissue preparation technique for regenerative function in SSc-DU, site of injection, timing and need for reinjection.

Periarterial sympathectomy is a surgical modality that resulted in a healing rate of SSc-DU of 35-80%; however, all of the studies were retrospective with high risk of bias ((16)). One study (22) added venous grafting to the surgical approach if vessel patency was occluded (used in 26 patients) and this modality resulted in 100% healing in DUs. Thus, in the choice of surgical techniques, sympathectomy may not be the best option due to lower evidence of published studies, and low reported healing rates. More research is needed to identify which surgical modality/timing is best in managing SSc-DUs. Better controlled studies are needed to evaluate the efficacy of sympathectomy and address if venous grafting may improve the outcome.

Bone Marrow Derived cells transplantation isa novel modality that resulted in complete healing in all ulcers (N=8). Increased blood flow volume and new capillary development by capillaroscopy were observed after 2 weeks of injection. Hence, this new modality has a potential role in DU management, however it needs further controlled studies to ascertain its efficacy in managing various SSc-DUs.

For all of the above techniques, their roles in the management of DUs in SSc still need to be defined, 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. 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.

Thus, due to the above limitations, our findings 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. Future studies that rigorously investigate DU surgical management, with selection of relevant primary endpoint/s, are required to build a stronger evidence-base to guide DU management.

In conclusion, our SLR highlights surgical techniques that have been utilized to manage DU: the local implantation of adipose tissue-derived cells, surgical sympathectomy and microvascular revascularization surgeries, which in addition to systemic treatments, could be considered as therapeutic options used to treat refractory DUs in patients with SSc

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Study	**Year**	**Intervention**	**Number of patients**	**Type of study**	**Primary outcome**	**comparator**	**Risk of bias**
Adipose tissue Grafting							
Del Bene (20)	2014	Autologous fat graft	9	Case series	DU healing	none	N/A

Del Papa(12)	2015	Adipose tissue grafting	15	Case series	Time to DU healing	none	N/A
Granel (13)	2015	Adipose derived SVF	12	Cohort	Number and the severity of adverse events	none	Moderate
Daumas(21)	2017	Adipose derived SVF	12	Cohort	Hand function	none	Moderate
Del Papa(11)	2019	Adipose tissue grafting)	25	RCT	DU healing	13 SSc received Sham injections	Low
Pignatti (10)	2020	Adipose tissue grafting	12	Cohort	DU healing/ hand pain	none	Moderate
Park(14)	2020	Adipose derived SVF	18	Cohort	Not stated	none	Moderate
Surgical Sympathectomy							
Agarwal (15)	2004	Sympathectomy	6	Case series	Not stated	none	N/A
Hartzel (16)	2009	Sympathectomy	13	Case series	Du healing	none	N/A
Momeni (22)	2015	Sympathectomy, vascular bypass	17	Cohort	DU healing	none	serious
Bone marrow derived cells transplantation							
Ishigatsubo (17)	2010	Bone marrow derived cells transplantation	8	Case series	VAS pain	none	N/A
Other Microsurgical modalities							
Tham (19)	1997	Limited microsurgical arteriolysis (adventitial stripping)	6	Case series	Not stated	none	N/A
Kryger (18)	2007	Direct microsurgical revascularization (radial to digital artery bypass graft)	4	Case series	Healing of fingertip ulcers and avoiding amputation	none	N/A

Table 1. Characteristics of the studies included in the SLR on surgical treatment for SSc-DU.

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

	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)(20)	.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)(12)	15	no	no	no	no	no	no	no	no	2	15(100%)	Signifiant pain relief 0.001	NR
3. Adipose derived SVF (Granel)(13)	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)(21)	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) (11)	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)(10)	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)(14)	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
Sympathectomy 1- Sympathectomy (Agarwal)(15)	11	no	100	no	no	no	no	no	no	20	9 (81%)	Improved in in 81% of SSc pts	Slight wound separation in 2 pts
2- Sympathectomy (Hartzel)(16)	35	NR	NR	NR	NR	NR	NR	NR	NR	23	12 (35%)	NR	-Flexion contracture in 1pt, delayed WH in 1 pt - 26% required amputation
3- Sympathectomy, vascular bypass (Momeni) (22) +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 in 2
Bone marrow derived cells transplantation (Ishigatsubo)(17)	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(19)	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)(18)	4	NR	NR	NR	NR	NR	NR	NR	NR	4	100%	Significant pain reduction in 100% of pts	NR

Table 2: Characteristics of extracted studies.

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.

	Total ATDC (4 studies)	SVF (3 studies)
Healing rates	-66% in 9 pts (10/15 ulcers)(20) -92% in treatment group (23/25 ulcers in treatment group vs. 7% in placebo)(11) -100% (15/15)(12) -88% (8/9 DU)(10)	-60% (9/15 DUs)(21) -63% (8/15 DUs)(13) -32% (6/19 DU)(14)
Randomized trials	1	-
Background therapies	Given in all except 1 study(12), which also resulted in 100% healing	Continued in all studies

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

Table 3: Difference between (total) Adipose tissue derived cells (ATDCs) and Stromal Vascular Fraction (SVF)