Autologous Fat Grafting for the Oral and Digital Complications of Systemic Sclerosis: Results of a Prospective Study

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Abstract

Background Systemic sclerosis is a connective tissue disease. Skin involvement of the mouth and hand may compromise function and quality of life. Autologous fat grafting has been described as a specific treatment of these clinical features. We report the results of our prospective study designed to treat and prevent skin complications in systemic sclerosis.

Materials and Methods We treated 25 patients with mouth and/or hand involvement (microstomia, xerostomia, skin sclerosis, Raynaud’s phenomenon and long-lasting digital ulcers) with autologous fat grafting, according to the Coleman’s technique, around the mouth and/or at the base of each finger. The surgical procedures were repeated in each patient every 6 months for a total of two or three times. Clinical data were collected before the first surgery and again 6 months after each surgical procedure. Pain, skin thickness, saliva production and disability were assessed with validated tests.

Results Overall we performed 63 autologous fat grafting sessions (either on the mouth, on the hands or on both anatomical areas). Results at 6 months after the last session included improvement of xerostomia evaluated with a sialogram, reduction of the skin tension around the mouth and, in the hands, reduction of the Raynaud phenomenon as well as skin thickness. Pain was reduced while the
perception of disability improved. Digital ulcers healed completely in 8/9 patients.

**Conclusions** Our results confirm the efficacy and safety of autologous fat grafting for the treatment of skin complications and digital ulcers due to systemic sclerosis. In addition, the patients’ subjective well-being improved.

**Level of evidence** V This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

**Keywords** Systemic sclerosis · Autologous fat grafting · Stem cell transplantation · Xerostomia · Microstomia · Digital ulcers

**Introduction**

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial dysfunction, specific autoimmune abnormalities and accumulation of collagen and other matrix component in the skin and target internal organs [2–4]. The multifaceted clinical features of SSc appear to be related to the variable contribution of the above mentioned pathogenetic mechanism that together with a multistep process are responsible for the heterogeneous clinical manifestations of SSc. (REF) Fibrotic and vascular manifestations such as Raynaud’s phenomenon, digital ulcers (DUs), pulmonary hypertension and cutaneous and visceral fibrosis are the most frequent manifestation of scleroderma [5–9]. The extent of skin fibrosis led to the classification in two distinct clinical subset of SSc namely, limited cutaneous SSc with skin involvement distal to the elbows and knees and diffused cutaneous SSc with skin involvement extending to the proximal limbs and/or trunk [2, 10–12]. Facial involvement frequently present in both subtypes is associated with disfiguring mask-like stiffness of the face [13–15], together with xerostomia and the loss of elasticity and fibrosis of the perioral area, makes eating, drinking, and personal and dental care difficult [9]. DUs are one of the most frequent and severe manifestation of SSc, they are present in up to 50% of patients [7, 16–18]. DUs are very painful, hard to heal, may be complicated by infections and gangrene, sometimes requiring amputation [19]. DUs are also related to functional disability with negative impact on the patients’ quality of life [18–23]. The complex and multifactorial nature of SSc constitutes a great therapeutic challenge.

The discovery of adipose tissue-derived stem cells has opened new therapeutic possibilities in plastic and regenerative surgery. In the last decades autologous fat grafting (AFG) has been successfully used to treat a progressively larger number of clinical conditions characterized by skin atrophy or fibrosis such as radio-induced tissue damage, scars, post-surgical pain [24–29]. Recently, also patients affected by scleroderma have been treated by grafting of autologous fat, with different techniques [30, 31].

In this prospective study, we report the results of our treatment protocol with multiple sessions of autologous fat grafting for facial and hand dysfunctions related to systemic sclerosis.

The study was approved by the local ethical committee of the University of Modena and Reggio Emilia (number 275/16) and performed according to the criteria of the Helsinki declaration. All patients gave their written consent.

**Materials and Methods**

We performed repeated surgical procedures in 25 scleroderma patients affected by mouth and/or hand involvement: microstomia, xerostomia, skin sclerosis, and long-lasting digital ulcers. All patients fulfilled the American College of Rheumatology criteria for SSc [8]. The clinical features of the patients at the time of treatment and number of procedures are reported in Table 1. To be included in the study, the SSc patients had to have an opening of oral commissure < 5 cm or/and skin involvement of the hands, with functional limitation consisting in abnormal finger flexion and extension, an increased skin thickness as measured by the modified Rodnan Skin Score (mRSS), presence of Raynaud phenomenon, evaluated with Raynaud Condition Score (RCS).

Digital ulcers lasting for more than 6 months and not responding to conventional systemic and local treatments were present in 9 of the 25 patients. All the patients received standard medical therapy for scleroderma vasculopathy (i.e.: calcium channel blockers, prostanoids and/or anti-endothelin receptors), therapy that they did not discontinue during the surgical treatment.

Exclusion criteria were: severe SSc cardio-pulmonary involvement not allowing the patients to undergo surgery; insufficient subcutaneous fat for harvesting; refusal to participate in the study and age under 18 years or over 85 years.

The treatment plan included three sessions of surgery, each one consisting in autologous fat grafting of the affected areas (either the mouth area or the hands or both) performed at intervals of 6 months from each other Fig. 1.

When patients required both mouth and hand treatment, the two sites were operated on during the same surgical session, and that was considered as a single procedure.

Three procedures, planned every 6 months, of AFG were recommended to all patients even if improved after
the first procedure, in the belief, derived from the experience with AFG in other clinical conditions (such as breast reconstruction and radiodermitis) [32], that they were necessary to induce and maintain the beneficial effects of AFG.

Not every patient completed the three surgical sessions as planned, due to worsening of the clinical condition (not related to treatment) or to personal choice.

The patients’ clinical data were collected before the first surgery and again 6 months after each surgical procedure, just before the following procedure. A final follow-up evaluation was performed 6 months after the last surgical procedure, and therefore 12 months (two sessions) or 18 months (three sessions) after the first autologous fat grafting.

The data collected included clinical and serological features of SSc and clinimetric assessment of hands and mouth, sialometry, and the evolution of the digital ulcers, when present.

Clinimetric measures included mouth opening (taken on the midline at maximum forced opening, between the upper and lower lip margin); middle finger-wrist distance (length taken from the tip of middle finger to the distal volar wrist crease with the hand fully extended and supinated); middle finger-palm distance (distance between middle finger tip and palmar skin when the patient was asked to make a fist as a measure of the flexion of fingers on the palm).

Skin thickness was measured with the modified Rodnan Skin Score (mRSS), the Raynaud phenomenon with the Raynaud Condition Score (RCS).

Sialometry, the measurement of the amount of the unstimulated whole saliva (UWS) per minute, is necessary for the diagnosis of hyposalivation. The sialometry, that was performed according to the technique reported in the literature, is considered to be positive for hyposalivation if less than 1.5 mL of saliva are collected in 15 min, a production of 0.1 mL/min representing the cut-off limit for diagnosis [33–36].

Furthermore, the patients were asked to fill out a questionnaire in order to express their level of satisfaction with hand and mouth function.

Pain was evaluated by the Visual Analog Scale (VAS) for pain and by the short-form McGill Pain Questionnaire (SF-MPQ), that investigates sensory and affective descriptors. The perception of disability was measured by the Health Assessment Questionnaire-HAQ and by the Mouth Handicap in Systemic Sclerosis scale-MHISS [23].

**Surgical Procedure**

All the patients received one preoperative dose of 2 g of Cefazolin e.v. (Clindamycin 600 mg, if allergic to cephalosporins).

The procedure was performed under sedation and regional block with local anesthetic, to obtain adequate analgesia on the areas where the fat was harvested and where it was injected. Local anesthetic alone would be insufficient to control pain and maintain comfort while repeated sessions of general anesthesia would have been more invasive and unnecessary. Furthermore, orotracheal intubation is difficult in patients affected by microstomia.

We performed tumescent infiltration of the donor areas (flanks or trochanteric areas) with a modified Klein solution (50 mL of saline solution, 0.5 mL of 1:1.000 adrenalin and 10 mL of 2% Mepivacain) through an epidural 23 Gauge needle attached to a 20 mL Luer-lock syringe.

The original Coleman’s technique for harvesting and purification of the fat was used [37].

An aspiration cannula (Micro Aspiration Cannulas Black and Black Surgical FAC, 12 gauge × 15 cm Luer-lock) was introduced through a 3 mm incision and a total volume of 30–50 mL of fat and fluids was aspirated in 10 mL Luer-lock syringes. The syringes were centrifuged for 3 min at 3000 rpm/1900 RCF (MPW-223e centrifuge, “Mpw Medical Instruments” Spółdzielnia Pracy, Warsaw, Poland) and the infranatant fat was isolated and transferred to 2.5 mL syringes.

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**Table 1 Clinical features of SSc patients before treatment**

| Feature                          | Number  |
|----------------------------------|---------|
| Number of patients               | 25      |
| Female/male                      | 19/6    |
| Age                              | 55.69 ± 9.25—SD—years |
| Median disease duration          | 184.68 ± 121.09—SD—months |
| lcSSc-L/dcSSc-D                  | 21/4    |
| ScI70/ACA                        | 18/7    |
| Digital ulcers                   | 9/25    |
| Puffy hands                      | 7/25    |
| Melanoderma face                 | 15/25   |
| Melanoderma hands                | 10/25   |
| Skin stiffness of face           | 15/25   |
| Skin stiffness of hands          | 16/25   |
| Xerostomia                       | 14/25   |
| RCS                              | 6.00 ± 1.8 |
| mRSS                             | 9.5 ± 6.1 |
| Mouth procedures (tot)           | 30      |
| Hands procedures (tot)           | 22      |
| Mouth + hands procedures         | 11      |

Number of procedures

lcSSc-L/dcSSc-D, limited/diffuse cutaneous systemic sclerosis; ScI70/ACA, anti-topoisomerase I or anti-ScI 70 antibodies/anti-centromere antibodies; RCS, Raynaud Condition Score (0–10); mRSS, modified Rodnan Skin Score.
Mouth

For the treatment of the mouth, after infraorbital block and mental nerve block with mepivacaine 1%, a skin access was created at each naso-jugal crease at the level of the oral commissure with a 19 gauge needle to introduce a Coleman injection cannula (Tissue Injection Cannulas Type I Black and Black Surgical 19 gauge × 7 cm). The cannula was connected to the 2.5 mL syringes loaded with the centrifuged, purified autologous fat that was then injected in the subcutaneous and submucosal plane with the retrograde technique, as shown in Fig. 2.

Two ml of fat were grafted in each of the eight sites around the mouth, for a total of 16 mL (Fig. 3).

The amount of AFG was standardized. For the perioral area previous experience showed us that due to the thin subcutaneous tissue and the stiff skin and mucosa a volume of 2 mL per each subunit, was adequate to obtain a filling effect, avoiding excessive tissue tension and hypoperfusion. A total of 16 mL was therefore used for the area.

Hands

After wrist block (median, ulnar and dorsal radial nerve) with 5 mL of mepivacaine 1%, skin accesses were created with a 19 gauge needle at each finger commissure and/or dorsum of proximal phalanx depending on the tightness of the skin which also determined the maximum amount of fat.
injected. The fat was grafted around the neurovascular bundle at the base of the fingers in an amount ranging from 0.5 to 1 mL on each side of each finger, for a total of up to 10 mL per hand (Fig. 4). The volume injected was never more than 1 mL for each neurovascular bundle to prevent the potentially severe complication of finger ischemia.

Patients that required mouth and hand treatment were treated at both sites during the same session.

Statistical Analysis

All descriptive data were expressed as mean ± standard deviation (SD). Comparison between values at the baseline and after treatment was performed by paired t test and Wilcoxon’s test for continuous and non-continuous variables, respectively. Data analysis was carried out using an SPSS statistical package (version 22.0, IBM Software, USA) and P value was considered to be significant when < 0.05.

Results

Overall, we performed 63 surgical procedures.

Of the 25 patients treated, 12 interrupted the treatment after the second surgical procedure: six because of other SSc-related medical problems, four because they were satisfied with the benefits already achieved after the first two procedures, and two because no longer followed by our Rheumatology center. The number of patients who received two or three treatments and the sites treated are reported in Table 2.

The results obtained are reported below.
corresponded to a subjective amelioration of xerostomia in 10/14 subjects \( (p = 0.0269) \).

**Hands**

There was a complete healing of digital ulcers in 8/9 patients \( (p = 0.0297) \) and an improvement in the remaining patient Figs. 7, 8 and 9.

All the 12 patients with hand involvement reported an improvement in hand tension \( (p = 0.0037) \), but the improvement of the clinimetric measures was not significant \( (p = \text{ns}) \).

The Raynaud phenomenon, measured with the Raynaud Condition Score, significantly improved from 6.0 ± 1.8 to 3.8 ± 1.6 \( (p < 0.0001) \), while the Modified Rodnan Skin Score showed only a trend towards improvement (from 9.5 ± 6.1 to 8.9 ± 5.7; \( p = 0.083 \)).

Pain, evaluated by SF-MPQ, scrutinizing sensory \( (p = 0.3340) \) and affective \( (p = 0.2234) \) descriptors,

Table 2  The number of patients who received two or three treatments and the sites treated are reported

|                  | 3 Treatments | 2 Treatments | Total N of patients |
|------------------|--------------|--------------|---------------------|
| Mouth            | 4            | 9            | 13                  |
| Hands            | 6            | 2            | 8                   |
| Mouth and hands  | 3            | 1            | 4                   |
| Total            | 13           | 12           | 25                  |

Fig. 5  Before (a, c) and after (b, d) treatment pictures of one patient with closed and open mouth. Improvement of lip thickness (comparison a–b) and mouth opening (c–d)
Fig. 6 Before (a, c) and after (b, d) treatment pictures of one patient with closed and open mouth. Improvement of lip thickness (comparison a–b) and mouth opening (c–d).

Fig. 7 Second finger of the right hand. Proximal inter phalangeal joint exposure. a Pre-operative image, b 1 week after AFG, c 1 month after AFG.
decreased, although not significantly, in all patients, who required lower doses of analgesic drugs.

The clinical changes were mirrored by the subjective feeling of increased well being. In particular, the perception of disability decreased with a trend towards amelioration, when measured with the tests cited above (HAQ, \( p = 0.063 \) and MHISS, \( p = 0.097 \)). The subjective assessment and clinimetric measures before and after the last treatment are reported in Table 3.

**Side Effects**

Side effects of the treatment included small ecchymotic areas around the mouth, and temporary edema and paresthesia in the hands of two patients. Both problems resolved within the first month after treatment. No other complications, in particular, no vascular occlusions or infections, were recorded.
Subcutaneous fat is an excellent source of adult stem cells and it has the advantage of being easy to harvest. Adipose-derived stem cells (ADSCs), similar to bone-marrow-derived stem cells, are able to differentiate into multiple mesodermal tissue types. In contrast to bone-marrow-derived stem cells, ADSCs can be easily harvested by liposuction, and their abundance avoids the need for expansion in culture. For these reasons the adipose tissue can be considered an innovative source of mesenchymal stem cells suitable for cell-based therapy in regenerative medicine [14, 28, 38]. ADSC in addition to function as filler, have immunomodulatory properties and are able to secrete angiogenetic factors that facilitate tissue repair [38].

Increasing evidence shows that AFG in sclerotic tissues may decrease collagen deposition and increase elasticity and vascularization [38]. In fact, the procedure has been successfully used to regenerate atrophic or fibrotic skin in a large number of clinical conditions such as radio-dermatitis, burn scars, linear scleroderma, and various types of morphea [25–28, 39].

Several studies have reported the use of fat grafting to treat either mouth or hand SSc complications [30, 31].

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**Table 3** Subjective assessment and clinimetric measures before and after treatment

| Measure                                      | Before treatment | After treatments | p    |
|----------------------------------------------|------------------|------------------|------|
| RCS                                          | 6.0 ± 1.8        | 3.8 ± 1.6        | < 0.0001 |
| mRSS                                         | 9.5 ± 6.1        | 8.9 ± 5.7        | 0.083 |
| HAQ                                          | 1.4 ± 0.5        | 0.8 ± 0.5        | 0.063 |
| VAS                                          | 74.5 ± 18.5      | 65.80 ± 11.9     | 0.097 |
| SF-MPQ sensory                               | 5.48 ± 9.0       | 5.44 ± 7.8       | ns   |
| SF-MPQ affective                             | 2.1 ± 3.1        | 2 ± 3.5          | ns   |
| MHISS total                                  | 19.9 ± 13.2      | 20.7 ± 11.7      | 0.097 |
| Mouth opening (cm)                           | 4.3 ± 0.7        | 4.4 ± 0.7        | ns   |
| Right middle finger-wrist distance (cm)      | 16.6 ± 1.4       | 17 ± 1.5         | ns   |
| Left middle finger-wrist distance (cm)       | 16.1 ± 1.0       | 16.8 ± 1.3       | ns   |
| Right middle finger-palm distance (cm)       | 0.1 ± 0.3        | 0.1 ± 0.2        | ns   |
| Left middle finger-palm distance (cm)        | 0.2 ± 0.3        | 0.2 ± 0.2        | ns   |

RCS: Raynaud Condition Score, mRSS: modified Rodnan Skin Score, HAQ: Health Assessment Questionnaire. Perception of disability measure, VAS: Visual Analog Scale, SF-MPQ: Short-form McGill Pain Questionnaire. Pain measure, scrutinizing sensory and affective descriptors, MHISS: Mouth Handicap in Systemic Sclerosis scale-Perception of disability measure, ns: not significant

**Discussion**

Fig. 9 Gradual healing of the middle fingertip ulcer. a Before treatment, b six months after the first session of AFG, c six months after the second session of AFG, d two years after the third session of AFG
We conducted a comprehensive literature search in the MEDLINE, EMBASE, Pub Med, Science Citation Index, and Google Scholar databases (up to June 2019) using the keywords “systemic sclerosis”, “scleroderma”, “microstomia”, “digital ulcers”, “autologous fat grafting”.

A list of the published articles on the topic is reported in Table 4.

Blezien et al. [40] recently reported in this journal the treatment of oral complications of systemic sclerosis in seven patients by fat grafting, demonstrating satisfying results in most of the observed parameters. Of particular interest is the study by Del Papa et al. [41] who performed a randomized controlled trial comparing AFG with a sham procedure, confirming their previous data [42, 43] on the efficacy of AFG for the treatment of indolent digital ulcers and mouth opening in SSc patients. Furthermore, they showed an increase in the neovascularization of the treated perioral skin [43].

After collection, fat can be processed in various ways, including the Coleman’s technique, as in our study [37]. There is no agreement among authors regarding the best method for processing fat transfer. We chose the original Coleman’s technique because of our previous experience with it in other conditions.

It would have been interesting to have a control group to try a different fat injection technique, but the number of our patients was not sufficient to obtain statistically significant results. However, the other reported techniques were not shown to have a superior success rate [14].

A few years ago, Onesti et al. used sedimentation by gravity as a method to eliminate nonviable components of the lipoaspirate in five patients with mouth functional disability while five more were treated with cell-factory prepared adipose-derived stromal cells. At the one-year follow-up they noticed that both procedures obtained significant results in mouth opening capacity and MHISS scores but neither one emerged as the first-choice technique [44].

Fat tissue provides an abundant source of stromal vascular fraction cells for immediate administration and can also give rise to a substantial number of cultured, multipotent adipose-derived stromal cells [45].

Recently Magalon et al. [46] reported the results of a study on the molecular profile and proangiogenic activity of the adipose-derived stromal vascular fraction. The autologous stromal vascular fraction from adipose tissue is an alternative to cultured adipose-derived stem cells. They concluded that the stromal vascular fraction from patients with SSc presents similar distribution of hematopoietic and regenerative subpopulations compared with healthy donors, supporting the rationale for the therapeutic use of autologous SSc-stromal vascular fraction [46].

Whether autologous adipose-derived stromal vascular fraction could turn out to be an unwanted source of profibrotic myofibroblasts in SSc [47] does not seem likely, on the basis of our results in a SSc cohort with an 18 months follow-up. Also, Capelli et al. [48] showed that ADSCs obtained from patients with SSc exhibit phenotypic pattern, proliferation, immunosuppressive properties and differentiation potential that are similar to the ones observed in healthy controls.

The actual mechanism of fat graft survival is not completely understood [49], but no significant difference appears to exist in survival of grafted fat obtained from different harvest and implantation techniques [14, 24].

Improvement of safety and outcomes of autologous fat grafting procedures may come from so-called “enrichment strategies”.

A recent review of the literature found that platelet-rich plasma and adipose-derived stem cells appeared to have a beneficial effect when used to augment and improve the viability of fat grafts. However, randomized controlled clinical studies are still needed [50, 51].

On the contrary, differences in the disease process, in the number of stromal adipose stem cells obtained by lipoaspirate, and in the underlying conditions associated with poor revascularization, may significantly impact the engraftment [14, 46].

Our study including 25 SSc patients treated with two or three grafting of autologous fat and followed for up to 18 months, confirmed the role of the AFG technique in the treatment of SSc complications [52–56].

Our study, in comparison to previous published ones, has a large patient population sample, a long follow up, includes treatment of hands in addition to the perioral area, provides a detailed surgical technique description and adds the use of salivation test to obtain objective data on improvement of xerostomia.

In particular, we observed complete healing of long-lasting digital ulcers in 8/9 patients and a significant improvement in hand tension and in the Raynaud phenomenon as evaluated by means of RCS (Figs. 7, 8 and 9). A subjective improvement in perioral skin tension and in the sensation of xerostomia was also reported. Almadori et al. in 2019 reported similar results when investigating mouth function following treatment with lipotransfer in 62 SSc patients (6.85±5.07) (p < 0.0001). All of treated patients had manifestation of sicca syndrome, followed by post-operative improvement that contributed of 21.6% (1.51±1.2, p < 0.0001) to MHISS overall score [57].

In addition we report data of 5 patients in which sialometry was evaluated pre- and post-operatively to provide more evidence to the subjective results.

Despite the limited number of cases, a positive trend in saliva flow rate was observed confirming the improvements reported by the patients.
Several articles report on the use of stem cells therapy in salivary glands hypofunction in animal models [58, 59]. In addition, the differentiation of ADSc in salivary gland cells in association with platelet-rich fibrin (PRF) has been showed in vitro [60].

Therefore, we hypothesize that, with the support of well-designed clinical and histological studies, AFG could be proposed not only for scleroderma but also for the treatment of “dry mouth” in other rheumatic conditions.

However, the clinimetric measures of mouth opening and of hand flexion and extension did not improve. We believe that the improvement in mouth opening and perioral elasticity could be masked by the concomitant increase of lip volume. Concerning hands, clinimetric assessment did not show significant enhancement, probably because joint involvement and tendon retraction, frequently observed in SSc, were responsible for the hand disability, and were therefore less influenced by AFG treatment.

Finally, our patients reported an overall subjective amelioration in their quality of life and did not complain of any significant adverse effect, demonstrating a good safety profile of the technique.

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Table 4 Published studies on AFG in cohorts of SSc patients

| Authors          | Year | Pts     | Mouth | Fingers | F-U  | Kind of graft | Results                                                                                                      |
|------------------|------|---------|-------|---------|------|---------------|---------------------------------------------------------------------------------------------------------------|
| Bene [31]        | 2014 | 9       | –     | 9 pts/15 DUs | 8–12 w | AFG           | 10/15 DUs healed, 7/9 patients reduced pain                                                                    |
| Blezien [40]     | 2017 | 7       | 7     | 0       | –    | AFG + PRP     | Remarkable improvement of the oral opening and of lips thickness. Noticeable improvement in quality of life at MHISS score. 3/7 pts focal reduction of dermal fibrosis in some areas of the biopsy’, 2/7 pts unchanged |
| Del Papa [42]    | 2015 | 15      | 0     | 15      | 3–6 mo | AFG           | Ulcer healing in all patients (in a median time of 4.2 weeks). Significant pain relief. VAS significantly lower. No variation of digital artery structure and related perfusion was observed by echocolor-Doppler |
| Del Papa [43]    | 2015 | 20      | 20    | 0       | 1–3 mo | AFG           | Increase mouth perimeter and labial capillaries. Increased dermal papillae                                    |
| Del Papa [41]    | 2019 | 25–13   | 0     | 25      | –    | AFG-Sham      | DUs healing in 23/25 and 1/13 sham, and in 12 rescued. Reduction of pain intensity. Increase of capillary numbers |
| Gheisari [56]    | 2018 | 16      | 16    | 0       | 3 mo  | AFG           | Significant improvement of mouth opening capacity, MHISS and Rodnan score of patients with facial scleroderma (p value < .001). The aesthetic and/or functional results of fat injection were satisfying to about 80% of the patients. The changes in CRRT values were not significant. |
| Granel [49]      | 2015 | 12      | 0     | 12      | 6 mo  | ADSVF         | Significant improvement in hand disability and pain, Raynaud’s phenomenon, finger oedema and quality of life Results of 6mo FU confirmed. Benefits extend for at least 1 yr |
| Guillaume-Jugnot [52] | 2016 | Same 12 | 0     | 12      | 1 yr  | ADSVF         | Results of 6mo FU confirmed at 22-30 mo                                                                 |
| Daumas [53]      | 2016 | Same 12 | 0     | 12      | 22–30 mo | ADSVF       | Results of 6mo FU confirmed at 22-30 mo                                                                 |
| Onesti [44]      | 2016 | 10      | 10    | 0       | 1 yr  | AFG versus ADSCs | Satisfactory results. No difference between two groups                                                       |
| Sautereau [54]   | 2016 | 14      | 14    | 0       | 6 mo  | AFG           | Decrease in the MHISS score. Improvement of perioral skin sclerosis, mouth opening, sicca syndrome, facial pain. 75% satisfied/very satisfied |
| Scuderi [30]     | 2013 | 6       | 2 Face| 2 Arms, 1 feet, 1 upper limbs | 1 yr  | Expanded ASCs after 3 weeks | All pts improvement in wellness of the skin judged by clinical examination. All pts improved and satisfied |
| Virzi [55]       | 2017 | 6       | 6     | 0       | –    | AFG + PRP     | Substantial increase of morphofunctional parameters and capillary density in the maxillofacial region |

MHISS: Mouth Handicap in Systemic Sclerosis. CRRT: cutaneous resonance running time. Kind of graft: AFG: autologous fat grafting; PRP: platelet rich plasma; ADSVF: autologous adipose-derived stromal vascular fraction; ADSCs: adipose-derived stem cells. ASCs: adipose-derived stromal cells. Pts: patients; DUs: digital ulcers. w: weeks; mo: months; yr: years
Conclusions

In conclusion, the results obtained in 25 patients treated with two or three sessions of AFG and evaluated by multiple tests, including the spit test, confirmed the efficacy of AFG to treat the perioral complications of SSc. In addition, there was a modest healing of digital ulcers, associated to a subjective improvement of pain. These clinical results were reflected by the subjective improvement in well-being of the patients.

Compliance with Ethical Standards

Conflict of interest None of the authors has any commercial interest in the subject of study and does not have received any financial or material support.

Ethical Approved The study was approved by the local ethical committee of the University of Modena and Reggio Emilia (number 275/16) and performed according to the criteria of the Helsinki declaration.

Informed Consent All patients gave their written consent.

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