Autologous fat or adipose-derived stem cell grafting in systemic sclerosis treatment: a systematic review and meta-analysis

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Abstract

Objective

Systemic sclerosis (SSc) is characterised by vasculopathy and progressive fibrosis of the skin. The aim of this article is to analyse and summarise the efficacy and safety of autologous fat (AF), stromal vascular fraction (SVF) and adipose-derived stem cell (ADSC) grafting in the treatment of SSc, providing evidence for clinical application.

Methods

The research involves the efficacy and safety of AF, SVF and ADSC grafting in the treatment of patients with SSc. The studies were screened and selected independently by two authors based on pre-specified criteria. The data extraction and quality assessment were also performed independently by two authors.

Results

Fifteen studies were eligible for inclusion. Skin thickness reduced following SVF or AF therapy, but there was no significant difference. All measures used to assess fingertip symptoms revealed a significant improvement. Notably, SVF and AF were found to have the most impact on Raynaud's phenomenon improvement. The ADSC group improved the most in terms of finger pain alleviation. SVF reported the highest proportion of adverse events, accounting for approximately half of the cases.

Conclusion

AF, SVF, and ADSC all displayed therapeutic effects of improving SSc, but differences existed in the effects on different symptoms. Plastic surgeons should choose the most suitable treatment strategy after comprehensively evaluating the patient's clinical manifestations.

Key words

systemic sclerosis, scleroderma, autologous fat grafting, adipose-derived stem cells, stromal vascular fraction

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Introduction

Systemic sclerosis (SSc), also called scleroderma, is an autoimmune disease, which is characterised by vasculopathy and progressive fibrosis that typically affects the skin, with diverse internal organ involvement (1-3). Patients may present with tight skin, Raynaud's phenomenon, digital ulcer (DU), pulmonary hypertension and visceral fibrosis. It affects mostly young and middle-aged women and usually indicates poor prognosis or even death when cardiopulmonary complications occur (1). DU is one of the most common symptoms of SSc, affecting up to 50% of patients (4, 5). It is hard to heal and leads to extreme pain and functional disability. Amputation may be required in certain cases when infection and gangrene are complicated (6). Facial involvement, despite not being life-threatening, is associated with mask-like stiffness of the face, perioral fibrosis, and xerostomia, resulting in disfiguring appearance and difficulty with daily eating, drinking, and personal care (7). The symptoms described above significantly lower the patient's quality of life and may produce a heavy impact on the patient's physical and mental health (8, 9). Currently, the drug treatments have shown limited efficacy in improving facial lesions and DU, posing a great therapeutic challenge for plastic surgeons (10).

The use of adipose tissue as a filling material to achieve structural modifications in plastic and aesthetic surgery is an ancient technique, taking advantage of its abundance and accessibility (10). In 2006, Coleman *et al*. proposed that fat grafting may also promote tissue regeneration, rather than merely serve as soft tissue fillers (11). In the last decades, autologous fat grafting (AFG) has been successfully applied to treat an increasing range of clinical disorders marked by skin atrophy or fibrosis such as radio-induced tissue damage, posttraumatic or burning scars, breast reconstruction after surgery, and craniofacial deformities (10, 12). Recently, AFG has also been used to treat individuals with SSc-related face and hand dysfunctions. Adipose tissue is a valuable source of cells with multipotency, angiogenic, and immunomodulatory properties that facilitate tissue repair (13, 14). Since Zuk *et al*. suggested the removal and administration of stromal vascular fraction (SVF) from adipose tissue in 2002, based on its regenerative and anti-inflammatory effects, it has emerged as a potential treatment option for SSc (15). SVF is composed of a population of multipotent cells known as adipose-derived stem cells (ASCs), various growth factors, and cytokines. SVF can be obtained from adipose tissue that has been subjected to washing, enzymatic digestion, filtration, and centrifugation. Subsequent tissue culture passages allowed for self-selection of ASCs from SVF due to their adherence to the plastic tissue culture ware (13). Compared with traditional stem cells, such as bone marrow stem cells, adipose stem cells are abundant and easy to separate, so they have opened new therapeutic possibilities. Adipose stem cells can release angiogenic, immunomodulatory, and anti-apoptotic substances, as well as proliferate and differentiate. SSc can be effectively treated using ADSCs and SVF, and their acquisition techniques have been created. They can avoid the issue of localised pressure from fat injection causing tissue ischaemia. However, no study has in-depth compared the variations in treatment efficacy and security between AF, SVF, and ADSCs grafting (16, 17). Herein, we aimed to conduct a systematic literature review and meta-analysis of all the published data in order to assess the efficacy and safety of AF, SVF and ADSC grafting in the treatment of patients with SSc and to provide evidence for clinical application.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (18) and was registered in the PROSPERO (registration no. CRD42023341722).

Literature search strategy

A comprehensive literature search was performed to identify the relevant publications in PubMed, Embase and

Cochrane Library databases from their inception to July 1, 2022. The search strategies typically use a combination of terms from medical subject headings (MeSH) and free-text keywords. The English subject headings were "scleroderma, systemic" AND "mesenchymal stem cells", combined with free words as follows: (systemic sclerosis OR scleroderma, diffuse OR scleroderma, progressive OR CREST syndrome) AND (mesenchymal stromal cells OR MSC OR multipotent stromal cells OR mesenchymal progenitor cells OR adipose-derived mesenchymal stem cells OR autologous fat grafting OR stromal vascular fraction). The records were managed with EndNote (version 20) to exclude duplicates. The remaining were further reviewed to determine whether to include in further analysis. Each included reference was scrutinised to find any more relevant records that the first search missed.

Inclusion and exclusion criteria

This review focused on the all the published data containing the efficacy and safety of AF, SVF, and ADSC grafting in the treatment of patients with SSc, regardless of age, gender, disease duration and severity. Exclusion criteria were as follows: (i) non-English literatures; (ii) animal or in vitro studies; (iii) literature with incomplete data or lacked target indicators; (iv) review articles, case reports, conference reports, replies, patents, or protocols. The title and abstract were first screened, followed by the full text. The literature search and filter were carried out separately by two authors, with disagreements resolved by consensus. If the authors were unable to reach an agreement, a third writer made the ultimate decision. If the full text was not available, the information was obtained by getting in touch with the original author by phone or e-mail.

Outcome assessment

The effective outcome endpoints included at least one of the following aspects of the modified parameters of disease activity in SSc patients, including: a) skin changes, *i.e.* modified Rodnan skin score (mRSS); b) vascular changes in fingers, such as DU, Cochin hand function scale (CHFS), Raynaud's Condition Score (RCS) and visual analog scale (VAS); c) perioral conditions, evaluated by mouth Handicap in Systemic Sclerosis scale (MHISS) and maximal mouth opening (MMO). Adverse events (AEs) were selected as safety outcome measures.

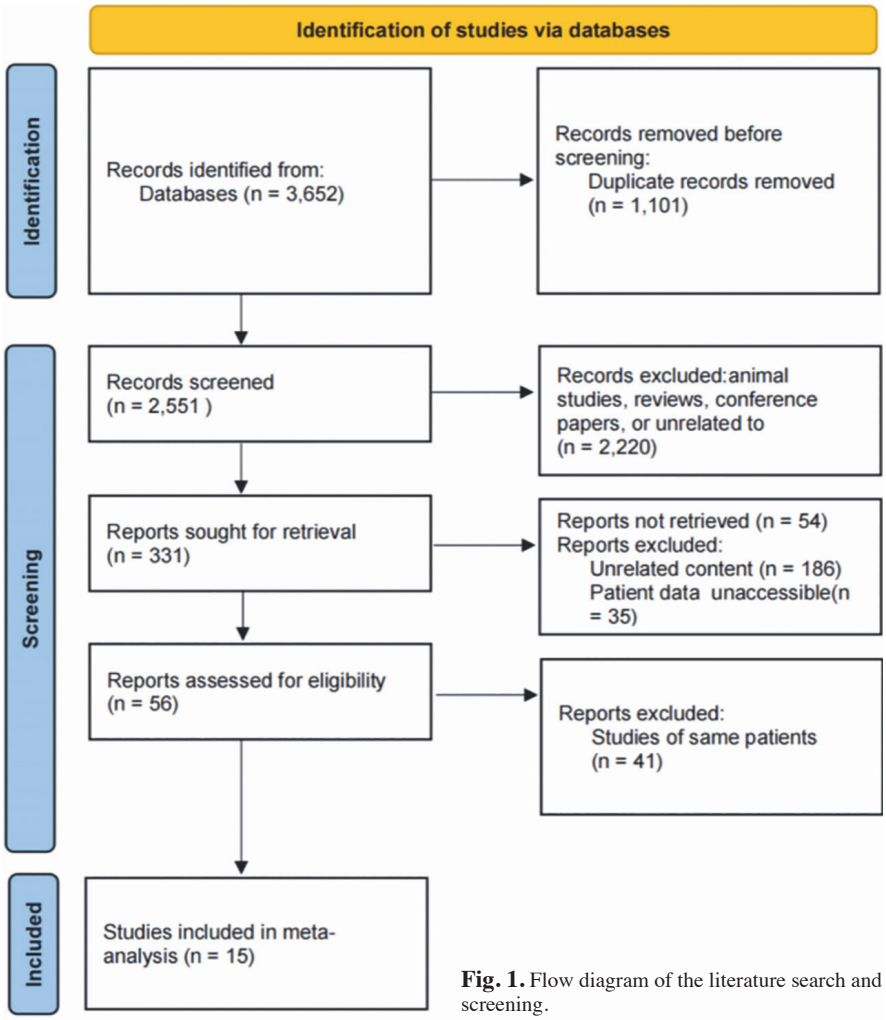

Fig. 1. Flow diagram of the literature search and screening.

Data abstraction and quality assessment

Two researchers separately extracted the data from the final included studies and disagreements were resolved by consensus. The following information was extracted and recorded: the first author/published year, country, research type, participants' data, mean age, follow-up time, injection method, post-treatment outcomes and standard deviations. The quality of evidence was assessed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (19). Two investigators mutually cross-checked the included literature and conducted a quality assessment, and the third investigator decided the final result in case of any difference. The certainty of the evidence was then classified as high, moderate, low, or very low.

Statistical analysis

The extracted data were pooled and analysed using the Review Manager software (RevMan, v. 5.3; Cochrane Collaboration, Copenhagen, Denmark) (20). For dichotomous data, pooled outcomes were presented as odds ratio (OR) and 95% confidence interval (CI), while continuous outcomes were expressed as a mean difference (MD) and 95% CI for analysis. Heterogeneity was statistically evaluated by I^2 value, indicating low, moderate, and high heterogeneity with the thresholds of

Table I. Characteristics of the 15 studies included.

Reference	Sample size	Follow-up	Treatment	Skin		Vacular				Perioral		RCT	AEs
				Global mRSS	Hand mRSS	RCS	DU	CHFS	VAS	MHISS	MMO		
Del Bene, 2014 (21)	9		AF				*						
Del Papa, 2015 (22)	20	1/3 m	AF								*		
Granel, 2015 (23)	12	2/6 m	SVF	*		*	*	*	*				*
Del Papa, 2015 (24)	15	1/3/6 m	ADSCs				*		*				
Onesti, 2016 (25)	10	12 m	AF &							*			
Sautereau, 2016 (26)	14	3/6 m	AF	*						*	*		*
Blezien, 2017 (27)	7	1/6/12 m	AF							*	*		
Daumas, 2017 (28)	11	6/30 m	SVF		*	*		*	*				
Gheisari, 2018 (29)	16	3 m	AF							*			*
Almadori, 2019 (30)	62		ADSCs							*			*
Del Papa, 2019 (31)	25	1/2 m	AF				*		*			Y	
Park, 2020 (32)	20	3/6 m	SVF	*	*	*	*	*	*				*
Pignatti, 2020 (33)	25	6/12 m	AF	*		*	*		*	*	*		
Daumas, 2022 (34)	20	1/3/6 m	SVF		*		*	*	*			Y	*
Khanna, 2022 (35)	48	6/12 m	ADSCs			*		*				Y	*

* Represents the measure is included in the results of the corresponding study.

>25%, >50% and >75%, respectively. Typically, I^2>50% indicates substantial heterogeneity. In this study, the fixed-effect model was applied for analysis if trials were homogeneous (I^2≤50% and p>0.1) and the random-effect model was applied for the meta-analysis if statistical heterogeneity was identified (I^2>50% and p<0.1); p<0.05 indicated statistical significance.

Results

Flow diagram and basic characteristics of studies

According to the above search strategy, 3652 articles were initially retrieved from three databases, and 2551 were obtained after the removal of duplicates. Then the titles and abstracts were screened for potential eligibility, and 277 articles were considered for full-text review. After further full-text screening, 56 studies were identified. Next, we checked the data of researchers and participants, removing duplicated studies that shared the same patient population but with different follow-up durations. And 15 studies were finally included and meta-analysed (21-35). The specific screening process is illustrated in Figure 1.

The characteristics of included studies are summarised in Table I. The total number of participants was 314. The follow-up period was 1 to 12 months. The treatments were AFG, SVF and ADSCs. The outcome measures observed were skin changes (Global and Hand mRSS), vascular changes (RCS, DU, VAS, and CHFS), and perioral changes (MMO, MHISS). Quality of life scores were also assessed in some studies. In addition, the incidence of adverse reactions was included in our statistics.

Evidence certainty evaluation

Both the global and hand mRSS are employed in this study to assess skin changes. The terms used to describe vascular changes are RCS, VAS, CHFS, and DU values. Oral function is addressed by MMO and MHISS. A total of eight aspects were evaluated using the GRADE, of which four aspects were moderate quality, and four were low quality. As shown in Table II, the evidence was judged to be of low quality for the RCS, VAS, CHFS, and DU numbers. For mRSS, MMO, MHISS outcomes, their evidence was judged to be moderate.

Skin changes in SSc patients

Global mRSS assigns three points to each part of 17 body parts, with a total of 51 points. In our study, four studies involving 68 SSc patients were compared using Global mRSS changes before and after the treatment (23, 26, 32, 33). The fixed-effect model was applied for the low heterogeneity among these studies (I^2=32.7%, p=0.22, Fig. 2) and meta-analyses showed that the score was lower than before the treatment (MD=-1.61, 95%CI -3.99 to 0.77), indicating improved skin thickening; however, the difference was not significant with a p-value of 0.19. Subgroup analyses were also conducted according to different treatments, divided into the group of SVF (23, 32) and AF (26, 33). And results showed that the Global mRSS of SSc patients after SVF treatment was lower than before the treatment, suggesting that the degree of skin thickening was reduced (MD=-3.66, 95%CI -7.73 to 0.41, p=0.08, Fig. 2), while the change in AF group was limited compared with baseline (MD=-0.54, 95%CI -3.48 to 2.39, p=0.72, Fig. 2). The findings revealed that SVF might lower the Global mRSS, AF could not.

For hand mRSS, six parts of the hands were evaluated, with a total of 18 points and three articles involving 50 patients were analysed (28, 32, 34). Due to the low intra-group heterogeneity among the studies included, a fixed-effect model was used (p>0.1, I^2≤50%, Fig. 3). Meta-analyses showed that the score was slightly lower than before the treatment (MD=-0.59, 95%CI -1.35 to 0.17), but the difference was not significant (p=0.13), shown in Figure 3. One randomised controlled trial in this group did not show any improvement

Table II. Summary of findings and GRADE evaluation of evidence certainty.

Participants (studies) Follow-up	Certainty assessment				Publication bias	Summary of findings					
	Risk of bias	Inconsistency	Indirectness	Imprecision		Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With treatment		Mean difference /Risk with placebo	Mean difference /Risk difference with Treatment
MMO 125 (5 studies) (22, 25, 26, 27, 33)	Downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Moderate	63	62	-	The mean MMO was **0**	MD **0.57 higher** (0.31 higher to 0.83 higher)
MHISS 245 (5 studies) (26, 27, 29, 30, 33)	Downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Moderate	123	122	-	The mean MHISS was **0**	MD **5.92 lower** (7.39 lower to 4.45 lower)
Global mRSS 136 (4 studies) (23, 26, 32, 33)	Downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Moderate	68	68	-	The mean global mRSS was **0**	MD **1.61 lower** (3.99 lower to 0.77 higher)
Hand mRSS - SVF 100 (3 studies) (28, 32, 34)	Downgraded	Not downgraded	Not downgraded	Not downgraded	Not downgraded	Moderate	50	50	-	The mean hand mRSS - SVF was **0**	MD **0.20 higher** (0.54 lower to 0.95 higher)
RCS 196 (5 studies) (23, 28, 32, 33, 35)	Downgraded	Downgraded	Not downgraded	Not downgraded	Not downgraded	Low	114	106	-	The mean RCS was **0**	MD **2.79 lower** (5.04 lower to 0.53 lower)
CHFS 186 (5 studies) (23, 28, 32, 34, 35)	Downgraded	Downgraded	Not downgraded	Not downgraded	Not downgraded	Low	101	109	-	The mean CHFS was **0**	MD 8.88 **lower** (23.26 lower to 5.5 higher)
VAS 227 (7studies) (23, 24, 28, 32-35)	Downgraded	Downgraded	Not downgraded	Not downgraded	Not downgraded	Low	102	113	-	The mean VAS was **0**	MD **32.74 lower** (64.99 lower to 0.5 lower)
DU numbers 254 (7 studies) (21, 23, 24, 32-35)	Downgraded	Downgraded	Not downgraded	Not downgraded	Not downgraded	Low	83/115 (72.2%)	32/127 (25.2%)	**OR 0.03** (0.01 to 0.26)	722 per 1,000	**470 fewer per 1,000**

in hand mRSS with the use of SVF, indicating that further research is needed to determine the efficacy of SVF for treating hand mRSS in SSc patients.

Vascular changes in fingers of SSc patients

Raynaud's Condition Score (RCS). We included five studies and compared the RCS changes of 98 SSc patients after the injection of AF, SVF, or ADSCs (23, 28, 32, 33, 35). Due to high heterogeneity (p<0.00001, I^2=96%,), the random effects model was used. And the results showed that the overall RCS in these patients improved significantly (MD=-2.67, 95%CI -5.04 to -0.31, p=0.03, Fig. 4). In terms of subgroup analysis, there were three studies containing 41 patients who have the received SVF injection, of which two studies showed significant improvement of RCS in 23 patients (23, 28), while one research showed no improvement in 18 cases (32). On the whole, RCS reduced significantly after the treatment of SVF (MD=-3.59, 95%CI -6.35 to 0.83, p<0.01, Fig. 4). The use of AF (33) and ADSCs (35) has also been shown to have certain benefits in the improvement of RCS and the effect of AF is significant (MD=-2.20, 95%CI -3.14 to 1.26, p<0.01, Fig. 4). One randomised controlled trial in this group found that ADSCs significantly improved RCS, suggesting that ADSCs may be a promising treatment option for improving RCS in SSc patients.

Digital ulcers (DU). As shown in Figure 5, a total of seven studies comprising 127 individuals investigated the effect of AF, SVF, or ADSCs on DU (21, 23, 24, 31-34). Due to the high heterogeneity (p=0.0001, I^2=78%), the random effects model was adopted. The DU symptoms significantly alleviated in these patients (odds ratio 0.03, 95%CI 0.00 to 01.30, p=0.003). One randomised controlled trial found that SVF did not reduce the number of digital ulcers, while another randomised controlled trial indicated that the autologous fat treatment group had

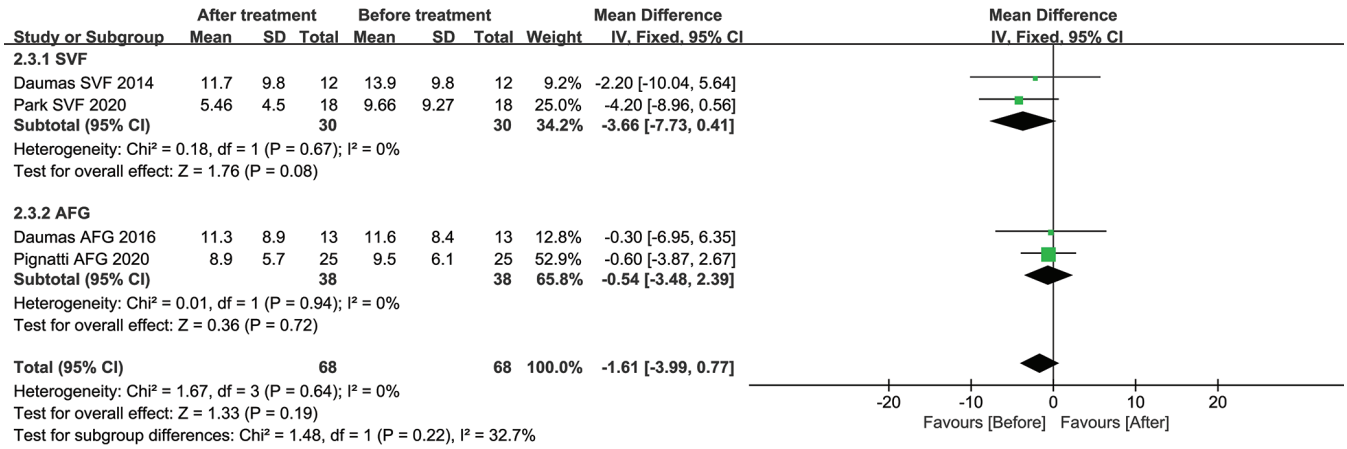

Fig. 2. Forest plot of global mRSS changes before and after treatment with SVF or AF.

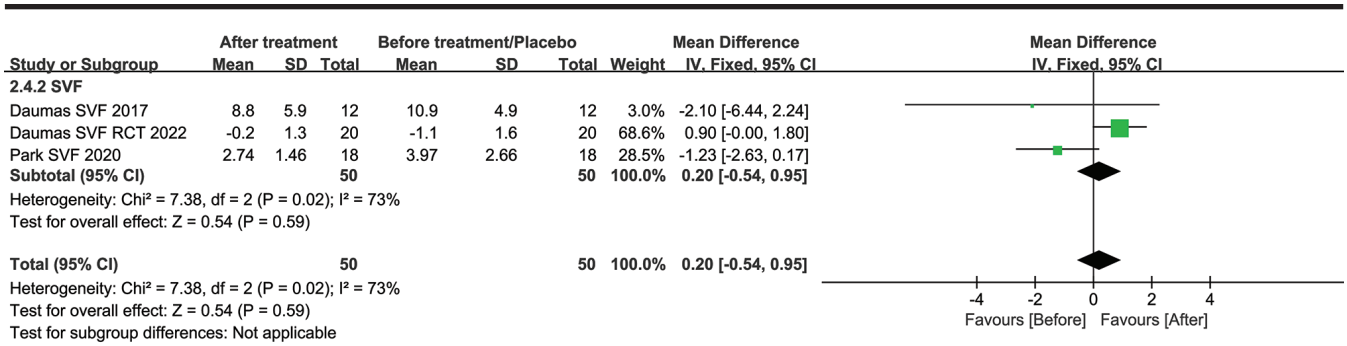

Fig. 3. Forest plot of hand mRSS changes before and after treatment with SVF.

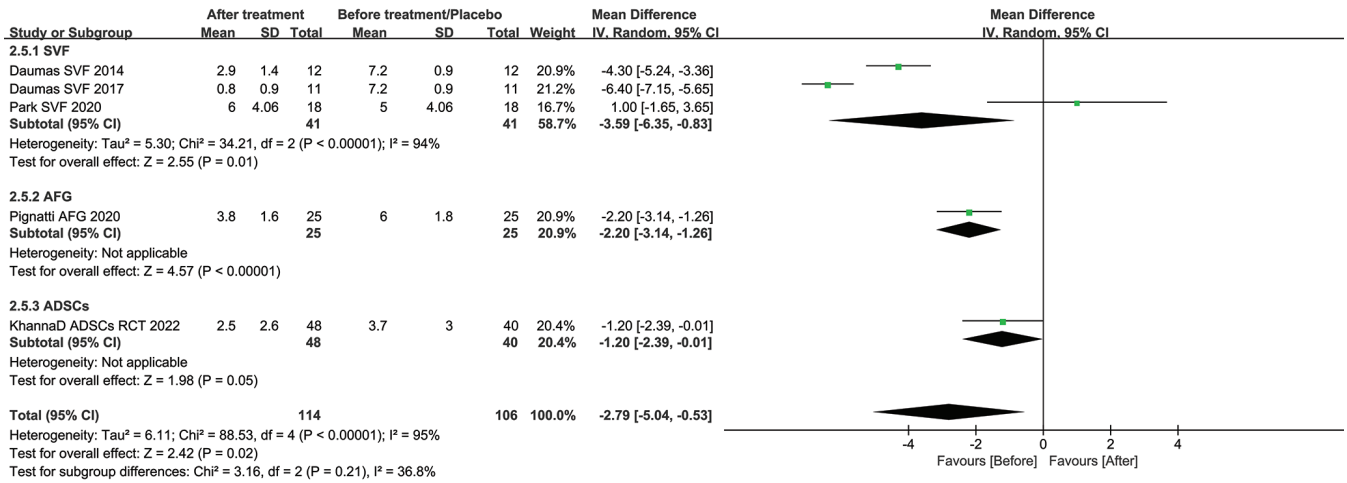

Fig. 4. Forest plot of RCS changes before and after treatment with SVF, AF or ADSCs.

a significantly lower number of digital ulcers than the control group.

Cochin hand function scale (CHFS)

The CHFS is a questionnaire assessing the extent of hand involvement in SSc patients. It includes 18 items related to the capacity to work and complete daily activities such as dressing and washing (37). The total score ranges from 0 (normal hand function) to 90 (severely impaired hand function). In this study, five research compared CHFS changes before and after treatment with SVF or ADSCs in SSc patients (23, 28, 32, 34, 35). The random effects model was performed for high heterogeneity (p<0.00001, I^2=87%, Fig. 6). The results revealed that these patients' CHFS in these patients decreased significantly (MD=-13.70, 95%CI -24.55 to -2.84, p=0.01, Fig. 6). Regarding subgroup analysis, four trials with 61 patients who underwent SVF injection were included and CHFS decreased following SVF therapy (MD=-14.06, 95%CI -30.12 to 1.99, p=0.09, Fig. 6). Granel *et al*. showed that autologous SVF injections improved gripping abilities in SSc patients (23). One research (35) investigated the effect of ADSCs on CHFS in 32 patients and found a substantial decrease (MD=-12.10,

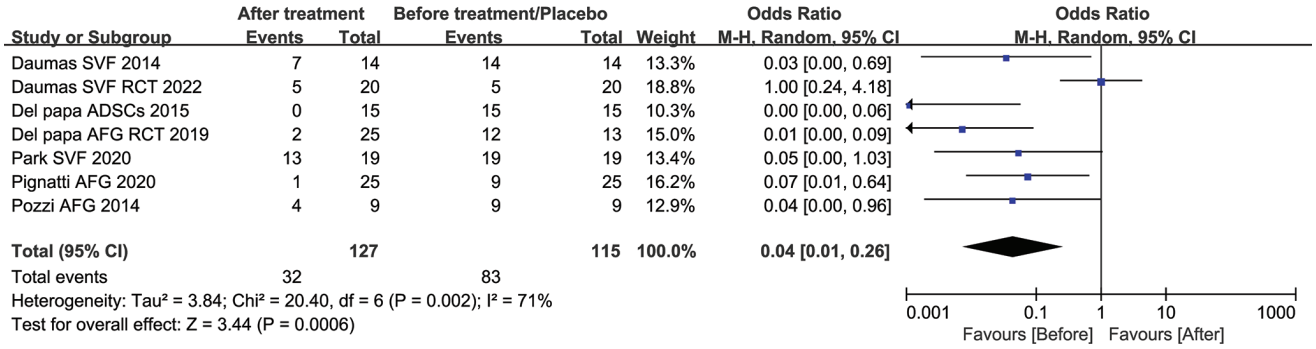

Fig. 5. Forest plot of DU changes before and after treatment.

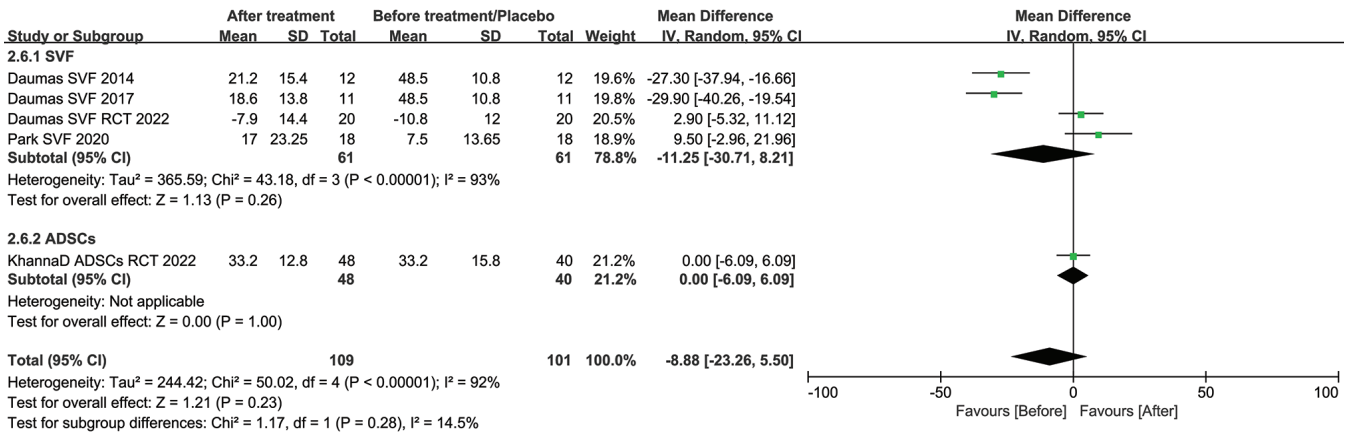

Fig. 6. Forest plot of CHFS changes before and after treatment with SVF or ADSCs.

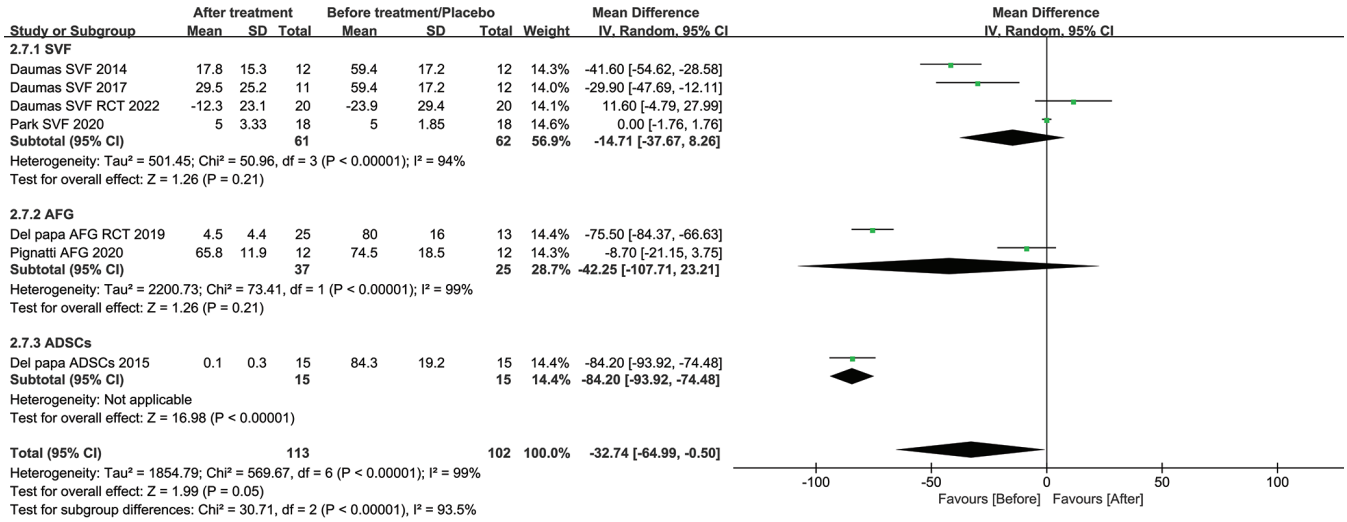

Fig. 7. Forest plot of VAS changes before and after treatment with SVF, AF or ADSCs.

95%CI -17.60 to -6.60, $p<0.0001$, Fig. 6). Two randomised controlled trials in this group did not find that SVF or ADSCs were effective in reducing CHFS in SSc patients.

Visual analogue scale (VAS). As shown in Figure 7, seven studies included in our meta-analysis compared the VAS in SSc patients before and after therapy, four of which used SVF (23, 28, 32, 34), two used AF (31, 33) and one used ADSCs (24). There was high heterogeneity among the trials ($p<0.00001$, $I^2=99\%$). The treatment lowered the VAS, significantly decreasing the pain of hand ulcers in SSc patients (MD=-36.26, 95% CI -69.78 to -2.74, $p=0.03$). One randomised controlled trial found that SVF did not reduce patient-reported VAS scores, while another randomised controlled trial found that autologous fat significantly improved VAS scores.

Perioral severity

The MHISS comprises of 12 items that

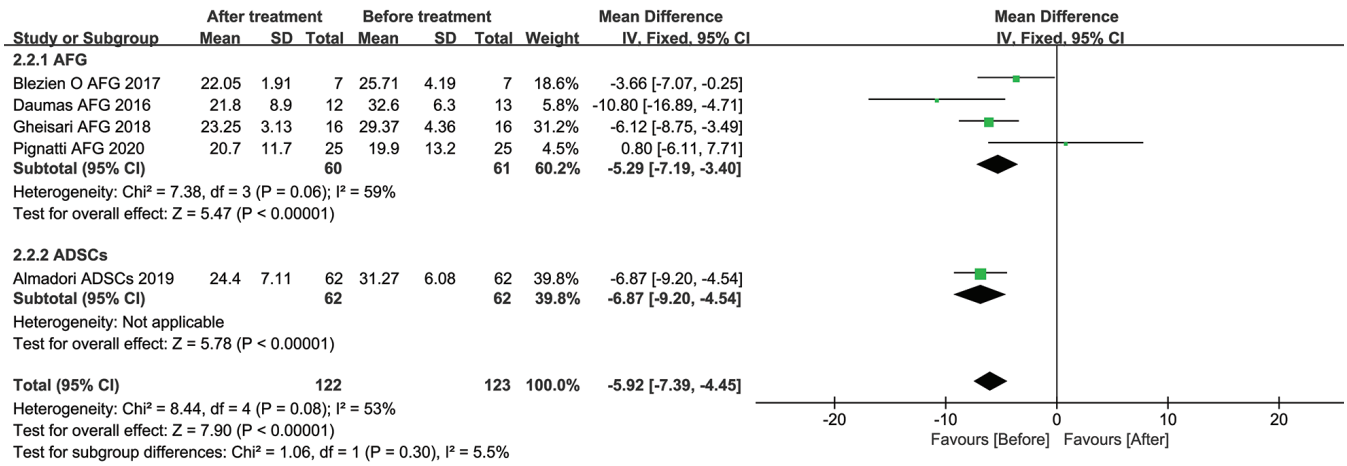

Fig. 8. Forest plot of MHISS changes in SSc patients.

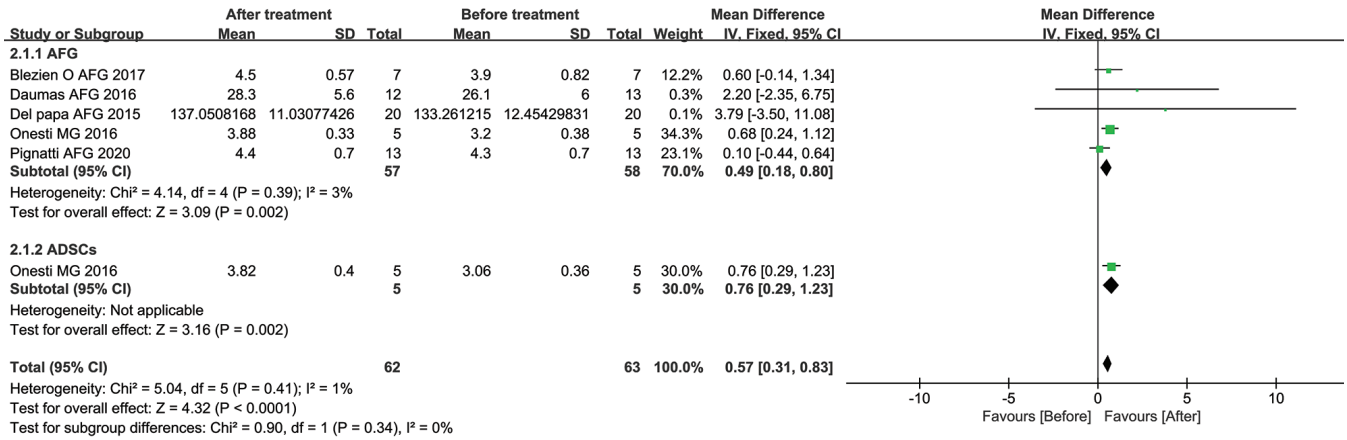

Fig. 9. Forest plot of MMO in SSc patients.

can effectively assess oral dysfunction in individuals with SSc (37). Each item was scored from 0 to 4, with a total score ranging from 0 (no disorder) to 48 (severe disorder). The 12 elements can be divided into three aspects: mouth opening, salivary gland involvement, and aesthetic score (37).

Five articles examined the MHISS changes in 123 SSc patients before and after therapy with ADSCs or AF administered via facial injection (26, 27, 29, 30, 33). A random-effects model was applied for low heterogeneity (p=0.08, I^2=53%, Fig. 8), and the results showed that both treatments improved mouth opening, oral swallowing, masticatory function, and maxillofacial morphology in SSc patients. (MD=-5.92, 95%CI -7.39 to -4.45, p<0.00001, Fig. 8). The distance between the tips of the upper and lower right incisive teeth was measured in centimetres to determine MMO.

Four investigations compared MMO before and after the injection of AF or ADSCs (25-27, 33). Both therapies enhanced the opening distance in SSc patients significantly (MD=0.48, 95% CI 0.25 to 0.70, p<0.0001, Fig. 9).

Safety outcomes

With regards to safety, seven of fifteen trials documented 56 AEs (23, 26, 29, 30, 32, 34, 35), including 21 of 121 (17.4%) patients treated with AF, 28 of 63 (44.4%) patients treated with SVF, and 7 of 130 (5.38%) patients treated with ADSCs. The most common AEs in patients were skin bruising and pain at the injection site and fat harvesting site. A total of two serious AEs occurred, one after the treatment with SVF (SSc worsening) (34) and one after ADSCs (injection related) (35).

Generally, the three treatments mentioned above were found to be safe for SSc patients.

Discussion

To date, the pathogenesis of SSc has remained unexplained, and there are no specific treatments available. The therapy of SSc is now primarily focused on relief of inflammation, immunological modulation, and fibrosis repair. Vasodilators, immunosuppressants, collagen synthesis inhibitors are common medications (38, 39). However, these drugs can only provide limited clinical improvement and cannot repair pre-existing facial abnormalities (40), and they come with a variety of adverse effects such as systemic toxicity and immunosuppression. Many patients have to seek surgical treatment, especially those with facial handicap and DU, which is often overlooked but highly important to enhance quality of life. Three common approaches used in plastic surgery are AF, SVF and ADSCs. Fat grafting is relatively well-established and classic plastic and

aesthetic surgical technique that has been confirmed safe and well tolerated. In recent years, there has been growing emphasis on the use of mesenchymal stem cells. The SVF is composed of blood cells, fibroblasts, endothelial cells, and their progenitors, pericytes, adipose stromal/stem cell and preadipocytes, which has been reported to possess angiogenic, anti-inflammatory, immunomodulatory and regenerative properties (41). In particular, ADSCs, isolated from SVF, can differentiate into multiple mesodermal tissue types, like bone marrow-derived stem cells, but are considerably easier to harvest by liposuction (42). Thus, subcutaneous adipose tissue can be considered an innovative source of mesenchymal stem cells suitable for cell-based therapy in regenerative medicine, and their abundance eliminates the necessity for cultural growth. The effects of adipose stem cells on fibrotic pathways can be roughly summarised as follows (43, 44): a. downregulation of transforming growth factor-β; b. reduction of local collagen accumulation and dermal thickening, and promotion of angiogenesis under fibrosis; c. participation in immune regulation and inflammatory response to improve wound healing at the site of transplantation.

After a comprehensive literature search, fifteen publications concentrating on these three strategies for the treatment of SSc patients were eventually included, comprising thirteen self-controlled research and two randomised controlled trials concerning a total of 314 patients. In our study, eight out of fifteen studies involved AF, with the first being performed in 2014 by Bene *et al*. on nine patients with DUs induced by scleroderma (21). SVF and ADSCs were discussed in four articles, respectively. The number of reported AEs differed obviously among the three groups. For one thing, it may be related to the level of detail in the paper writing. Another factor is the doctor's skills and experience. Injection-related adverse effects, such as bruising, sensory anomalies, and pain at the injection site, have the highest incidence of adverse events. These injection-related symptoms will subside on their own over time. The little volume of adipose tissue needed for subcutaneous injection of ADSCs in the fingers results in relatively brief local pain and minor bruising even though SSc patients are frequently skinny and prone to skin ulcers. While temporary adverse reactions like pain and bruising may result from injection, serious complications are rare. Doctors and patients can decide whether to pursue surgical treatment after weighing the benefits and dangers.

In terms of efficacy, skin thickness has been lowered to some extent but there is no significant difference, no matter with the SVF or AF. Currently, no studies have discussed changes in skin thickness after ADSCs. The effectiveness of skin fibrosis is now assessed solely by the MRSS index, which may restrict the evaluation of the efficacy of surgical treatment for skin sclerosis both before and after treatment. To enable a more thorough assessment and the development of associated technologies, more research is required. RCS, DU, CHFS, and VAS all showed a significant recovery. Notably, SVF and AF grafting proved to have the most influence on the improvement of RCS, which assesses the frequency and severity of Raynaud's phenomenon. But in terms of VAS ratings, the ADSC group exhibited the highest improvement and the SVF group showed the least change. In terms of ischaemia damage and microscopic findings in the affected patients' hands, statistics show that grafting with AF, SVF, and ADSCs has led to satisfactory recovery of DU and a steady increase in the number of nailfold capillaries (23). The molecular mechanisms may be explained by the ability of ASCs to stimulate angiogenesis through paracrine pathways in ischaemic tissues (45). Other cellular elements in SVF, including fibroblasts, pericytes, and various precursor cells, support the mechanical framework of repaired tissues and aid in the regeneration of damaged tissues by secreting cytokines (46). In general, AF, SVF and ADSCs displayed the similar therapeutic effects of improving skin sclerosis, which is in line with our expectations given that the mechanisms of the three are thought to be consistent.

To the best of our knowledge, this is the first systematic review and meta-analysis to carry out a comprehensive assessment and comparison of the efficacy and safety of AF, SVF and ADSCs. These findings are expected to provide some clinical evidence for the unmet needs regarding SSc therapy. However, this study still has several shortcomings. First off, the research included are mostly self-controlled and only three RCTs have been retrieved in SSc treatment so far. Consequently, the natural course of the disease may interfere with clinical outcomes, since the comparison with control group was lacking. The pilot studies, which utilised self-comparison, showed significant improvements in multiple indicators. However, in the randomised controlled studies, several indicators did not improve, indicating that the placebo effect still needs to be identified. Therefore, more randomised controlled studies should be conducted to address this issue. Secondly, part of the results involves qualitative description, such as adverse events and quality of life, which may cause reporting bias. Finally, although we included fifteen research in our analysis, the numbers of cases are still limited. Also, period of therapy and follow-up is insufficient. Further studies with larger sample sizes and long-term follow-up are needed.

Take home messages

- Surgical treatment with AF, SVF, and ADSCs is becoming more common due to their angiogenic, anti-inflammatory, immunomodulatory, and regenerative properties and ability to improve quality of life for SSc patients.
- AF, SVF, and ADSCs all showed similar therapeutic effects in improving skin sclerosis, while RCS, DU, CHFS, and VAS showed varying degrees of improvement after treatment with these methods, suggesting the need for further studies to assess the efficacy of surgical treatment for skin sclerosis and to explore the underlying molecular mechanisms.
- This systematic review and meta-analysis provide the first comprehen-

sive assessment and comparison of AF, SVF, and ADSCs for SSc therapy, but more randomised controlled studies with larger sample sizes and longer follow-up periods are needed to address limitations such as the lack of control groups, reporting bias, and limited sample sizes.

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