Regenerative treatments for scleroderma in cutaneous manifestations of the face: a systematic review

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ABSTRACT

Objective. *Scleroderma is a heterogeneous chronic autoimmune disease affecting connective tissue, characterised by chronic inflammation and fibrosis, particularly affecting internal organs and skin. Orofacial involvement is common, leading to facial atrophy, mask-like appearance and difficulties in function that significantly impact patients' quality of life. This systematic review evaluates different autologous regenerative treatments of facial manifestations of scleroderma, aiming to provide comprehensive understanding of their effectiveness in reducing fibrosis, and thereby improving function and skin quality.*

Methods. *A search in PubMed, Embase, Web of Science Core Collection, Cochrane CENTRAL, and CINAHL was conducted. Studies assessing autologous regenerative treatments in cutaneous manifestations of the face in scleroderma patients were included. Outcomes of interest were treatment characteristics, characterisation of biomaterials, outcome measurements and patient satisfaction. Methodological quality was assessed with the Effective Public Health Practice Project tool.*

Results. *In total 18 studies were included. Methodological quality of studies was weak (n=15) and moderate (n=3). Treatments consisted of autologous fat grafting, platelet-rich plasma, stromal vascular fraction, and adipose-derived stem cells. In general, most studies showed improvements of symptoms, but no treatment was considered superior.*

Conclusion. *Autologous regenerative treatments hold potential for alleviating cutaneous manifestations of the face in scleroderma. Further clinical trials should be well-designed to improve the quality of clinical evidence.*

Introduction

Scleroderma is a heterogeneous chronic autoimmune disease affecting connective tissue. It is characterised by specific autoantibodies and T lymphocytes activation particularly T_H2 cells producing pro-inflammatory cytokines, such as interleukin-1β (IL-1β) (1-7). Production of cytokines recruits and activates local fibroblasts, upregulates pro-fibrotic growth factors such as transforming growth factor-β1 (TGF-β1) which causes differentiation of fibroblasts to myofibroblasts. Myofibroblasts facilitate and maintain fibrosis through deposition and crosslinking of collagens and other extra-cellular matrix components (8, 9). The inflammatory infiltrate present at the dermal subcutaneous junction is associated with small blood vessel pathology and panniculitis which leads to subcutaneous fat atrophy and progressively substitution of fat by collagen (10, 11).

The main pathological changes in scleroderma are progressive fibrosis and subcutaneous fat atrophy in both the skin and internal organs (10, 12). Scleroderma can manifest in two forms: localised scleroderma (LoS) and systemic scleroderma (SSc), with further distinction of SSc into limited cutaneous systemic scleroderma (lcSSc) and diffuse cutaneous systemic scleroderma (dcSSc). The etiology of scleroderma remains largely unknown. Risk factors include trauma, genetic factors, disorders of the immune system or hormone metabolism, viral infections, toxic substances or pharmaceutical agents, radiation, and neurogenic factors (10, 13).

The face and mouth are often affected in scleroderma as a result of (peri-oral) fibrosis and are reported in 34.1% of dcSSc patients and in 23.7% lcSSc patients and they are predominately identified in women (84.5%) (14-16). Patients present with loss of mimic, mask-like appearance, facial atrophy, microstomia, microcheilia, increased peri-oral rhytids, "en coup de sabre" (a linear scar that indents the skin and underlying bone), telangiectasia and hypo- or hyperpigmentation of the skin (10, 13). Patients are often affected by microstomia (70%) and xerostomia (63%), leading to difficulties in speech, mastication, adequate dental self-care, and dysphagia, and are therefore at an increased risk of dental caries and periodontitis (14, 16-19). Oral disability can be evaluated with the patient-reported mouth handicap in systemic sclerosis scale (MHISS) questionnaire (20). The Rodnan Skin Score (RSS) assesses the skin thickness (21, 22).

Orofacial disabilities of scleroderma significantly affect quality of life and therefore necessitate appropriate treatment (23). Therapeutic options are disease-modifying- or symptomatic treatment. Disease modifying treatment attempts to block the progression of scleroderma, for example through use of immunosuppressants, such as Mycofenolate mofetilò and methotrexate, to suppress the inflammation. These interventions are generally only effective early in the disease course and do not reverse atrophic and fibrotic skin changes. Multiple treatments for orofacial symptoms exist, such as fat grafting to restore volume or correct asymmetries. Less invasive treatments, such as local phototherapy with ultraviolet A(UV-A), carbon dioxide (CO_2) laser therapy, or intense pulsed light (IPL) therapy, aim to relieve oral-facial symptoms. Synthetic injectables primarily focusing on enhancing facial aesthetics include hyaluronic acid (HA), calcium hydroxyapatite, polymethyl methacrylate, or poly-l-lactic-acid. Moreover, several fat-derived or blood-derived autologous injectables have been investigated to regenerate affected tissue by reducing fibrosis. Autologous regenerative treatments are easy to isolate either from fat by autologous fat grafting, or blood through blood collection (12, 24, 25).

Fat-derived regenerative treatments involve grafting of adipose tissue, consisting mostly of adipocytes, along with the stromal vascular fraction (SVF) that consists of fibroblasts, adipose-derived stromal cells (ASCs), immune cells, endothelial cells, among other cell types. Specifically, ASCs possess the ability to suppress excessive collagen synthesis and expedite collagen remodelling (26). These fat-derived regenerative treatments such as autologous fat grafting, ASCs and SVF have shown antifibrotic and proangiogenic action through paracrine factors by decreasing collagen content, increasing dermal thickness, creating greater alignment of collagen fibre networks, and increasing skin perfusion (27-30). Also, it is suggested that they modulate the local immune- and inflammatory response, inhibiting chronic inflammation (30, 31). These properties are favourable in lipotransfer engraftment, tissue regeneration, and counteraction of scleroderma's pathological mechanisms (24, 32). Furthermore, fat-derived injectables are suggested to be effective in reducing scar tissue, and improving micro-circulation, contour, volume, and skin elasticity (27, 29, 33).

Blood-derived regenerative treatments like platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) contain, platelets, cytokines and growth factors, which could potentially reduce fibrosis (34). These components promote coagulation, expedite wound healing, exert anti-inflammatory effects on the graft, and boost the regenerative potential of ASCs (35-37).

Multiple regenerative treatments are investigated due to their potential to enhance peri-oral volume and skin quality, resulting in increased facial expression, increased interincisal distance, enhanced mastication and speech, and a reduction of facial pain (38, 39). These developments warrant systematic evaluation of the available clinical evidence. Several systematic reviews were published on fat-derived regenerative treatments in scleroderma, however, none of these focused specifically on the face. The aim of this study was to systematically review the literature on efficacy of autologous regenerative treatments in facial manifestations of scleroderma. Efficacy was defined as the potential of these treatments to stop or reverse the fibrosis associated with scleroderma and therefore to improve its associated aesthetic and functional symptoms.

Methods

Protocol and registration

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. This study protocol was registered in PROSPERO (register code: CRD42022344488).

Search strategy and information sources

A systematic search was conducted in PubMed, Embase (embase.com), the Web of Science Core Collection, Cochrane Central Register of Controlled Trials and CINAHL (EBSCO) from inception to the final search date, January 10th, 2024. The search strategy was developed by one of the reviewers (L.L.V.) in collaboration with an experienced information specialist (S.v.d.W.). The strategy combined search blocks for: 1. Scleroderma 2. Types of regenerative treatments and 3. Head and face.

In each search block, indexing terms such as MeSH were combined with a variety of text words. There were no restrictions, except the exclusion of animal studies and meeting abstracts. The full search strategies are added (Supplementary Table S1).

Eligibility criteria

Papers were considered eligible if they concerned autologous regenerative treatments for facial manifestations in scleroderma patients. The regenerative treatments included were fat grafting or lipofilling (and similar treatments such as nano-fat, micro-fat, macro-fat etc.), stromal vascular fraction (SVF), adipose (derived) stromal cells (A(D)SC) (and similar treatments such as adipose derived regenerative cells (ADRC), cultured adipose stromal cells (cASC)), mesenchymal stem cells (MSC), platelet-rich plasma (PRP), platelet-rich fibrin (PRF) and bone marrow (derived) stem cells (BM(D)SC), or any combinations thereof. Systematic reviews, case studies, conference abstracts, letters to the editor, animal studies and *in vitro* studies were excluded. Also, Papers that described concomitant procedures were excluded (Suppl. Table S2). Reference lists of the included studies were analysed to identify relevant studies missed in the searches.

Study selection and data collection process

Two reviewers (L.L.V., J.A.M.S.) independently assessed titles, abstracts, and selected full texts. Disagreements between reviewers were discussed until consensus was reached. Persistent disagreement was resolved by a senior author (J.J. or R.H.S.), who gave a binding verdict.

Data extraction

Data were extracted by the two authors (L.L.V., J.A.M.S.). We collected data of study, treatment and biomaterials characteristics, and reported outcomes. Characteristics of autologous fat grafting were extracted such as donor site, type of anaesthesia, details regarding infiltration and aspiration, processing methods, the site and plane of injection, injection techniques, cannula specifications, the volume injected, the number of sessions, and administration of pre- and/or post medication. Biomaterials were characterised by platelet count of PRP, as well as the stem cell count and passages of ASCs and SVF. Patient-reported questionnaires such as MHISS, RSS, and patient satisfaction were also extracted. Complications were categorised as minor: erythema, hematoma, mild oedema, local pain at incision/injection site, and oily cyst, or major: infection, tissue loss, skin necrosis, severe oedema, pain extending beyond injection- or incision site, cellulitis, fat embolism, and embolism causing blindness.

Risk of bias in included studies

Two reviewers (L.L.V., J.A.M.S.) independently assessed the risk of bias and quality with the Effective Public Health Practice Project tool (EPHPP) (40). This tool enabled quality assessment of different study designs. Based on ratings of study design, selection bias, confounders, data blinding, data collection and dropouts, the quality of studies was scored as 'strong', 'moderate', or 'weak'.

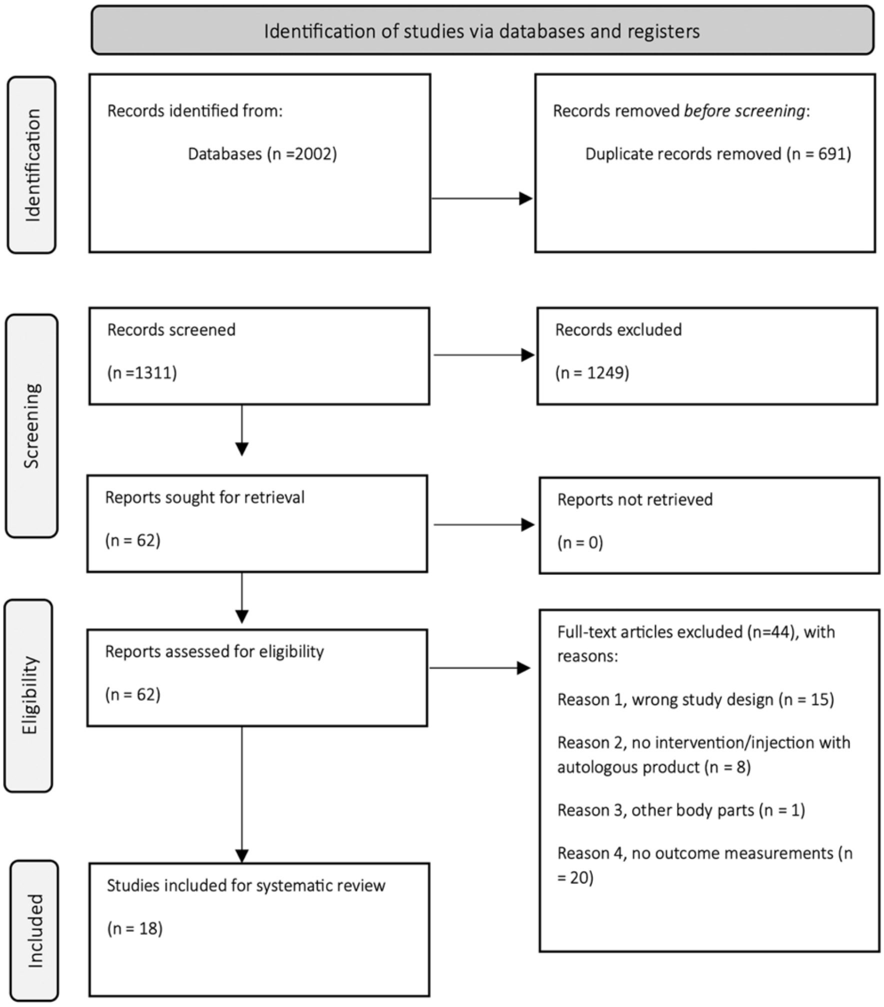

Fig. 1. Flow chart of study selection.

Results

Study selection and characteristics

In total, 1311 records were identified. After title- and abstract screening, 62 studies remained for full-text assessment. 44 studies were excluded, and a total of 18 studies were included. (Fig. 1) Studies were published between 2008 and 2023, with follow-up ranging from 3 to 94 months. They included 317 participants, range 7 to 62 per study. The mean age ranged between 10 and 85 years, 83.2% of the participants was female (range 57–100%), 6 studies included exclusively females (39, 41-45). Different types of scleroderma were treated: SSc (2.5%), lcSSc (54.9%), dcSSc (30.3%), 'en coup de sabre' (2.2%), 'en coup de sabre' combined with lcSSc (0.3%), and an unknown form (2.2%). Four studies also included patients with Parry-Romberg syndrome (4.4%) and progressive hemifacial atrophy (1.6%) (46-49).The majority of studies (13/18) used autologous fat grafts (39, 43, 44, 46-55), 3 studies used a combination of autologous fat grafts and PRP (41, 42, 56); while 1 study used PRP in combination with HA (45). Of the remaining studies, 3 treated their patients with ASCs (50, 52, 57), and 1 with cellular SVF (cSVF) (52). (Table I. We categorised studies by type of intervention (autologous fat grafts, PRP, ASCs, SVF) for analysis of biomaterial characteristics and outcomes.

Study design and quality

The EPHPP tool rated 15 studies weak, and 3 studies moderate (50, 52, 53) (Table II). Study designs included randomised controlled trial (n=1) (52), cohort studies (1 group with pre- and posttreatment evaluation, n=10) (39, 41-45, 51, 53, 55, 57), cohort studies (2 groups with pre- and posttreatment evaluation, n=2) (46, 56), and retrospective studies

Table I. Study characteristics.

Study	Study design	Total (N)	Form Sclero-	Mean age	Age range	BMI (kg/m2)	Female (n)	Sex (%female)	Comorbidities	Intervention erma	Intervention (n) (years)	Control (years)	Control (n)	Repeated interven-	Follow-up (months)	Disease duration	Immuno-suppressants	Minor complications tion	Major complications (years)
Abellan Lopez *et al*. 2022	C1G	13	lcSSc n= 7 dcSSc n= 6	53 [14]	46-64	22 (19-26)	13	100%	NR	PRP + AFG	13	-	-	-	6	12	NR	+, n=9	-
Almadori *et al*. 2015	C1G	62	lcSSc n= 36 dcSSc n= 26	56 [12]	NR	NR	61	98%	NR	ASCs	62	-	-	+	12(±9)	15 [9]	50%	+	n=1 (superficial wound infection)
Baserga *et al*. 2020	C2G	18	lcSSc n= 4 ECDS n= 7	33	14-75	NR	11	14%	NR PRS n= 7	AFG	18	healthy subjects matched for sex, age and ethnicity.	60	+	12	NR	NR	NR	NR
Berl *et al*. 2022	RC	17	dcSSc n=8 SSc n=8 lcSSc n=1	51	27-72	23	14	82%	NR	AFG	17	-	-	+	3	14 (2-29)	34%	postoperative hematoma n=3, postoperative pain n=10	-
Blezien *et al*. 2017	C1G	7	NR	46 [6]	31-65	NR	7	100%	NR	PRP+ AFG	7	-	-	-	12	10 [4]	NR	3% graft area oedema, 5% harvesting site ecchymosis, 11% persistent post-operative pain >3 days	-
Del Papa *et al*. 2015	C1G	20	dcSSc n=20	40 [13]	NR	NR	20	100%	NR	AFG	20	-	-	-	3	10 [6]	NR	+	-
Gheisari *et al*. 2018	C1G	16	lcSSc n= 6 dcSSc n= 10	39 [8]	29-54	NR	16	100%	NR	AFG	16	-	-	-	3	7 [2]	Not more than 10mg/d	n=10	-
Li *et al*. 2023	C1G	14	lcSSc n=14	21 [8]	10-36	23 [4]	9	64%	Exclusion: diseases that require long-term medication or with immuno-deficiency.	AFG	14	-	-	-	3	10 [4]	-	NR	NR
Onesti *et al*. 2016	RC	10	lcSSc n= 10	NR	23-28	NR	8	80%	NR	ASCs	5	AFG	5	+	12	3-18	-	NR	NR
Pignatti *et al*. 2020	C1G	25	lcSSc n= 21 dcSSc n= 4	56 [9]	NR	NR	19	76%	NR	AFG	25	-	-	+	6	15 [10]	NR	N=2	-
Pirrello *et al*. 2019	C1G	10	lcSSc n= 2 dcSSc n= 8	NR	33-62	NR	10	100%	Exclusion: infectious diseases	PRP+ HA	10	-	-	-	24	2-9	NR	+	-
Roh *et al*. 2008	RC	20	lcSSc n=18 PRS n=2	26	10–55	NR	17	85%	NR	AFG	20	-	-	+	94	7 (1–15)	-	+	-
Sautereau *et al*. 2016	C1G	14	lcSSc n= 6 dcSSc n= 8	54 [10]	50-60	23 [2]	14	100%	NR	AFG	14	-	-	-	6	NR	Not more than 1 0mg/d	bruises harvesting zone n=8, local pain harvesting zone n=3, injection site bruising n=3, Injection site pain n=3, peri-oral sensitive manifestation n=1, Trigeminalì +neuralgia n=1.	-
Segna *et al*. 2017	RC	8	lcSSc n= 2 PRS n= 5 ECDS+ lcSSc n=1	NR	11-17	NR	5	63%	NR	AFG	8	-	-	+	65	NR	NR	NR	NR
Virzi *et al*. 2017	C2G	11	dcSSc n= 6	NR	41-64	NR	7	64%	NR	PRP	6	healthy group	5	-	3	3-20	-	NR	NR
Wang *et al*. 2021	RCT	18	lcSSc n= 18	27 [1]	NR	21 [0.3]	11	61%	Exclusion: chronic diseases that require long-term medication	ASCs, cSVF	ASCs n=6 cSVF n=6	AFG	6	-	10	NR	-	-	-
Wang *et al*. 2022	C1G	23	lcSSc n= 23	25 [6]	NR	22 [2]	13	57%	Exclusion: chronic diseases that require long-term medication	AFG	23	-	-	-	6	12 [4]	-	-	-
Wang *et al*. 2023	RC	11	lcSSc n= 6 PHA n= 5	32	25-35	NR	9	81%	NR	AFG	8	-	-	+	6	NR	NR	-	-

Where indicated, values are mean [standard deviation] or mean(range). NR: not reported; +: applicable; -: not applicable. Study design: RCT: randomised controlled trial; C2G: cohort study (2 groups, pre- + postoperative); C1G: cohort study (1 group pre- + postoperative); RC: retrospective cohort study. Form scleroderma: lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ECDS: en coup de sabre; PRS: Parry Romberg syndrome; PHA: progressive hemifacial atrophy. Intervention: PRP: platelet rich plasma; AFG: autologous fat graft; ASCs: adipose derived stem cells; cSVF: cellular stromal vascular fraction; DBM: demineralised bone matrix; HA: hyaluronic acid.

Table II. Methodological quality of the studies based on the effective public health practice project tool.

Study	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals & dropouts	Global rating/ overall quality score
Roh *et al*. 2008	-	-	-	0	-	NA	-
Del Papa *et al*. 2015	-	0	-	0	+	-	-
Onesti *et al*. 2016	0	0	+	0	+	-	0
Sautereau *et al*. 2016	-	0	-	0	+	-	-
Blezien *et al*. 2017	-	0	-	0	+	-	-
Segna *et al*. 2017	-	-	-	0	-	NA	-
Virzi *et al*. 2017	-	0	-	0	+	-	-
Gheisari *et al*. 2018	-	0	-	0	+	-	-
Almadori *et al*. 2019	-	0	-	0	+	-	-
Pirrello *et al*. 2019	-	0	-	0	+	-	-
Baserga *et al*. 2020	0	0	+	0	+	-	0
Pignatti *et al*. 2020	-	0	-	0	+	-	-
Wang *et al*. 2021	-	+	+	0	0	+	0
Abellan Lopez *et al*. 2022	-	0	-	0	+	+	-
Berl *et al*. 2022	-	-	-	0	+	NA	-
Wang *et al*. 2022	-	0	-	0	0	+	-
Li *et al*. 2023	0	0	-	0	+	-	-
Wang *et al*. 2023	-	-	-	0	+	NA	-
Totals							
Weak, n (%)	*15 (83%)*	*4 (22%)*	*15 (83%)*	*0 (0%)*	*2 (11%)*	*11 (61%)*	*15 (83%)*
Moderate, n (%)	*3 (17%)*	*13 (72%)*	*0 (0%)*	*18 (100%)*	*2 (11%)*	*0 (0%)*	*3 (17%)*
Strong, n (%)	*0 (0%)*	*1 (6%)*	*3 (17%)*	*0 (0%)*	*14 (78%)*	*3 (17%)*	*0 (0%)*
NA, n (%)						*4 (22%)*	

-: weak; 0: moderate; +: strong; NA: not applicable.

(n=5) (47-50, 54). Confounding factors were controlled in 1 study (46). In two studies reliability and validity of outcome measurements was weak (47, 48). Three studies documented dropouts and reported the number of participants who completed the follow-up (41, 52, 53).

Treatment characteristics
The abdomen was used as donor site for autologous fat grafting in 16 studies (39, 41-44, 46-50, 52-57). Twelve studies reported to use an infiltration solution prior to aspiration (39, 41, 43, 44, 46-51, 54, 56). In nine studies a 10 ml Luer-Lock syringe was used to manually generate negative pressure during aspiration (39, 41, 44, 47, 48, 50, 51, 55, 57). The harvested volume of fat was reported in six studies and ranged from 30 to 140 ml of fat (39, 41, 45, 50, 51, 56). Five studies processed the autologous fat graft by centrifugation (43, 46, 48, 51, 56); in four studies by decantation (42, 44, 50, 54). In four studies the fat graft was washed and filtered with a closed wash system (39, 41, 49, 55), and in one study fat was rinsed with Hartmann dextrose (47). The characterisation of the biomaterials was reported by platelet count, stem cell count, cell viability, passages, and/or fluorescence-activated cell sorting (Table III).
The most frequently injected site was the peri-oral region (39, 41, 44, 45, 50, 51, 56); along with the upper- and lower lips (42-45, 54). Additional injection sites were buccal, chin, forehead, infraorbital, malar region, corner of mouth and nose. Four studies did not disclose specific injection sites (46, 48, 52, 57). Injected volumes varied from 3 to 140 ml, with two studies reporting to overcorrect (47, 53). Six studies did not specify the injected volume (39, 45, 46, 52, 56, 57) (Table IV).

Effects of regenerative therapy on scleroderma
Autologous fat grafts. Autologous fat grafts showed marked improvement in mouth handicap measured by MHISS, fat retention, aesthetics, skin thickness measured by Rodnan Skin Score (RSS), facial blood flow perfusion and mouth opening. Two studies showed a reduced MHISS, which indicates an improvement in mouth handicap (39, 44). One study reported a significant decrease in HAQ (51), while another found no significant change in SSc-HAQ (39). 3D analysis of images showed that symmetry of the middle facial third in scleroderma patients improved after the first treatment. Following the second treatment, symmetry also improved in the upper- and lower facial thirds of the face (46). Moreover, facial aesthetics saw further enhancement, as one study found a significant decrease in hyperpigmentation, as measured by the Melanin Index (p=0.008). Oral function was assessed by measurement of the mouth opening, in four studies the mouth opening had significantly increased, ranging from 2.6 to 8.5 mm (39, 43, 44, 54). Additionally, when examining sicca syndrome, normalisation was measured in saliva production of all patients, with 71% subjective amelioration of xerostomia (p=0.0269) (51). Patient satisfaction, which was most frequently assessed in the autologous fat grafts group, indicated that more than 60% of the patients were either satisfied or very satisfied with the treatment outcomes (39, 43, 44, 50) (Table V).

Platelet-rich plasma. The use of PRP markedly improved mouth handicap measured with MHISS, mouth opening,

Table III. Biomaterials.

Study	Intervention				
AFG		*Histopathological analysis*			
Baserga *et al*. 2020	AFG	NR			
Berl *et al*. 2022	AFG	NR			
Del Papa *et al*. 2015	AFG	NR			
Gheisari *et al*. 2018	AFG	NR			
Li *et al*. 2023	AFG	NR			
Onesti *et al*. 2016	AFG	NR			
Pignatti *et al*. 2020	AFG	NR			
Roh *et al*. 2008	AFG	NR			
Sautereau *et al*. 2016	AFG	NR			
Segna *et al*. 2017	AFG	NR			
Wang *et al*. 2021	AFG	NR			
Wang *et al*. 2022	AFG	NR			
Wang *et al*. 2023	AFG	NR			
PRP		*Platelet count*			
Abellan Lopez *et al*. 2022	PRP + AFG	Mean total dose platelet s of 2.7 billion (±1.3)			
Blezien *et al*. 2017	PRP + AFG	NR			
Virzi *et al*. 2017	PRP + AFG	NR			
Pirrello *et al*. 2019	PRP + HA	NR			
ADSC		*Stem cell count*	*Cell viability*	*Passage*	*Characterisation (FACS)*
Almadori *et al*. 2019	ASCs + AFG	Expanded ASCs	NR	NR	NR
Onesti *et al*. 2016	ASCs + HA	8 × 105 expanded ASCs /ml fat *	NR	after 3 weeks	NR
Wang *et al*. 2021	ASCs + AFG	5 × 105 expanded ASCs/ml fat	>90% viable	2-3	positive: CD13, CD29, CD44, CD73, CD90, and CD105 (>80%); negative: CD31, CD45, and CD235a (<2%)
SVF		*Stem cell count*	*Cell viability*		*Characterisation (FACS)*
Wang *et al*. 2021	cSVF + AFG	Approximately 6 × 105 cSVF cells/ml fat	range 85- 95% (>70% viable)		positive, CD13, CD29, CD44, CD73, CD90 (>40%), CD34 (>20%); negative: CD31 (<20%), CD45 (<50%).

Where indicated, values are mean [standard deviation] or mean (range). NR: not reported.
Intervention: PRP: platelet rich plasma; AFG: autologous fat graft; ASCs: adipose derived stem cells; cSVF: cellular stromal vascular fraction; DBM: demineralised bone matrix; HA: hyaluronic acid.
*converted to ASCs/ml fat; FACS: fluorescence-activated cell sorting.

xerostomia, and lip thickness, but PRP did not affect the VAS score for mouth opening limitation, sicca syndrome and facial pain, vascular ectasia, and RSS. The MHISS significantly reduced in two studies, indicating an improvement in mouth handicap (41, 42). Quantitative assessment of fibrosis by biopsy showed that 5/7 patients had a focal reduction of dermal fibrosis in some areas (42). Other fibrosis-related outcomes showed that the RSS on the cheek 0.2 (SD 1.3) (p=0.640), and RSS on the lips -0.2 (SD 0.8) (p=0.447) did not change (41). Oral function was measured by mouth opening in three studies, which was significantly increased in one study from baseline 47.6 mm (SD 4.6) to 48.6 mm (SD 5.3) after 24 months (p=0.0093) (45). O Patient satisfaction was assessed in one study, and patients revealed to be very satisfied (46%), satisfied (36%), moderately satisfied (9%), and unsatisfied (9%) (41) (Table V).

Stromal vascular fraction. Treatment with cSVF markedly improved fat retention in comparison with autologous fat grafting, but none of the studies included patient reported questionnaires, fibrosis-related assessments, or oral function assessments as part of their outcome measurements. MRI analysis revealed a fat retention rate of 31.8% (SD 1.7%) (52) (Table V).

Adipose derived stem cells. Two out of the three studies used a combination of ASCs with autologous fat grafts (52, 57), the other study used a combination of ASCs with hyaluronic acid (HA) (50). ASCs showed marked improvement on mouth handicap measured with MHISS, psychological state, volume retention and mouth opening. The MHISS was significantly reduced in two studies, marking an improvement in mouth handicap (50, 57). Furthermore, the study by Almadori *et al*. found improved mental well-being after ASCs injection. All questionnaires demonstrated significant improvement: DAS 24 (12.1 (SD 9.5), p<0.0001), HADS-anxiety (2.8 (SD 3.2), p<0.0001), HADS-depression (2.0 (SD 3.1), p<0.0001); and BFNE (2.9 (SD 4.3), p<0.0001) (57). However, the neurobiological mechanism by which ASCs injection could influence psychological well-being remains unclear. Oral function assessment showed an increased mouth opening (p=0.0322) (50). One study in the ASCs group reported patients to be very satisfied (80%), and rather satisfied (20%) (50) (Table V).

Comparison of regenerative treatments. Two studies compared two or more regenerative treatments (50, 52). Co-administration of ASCs with fat grafts increased fat retention (49.8% (SD 3.61)) compared to co-administration of cSVF with fat grafts (31.8% (SD 1.7) (p=0.0004)) or fat grafting controls (21.9% (SD 1.7) (p<0.0001)) at six months follow-up (52). Also, co-administration of cSVF with fat grafts increased fat retention compared to fat grafting controls (p=0.0346). Even more, expert satisfaction of co-administration of ASCs with fat grafts was higher (4.0 (SD 0.1)) compared to the co-administration of cSVF with fat grafts (3.1 (SD 0.2) (p=0.0092)) or fat grafting controls (2.2 (SD 0.2) (p<0.0001)). Also, co-administration of cSVF with fat grafts increased expert satisfaction compared to fat grafting controls (p=0.0119). There was no difference in increase in IvMHISS after co-administration of ASCs and HA compared to the fat graft controls (p=0.9619) (50) (Table V).

Complications

In 9 studies, minor complications were reported, of which 2 studies described the nature of these minor complications (39, 42). Bruising and local pain at the harvesting and injection site were most often reported. One study reported a major complication of superficial wound infection (n=1) after ASCs injection (57).

Data pooling and meta-analysis were precluded due to heterogeneity across studies, stemming from variations in interventions and reported outcomes.

Discussion

We systematically reviewed the efficacy of autologous regenerative treatments for cutaneous manifestations of the face in scleroderma. Our primary findings are: (1) overall study quality was weak, (2) there is a general lack of standardised outcome measurements to evaluate the efficacy of these treatments on scleroderma, (3) the studies are heterogenous with respect to (a) form of scleroderma, (b) age, (c) type of autologous regenerative treatment, (d) processing technique, (e) intervention frequency, (f) injection technique, (g) injection volume, (h) follow-up time, (i) outcome variables and (j) use of controls; and therefore (4) the low number of studies and their profound heterogeneity did not allow for a meta-analysis neither for drawing firm conclusions.

Functional and/or aesthetic symptoms of scleroderma are frequent, facing patients and health care professionals with a very difficult to treat clinical problem affecting daily quality of life. Symptoms generally arise from fibrosis, fat atrophy and chronic inflammation. For treatments to be considered regenerative, three criteria should be met: 1. suppression and remodelling of fibrosis 2. regeneration of fat, and putatively 3. modulation of both the immune and inflammatory response. Scleroderma, particularly if it has a rapid progressive character, can be life-threatening, with a 25% 5-year-mortality in dcSSc (58). Early start with immunomodulating treatment, commonly involving immunosuppressants and, in severe cases, autologous hematopoietic stem cell transplantation (HSCT), is vital to prevent progression and mortality. Studies showed that HSCT effectively stopped progression and improved survival, quality of life and skin fibrosis (59-61). Despite its benefits, HSCT has a high risk of adverse events and a 10% treatment-related mortality, therefore limiting its use to cases with rapid disease progression (61, 62). Conversely, local regenerative treatments are generally considered in people in a stable phase of the disease, ineligible for HSCT, aiming to address symptoms.

While autologous fat grafts, ASCs and SVF have therapeutic benefit to treat facial manifestations of scleroderma, the underlying mechanisms are only partially understood. It is proposed that these treatments containing progenitor cells act in paracrine fashion to stimulate adipocyte regeneration, extracellular matrix remodelling and angiogenesis (63-65). Also, ASCs are able to differentiate into multiple mesodermal tissue types, reduce collagen accumulation, and modulate immune regulation and inflammatory response (30, 31, 66) Blood-derived products, like PRP, consist out of a gel fraction obtained from peripheral blood, and contain high number of platelets, cytokines, and growth factors (56). *In vitro*, they stimulate MSC proliferation and preserve MSCs multipotency (36). Thus, it is suggested that fat- and blood-derived treatments counteract the pathological changes seen in scleroderma and regenerate the affected tissue.

To substantiate evidence for the regenerative action of these treatments, being more than only a filler, (immuno)histochemical analysis should be performed by pre- and post-treatment biopsies of patients. However, none of the included studies in this review performed a (immuno)histochemical analysis of injected tissue. However, the face is not an obvious anatomical region to perform a biopsy because of ethical concerns. Biopsies from patients with (burn) scars following autologous fat grafting showed improvement of skin structure, collagen remodelling (*i.e,* a better organisation and alignment), an increase in vascularisation of dermal papillae, less melanocytic activity in the epidermis, and an increase of the amount of elastin fibres (31, 67). This substantiates the regenerative potential of the fat-derived regenerative treatments. Unfortunately, no study has yet been published on the effect of PRP at a histological level in scleroderma patients. Nevertheless, Blezien *et al.* did a quantitative assessment of fibrosis by microscopic histological examination of labial punch biopsies taken pre- and post-treatment. The study reported that 5 out of 7 labial biopsies displayed a thickened squamous epithelium with superficial parakeratosis post-treatment, indicating a localised reduction of dermal fibrosis, suggestive of regeneration (42). It is essential to highlight that the PRP was co-administrated with the micro-fat graft, and that study lacked a control group. Given the lacuna in literature on histological evidence, the working mechanism of PRP remains unclear.

Histological analysis by biopsy as outcomes in clinical trials may raise ethical concerns. Outcomes based on

Table IV. Treatment characteristics.

Study characteristics				Infiltration					Aspiration		
Study	Intervention	Donor site	Anesthetic	Infiltration	Fluid	Lidocaine	Epinephrine	NaHCO3	Cannula diameter	Cannula brand	Syringe (ml)
Abellan Lopez *et al*. 2022	**PRP + AFG**	AFG:A, H, K, T, PRP: blood	GA, LA	+	S	40 ml 1%	1 mg/L	-	AFG: 2.0 mm PRP: 0.71 mm*	Strim	AFG: 10
Almadori *et al*. 2019	**ASCs**	A, T	NR	NR	NR	NR	NR	NR	3.0 mm	NR	10
Baserga *et al*. 2020	**AFG**	A, H, T	GA, LA	+	S	20 ml a 2%, 20 ml b 7.5 mg/ml	1mL	+	2.6 mm*	Coleman	+
Berl *et al*. 2022	**AFG**	A, F, T	GA	+	S	-	1mL	-	3-4 mm	NR	NR
Blezien *et al*. 2017	**PRP + AFG**	A	NR	NR	NR	NR	NR	NR	0.5-0.7 mm	NR	NR
Del Papa *et al*. 2015	**AFG**	A, H	LA	+	S	20 ml a 2% 20 ml b 7.5 mg/ml	1mL	+	2.6 mm*	Coleman	+
Gheisari *et al*. 2018	**AFG**	A, B, F, H	LA	+	S	25 ml	5ml 1:1000	-	3.0 mm	NR	10
Li *et al*. 2023	**AFG**	A	GA	NR	NR	NR	NR	NR	3.0 mm	NR	10
Onesti *et al*. 2016	**ASCs, AFG**	A	NR	+	S	20 ml 2%	04:20,0	-	3.0 mm	NR	10
Pignatti *et al*. 2020	**AFG**	F, H	Sed, LA	+	S	10 ml of 2% a	1:1000	-	2.6 mm*	Black and Black	10
Pirrello *et al*. 2019	**PRP + HA**	PRP: blood peripheral vein	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roh *et al*. 2008	**AFG**	A, B	Kl	+	NR	NR	NR	NR	2.0 mm*	NR	10
Sautereau *et al*. 2016	**AFG**	A, K, H	LA	+	S	10 ml	10 mL 1%	-	0.31 mm*	NR	10
Segna *et al*. 2017	**AFG**	A, T	GA	+	S	-	3 mL 3:500	-	3.0 mm	NR	10
Virzi *et al*. 2017	**PRP + AFG**	A, K	Sed	+	NR	NR	NR	NR	3.2 mm*	NR	NR
Wang *et al*. 2021	**ASCs, cSVF, AFG**	A	LA	NR	NR	NR	NR	NR	NR	NR	50
Wang *et al*. 2022	**AFG**	A	NR	NR	NR	NR	NR	NR	3.0 mm	NR	20
Wang *et al*. 2023	**AFG**	A, T	NR	+	R	NR	1:1000	NR	2.4 mm	Tulip	-

Where indicated, values are mean [standard deviation] or mean(range).
NR: not reported; +: applicable; -: not applicable.
Intervention: PRP: platelet rich plasma; AFG: autologous fat graft; ASCs: adipose derived stem cells; cSVF: cellular stromal vascular fraction; DBM: demineralised bone matrix; HA: hyaluronic acid.
Donor site: A: abdomen; B: buttock area; H: trochanteric region/hips; F: flank; K: knee; T: thighs.
Anesthetic: GA: general anesthesia; LA: local anesthesia; Sed: sedation; Kl: Klein solution.
Fluid: S: Saline; R: Ringer's lactate.
Lidocaine: a: Mepivacain; B: Ropivacaine.
Pressure: neg: negative pressure (manual).
Processing: C: centrifugation; D: decantation; Fil: filtration; W: washed.
Injection site: B: buccal/cheek; Ch: chin; Fh: forehead; Io: infraorbital; LL: lower lip; M: malar; MC: mouth corner; N: nose; PO: peri-oral; UL: upper lip.
Volume: OC: overcorrection.
Pre- and post-medication: AB: antibiotics; prof: prophylaxis; analg: analgetic; antibac: antibacterial; corticoster: corticosteroids.
*converted from Gauge to mm.

		Processing	Injection								
Pressure	Volume	Processing	Injection/	Injection plane recipient site	Technique	Cannula	Cannula diameter	End cannula brand	Volume	no. of sessions	Pre-/post medication
neg	AFG: 60 ml PRP: 18 ml	PRP: C AFG: W	PO	NR	AFG: radiating ADSC: infiltration	0.8 mm*	Strim Kit	NR	PRP: 8.1 ± 1.8 ml AFG: 22.7 ±5.7 ml PRP+AFG: 30.8 ± 8.1 ml	NR	NR
neg	NR	C	NR	NR	retrograde	2.0 mm	NR	Blunt	NR	2-3	NR
neg	NR	C	NR	dermal-epidermal junction	retrograde	1.4 mm*	Coleman	Blunt	NR	1-2	AB prof, analg
NR	NR	D	Fh, T, B, UL, LL, Ch, N	NR	NR	1.2 mm*	Coleman	NR	20-140 ml	1-4	analg.
NR	NR	D	LL, UL	NR	NR	NR	NR	NR	3 ml	1-2	NR
neg	NR	C	UL, LL, MC	subcutaneous	radiating	1.4 mm*	Coleman	Blunt	(≤)16 ml	NR	NR
neg	NR	D	PO, UL, LL, MC, B, M, Io (periorbital)	subcutaneous	NR	1.2 mm*	NR	NR	15-40 ml	NR	NR
neg	NR	Fil	Fh	Supraperiosteal, submuscular, subdermal	fan-like pattern	1.0 mm	NR	Blunt	11 ml (6-17)	1	NR
neg	40 ml	AFG: D, ADSC:C, Wx2	PO	subcutaneous	AFG: radiating ADSC: infiltration	2.0 mm	NR	Blunt	AFG: 16 ml ADSC: 4 ml	NR	AB prof
neg	30-50 ml	C	PO	subcutaneous, submucosal	retrograde	1.0 mm*	Coleman	NR	16 ml	3	AB prof
NR	7 ml	C	Z, PO, N, UL, LL, Ch	NR	NR	NR	NR	NR	NR	3	Post: antibac. Cream.
neg	NR	W	Fh, Ch, N, Io	multiple	NR	1.2 mm*	NR	NR	OC	2-11	NR
neg	20-50 ml	Fil	PO	subcutaneous	radiating	0.8 mm*	NR	NR	NR	NR	NR
neg	NR	C	NR	NR	NR	NR	NR	NR	17-33 ml	NR	AB post, Analg
neg	AFG: 90-140 ml PRP: 10-12ml	PRP: C AFG: C	PO, M	NR	NR	1.8 mm*	NR	NR	NR	NR	Corticoster. Post.
neg	NR	cSVF:C (5x), W (2x), Fil	NR	subcutaneous	fan-like pattern	1.4 mm	NR	Blunt	NR	NR	NR
neg	NR	D, Fil	Fh, B	subcutaneous	fan-like pattern	1.4 mm	NR	Blunt	OC	NR	NR
neg	NR	Fil, W	Fh, B, Ch, Io, N	Intradermal	NR	0.9 mm	Tulip	NR	microfat: 9 ml (3.8-15.3) nanofat: 0.3 ml (0-2.1)	1-3	NR

Table V. Outcomes.

Study	Intervention	Outcome assessment	Results	Overall result	Conclusion
AFG					
Baserga *et al*. 2020	**AFG**	3D surface imaging	1st treatment; symmetry of the middle facial third among scleroderma patients was similar to the control group (p=0.263) 2nd treatment; upper- and lower facial thirds from scleroderma patients was similar to the control group (p>0.05)	+	NR
Berl *et al*. 2022	**AFG**	Mouth opening Patient satisfaction	Mouth opening increased 8.5 mm (2-25 mm) (p<0,05)* Overall satisfaction; high satisfaction rate (mean 5.2), 88% willing to repeat	+	Autologous fat grafting successfully increased the oral opening and improved facial manifestations in patients with SSc. The procedure is reproducible, safe and leads to improvements in facial manifestations and in patients' quality of life.
Del Papa *et al*. 2015	**AFG**	Skin hardness assessment Labial capillaroscopy Mouth opening Mouth perimeter measurement Patient satisfaction	Durometer scores reduced 10.7 (p<0.0001)* Number of capillaries increased 14.2 (4.3-25.0) (p<0.0001)* Mouth opening increased 2.6 mm (0.1- 6.0) (p<0.001)* Mouth perimeter measurement increased 9.2 mm (-2.3 - 15.4) (p<0.0001)* 80% was very satisfied, 20% rather satisfied	+	NR
Gheisari *et al*. 2018	**AFG**	Mouth handicap in systemic sclerosis (MHISS) Photograph analysis Rodnan skin score (RSS) Skin biophysical properties (CRRT) Mouth opening Patient satisfaction	MHISS reduced 23.3±3.1 (p<0.001)* 81% improved appearance RSS reduced 0.5±0.5 (p=0.001)* CRRT did not change; 131.6±150.7 (p=0.39) Mouth opening increased 0.8 cm (0.5-1.5) (p<0.001)* 63% was very satisfied, 13% was somewhat satisfied, 19% was unsatisfied	+	NR
Li *et al*. 2023	**AFG**	Melanin index Erythema index Localised scleroderma cutaneous assessment tool (LoSCAT) Clinical assessment of facial deformity using PUMC localised scleroderma facial aesthetic index (PUMC LSFAI)	Melanin index decreased (p=0.008)* Erythema index did not change (p=0.332) LoSCAT did not change (p=0.750) PUMC LSFAI reduced (p=0.002)*	±	Fat grafting could alleviate skin hyperpigmentation and skin damage of LS lesions while having little effect on skin erythema and disease activity.
Onesti *et al*. 2016	**ASCs + HA, AFG**	Italian version of Mouth Handicap in Systemic Sclerosis Scale (IvMHISS) VAS on compliance and physician and patient satisfaction Mouth opening Patient satisfaction	IvMHISS reduced in AFG (p=0.0234)* and ADSC (p=0.0022)*; no difference in improvement between AFG and ADSC (p=0.9619) Improvements VAS in AFG and ADSC; no difference between AFG and ADSC in terms of VAS (p=0.0339)* Mouth opening increased in AFG (p=0.0171)* and ADSC (p=0.0322)*; no difference of improvement between AFG and ADSC (p=0.5833) AFG: 80% satisfied, 20% very satisfied ADSC: 20% rather satisfied, 80% very satisfied	+	Autologous decanted fat transplantation allows us to obtain satisfactory results in terms of tissue trophism and mouth opening improvement, taking advantage of adipose- derived stromal cells properties and exploiting the fluidity of fat obtained from fat decantation especially to treat very fibrotic areas.
Pignatti *et al*. 2020	**AFG**	Mouth Handicap in Systemic Sclerosis (MHISS) Health Assessment Questionnaire (HAQ) Visual Analog Scale (VAS) for pain Mouth opening Sialometry	Perception of disability reduced; MHISS (p=0.097) and HAQ (p=0.063) VAS score reduced (p=0.097) Mouth opening did not change -0,1 (p=ns) Normalisation of saliva production to more than 0,1mL/min was documented in all patients. Subjective amelioration of xerostomia in 71% (p=0.0269)*	-	Confirmed the efficacy of AFG to treat the perioral complications of SSc.
Roh *et al*. 2008	**AFG**	Photograph analysis	51-75% improvement of the forehead (NSR) <25% improvement of the chin (NSR) Fair correction of the infraorbital area (NSR) Poor correction of the nose (NSR) 67% of the patients showed excellent results (NSR)	-	Autologous fat may be the best material for restoring volume loss when used for the right indication at the right location.
Sautereau *et al*. 2016	**AFG**	Mouth Handicap in Systemic Sclerosis (MHISS) Health Assessment Questionnaire adapted to SSc (SSC-HAQ) VAS for Sicca Syndrome VAS for facial pain Photograph analysis Modified Rodnan Skin Score (mRSS) Skin elasticity (suction skin elasticity meter) Mouth opening Sicca Syndrome Patient satisfaction	MHISS reduced 10.7±5.1 (p<0.001)* SSc-HAQ did not change r=0.30 (p=0.336) VAS for Sicca Syndrome reduced 53% (p=0.003)* VAS for facial pain reduced 62.8% (p=0.01)* Improvement of perioral folds and mouth opening was clinically obvious for some patients mRSS reduced 54.2% (p=0.016)* No significant change of skin elasticity Mouth opening increased 3.7 mm ± 4.4 (NSR) Sicca syndrome reduced of 5.2±4.9 (NSR) 33% was very satisfied, 42% satisfied, 17% moderately satisfied, 8% unsatisfied	±	NR

Study	Intervention	Outcome assessment	Results	Overall result	Conclusion
Segna *et al*. 2017	**AFG**	3D surface imaging Photographs analysis	No outcome measurements reported	-	NR
Wang *et al*. 2021	**ASCs + AFG, cSVF + AFG, AFG**	MRI analysis of facial atrophy volume Photographs analysis	Fat retention of ASCs 49.8% ±3.6, higher than cSVF 31.8% ±1.7% (*p*=0.0004)*, and AFG 21.9% ±1.7% (*p*<0.0001)* With difference in fat retention cSVF *vs*. AFG (p=0.0346)* Expert satisfaction rating of the ASCs 4.0±0.1, higher than cSVF 3.1±0.2 (*p*=0.0092)* and AFG 2.2 ±0.2 (*p*<0.0001)*	+	This pilot study suggests that ASCs-assisted AFG is a safe, feasible, and attractive alternative to conventional and cSVF-assisted AFG in the correction of facial atrophy of LoS patients. Future studies with large patient samples are needed for confirmation.
Wang *et al*. 2022	**AFG**	MRI for fat retention Clinical assessment of facial deformity using PUMC localised scleroderma facial aesthetic index (PUMC LSFAI) Measurement of facial blood flow Pprfusion	Fat retention 34.6% ±11.9 (NSR) PUMC LSFAI of all participants were improved at follow-up, except for the surface area of the lesion item (NSR) No association between fat retention and PUMC LSFAI scores r = –0.014 (*p*=0.967) Blood perfusion increased by 1.2±0.1 (*p*=0.01)* No association between increase in blood perfusion and fat graft retention r = –0.1 (*p*=0.811)	±	Autologous fat grafting significantly improved the impaired facial aesthetics, including soft tissue atrophy, skin thickness, dyspigmentation.
Wang *et al*. 2023	**AFG**	Photographs analysis Quality of life	Photograph analysis showed no difference in symmetry (*p*=0.48), volume (p=0.48) and skin texture (*p*=1) treating during active *vs*. stable phase Extremely satisfied (n = 1), very satisfied (n = 2), and somewhat satisfied (n = 1) to not at all satisfied (n = 1)	-	Autologous fat grafting during the active phase did not appear to be inferior to fat grafting during the stable phase in this small clinical case series. To understand challenges concerning fat resorption, further research is needed to determine whether the fat quality of this special patient population plays a significant role.
PRP					
Abellan Lopez *et al*. 2022	**PRP + AFG**	Mouth Handicap in Systemic Sclerosis (MHISS) VAS for mouth opening limitation VAS for sicca syndrome VAS for facial pain Photographs analysis Rodnan Skin Score (RSS) Mouth opening Xerostomia inventory score Sugar test Patient satisfaction	MHISS reduced -6.5±7.5 (*p*=0.016)* VAS for mouth opening limitation -0.9±3.1 (*p*=0.409) VAS for sicca syndrome 0.8±2.6 (*p*=0.402) VAS for facial pain 0.4±3.9 (*p*=0.740) Volume restoring and peri-oral folds attenuation were noticed RSS on cheek 0.2±1.3 (*p*=0.640), RSS on lips -0.2±0.8 (*p*=0.447) Mouth opening increased 0.6 mm ±4.0 (*p*=0.608) Xerostomia inventory score reduced -3.7±6.4 (*p*=0.124) Sugar test reduced -11.1±75.2 (*p*=0.709) 9% unsatisfied, 9% moderately satisfied, 36% satisfied, 46% very satisfied	-	We compared these results to our former cohort (2015) and did not find significant difference on MHISS score. PRP addition behaviour requires further investigations.
Blezien *et al*. 2017	**PRP + AFG**	Mouth Handicap in systemic sclerosis (MHISS) Quantitative assessment of fibrosis by biopsy Mouth opening Lip thickness	MHISS reduced 5.3 (*p*=0.00007)* 5/7 patients; focal reduction of dermal fibrosis in some areas (NSR) Mouth opening sup-inf increased 0.6 cm (*p*=0.031) Mouth opening lat increased of 0.2 cm (*p*= 0.098) Lower lip thickness increased 0.1 cm (*p*=0.0005)* Upper lip thickness increased 0.1 cm (*p*=0.00026)*	±	Autologous fat grafting containing stem cells allows us to obtain satisfactory results in terms of mouth opening improvement and tissue tropism, taking advantage of adipose-derived stromal cell properties especially to treat fibrotic labial areas, without significant surgical side effects.
Virzi *et al*. 2017	**PRP + AFG**	Videodermatoscopic analysis Morpho-dynamic analysis of labial rhyme Skin elasticity (Elastometer-EM 25) Patient satisfaction	Capillary density increased 67% and a decreased vascular ectasia 33% (NSR) Labial rhyme opening rate increased (83%), labial rhyme extension increased 100% (NSR) Substantial increase in skin elasticity or the lip 16.64% and for the cheek 17.80% (NSR) Increase patient satisfaction (Table III) (NSR)	-	Our evidence supports the hypothesis that co-injection of autologous SVF and PRP in SSc patients could provide the correct balance of angiogenic and growth factors to improve tissue regeneration, thus representing an optimal combinatorial therapy against SSc.
Pirrello *et al*. 2019	**PRP + HA**	Videodermatoscopic analysis Skin elasticity Mouth opening Lip thickness Questions on aesthetic and functional benefits	100% of the capillary density remained stable, vascular ectasia: 40% slightly increased, 30% stable, 30% undetectable (NSR) Skin elasticity significantly increased in 100% of the patients (NSR) Mouth opening increased (*p*=0.0093)* Upper lip thickness increased (*p*=0.15) Lower lip thickness increased (*p*=0.0163)* 40% more hydrated and softer, 30% increased skin elasticity, 70% regained the feeling of their own skin and skin sensitivity, 40% suffered less in mouth opening, (30%) gradual decrease of flushing and hematoma (NSR)	±	This study has shown the efficacy of hyaluronic acid and platelet-rich plasma infiltrations in the treatment of facial skin lesions in SSc patients.

Study	Intervention	Outcome assessment	Results	Overall result	Conclusion
ADSC					
Almadori *et al*. 2019	**ASCs + AFG**	Mouth Handicap in systemic sclerosis (MHISS) Psychological status Derriford Appearance scale (DAS24) The Hospital Anxiety and Depression Scale (HADS) The Brief Fear of Negative Evaluation Scale (BFNES) VAS for mood, emotion, distress 3D surface imaging for volume augmentation Photographs analysis	MHISS reduced 6.9±5.1 (p<0.0001)* DAS 24 improved 12.1±9.5 (p<0.0001)* HADS-anxiety improved 2.8±3.2 (p<0.0001)* HADS-depression improved 2.0±3.1 (p<0.0001)* BFNE improved 2.9±4.3 (p<0.0001)* VAS improved 3.6±4.1 (p<0.0001)* Volume retention: 93.7% cheeks, 81.9% nasolabial folds, 67.4% nose, 68.2% chin, 35.5% upper- and 27.3% lower lips (NSR) Patients graded according to disease severity: 0% severe, 13% severe/moderate and moderate, 40% mild	+	Autologous stem cell enriched lipo- transfer offers a potentially effective regenerative option to treat orofacial fibrosis in SSc that operates independently of immunosuppression and disease subset.
Onesti *et al*. 2016	**ASCs + HA, AFG**	Italian version of Mouth Handicap in Systemic Sclerosis Scale (IvMHISS) VAS on compliance and physician and patient satisfaction Mouth opening Patient satisfaction	IvMHISS reduced in AFG (p=0.0234)* and ADSC (p= 0.0022)*; no difference in improvement between AFG and ADSC (p=0.9619) Improvements VAS in AFG and ADSC; no difference between AFG and ADSC in terms of VAS (p=0.0339)* Mouth opening increased in AFG (p=0.0171)* and ADSC (p=0.0322)*; no difference of improvement between AFG and ADSC (p=0.5833) AFG: 80% satisfied, 20% very satisfied ADSC: 20% rather satisfied, 80% very satisfied	+	Autologous decanted fat transplantation allows us to obtain satisfactory results in terms of tissue trophism and mouth opening improvement, taking advantage of adipose- derived stromal cells properties and exploiting the fluidity of fat obtained from fat decantation especially to treat very fibrotic areas.
Wang *et al*. 2021	**ASCs + AFG, cSVF + AFG, AFG**	MRI analysis of facial atrophy volume Photographs analysis	Fat retention of ASCs 49.8% ±3.6, higher than cSVF 31.8% ±1.7% (p=0.0004)*, and AFG 21.9% ±1.7% (p<0.0001)* With difference in fat retention cSVF *vs*. AFG (p=0.0346)* Expert satisfaction rating of the ASCs 4.0±0.1, higher than cSVF 3.1±0.2 (p=0.0092)* and AFG 2.2±0.2 (p<0.0001)*	+	This pilot study suggests that ASCs-assisted AFG is a safe, feasible, and attractive alternative to conventional and cSVF-assisted AFG in the correction of facial atrophy of LoS patients. Future studies with large patient samples are needed for confirmation.
SVF					
Wang *et al*. 2021	**ASCs + AFG, cSVF + AFG, AFG**	MRI analysis of facial atrophy volume Photographs analysis	Fat retention of ASCs 49.8% ±3.6, higher than cSVF 31.8% ±1.7% (p=0.0004)*, and AFG 21.9% ±1.7% (p<0.0001)* With difference in fat retention cSVF *vs*. AFG (p=0.0346)* Expert satisfaction rating of the ASCs 4.0±0.1, higher than cSVF 3.1±0.2 (p=0.0092)* and AFG 2.2 ±0.2 (p<0.0001)*	+	This pilot study suggests that ASCs-assisted AFG is a safe, feasible, and attractive alternative to conventional and cSVF-assisted AFG in the correction of facial atrophy of LoS patients. Future studies with large patient samples are needed for confirmation.

Where indicated, values are mean [standard deviation] or mean(range); NR: not reported; +: positive; -: negative.
Intervention: PRP: platelet rich plasma; AFG: autologous fat graft; ASCs: adipose derived stem cells; cSVF: cellular stromal vascular fraction; DBM: demineralised bone matrix; HA: hyaluronic acid. *statistically significant.

PROM's, imaging tools and oral function are less invasive to perform and were more frequently used in the included studies. Distinguishing between aesthetic and functional outcomes is crucial, with questions arising about how aesthetic outcomes truly reflect regeneration of fibrosis. Imaging tools showed that autologous fat grafts, SVF and ASCs improve fat retention. However, the absence of comparisons to healthy controls makes it impossible to make a statement about the regenerative potential. Measuring fat retention, primarily an aesthetic outcome, differs from assessing regeneration in fat atrophy seen in scleroderma. Functional outcomes, such as the MHISS, might be considered more valuable in assessing regeneration of fibrosis. Autologous fat grafting, PRP and ASCs reduced the MHISS, with corresponding patient satisfactions reports. Another important factor is how patients experience their oral function. AFG, PRP and ASCs showed a significant improvement in mouth opening. AFG and PRP also improved sicca syndrome and saliva production. By improving mouth opening and relieving xerostomia, patients should experience less difficulties in speech, mastication, adequate dental self-care, and dysphagia. To date the limited number of studies revealed that AFG alone or supplemented with PRP, SVF or ASCs, had a similar therapeutic benefit. Yet, investigations lack that assessed timing, dosing, and frequency of administrations to optimise treatment regiments. Moreover, long-term potency of the treatments remains unknown as 10 of the cited studies had a follow- up period of no more than 6 months.

This systematic review is distinctive in its specific focus on autologous regenerative treatments for cutaneous manifestations of scleroderma in the face. A similar study by Gonzales *et al*. reviewed medical and surgical treatment options for microstomia in scleroderma. Some overlapping studies were reviewed, but with an emphasis on microstomia, particularly assessing MHISS and mouth opening. They reviewed various treatments and concluded that "autologous fat grafting seems to have the most substantial evidence" in treating microstomia (68). Furthermore, similar studies concentrate on SSc, but lack the specific emphasis on the cutaneous manifestations of the face. For instance, a systematic review on the efficacy and safety of MSCs in treating SSc, and the study by Cao et al. that reviewed studies on AFG and ASCs in SSc treatment (69, 70). However, both reviews concluded that the treatment had an improving effect on SSc, but there was a difference in effect on different symptoms of the disease. In summary, this systematic review stands out by taking up on the regenerative potential of autologous treatments for scleroderma in cutaneous manifestations of the face, thereby addressing a specific gap in the existing literature, and offering potentially valuable insights into improving future treatment and research.

This review has its limitations. The significant variation in outcome variables across studies has posed a challenge in performing meaningful comparisons (23 outcome variables in 17 studies). Furthermore, there was a lack of comprehensive descriptions and standardised procedures in most of the analysed studies, as well as the absence of control groups in several studies. We were therefore unable to establish superiority of any of the investigated treatments. Often, no validated outcome measurement tools were used. Some studies did however use validated outcome measures, such as patient reported MHISS and RSS. Others utilised imaging-methods, such as 3D imaging, MRI, and photographs. However, often no inter-, and intra-measurement variations were reported, which makes it impossible to determine the reliability of these measurements. Moreover, statistical testing of outcomes was neglected in several studies, which diminishes the value of potentially relevant clinical trials to a minimum.

The use of adipose-derived regenerative treatments in scleroderma, whether or not in combination with blood-derived regenerative treatments, can be considered an easily accessible and minimally invasive treatment, holding the potential for widespread applicability. This review aimed to identify studies that reported the efficacy of autologous regenerative treatments for scleroderma in cutaneous manifestations of the face. However, we could neither corroborate nor dispute these findings based on the outcomes of our current review. This systematic review focused on regenerative treatments for scleroderma in the facial area, thereby limiting the scope of our findings. To improve quality of evidence and reduce variations across studies, future studies should focus on conducting randomised controlled clinical trials with standardisation of the processes of harvesting, processing and injection of the regenerative treatments. Detailed documentation of treatment procedures would considerably contribute to advancing our understanding of these treatments. Additionally, to minimise potential recall bias, validated patient-reported outcome questionnaires should be used both pre- and postoperative.

In conclusion, autologous regenerative treatments, including autologous fat grafts, PRP, SVF, and ASCs, show promise in addressing cutaneous manifestations in scleroderma patients. While some treatments demonstrated positive outcomes, the heterogeneity in study designs and variations in results made it impossible to objectify clinical superiority of regenerative treatment. These outcomes highlight the need for more standardised research methodologies to better understand the potential benefits of these treatments in scleroderma management. Further research is warranted to establish the effectiveness of these interventions.

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