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ReviewArticle

Adipose-Derived Stromal Vascular Fraction-Fat Mixture for Hand Treatment in Patients with Systemic Sclerosis: Surgical Technique

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Abstract

Surgery For Systemic Sclerosis (SSc)-related hand manifestations has a high probability of complications, with Adipose-Derived Stromal Vascular Fraction (ADSVF) having emerged as an alternative treatment option for these manifestations. Different techniques for processing ADSVF and its application in the hand have been described. We aimed to describe the process, surgical technique, and clinical changes concerning our treatment of these manifestations using an ADSVF injection. Fat grafts (100 cc) were obtained through abdominal liposuction from ten patients with SSc-related hand deformities, of which 60 cc was processed through enzymatic digestion in a laboratory to obtain ADSVF. This was then mixed with the remaining 40 cc of fat to form an ADSVF-fat mixture, of which 1.5 mL was injected into each neurovascular digital pedicle of the patients' right hands. We evaluated total nucleated cells, viability, and the characterization of ADSVF. Acute clinical changes were noted for a follow-up period of 168 days. No adverse events such as delayed healing, intractable pain, infection, or compartment syndrome were reported in either the fat donor site or the hand. The median cellular population in ADSVF was 167 x 10^6 (min-max, 39.8-543.0), the cell viability median was 82% (min-max, 59.3-95.1), and its cellular characterization was consistent with International Society for Cellular Therapy requirements, with 4% of stromal cells. There was a significant improvement in pain, quality of life scores (using the 36-Item Short Form Survey [SF-36]), and the frequency, intensity, and duration of Reynaud's phenomenon at 168 days. Moreover, the digital ulcers had healed within 28 days. Our study findings showed that the application of an ADSVF-fat mixture in the hands of patients with SSc was safe. Moreover, this treatment significantly improved pain, digital ulcer healing rates, Raynaud's phenomenon, and patient quality of life when combined with conventional medical therapies.

Keywords: Adipose derived stromal vascular fraction; Adipose mesenchymal stem cell; Hand therapy; Regenerative medicine in the hand; Systemic sclerosis

Introduction

Plastic surgeons are frequently consulted regarding Systemic Sclerosis (SSc)-related hand complications such as pain, deforming joint contractures due to cutaneous fibrosis and tendon retraction, digital mobility loss and, occasionally, infected digital ulcers [1,2]. However, the role of surgery is limited due to fibrosis of the hand's anatomical structures and digital ischemia, which delays wound healing. Therefore, surgery is restricted to treatment

for pain, severe contractures with loss of function, digital ulcers, and calcinosis [3]. Surgical complication rates such as slow wound healing (20-67%), marginal wound necrosis (50%), finger amputation (8-20%), infection (10-15%), and recurrent ulcers (27-33%) have been reported [3].

Adipose-Derived Stromal Vascular Fraction (ADSVF) is a heterogeneous cellular mixture obtained using mechanical treatment or enzymatic digestion of adipose tissue [4]. It contains pre-adipocytes, pericytes, and hematopoietic, stromal, stem, endothelial, and various immune cells, thus contributing to regulation of the stemness of Adipose-Derived Stem Cells (ASCs) [5,6]. Therefore, ADSVF has been considered an option in which to administer ASCs into the body [7]. Its main actions are proangiogenic, antiapoptotic, antifibrotic, immunoregulatory, and anti-inflammatory, along with having trophic effects. Some of these actions have been attributed to the presence of ASCs (2%-10%), the vascular role of ADSVF, and interactions between all cell phenotypes contained in ADSVF. ADSVF's specific mechanism of action remains unknown, although it appears to be regulated by the local host tissue microenvironment [4]. ADSVF has been used to treat multiple pathologies [8-16]. The application of ADSVF is considered safe, with no adverse events having been reported [4]. For these reasons, the use of ADSVF as a regenerative medicine approach has emerged as a treatment to control and/or prevent of some manifestations in the hands of patients with SSc [11,12,17-22].

In uncontrolled studies, the administration of ADSVF has consistently and significantly been shown to improve pain, Raynaud's Phenomenon (RP), and healing of digital ulcers in the hands of patients with SSc, without adverse events. It has also been found to have improved patients' quality of life [11,12,17-22]; however, different techniques in terms of obtaining fat grafts, processing to obtain ADSVF, the amount of ADSVF applied, as well as the application technique into the hand have been reported [11,12,21,22]. As such, a new therapeutic possibility for some hand complications due to SSc has emerged, and plastic surgeons, hand surgeons, and orthopedists need to be aware of this new technique.

This study aimed to describe our technique for processing and injecting ADSVF into the hands of patients with SSc and to report on the safety of our technique and any clinical changes within a 168-day follow-up period.

Materials and Methods

This open-label study was approved by the Institutional Review Committee of our institution (reference no. SCI-1505-15/15-1. Ten patients aged >18 years, who had been diagnosed with SSc and who fulfilled 1980 American College of Rheumatology and 1988 LeRoy-Medsger criteria were included in the study and then the consent informed was signed by the patient and relatives. All ten patients were undergoing regular and stable medical treatment that remained unchanged throughout the study period. Exclusion criteria comprised patients with a body mass index <18 kg/m^2, with infected digital ulcers, with comorbidities that could affect hand function, pregnant patients, and patients with a history of alcohol and/or drug abuse. The study was conducted between November 2018 and April 2019. Fat micrografts enriched with ADSVF were injected into the patients' right hands, which were the hands most affected. Patient demographic data and disease severity, according to the Medsger severity scale, were recorded. The variables evaluated were: pain, on a numerical scale from 1 to 10; transcutaneous digital oximetry; the number of RP-related events per day/week; the duration (in minutes) of every RP event; intensity, according to the color of the digits, during an RP event; healing of digital ulcers (in days); total active range of motion of the digits; Kapandji test results; vascular density of the nail bed, assessed using nailfold videocapillaroscopy; and results of the Success and Happiness Attributes Questionnaire (SHAQ) and of the Cochin Hand Function Scale (CHFS), the SF-36, and a modified Rodnan skin score. These variables were recorded at baseline and 168 days post-treatment.

Fat Harvesting and ADSVF Processing

Fat grafts (100 mL) were obtained using liposuction under local anesthesia, from which 60 mL was sent to the laboratory. The harvested tissue was decanted into a sterile flask for 10 min. Subsequently, three tissue fractions were formed. The upper fraction contained mature adipocytes and oil supernatant. The lower fraction contained blood and plasma residuals. The upper and lower fractions were removed. The middle fraction was washed twice in Phosphate-Buffered Saline (PBS) and subsequently incubated for 20 min in a type II collagenase solution in PBS at a lipoaspirate concentration of 2 mg/mL. Ethylenediaminetetraacetic acid in PBS was then added. To separate the ADSVF from floating adipocytes, the digested tissue was centrifuged at 800 × g for 10 min. The compacted cells were resuspended in 3 mL of PBS and filtered through a 100 μm mesh cell strainer. Next, 2 mL of ADSVF was returned to the operating room and was mixed with the remaining 40 mL of fat grafts, forming the ADSVF-fat mixture for the autologous transplantation procedure, and the remaining 1 mL sample was used for cell quantification, viability determination, and cell culturing to determine the adipocyte differentiation capacity.

ADSVF Injection Technique Into The Hands

Local anesthesia with lidocaine (2%) and sodium bicarbonate was injected around the median, ulnar, and radial nerves at the wrist level. Using a number 11-sized scalpel blade, incisions were made at the radial and ulnar edges of each of the Metacarpophalangeal (MCP) and Interphalangeal (IP) joints. Using a 20-gauge blunt cannula (0.9 mm), the ADSVF-fat mixture (1.5 mL) was injected into the radial and ulnar edges of each neurovascular digital pedicle.

A total volume of 3 mL of the ADSVF-fat mixture was injected into each finger. The injections were performed using the retro-tracing technique. In the thumb, 3 mL was injected into each side of the trapezio-metacarpal joint and 1 mL was injected into each radial and ulnar edge of each neurovascular digital pedicle. Additionally, 10 mL of the ADSVF-fat mixture was distributed subcutaneously throughout the palm of the hand, and 10 mL was evenly distributed throughout the back of the hand (Video Technique).

Digit color, temperature, oximetry, and any complications (e.g., compartment syndrome or infection) were recorded daily for 1 week at both the donor sites and the treated hand.

Continuous variables are expressed as medians with 95% confidence intervals. Dichotomous variables are expressed as frequencies and percentages. Categorical or dichotomous variables were analyzed using Fisher's exact test. Pre- and post-intervention differences were analyzed using a Wilcoxon range test. Differences were considered statistically significant at a *P* value of <0.05. Data were analyzed using SPSS for Windows (version 24.00; IBM Corp., Armonk, NY, USA) and GraphPad Prism software version 7 (GraphPad Software, San Diego, CA, USA) software.

Results

Demographic and disease severity data are presented in Table 1. One patient in the control group withdrew from the study for personal reasons. The total time of the procedure including harvesting of abdominal fat, processing the ADSVF in the laboratory and its injection into the hand was 120 minutes. At the end of the ADSVF application, the digits had no capillary filling, but the circulation was reestablished after 2 h (Figure 1). In both the fat donor site and the hand, no adverse events were reported, such as delayed healing, intractable pain, infection, or compartment syndrome. The postoperative pain score in the hand increased from 4.6 to 7.5 in the first week and gradually decreased to reach basal values at day 7, and subsequently began to decrease further (Graphic 1). All patients reported mild abdominal pain and some patients reported ecchymoses, which improved after 4 to 5 days. The total number of viable nucleated cells was 167.5 x106 (39.8-543), with a cell-viability percentage of 82.0% (59.3-95.1). The percentages of cell markers as follows: CD34+ cells, 4.72% (0.50-18.2); CD45+ cells, 43.9% (1.39-67.5); CD44+ cells, 36.3% (13.8-39.6); CD73+ cells, 6.18% (3.91-12.3); CD90+ cells, 34.4% (6.43-52.3); CD105+ cells, 7.27% (1.19-54.9); and HLA-DR+ cells, 12.1% (6.26-33.5). The percentage of stromal cells was 4.05% (2.51-6.83). All these data are presented as median (min-max). The adherence capacity to plastic, as well as the differentiation towards adipocytes, was found with greater amount of fat content in cell cultures induced towards adipocytes than in the controls (p = 0.0001). The acquisition and processing of ADSVF was constant and reproducible.

General Data	0 days
Patient n (%)	**10**
Female	10 (100 %)
Age, mean (95%IC)	55.0(43.4,58.7)
Diffuse Sclerosis	8 (80 %)
Antibodies	
ANA positives	8 (80 %)
Anti-Topoisomerase I	3 (30 %)
Anti-centromere	3 (30 %)
Anti-U1-RNP	2 (20 %)
Organ Involvement	
mRSS, mean (95%IC)	15.0(6.84,17.7)
Vascular	10 (100 %)
Severe vascular	6 (60 %)
Articular	10 (100 %)
Severe articular	6 (60 %)
FTP, mean (95%IC)	3.15(2.30,3.71)
Muscular	1 (10 %)
Severe muscular	0 (-)
Gastrointestinal	4 (40 %)
Severe gastrointestinal	1 (10 %)
Pulmonary	6 (60 %)
Severe pulmonary	1 (10 %)
HAP	2 (20 %)
Severe HAP	0 (-)
Cardiac,	1 (10 %)
Severe cardiac	0 (-)
Renal	0 (-)
Severe renal	0 (-)

Table 1: Demographic, Surgical and Severity Data.

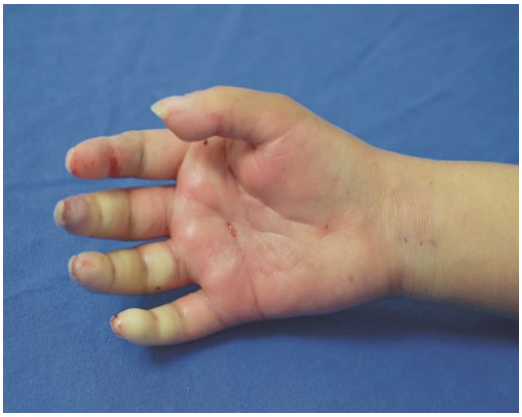


Figure 1: Patient 4. Immediate clinical status after treatment. The third, fourth, and fifth fingers have no capillary perfusion at 2 hours. The perfusion was reestablished after this time.

Concept	Day 0	Day 168	P
Pain	5.00(3.08,6.12)	0.00(0.00,2.95)*	**0.006**
Quality of Life (SF-36)	37.5(32.1-57.8)	45.0(38.7-62.2)	**0.04**
Raynaud Phenomenon Frequency n/week	4.50(2.87,6.33)	0.50(0.10,1.10)	**0.005**
Raynaud Phenomenon Intensity	2.00(1.50,2.10)	0.50(0.10,1.10)	**0.006**
Raynaud Phenomenon duration in minutes	12.5(6.55,35.6)	0.00(0.00,6.82)	**0.005**

Table 2: Results with statistical significance.

Transcutaneous digital oximetry, the Kapandji score, vascular density of the nail bed, the CHFS, the SHAQ, and the modified Rodnan skin score results did not differ significantly at the end of the study. Results in regard to pain, frequency, intensity, and duration of RP, and quality of life (SF-36) improved significantly at 168 days (Table 2). The basal median (25^{th} and 75^{th} percentile) of the active range of motion of the metacarpophalangeal joints was 40º (20º and 55º, respectively), compared with the median (25^{th} and 75^{th} percentile) at 168 postoperative days, which was 55° (23.7º and 71.2º, respectively), p = 0.0001. All the digital ulcers had healed within 28 days. Ulcer recurrence during the follow-up period was observed in one patient. Clinically, the treated hands of the patients had more volume, warmer temperature, and faster capillary filling than the contralateral hands of the same patients (Figures 2, Video Results).

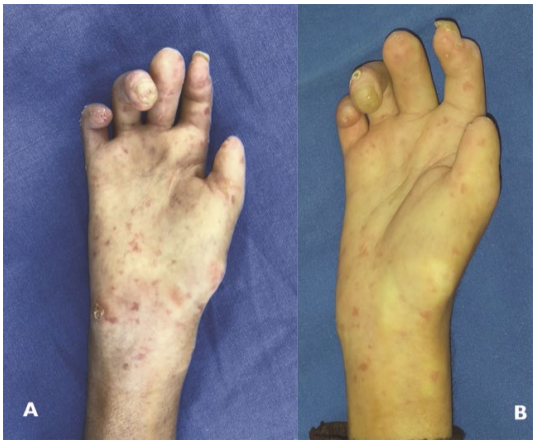
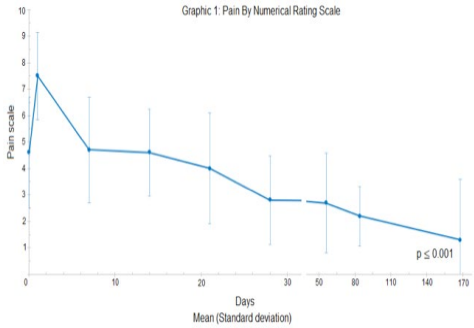


Figure 2: Patient 3. Female 48 y/o, with Cochin 40. A. Clinical appearance pre-treatment. B Clinical appearance pos treatment.



Graphic 1. Pain evolution during the treatment

Discussion

Hand surgery for patients with SSc can be stressful for both patients and surgeons because of the high probability of complications and the minimal benefit obtained. Therefore, surgery is advised in only a few cases and should be performed by an experienced surgeon [23]. Regenerative medicine can be a preferred option for hand surgeons, especially for patients with impaired wound healing, as it is less invasive. In 2002, Zuk et al. first described the regenerative properties of ASCs in a mixed cell fraction obtained through enzymatic digestion of adipose tissue, termed ADSVF [24]. Since then, ADSVF application has been used more frequently because of the ease in obtaining fat, the large amount of MCS present in ADSVF, its simple processing, and its almost immediate administration. The abdomen has been the most frequently chosen site for obtaining fat grafts rather than the hips or thighs, as the amount of MSC is higher in the abdomen (5.1 ± 1.1%, mean ± SEM) than at those other sites (1.2 ± 0.7%), while the number of viable nucleated cells is the same at all anatomical sites [25]. Therefore, the abdomen was selected as the donor site for patients with SSc in our study. Excised adipose tissue in a block yields twice the number of ASCs than lipoaspirate adipose tissue [26]. However, liposuction has been selected to harvest adipose tissue in all studies involving treatment of hands of patients with SSc, due to problems with wound healing. Only minor adverse events have been reported such as pain and bruising [11].

Harvesting of viable cells differs between different commercial systems by up to 100-fold per gram of fat grafts [27]. The total amount of viable cells obtained in Granel et al.'s study using the collagenase-based commercial Celution800/CRS system (Cytori Therapeutics, San Diego, Cal., USA) was 50.5 ± 23.8 x 10^6 in 181.33 cc of liposuctioned fat, whereas, in Park's study, using the collagenase-based commercial system SmartX kit (DongKoo Bio & Pharma Co., Ltd., Seoul, Korea), the total amount of viable cells obtained was 42.1 ± 5.06 x 10^6 in 91.3 cc of liposuctioned fat [11,28]. In our study, ADSVF was obtained through enzymatic digestion in a cell therapy laboratory, and the total amount of viable cells obtained was 167.5 (39.8-543) x 10^6 in 60 cc of liposuctioned fat. This amount was greater than that reported in previous studies but the results were similar. Determining which is the best method to obtain ADSVF remains controversial. The amount of cells administered did not appear to influence the clinical results in our study, given our results were similar to those previously reported; thus, it appears that the clinical response may be qualitative. Bank et al. injected only decanted fat [29]. Del Papa et al. processed harvested fat at 920 × g for 3 min. The upper and lower phases were then discharged. Only the intermediate layer was injected into the digits [12,21]. In these two studies, ADSVF was not processed, yet the results of both studies were similar to those using ADSVF.

The application sites, along with the reported amount of ADSVF injected, have also differed between studies. Del Papa et al. administered centrifuged fat (from 0.5 to 1 mL) at the base of each finger with a digital ulcer [12,21]. Granel et al. administered 0.5 mL of ADSVF to each neurovascular pedicle, with a total of 1 mL in each finger [11]. Park injected 0.3 mL of ADSVF to each digital vascular pedicle for a total of 0.6 mL per finger [28,30]. In our study, we applied a 1.5 cc ADSVF-fat mixture in each digital vascular pedicle, for a total of 3 cc per finger, even in patients with significant digital fibrosis and with a CHFS as high as 63. Digital pallor appeared in almost all our study patients. This suspended flow lasted up to 2 h and flow then returned with no further intervention, without severe pain or acute or long-term complications. This ADSVF-fat mixture produces the widely known volumetric effect of lipo-injection as well as the benefits of tissue regeneration conferred using ADSVF. The treated hands presented with a clinically greater volume than the contralateral hands. This greater volume could help prevent the recurrence of ulcers on bony prominences. We consider that the warmer skin temperature, faster capillary filling, and less pain in the treated hands compared with the contralateral hands resulted from the well-known angiogenic effect of ADSVF. Due to its great biological properties of ADSVF, the ADSVF fat-mixture can be used to treat ischemia and fibrosis also in the toes, as well as in the lips and nose of patients suffering from systemic sclerosis.

Conclusion

Our study findings indicated that the application of ADSVF-fat mixture to the hands of patients with SSc was safe, without involving the commonly reported surgical complications, and was easy to perform with local anesthesia, and reproducible. This technique is semi-invasive and significantly improves pain, MCP joints movement, RP, SF-36 and digital ulcer healing when combined with conventional medical therapies. Given these advantages, the regenerative medicine benefit conferred using ADSVF can be considered an important aid to plastic and hand surgeons before or during the treatment of hand complications in patients with SSs. Studies with larger numbers of patients are necessary to demonstrate more comprehensively that this method can improve pain, digital ulcer healing, RP, digital perfusion, and hand function.

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