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Commentary

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Novel indications for autologous fat grafting in reconstruction: scleroderma

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Abstract

Scleroderma is a chronic connective tissue disease characterized by inflammation, vascular injury, and progressive skin fibrosis, resulting in significant aesthetic and functional impairments for patients. Current therapies are limited and insufficiently treat the cutaneous manifestations of scleroderma. Autologous fat transfer (AFT) is a surgical technique that has been utilized for many decades for facial rejuvenation. The adipose stem cells (ASCs) present in fat grafts have also shown significant promise for their anti-inflammatory and regenerative properties. Recently, AFT has been repurposed to treat the skin manifestations of systemic sclerosis and localized scleroderma. Studies suggest that AFT in scleroderma patients improves mouth and hand functions, Raynaud's symptoms, and digital ulcerations. AFT is a safe procedure with rare postoperative complications, making it a promising intervention for the treatment of scleroderma. Further studies are required to better characterize the influence of fat grafts on the recipient site and to establish standards for fat transfer in fibrotic skin diseases.

Keywords: Scleroderma, systemic sclerosis, localized scleroderma, AFT

INTRODUCTION

Scleroderma is a rare heterogeneous autoimmune connective tissue disorder characterized by widespread inflammation, vascular damage, and fibrosis[1]. Scleroderma has a variety of clinical manifestations in the face, hand, and body that vary based on subtype. The two main clinical subtypes include localized

scleroderma, limited to the skin and underlying tissue, and systemic scleroderma, which includes internal organ involvement[2,3]. All patients experience some degree of cutaneous involvement of the face and hands regardless of scleroderma subtype, which results in significant aesthetic and functional concerns for patients[1,4]. Current oral and topical therapies have been shown to have some efficacy in slowing the progression of the cutaneous manifestations of scleroderma; however, these therapies have limited efficacy and do not reverse skin fibrosis[5-7].

AFT has been used safely for decades in facial rejuvenation and, more recently, has become a highly efficacious surgical procedure performed to optimize breast reconstructions, scar treatments, hand rejuvenation, and correction of deformities related to congenital anomalies[8-15]. Adipose tissue is composed of mature adipocytes and a heterogenous stromal vascular fraction (SVF), which includes ASCs, preadipocytes, endothelial cells, immune cells, and hematopoietic stem cells[16]. ASCs have recently been shown to have immunomodulatory, angiogenic, and regenerative potential. Given its rich source of growth factors, it is believed that AFT can mitigate inflammation, promote angiogenesis, and reverse skin fibrosis in scleroderma patients, in addition to providing structural volume restoration[9,17].

PATHOPHYSIOLOGY AND CURRENT TREATMENT OF SCLERODERMA

Scleroderma is the result of microvascular dysfunction and immune cell activation that leads to progressive tissue fibrosis. In early stages, immune inflammation is characterized by immune cell infiltration leading to increased levels of proinflammatory cytokines and growth factors (TGF-β, IL-10, PDGF)[18-20]. The degree of mononuclear cell infiltration correlates with the severity and progression of skin thickening[20]. The widespread inflammation eventually results in vascular damage to small arteries and arterioles with intima swelling and proliferation, which all lead to blood vessel narrowing[18,21-23]. This vascular injury leads to chronic hypoxia and ischemic changes that result in the differentiation of fibroblasts into myofibroblasts[24,25]. Myofibroblasts play a critical role in the pathologic changes associated with scleroderma and are thought to be in a persistently activated state, depositing extracellular matrix proteins that lead to skin fibrosis[26-29]. Fibrosis generally affects the lower dermis first, prior to spreading to deeper structures and leading to skin thickening and hair follicle injury[19].

Current treatments for scleroderma are systemic. Immunomodulatory agents target the overactive immune system, antiplatelet and vasodilatory agents improve circulation, and antifibrinolytic agents decrease fibrosis by targeting collagen synthesis[30]. These agents have been used alone or in combination, depending on the severity of symptoms. However, medical management of scleroderma remains challenging given the significant side effects of the medications and their limited efficacy in preventing and treating the skin changes seen in scleroderma[30]. Side effects of current medical therapies include systemic toxicity, chronic immune suppression, and bleeding[19]. Moreover, the extensive skin fibrosis seen in scleroderma limits the perfusion of systemic medications to the dermis and restricts their efficacy[19]. Current systemic treatments have also shown to be ineffective at reversing skin fibrosis or improving contour irregularities in scleroderma, prompting the need to identify alternative therapies.

THE SCIENCE OF FAT GRAFTING

AFT has the potential to attenuate and reverse the pathophysiologic processes that underly scleroderma. ASCs have strong immunomodulatory effects that mitigate the widespread inflammation essential to the progression of scleroderma[31-36]. ASCs also exhibit pro-angiogenic effects by secreting growth factors that synergistically interact with endothelial cells to stimulate rapid neoangiogenesis[9,19,37,38]. This enhanced blood vessel formation has the potential to revascularize fibrotic skin in scleroderma patients and promote tissue regeneration[19,39]. With respect to skin fibrosis, ASCs are a host for matrix metalloproteinases and various

other proteases, which play a role in not only inhibiting skin fibrosis but also remodeling the extracellular matrix[19,40]. Finally, AFT can effectively improve the contour irregularities that result from the cutaneous involvement of different subtypes of scleroderma by providing structural support and volume restoration[19,41].

FAT GRAFTING TECHNIQUE

Fat is harvested from the abdomen and/or thighs using a 3.0-mm liposuction cannula under hand-held suction. The lipoaspirate is carefully transferred to 10 cc syringes and processed by centrifugation at 3000 rpm (1228 x g) for 3 min, according to the Coleman method[42]. Centrifugation produces concentrated lipoaspirates and allows for efficient decantation of oil and debris. The fat is then transferred to 3 cc syringes for injection. For fat transfer to the face, small incisions are made along the lateral commissures using an 11-blade. Multiple tunnels are created and small volumes of fat (0.1-0.2 mL) are injected with each pass only at the withdrawal of the cannula. Over 30 patients with a diagnosis of scleroderma have been treated at the University of Michigan between March 2015 and March 2023[7]. Patients received 1-4 rounds of fat grafting based on the severity of their disease at presentation and were evaluated at 1, 3, 6, and 12 weeks postoperatively[7].

FAT GRAFTING FOR THE TREATMENT OF SCLERODERMA

Systemic scleroderma

Face

Orofacial manifestations of scleroderma are disabling and contribute to significant functional and aesthetic concerns for patients[43]. Facial involvement presents as hardened or atrophic skin, loss of mimic folds, deep wrinkles in the upper and lower face, and hair loss[19,44,45]. Microstomia is a common oral manifestation of systemic scleroderma due to perioral tissue sclerosis[46,47]. AFT to the face improves oral opening, reduces facial skin sclerosis, and improves oral incompetence[48,49]. The procedure is safe and has minimal complications postoperatively[48,49]. Figure 1 demonstrates a 52-year-old patient with improved lip contour and volume after facial fat grafting.

Fat transfer to the face in scleroderma patients should ideally be performed at a subdermal level to correct contour abnormalities and improve skin fibrosis. Both macrofat and microfat have been shown to improve the contour irregularities observed in patients with scleroderma. However, microfat, which is lipoaspirate isolated with a smaller cannula port size or macrofat further processed with filters, yields smaller fat grafts compared to traditional liposuction and provides many advantages over macrofat[50]. The utilization of microfat has the advantage of improving superficial contour abnormalities as the parcel size of microfat is small. This micronized fat allows for the injection of fat grafts in a more superficial plane to reduce skin fibrosis without the contour irregularities associated with fat necrosis or oil cysts from the injection of macrofat[51,52]. Various techniques have been described in the literature to generate microfat[51,53]. In our practice, the Coleman technique is utilized to process and harvest macrofat, which is subsequently passed through two Luer-Lok syringes connected to a three-way stopcock for a total of 10 times to generate microfat. The microfat is subsequently injected using a 25-gauge cannula to the desired region of the face and hands. Subcutaneous perioral microfat injection in systemic sclerosis patients has been shown to improve facial animation, skin sclerosis, and oral opening[52]. Other studies have shown that microfat provides symptomatic improvement of xerostomia, as assessed by the xerostomia inventory index[54]. While the results of microfat alone have been shown to be promising, additional studies have investigated the addition of platelet-rich plasma (PRP) to fat grafts[43]. Systemic sclerosis patients treated with AFT and PRP demonstrated significant improvements in oral opening and lip thickness with aesthetically pleasing outcomes. It has also been reported that the addition of PRP to fat graft improves skin elasticity and

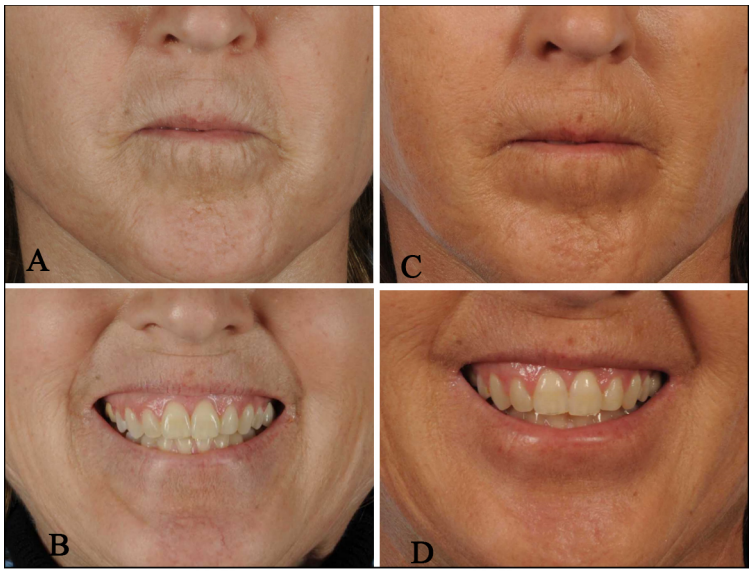

Figure 1. Improvement in perioral skin fibrosis following fat grafting. (A) (B) Preoperative photographs of a 52-year-old woman with facial manifestations of scleroderma, including perioral skin tightening and deficient lip contour. (C) (D) Postoperative photographs at 2 months follow up after 1 round of autologous fat grafting to the upper lip (4.5 cc) and lower lip (5 cc). Patient demonstrated improvements in lip contour and volume and decreased perioral rhytids.

vascularization of the perioral and malar areas of systemic sclerosis patients[55]. The results are likely from enhanced graft survival and proliferation of preadipocytes in the presence of PRP[43]. However, controversy remains regarding the efficacy of PRP supplementation to fat grafts as a number of studies reported contradictory results, where PRP did not consistently improve graft volume maintenance or skin elasticity in facial rejuvenation[56]. Thus, while AFT, with either macrofat or microfat, has been shown to have promising results on contour abnormalities and skin fibrosis, the addition of PRP to the fat grafting process has not been shown to conclusively improve outcomes.

Hand

Scleroderma patients with hand involvement present with skin fibrosis, Raynaud's phenomenon, and digital ulcers. Commonly, scleroderma progresses in a stepwise fashion, initially with tissue fibrosis and Raynaud's phenomenon, followed by the development of end-stage ulcers[45]. Digital ulcerations are the result of prolonged and repeated ischemic events from worsening disease and lead to significant pain, deformity, recurrent infections, and reduced range of motion[57,58]. Current management of digital ulcers includes the avoidance of triggers, such as cold temperatures or stress, and pharmacologic therapy with vasodilatory and vasoprotective medications[59]. These interventions have limited efficacy and result in high ulcer recurrence rates[60]. AFT has been shown to improve digital ulcer healing, pain, hand strength, and functional capacity in these patients[58,61-63]. AFT for the treatment of Raynaud's phenomenon leads to significant improvements in pain management and frequency and severity of episodes[64]. Furthermore, the injection of SVF has been shown to improve the severity of Reynaud's phenomenon, skin thickness, and quality of life in scleroderma patients[54]. While the isolation of SVF is not approved for clinical use in the United States, these results are likely comparable to the isolation and injection of nanofat[65]. The use of AFT for the treatment of scleroderma of the hand is safe and is not associated with significant adverse events during the procedure or postoperatively[54,64].

Body

The cutaneous manifestations of systemic sclerosis can involve the extremities and trunk. Transplantation of ASCs in the upper and lower extremities can correct contour irregularities, improve dyschromia and sensitivity, and stop disease progression[66].

LOCALIZED SCLERODERMA

Linear scleroderma manifests as an indurated linear deformity involving the face or extremities. Linear scleroderma is a subtype of localized scleroderma, which presents as a depressed linear lesion due to hardening of the skin, progressive loss of subcutaneous fat, and possible involvement of the muscle and underlying bone[67]. It typically affects children and young adults and occurs on the scalp, face, or extremities. Scleroderma "En Coup de Sabre" is a subtype of linear scleroderma limited to the hemiface, affecting the frontoparietal scalp and forehead[67]. Other subtypes of limited scleroderma affect differing depths of tissue in various areas of the body and include plaque morphea, generalized morphea, and deep morphea[2]. Traditionally, linear scleroderma has been treated with scar release, negative-pressure wound therapy, and hyaluronic acid fillers[67]. Skin excision with tissue expansion and primary closure yields reasonable aesthetic results in patients with scleroderma "En Coup de Sabre". However, it requires several procedures and multiple clinic visits for tissue expansion, which can be burdensome to the patient[68]. In addition, if a noticeable scar remains on the forehead following the serial excision, this may be a suboptimal aesthetic outcome for the patient. Clinicians have also attempted to use less invasive approaches to correct the deformities related to scleroderma, including the use of hyaluronic acid fillers to correct contour irregularities in the scalp[69]. However, high resorption rates, the need for repeated injections, and high costs are significant disadvantages.

More recently, AFT has provided an advantage compared to current treatment options for local scleroderma as it improves structural volume and contour irregularities and has ASCs that improve the quality of the overlying skin[66]. AFT can present significant advantages over other surgical interventions, including low donor site morbidity, uncomplicated postoperative course, and the ability to achieve natural contours and durable results. Clinically, the treatment of linear scleroderma of the frontal scalp with AFT demonstrates significant improvement in the appearance of the lesion with minimal reportion rates[70,71]. In cases where forehead depressions associated with linear scleroderma are significant, serial AFT can be considered or AFT in conjunction with implant-based reconstruction (porous polyethylene) can be used to further improve contour irregularities[69]. Our preferred method of treatment is serial AFT for linear scleroderma, as this surgical procedure has proven to be effective with low donor site morbidity and low complication rates.

SPECIAL CONSIDERATIONS FOR FAT GRAFTING IN SCLERODERMA

AFT is a safe and effective surgical technique for the treatment of cutaneous scleroderma. However, several questions remain. Currently, there is no standardized protocol for fat graft harvesting, processing, or injection methods. Variations between studies limit outcome comparisons and study generalizability. Further research is required to establish AFT protocols in the scleroderma population to produce maximal aesthetic and functional outcomes. This is currently limited by unclear fat retention rates. Current research efforts involve investigating the optimal AFT techniques to identify factors that minimize graft resorption.

It has been well established that vascularity of the recipient site is an important factor for graft survival. The involvement of blood vessels and fibrosis of the tissue in scleroderma can decrease vascularity in those lesions and potentially negatively impact graft survival[72]. Therefore, repeat AFT procedures can be beneficial, where the cumulative pro-angiogenic benefit provided by fat grafts gradually improves recipient

site vascularity and subsequently improves fat graft survival with future rounds. Furthermore, the ideal number of AFT rounds in scleroderma patients remains unclear and varies among studies. The first round of AFT favorably impacts the skin, which allows for larger volume AFT in subsequent rounds, increased graft retention, and more favorable long-term outcomes[7]. Overcorrection at the initial AFT surgery can compensate for expected partial resorption and reduce the need for repeat procedures[72]. However, as the skin in scleroderma patients is not as elastic due to fibrosis, it is essential to stop fat grafting when the skin begins to blanch to prevent skin necrosis. Although repeat procedures might be indicated due to partial graft resorption, long-term satisfactory outcomes are often achieved[7,73,74].

CONCLUSION

AFT can be utilized for its regenerative and volume-enhancing properties for the treatment of scleroderma. The growing body of data supports the use of AFT to reverse fibrosis, mitigate inflammation, and promote angiogenesis, which are essential mechanisms that drive the progression of scleroderma. Our experience at the University of Michigan, utilizing the Coleman method for harvesting and processing fat, demonstrates that AFT improves various scleroderma manifestations of the hand and face, including perioral skin quality, facial animation, hand range of motion, and hand pain[7]. These findings, which are consistent with other published studies, open the door to AFT as a new potential intervention in treating the cutaneous manifestations of scleroderma with significant implications for improving the quality of life of patients. Large cohort studies are essential to further characterize the clinical outcomes observed in scleroderma patients treated with AFT and will shed light on the optimal timing for AFT, the volume needed in different locations, and the AFT practices that will maximize fat graft retention rates. In conclusion, AFT provides an advantage over current treatment options available for scleroderma patients and it merits further investigation clinically for the treatment of the hand and face manifestations of the disease.

DECLARATIONS

Authors' contributions

Wrote the manuscript, and the manuscript was reviewed and edited: Kawakibi AR, Khouri AN, Cederna PS, Strong AL

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Not applicable.

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