Regenerative Approach to Scleroderma with Fat Grafting

Guy Magalon, MD[a,b,*], Aurélie Daumas, MD[c], Nolwenn Sautereau, MD[c], Jérémy Magalon, PharmD[b], Florence Sabatier, PharmD, PhD[b,d], Brigitte Granel, MD[c,d]

KEYWORDS

• Systemic sclerosis • Cell therapy • Microfat injection • Stromal vascular fraction • Fat grafting • Autologous fat graft • Adipose tissue

KEY POINTS

- Systemic sclerosis (SSc) is a rare autoimmune disease characterized by skin fibrosis, microvascular damage, and organ dysfunction.
- Facial manifestations in SSc are disfiguring and lead to social disability with psychological distress.
- Hand involvement in SSc can lead to a severe disability, with no effective therapy.
- Adipose-tissue-derived stem cell therapy has emerged as a therapeutic alternative for regeneration and repair of damaged tissues.
- Patients with SSc can benefit from fat grafting: microfat injection in the face to improve skin pliability and quality with esthetic benefit, and injection of the autologous adipose-tissue-derived stromal vascular fraction (ADSVF) in fingers for a trophic effect.

Three surgical technique videos accompany this article showing the authors approach to the treatment of the face and of the hands in systemic sclerosis patients, and the inside of 2-mm, 14-gauge cannula harvesting and microfat injection with 0.8-mm, 21-gauge cannula at http://www.plasticsurgery.theclinics.com/

INTRODUCTION

SSc (scleroderma) is a chronic systemic autoimmune disease characterized by microvascular abnormalities and progressive skin and internal organ fibrosis.[1] Life-threatening organ lesions leading to pulmonary arterial hypertension, pulmonary fibrosis, and scleroderma renal crisis only affect a minority of patients. By contrast, lesions of the hands and face are almost always present. Although not life-threatening, these manifestations are very obvious, hard to conceal, and lead to disability and worsening quality of life.[2–4] Facial symptoms are associated with cosmetic

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[a] Plastic Surgery Department, Assistance Publique Hôpitaux de Marseilles (AP-HM), Aix-Marseilles University, 13005 Marseilles, France; [b] Culture and Cell Therapy Laboratory, INSERM CBT-1409, Assistance Publique Hôpitaux de Marseilles (AP-HM), Aix-Marseilles University, 13005 Marseilles, France; [c] Internal Medicine Department, Assistance Publique Hôpitaux de Marseilles (AP-HM), Aix-Marseilles University, 13010 Marseilles, France; [d] Vascular Research Center Marseilles, INSERM UMRS-1076, Aix-Marseilles University, 13005 Marseilles, France
* Corresponding author. Conception Hospital, Assistance Publique Hôpitaux de Marseilles (AP-HM), 13005 Marseilles, France.
E-mail address: secretariat.magalon@gmail.com

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disfigurement and limited expression with mask-like stiffness of the face. Lesions in the hand lead to substantial difficulty in performing everyday tasks (such as dressing, eating, and applying makeup) as well as an increased risk of chronic digital ulcers (DUs). Therapeutic interventions in this disease are mainly based on the use of vasodilators. No antifibrotic treatment has proven effective. Unlike other autoimmune diseases, immunosuppressive drugs have a limited clinical interest.[5–10] Thus, functional improvement of hand motion and face appearance represent a real challenge for physicians and a priority for patients who often feel that this aspect of their disease is neglected.

Use of adipose tissue as filling product in plastic and esthetic surgery is an ancient technique. Significant renewal of interest in this approach for the restoration of all volume defects was observed after the description of the LipoStructure® technique by Coleman.[11–13] Recently, identification and characterization of the ADSVF, a population that includes mesenchymal-like stem cells, endothelial progenitor cells, and hematopoietic cells, have revolutionized the science showing that adipose tissue is a valuable source of cells with multipotency as well as angiogenic and immunomodulatory properties that facilitate tissue repair. The ease of harvest by liposuction and the abundance of these cells (by comparison to bone marrow) avoid the need for ex vivo expansion before clinical use. Because of these practical factors and the stromal vascular fraction's ability to differentiate and secrete immunomodulatory, angiogenic, antiapoptotic, and hematopoietic factors, use of adipose tissue is becoming more attractive and is expanding in regenerative medicine.[14–19]

In this article, the authors present their clinical approach using adipose tissue in the treatment of the face and hands of patients with SSc.

PATHOLOGY OF SCLERODERMA

Face

Involvement of the face with associated oral complications, esthetic changes, and impairment of the patient's self-image is found in over 90% of patients with SSc.[3,20,21]

Fig. 1 and **Table 1** illustrate the main orofacial findings in patients with SSc.

Several validated tools have been developed for assessing the involvement of the face. Skin involvement is usually assessed by the Rodnan skin score. This semiquantitative score rates the severity of skin sclerosis from 0 (normal) to 3 (most severe). Xerostomia can be easily measured by sugar test (time to melt a sugar on the tongue, without crunching it) and with the xerostomia inventory index. Mouth opening is assessed in centimeters by measuring the distance between the tips of upper and lower incisive teeth. Elastosonography and three-dimensional photographs can also be used. Mouth-related disability can be assessed by the Mouth Handicap in Systemic Sclerosis (MHISS) scale, which is the first mouth-specific disability outcome measure designed for patients with SSc.[3] This scale evaluates 3 factors: reduced mouth opening, sicca syndrome, and esthetic concerns. Although mouth disability seems to have less weight than hand disability in total disability, the MHISS score explained up to 36% of the variance of the Health Assessment Questionnaire score. This fact highlights the need to specifically assess disability involving the mouth in patients with SSc. Rehabilitation and management of the face is mainly based on physiotherapy with mimic exercises, massage, and self-administered home-based exercises. Mouth and dental care are not specific.

Some case reports have shown the efficacy of autologous fat grafting in the treatment of linear scleroderma.[22,23] Besides the volumizing effect of mechanical lipofilling, autologous fat grafting also seems to produce trophic and angiogenic effects. The use of autologous grafting of adipose tissue seems to have substantial potential to correct signs of face involvement in SSc.

Hands

Involvement of the hand is common in patients with SSc and represents a large burden in work and daily activities. Hand disability has a multifactorial origin with microvascular lesions, skin sclerosis, tendon retraction, bone and articular involvement, and subcutaneous calcinosis.[4,24–31] Each of these lesions causes pain, functional impairment, esthetic issues, and psychological distress.

Vascular involvement

Vascular dysfunction including Raynaud's phenomenon (paroxysmal vasospasm) (**Fig. 2**), acrocyanosis (permanent ischemia), and subsequently DUs with their potential complications (infections, digital necrosis, autoamputation) are the main manifestations. Raynaud's phenomenon occurs in almost all (95%) patients with SSc. DUs, defined as necrotic lesions that occur either at the pulp of the digits (ischemic DUs) or over bony prominences (mechanical DUs), occur in up to 50% of patients with limited or diffuse SSc. DUs typically occur early in the course of SSc. A study assessing functional limitations owing to

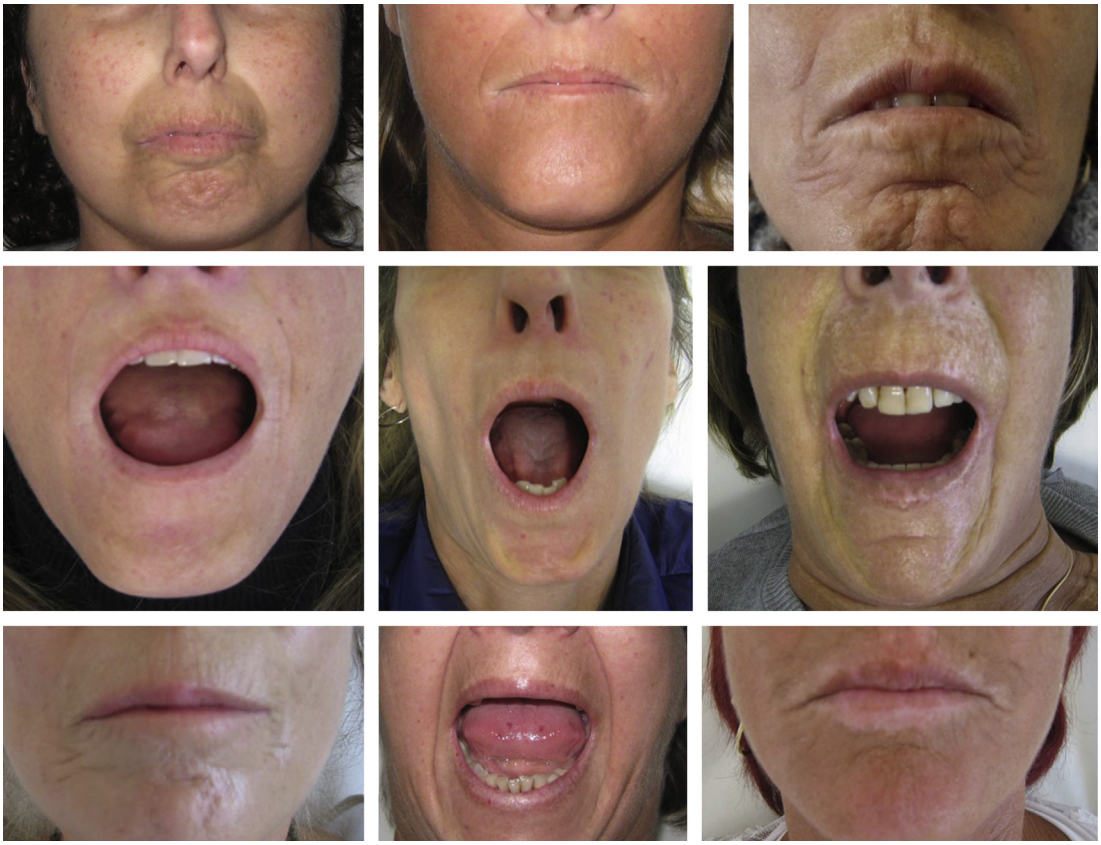

Fig. 1. Various aspects of SSc face involvement showing skin sclerosis, cutaneous wrinkles, vertical furrows that develop around the mouth, sharp nose and lip retraction, telangiectasia, hypopigmentation and hyperpigmentation, and reduction of mouth opening.

Table 1
Orofacial findings in patients with SSc

Orofacial Findings	Commentaries
Skin sclerosis of the face	Very frequent, around 90% of cases. The face becomes amimic or without expression, cutaneous wrinkles disappear, vertical furrows develop around the mouth because of retraction of the skin, the nose becomes sharp, and the lips thin
Telangiectasia	Especially located in the face, lips, or the inside of the mouth; they can lead to severe esthetic concerns
Skin pigmentation abnormalities	Hypopigmentation and hyperpigmentation mostly observed in the diffuse cutaneous form of scleroderma. Vitiligo is possible
Sicca syndrome	Sicca syndrome is detected in approximately 70% of patients with SSc. It is secondary to salivary gland fibrosis
Diminished mouth opening	Frequent, around 60%. Thinning of lips and reduction of mouth width (microcheilia) and opening (microstomia) with consequent difficult dental care
Osteolysis of mandibular angles	Mandibular bone resorption is mainly encountered in patients with marked facial skin fibrosis: chewing and swallowing movements may be impaired, pain is often reported
Altered dentition and difficulties during dental care	Oromucosal involvement include ulcerations, dry mouth, periodontitis, wide periodontal ligament space, dental root resorption, and loose teeth

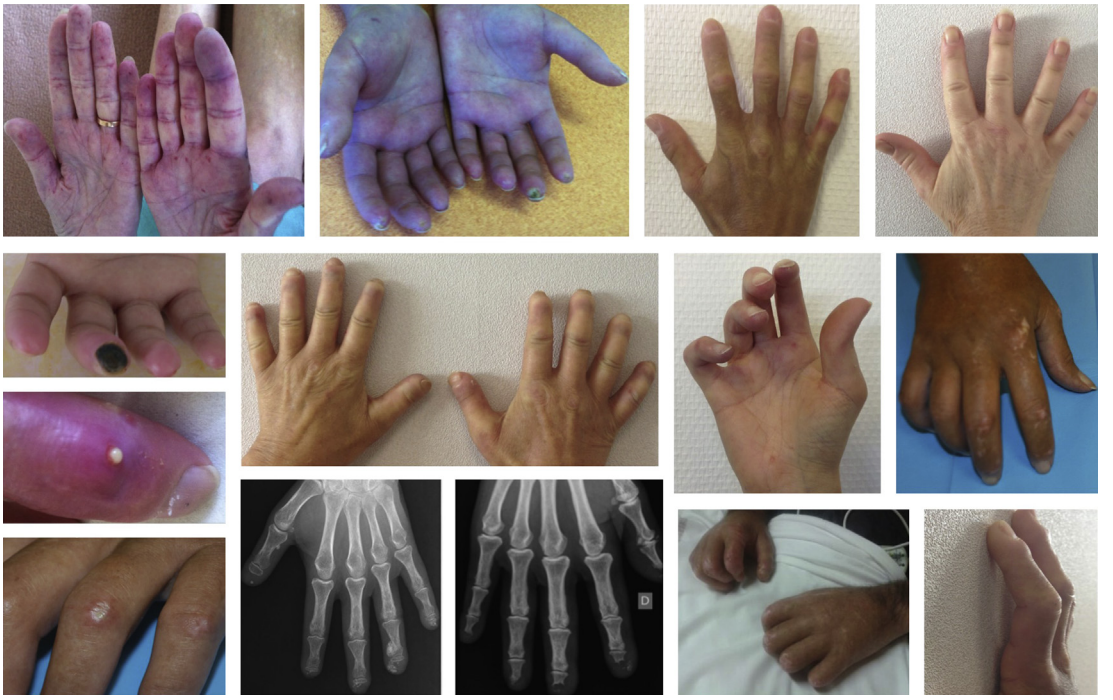

Fig. 2. Various aspects of SSc hand involvement showing acrocyanosis, palmar telangiectasia, sclerodactyly, puffing hand, tightened finger on the underlying bone, various types of DUs (ischemic, mechanic, and related to calcinosis), acro-osteolysis, and claw deformity.

DUs among patients enrolled in the Digital Ulcer Outcome (DUO) Registry showed for patients with 0, 1 to 2, and 3 or more DUs at enrollment an increasing mean overall work impairment. Similarly, the ability to perform daily activities was impaired in patients with DUs and this impairment increased with the number of DUs.

Skin involvement

Skin sclerosis is characterized by variable extent and severity of skin thickening and hardening. Edematous swelling and erythema may precede skin induration. On the hands, this condition is called sclerodactyly (see **Fig. 2**). As the disease progresses further, however, the skin loses its ability to stretch and becomes shiny because it tightens across the underlying bone. Eventually, in severe cases, the fingers may lose the ability to move, with vicious attitude leading to claw deformities (see **Fig. 2**).

Flat red marks, known as telangiectasias (see **Fig. 2**), may appear in various locations, especially in the palms. Although they can cause esthetic concerns, they do not cause functional disturbance.

Calcinosis (see **Fig. 2**) is characterized by calcium deposition in skin and subcutaneous tissues. Calcinosis is commonly associated with SSc; approximately 10% to 30% of patients develop calcinosis. These deposits are typically found on the fingers, hands, and on the skin above wrists, elbows, and knees. Calcinosis can lead to functional impairment, painful ulcers, and infections.

Bone and joint involvement

Distal phalangeal resorption with bone loss (acro-osteolysis) can be observed in SSc (see **Fig. 2**). Arthralgia and arthritis are observed in around 50% of cases. Metacarpophalangeal and proximal interphalangeal arthritis are also frequent. This joint destruction is not as severe as it is in rheumatoid arthritis but can lead to finger deformities and claw hand deformity.

Clinical measures for hand involvement evaluation include: (1) the semiquantitative estimation of skin thickness (modified Rodnan skin score applied to hands, score 0–18); (2) a visual analog scale of pain in the hands; (3) mobility and strength tests such as Kapandji test, grip and pinch strength, and measurement of the intercommissural distances; (4) the Hand Mobility in Scleroderma index, which specifically assesses hand global mobility in patients with SSc, but does not evaluate hand disability for activities of daily living; and (5) the Cochin Hand Function

Scale (CHFS), a functional disability questionnaire about daily activities validated in rheumatoid arthritis and hand osteoarthritis, as well as SSc. The CHFS is a valid instrument for assessing hand disability in patients with SSc. It was shown that hand functional disability is the major component of global disability, contributing to 75% of global disability in patients.[4]

To date, therapeutic interventions for patients with hands affected by SSc have mainly focused on the treatment of vascular manifestations such as Raynaud's phenomenon and DUs. Patients can get some relief with physiotherapy. Unfortunately, there is scant research showing that exercise stops the worsening of scleroderma (Videos 1 and 2). Full rehabilitation is rarely guaranteed, but function can be retained through physiotherapy. Movement can help retard the contractures and help the patient maintain strength and range of motion.[5–10]

ADIPOSE-TISSUE-BASED THERAPY IN SYSTEMIC SCLEROSIS

Over the past few years, stem cell therapy has emerged as a novel therapeutic approach for various diseases including ischemic diseases, wound repair, and tissue regeneration.[14–19,32] The adipose tissue contains various cells such as adipose-derived stem/stromal cells, endothelial progenitor cells, and immune cells, which act together for tissue repair and regeneration. The abundant supply of fat tissue, the ease of isolation, the ability to secrete angiogenic growth factors, and the abundance of stem/progenitor cells make adipose-based therapy ideal for ischemic and nonhealing wounds. In this disease, adipose-derived cell therapy seems to be an attractive source and worthy of attention for clinical translation.

TREATMENT OF THE FACE

Reinjection of autologous fat tissue has volumizing and trophic properties. This technique has been codified by Coleman.[11,12] However, the special context of SSc requires certain modifications to this approach, in particular, harvesting and implanting smaller morsels or packets of adipose tissue.[33] Thus, microreinjection is an evolution of the art. The tissue is aspirated by a 2-mm (14-gauge) cannula, with openings of less than 1-mm, which harvests fat lobules of about 600-μm. Tissue is reimplanted using a 0.8-mm (21-gauge) placement cannula. This minimally invasive technique is used to treat the face of the patient with scleroderma.

Surgical Technique

During the first consultation (after a clinical and photographic analysis), the surgeon defines the amount of adipose tissue necessary and the areas from which this tissue can be harvested (**Fig. 3**). Preferred harvesting areas include the abdomen, hips, and inner side of the knees; the most preferred location for small quantities is the inner side of the knees. The entire procedure takes place under local anesthesia (supplemented with conscious sedation if needed) and can be performed either as an outpatient or in inpatient care.

Sampling and infiltration

The first step is anesthesia of the entry point with a 3-mL syringe and a 30-gauge needle. An incision is then made with a 14-gauge needle, before inserting the infiltration cannula of the same diameter (14-gauge, 2-mm). For infiltration, the authors use a modified Klein solution containing 800 mg lidocaine and adrenaline 1/1,000,000 with a wet technique. Aspiration is performed using a 10-mL syringe with less than 1-mL vacuum.

Purification

Two techniques can be used for purification of the product:

- The standard for fat graft processing has long been centrifugation. For microfat, the authors recommend centrifugation for 1 or 2 minutes at 1200 *g*. The lower phase containing the infiltration liquid is removed. In the authors' experience, there is minimal oil from disrupted fat.
- Filtration using the PureGraft™ (Cytori Therapeutics, Inc, San Diego, CA, USA) closed membrane filtration system can be used as an alternative. Tumescent fluid, blood cells, debris, and oil are removed by this system leaving filtered living purified fat.

With both techniques, the pure fatty tissue is transferred via a Luer Lock connector from the 10-mL syringe into multiple 1-mL syringes for implantation. In order to prevent air bubbles, the connector is first placed on the 10-mL syringe and primed with tissue before connecting to the 1-mL syringe.

Placement/implantation

The entry points are anesthetized. The skin barrier is crossed with a 21-gauge needle or 0.8-mm cannula in the same direction in which the minicannula (21-gauge, 0.8-mm) needs to be introduced. Tissue may be injected in all areas, but especially in the superficial plane, as close to the skin level as can be achieved without risk of irregularities. The tissue can be implanted in several planes in

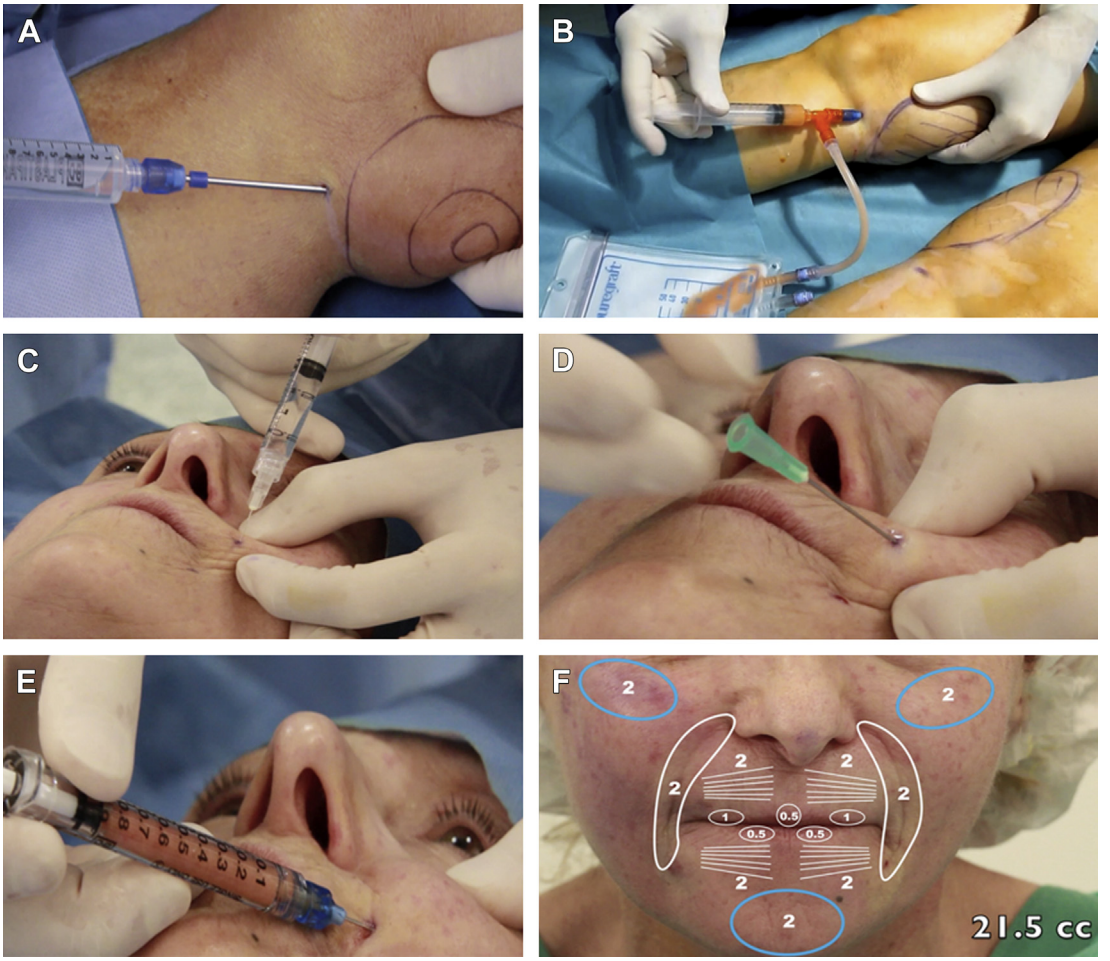

Fig. 3. Surgical technique using microfat in the treatment of the face. (*A*) Local infiltration in the inner part of the knee. (*B*) Microharvesting with a closed system. (*C*) Local anesthesia of the face. (*D*) Entry point with a 21-gauge needle (0.8-mm). (*E*). Fat injection with a 1-mL syringe and 21-gauge (0.8-mm) cannula. (*F*) Fat placement and quantities.

different directions knowing that micrografts are on the order of 500-μm and contain only a few hundred cells.

Postoperative period

The postoperative course is extremely simple. There are no painful symptoms, the swelling is extremely small, and there is normally little bruising. The result is stable after the second postoperative month. An improvement in the quality of skin, esthetic appearance, face pain, and mouth opening can be observed at 6 months.

Case 1 A 57-year-old woman with SSc consulted for functional and cosmetic improvement of her face. SSc was diagnosed in 2006 and was characterized by skin sclerosis above her forearm (diffuse cutaneous form of the disease), Raynaud's phenomenon complicated by ischemic DUs, polyarthritis, upper digestive tract symptoms with typical pattern of esophagus involvement at manometry, and sicca syndrome. Alteration of alveolar diffusion on pulmonary function test was observed, without a restrictive pattern. She did not have pulmonary arterial hypertension or renal crisis. She was taking low-dose steroids, methotrexate, folic acid, nifedipine, bosentan, and esomeprazole and applying emollient creams on her face twice a day. Her medical history did not include any other disease, alcohol, or smoking. Biological investigations showed positive results for anticentromere antibodies, with normal results of blood tests as well as renal and liver function tests and no deficiency of iron or vitamins B_{12} and B_9. Her physical examination revealed marked skin thickening on the face with a Rodnan skin

score applied to face at 2/3. At entry, the MHISS score was at 36/48, the Xerostomia Inventory Index was at 52/55, sugar test was at 4 minutes, 42 seconds, and mouth opening was at 25-mm. According to the surgical procedure described above, lipoaspiration of 50-mL of fat from the inner part of the knees was performed and the PureGraft™ filtration device was used. In the same operating time, 19.8-mL of microfat was reinjected around the lips. No specific medication was given after the treatment except for mild analgesics. Tolerance was good, and when asked 6 months later, the patient was very satisfied with all the following parameters showing improvement in comparison to baseline: MHISS score was at 23/48, Xerostomia Inventory Index was at 44/55, sugar test was at 2 minutes, 54 seconds, and mouth opening was at 35-mm. **Fig. 4** demonstrates a representative example.

TREATMENT OF THE HAND

The treatment for hands is performed using a cell therapy protocol, which uses ADSVF (Video 3). Because of skin fibrosis, microfat injection is unthinkable in the hands owing to the risk of ischemia related to the volume effect.[34] ADSVF is prepared using the Celution® System (Cytori Therapeutics, Inc).

Surgical Technique

In the operating room, adipose tissue collection and ADSVF injection are conducted under conscious sedation; harvesting areas are anesthetized (**Fig. 5**).

Sampling and infiltration

The entry points are anesthetized with a 3-mL syringe and a 30-gauge needle. For infiltration, the authors use a modified Klein solution containing 800 mg lidocaine and adrenaline 1/1,000,000 with the wet technique. After making the guidance hole with a 14-gauge needle, infiltration is performed with a 2-mm cannula in the knees, abdomen, and hips and, if necessary, in the back. For collection, the authors use a Khouri cannula with 12 holes 2.5-mm long × 1.5-mm wide or a standard Coleman harvesting cannula. Harvesting is performed with a 10-mL syringe in a closed circuit with 2 terminal 4 × 2-mm openings with a 2-way nonreturn adipose tissue valve, sterile tubing, and a 250-mL collection bag. Tissue is collected using low vacuum. When the bag is filled, it is placed in a sterile double pack and transported to the cell therapy laboratory.

Purification

Once harvesting is complete, the bag is immediately transported to the registered cell therapy unit. ADSVF is obtained within 2 h after lipoaspiration using the automated processing Celution800/CRS system (Cytori Therapeutics, Inc). Fat tissue is processed in the Celution® System according to the manufacturer's instructions. Briefly, tissue is transferred into the canister, washed, and rinsed with Ringer lactate at 37°C after which the processing enzyme is prepared and injected. Upon completion of digestion, the system automatically washes and concentrates the ADSVF cells. After the centrifugation step, 2.5-mL of ADSVF is collected from each side to make up a total of 5-mL. This sample is then diluted into 11-mL of Ringer lactate and then transferred in 10 doses (1-mL), one for each finger. The remaining volume is used for sterility testing and biological characterization. Total viable nucleated cell recovery and viability percentage are determined using the NucleoCounter® NC-100™ (ChemoMetec, Denmark). Cellular components are identified by flow cytometry using a Beckman Navios instrument (Beckman Coulter, Miami, FL, USA) with a

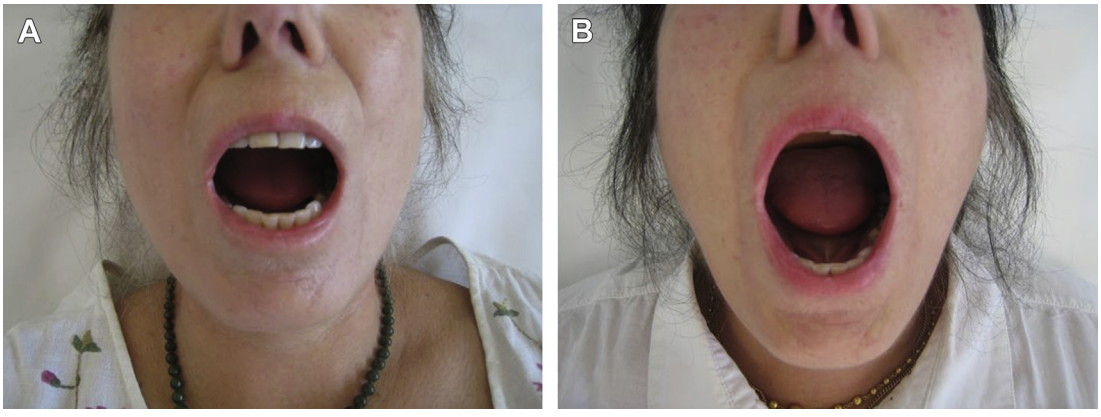

Fig. 4. Mouth opening before (*A*) and 6 months after (*B*) microfat injection.

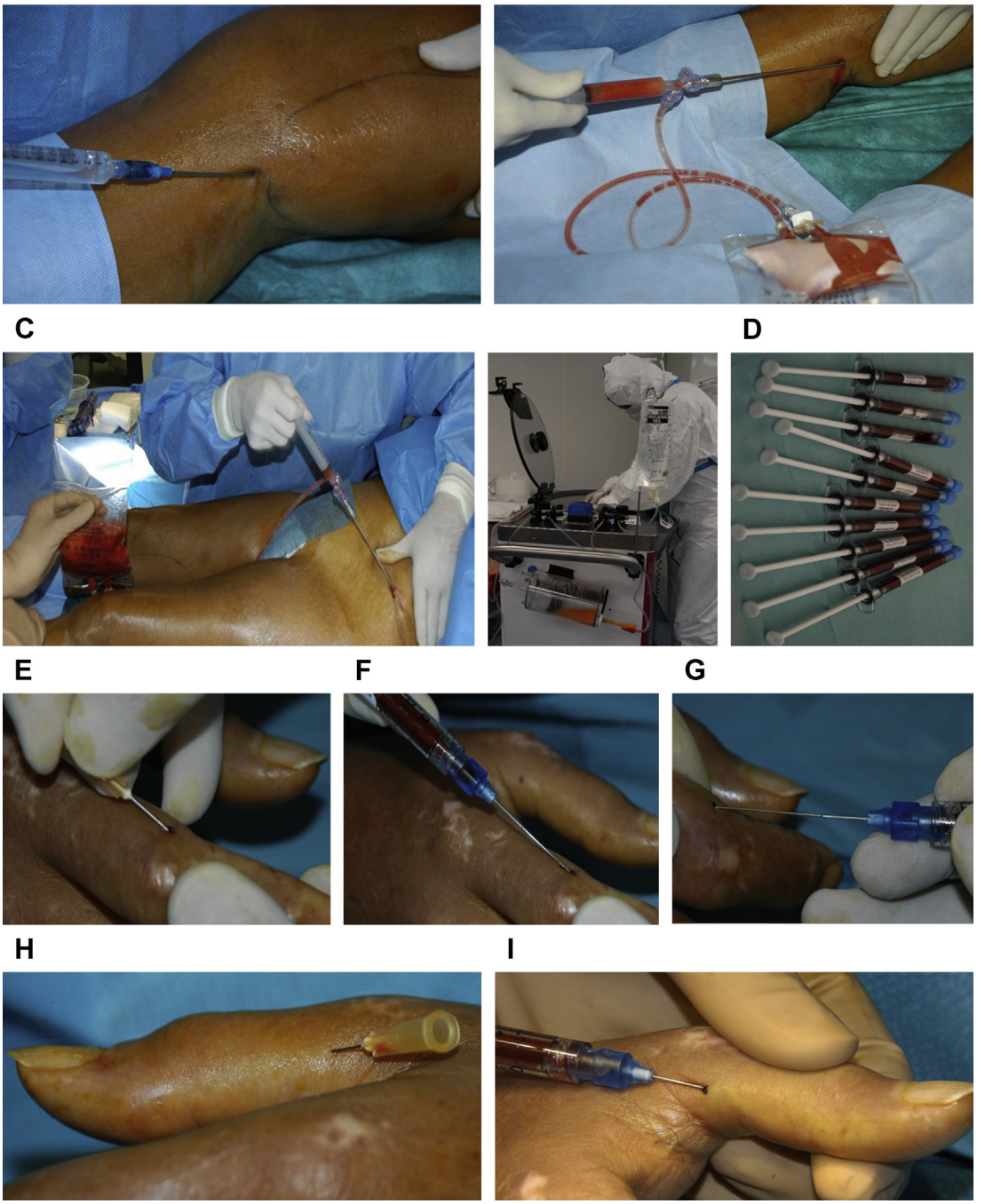

Fig. 5. Surgical technique using ADSVF in the treatment of the hands. (*A*) Local infiltration in the inner part of the knee. (*B*) Microharvesting with a closed system in the knee. (*C*) Microharvesting with a closed system in the hip. (*D*) ADSVF extraction with the Celution® System and obtaining 10 doses (1 for each finger) of diluted ADSVF. (*E*) Injection orifice for long fingers is located at the union of palmar and dorsal surfaces at the level of the proximal interphalangeal joints. Entry is performed using a 25-gauge needle (0.5-mm). (*F*) Injection of 0.25-mL of ADSVF using a 25-gauge (0.5-mm) reinforced cannula placed into the subcutaneous tissue in contact with the neurovascular pedicles using a retrotracing technique from distal to proximal. (*G*) Injection of 0.25-mL of ADSVF using a 25-gauge (0.5-mm) reinforced cannula placed into the subcutaneous tissue in contact with the neurovascular pedicles using a retrotracing technique from proximal to distal. (*H*) Injection orifice for the thumb is located at the level of metacarpophalangeal joint. Entry is performed using a 25-gauge needle (0.5-mm). (*I*) Injection of 0.5-mL of ADSVF into each lateral side of the thumb using a 25-gauge (0.5-mm) reinforced cannula placed into the subcutaneous tissue in contact with the neurovascular pedicles using a retrotracing technique from distal to proximal.

panel of cell surface makers in agreement with International Federation for Adipose Therapeutics and Science and the International Society for Cellular Therapy recommendations. The markers CD45, CD34, CD90, CD146, and CD14 are used in combination with deep red fluorescing anthraquinone (DRAQ5) and diamidinophenylindole (DAPI) to exclude debris, red blood cells, and dead cells. The frequency of adipose-derived mesenchymal-like stem cells is estimated using the colony-forming unit-fibroblast (CFU-F) clonogenic assay.

Placement

The ADSVF cells are transported in a controlled manner to the operating room. The injection points are marked on the edges of each finger, at the junction of palmar and dorsal faces. Entry is performed using a 25-gauge needle (0.5-mm). ADSVF cells are then injected using a 25-gauge (0.5-mm) reinforced cannula placed into the subcutaneous tissue in contact with the neurovascular pedicles: 0.5-mL of the solution is injected into lateral side of each digit, using a retrotracing technique, from distal to proximal. Entry points are positioned at the metacarpophalangeal joint for the thumb, and the proximal interphalangeal joint where the palmar and dorsal skin joins for long fingers. The operation is continued on all fingers of the first hand before proceeding with the same injections on the other hand. Both hands are treated over a period of approximately 20 minutes.

In order to have maximal visibility when introducing the cannula, it is essential that a magnifying glass be used. As the patient has received neuroleptanalgesia, the postsurgical recovery is simple.

Postoperative period

Patients are discharge from the hospital a few hours after surgery. No dressing is required. Resumption of normal activities is possible immediately. Abdominal lipoaspiration sample points heal rapidly, and the points of entry for ADSVF injection heal as soon as the next day. Abdominal bruises and pain induced by the lipoaspiration can be observed, but these symptoms spontaneously disappear within a few days.

Case 1 A 34-year old woman with SSc consulted for therapeutic advice. SSc was recently diagnosed based on the following criteria: rapidly progressive skin sclerosis (diffuse cutaneous form of the disease), Raynaud's phenomenon complicated by ischemic DUs, acrocyanosis and severe sclerodactyly, and upper digestive tract symptoms with typical pattern of esophagus involvement at manometry. Thoracic computed tomography revealed mild fibrosis with alteration of alveolar diffusion on pulmonary function test, without a restrictive pattern. She did not have pulmonary arterial hypertension or renal crisis. Biological investigations gave positive results for antitopoisomerase I antibodies, with normal results of blood tests as well as renal and liver function tests. She was taking lercanidipine and esomeprazole. She had been treated with intravenous iloprost without efficacy. Her medical history did not include any other disease, alcohol, or smoking. She was a dental prosthetist and stopped working because of disability of hands.

Her physical examination revealed marked skin thickening with a global Rodnan skin score of 32, acrocyanosis, sclerodactyly, and an ischemic DU on the pad of the third finger of the left hand. According to the surgical procedure described above, lipoaspiration of 165-mL of abdominal fat was performed and ADSVF was isolated with the Celution® System to be reinjected into her fingers. No specific medication was given after the treatment except for mild analgesics. Tolerance was good, and when asked 6 months later, the patient declared to be satisfied with all the following parameters showing improvement in comparison to baseline: decrease in Raynaud phenomenon's severity from 6/10 to 2/10 (Raynaud Condition Score), decrease in CHFS from 51/90 to 34/90, regression of the DU, decrease of mean circumference of the fingers, decrease in Rodnan skin score applied to hand from 18 to 15, and improvement in quality of life.

Fig. 6 demonstrates a representative example.

DISCUSSION

The authors carried out an open-label, single-arm, monocentric trial with 6-month follow-up among 12 female patients with SSc with CHFS greater than 20/90.[34] No severe adverse events occurred during the procedure and follow-up. Four minor adverse events reported by 4 patients were potentially related to the procedure: 2 abdominal bruises induced by the lipoaspiration of 7 and 15 days duration, 1 transient paresthesia on the lateral side of the left fifth finger persisting for 11 days postsurgery, and 1 pain located on the lateral side of the left thumb persisting for 13 days postsurgery. These events spontaneously resolved. Abdominal lipoaspiration sample points healed in less than 7 days postsurgery, and the points of entry for ADSVF injection healed as soon as the next day. Abdominal pain remained moderate and transient. A significant improvement in hand disability and pain, Raynaud's phenomenon, finger edema, and quality of life was observed. This study outlines the safety of the autologous ADSVF cell

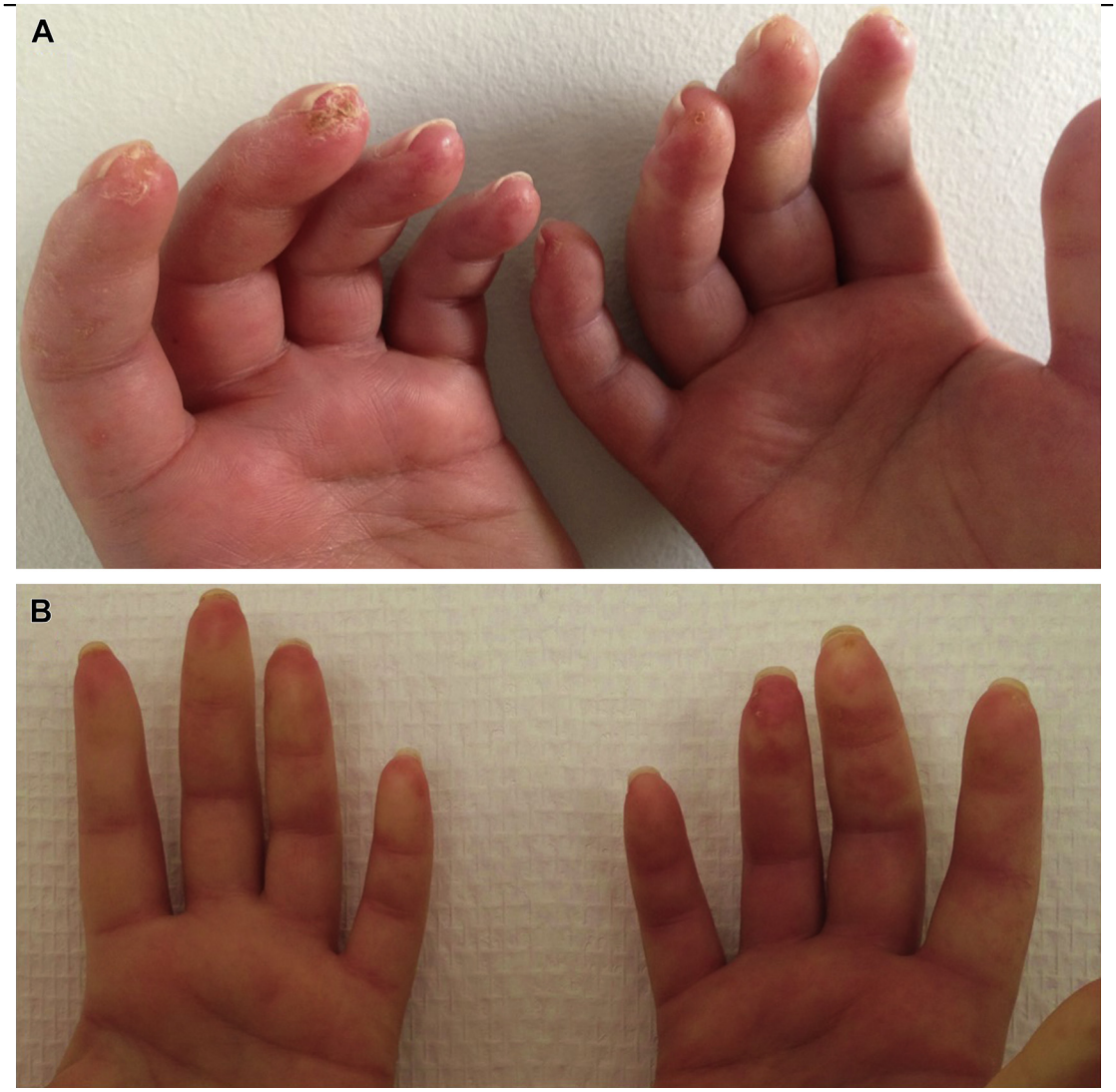

Fig. 6. Fingers before (*A*) and 6 months after (*B*) ADSVF injection.

injection in the hands of patients with SSc with encouraging results with regard to efficacy at 6 months with persistent effect at 12 months. Confirmation in a randomized placebo-controlled trial on a larger population of patients is required.

ADSVF therapy for the hands of patients with SSc is mainly indicated when hand disability is moderate to severe and persistent despite optimal medications, such as oral calcium channel blockers, endothelin 1 receptor antagonists, and phosphodiesterase 5 inhibitors, and regular physiotherapy. Patients with severe internal organ involvement, patients with finger infection, and patients with general anesthesia contraindication or taking antiplatelet agent or anticoagulant should be excluded. In the series of 12 patients with SSc, the benefit of ADSVF therapy was mainly observed on vascular manifestations, particularly of Raynaud's phenomenon severity, DUs outcome, and hand pain, the last of these being in major part related to chronic vasospasm and DUs. The decrease of finger circumference was probably related to an improvement of finger skin edema. All together, these effects could explain the positive benefit the authors observed in hand disability and pain. These observations also suggest that ADSVF may improve vasomotor tone and microvascular perfusion. Consistently, one of the main properties of ADSVF is to promote vascular repair and angiogenesis, as documented in various experimental models of tissue ischemia.[17,35] No significant correlation was observed in the authors' study between the characteristics of the injected ADSVF (number of viable cells, proportion

of the different subpopulations defined using flow cytometry, and CFU-F clonogenic test) and clinical outcomes (CHFS, hand pain, Raynaud phenomenon's severity, and quality of life). Further study in a larger cohort of patients will help delineate the phenotype of patients who best respond with this cell-based therapy.

Some limitations of this therapy are (1) a low body mass index preventing the aspiration of large quantity of fat, (2) severe and irreducible finger retractions, and (3) the need to isolate the ADSVF in an experimented cell therapy laboratory.

Concerning future perspectives, it will be interesting to evaluate the combination of fat grafting with ADSVF to have both filling and trophic effect for indications in which both these effects are wanted. By combining the lipostructure technique with the regenerative cell therapy tissue, graft longevity and positive effect could be enhanced. In SSc, applications could concern both hands and face: for hands, the association of both ischemic manifestations and mechanic ulcers related to skin tightening on bone relief, and for face, optimization of the regenerative effect of autologous fat grafting. Another perspective relies on the use of platelet-rich plasma combined with fat to ensure better survival of the grafted fat.

SUMMARY

Microfat injection in the face of patients with SSc is a safe and reliable procedure increasing facial volume and improving the quality of the skin and mouth opening. Implantation of autologous freshly isolated ADSVF population into the fingers of patients with SSc has a good safety profile with encouraging secondary efficacy end points.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cps.2015.03.009.

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