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Reconstructive

Autologous Fat Transfer for Scar Prevention and Remodeling: A Randomized, Blinded, Placebo-controlled Trial

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Background: Autologous fat transfer—also referred to as fat grafting—has been reported to provide beneficial effects to overlying scar and skin. Despite procedural frequency, there is a paucity of high-level evidence guiding the surgeon in technique, patient selection, and efficacy.

Methods: A multicenter, double-blinded, randomized, internally placebo-controlled trial was performed with an aim to qualitatively and quantitatively evaluate the impact of autologous fat transfer on the quality of overlying scar tissue. Fat-grafted scars were evaluated and compared with paired, saline-injected "control" scars. Subjective and objective metrics were evaluated in treated sites for 12 months after treatment.

Results: Blinded qualitative results demonstrated a statistically significant improvement in scar quality over time in fat-grafted scars. However, these improvements were not found to be statistically different from changes noted in scars treated with saline. In addition, objective metrics did not statistically differ between saline-injected and autologous fat-grafted scars.

Conclusions: Our results demonstrate that autologous fat grafting can improve the qualitative profile of a scar from both the patient and observer perspectives. However, there was no difference in improvement when compared with scars that were treated with saline in a randomized and blinded fashion. These results demonstrate that any improvements in scar quality related to fat grafting are also achieved using saline and suggest that mechanisms other than cell activity may be at play. Additional randomized, blinded, placebo-controlled trials are required to either corroborate or contest the putative beneficial effect(s) of adipose tissue on scar remodeling. *(Plast Reconstr Surg Glob Open 2020;8:e2830; doi: 10.1097/GOX.0000000000002830; Published online 27 May 2020.)*

INTRODUCTION

Scars impose significant quality-of-life burdens on patients and a financial load on the public healthcare system, with prospective market estimates for scar treatment exceeding $12 billion annually.[1] Skin and its appendages that are lost due to injury do not regenerate, and the subsequent scar that forms lacks important esthetic and functional qualities. Additionally, some scar beds are devoid of a hypodermis (also known as subcutaneous layer) composed of adipose tissue. An abundance of literature now suggests that adipose tissue contains a cellular fraction [adipose stromal cells and/or adipose-derived stem cells (ASCs)] that may facilitate wound healing, tissue repair, and extracellular matrix remodeling. These

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putative effects are thought to occur through mechanisms that impact angiogenesis, neovascularization, inflammation, and cell viability and proliferation via direct cell-mediated contact, release of soluble factors, and/or transfer of bioactive factors through exosomes and microvesicles.[2–9] In addition, ASCs have been reported to differentiate into lineages composing the epidermis and dermis[10,11] and to augment keratinocyte migration and tissue vascularization/deposition/remodeling via paracrine effects.[12–15] Therefore, the repair/replacement of a hypodermal layer beneath an existing scar bed has the potential to affect both the appearance and the histologic quality of a scar.

Autologous fat transfer (AFT) represents the most fundamental approach to exploring the potential effects of adipose on scar quality. Despite procedural frequency, there is a paucity of high-level evidence guiding the surgeon in technique, patient selection, and efficacy.[16] The majority of existing literature describing improved scar quality with AFT is either retrospective, or anecdotal, and those studies providing objective and quantitative analyses are limited in scope by their experimental design and potential for bias. This multicenter, double-blinded, randomized, placebo-controlled trial aimed to qualitatively and quantitatively evaluate the potential impact of AFT on the quality of overlying scar tissue.

MATERIALS AND METHODS

Study Design

A multicenter, double-blinded, randomized, internally placebo-controlled trial was performed. After completion of a pilot study evaluating safety and dose escalation, 17 total patients were enrolled over a 4-year period from 2012 to 2016. Complete inclusion and exclusion criteria are presented in Table 1.

Outcomes were measured at baseline and then at 6 and 12 months after treatment. Fat-grafted scars were evaluated and compared with paired, saline-injected "control" scars. To ensure same site acquisition for evaluation and treatment purposes, a scar map using ruled, E-Z Graph transparency film (Victoria, Inc., Victoria, Tex.) was created by topographically outlining the individual scar area and alphabetically designated evaluation sites within each area. Subjective and objective scar characteristics were evaluated by a single person at each clinical trial site.

Operative Technique

A single surgeon at each trial site performed Coleman-based lipo-harvests and AFTs.[17] All procedures were performed under institutional review board and Human Research Protection Office–approved protocols. Each subject had 2 scar areas treated: one randomized to saline treatment and the other randomized to fat grafting.

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Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
2 noncontiguous scars similar in anatomic location, <80 cm^2 in area
Any etiologic factor (burn, postsurgical, traumatic)
Any scar >6 mo
Age 18–65 y
Negative pregnancy test
Exclusion criteria
Sepsis
Life/limb threatening injury
Active psychiatric illness (excluding depression without suicidal ideation)
Diagnosis of cancer <5 y (excluding basal and squamous cell carcinoma)
Diagnosis of bleeding diathesis and/or INR >2.2
Differential site treatment (eg, steroid injections, pressure garment, or silicone sheeting)
Incarceration

INR, international normalized ratio.

The surgeon learned of the treatment allocations after the patient underwent general anesthesia via presealed envelopes generated through an online randomization scheme. The graft-harvest donor site was the abdomen. Fat tissue was harvested using a syringe-based technique after infiltration of tumescent solution. Fat was processed with centrifugation at 1200*g* for 3 minutes. The supra- and infranatants were decanted and wicked, respectively, and the remaining tissue was transferred into 3- or 10-ml syringes. A COL-19 cannula and/or a "V" dissector cannula (COL-V; Mentor Worldwide, LLC, Santa Barbara, Calif.) was used for fat graft injection. Manual infiltration of linear grafts was performed in retrograde fashion with each pass in a fan-like pattern. Subdermal/subscar injections were completed with either autologous fat or normal saline at a density of 1 ml/cm^2. Access sites were closed with suture. No dressings were applied. Additional tissue harvest samples were reserved for laboratory investigation.

Human Scar Biopsy Specimens

Two 3-mm punch biopsies were obtained from each treatment scar/site per patient at baseline, 6 months, and 1 year after treatment. Specimens were stained using haematoxylin and eosin stain, Verhoeff's (elastin), and Masson's trichrome (collagen). A human cluster of differentiation 31 (CD31) (platelet endothelial cell adhesion molecule [PECAM-1]) mouse monoclonal antibody (ThermoFisher Scientific, Waltham, Mass.) was used to evaluate vessel density. Histologic features (summarized in Table 2) were scored and recorded by a single, blinded pathologist.

Table 2. Histologic Scoring

Vascularity	1	2	3	4	5
	Decreased		Normal		Increased
Orientation	Horizontal		Vertical		Mixed
Inflammation	1	2	3	4	5
	Mild		Moderate		Severe
Chronicity	Acute		Chronic		Mixed
Collagen Organization	1	2	3	4	5
	Acellular		Hypocellular		Hypercellular
Remodeling	Haphazard	Nodules	Parallel	Wavy	
Epidermal Thickness	1	2	3	4	5

Quantitative Assessment: Scar Color, Firmness, Elasticity, and Histology

Skin/scar viscoelasticity was measured using a cutometer (Cutometer MPA 580; C&K Electronic GmbH, Cologne, Germany),[18–24] firmness using a durometer (Rex Durometer DD-3; Rex Gauge Company, Inc., Buffalo Grove, Ill.),[25–28] and color/pigment with a color meter (DSM-II ColorMeter; Cortex Technology, Hadsund, Denmark).

All quantitative continuous variables were normalized to measured values of each individual's "normal", unscarred skin in close proximity. Therefore, ratios approaching one are consistent with improvement in scar tissue toward normal.

Characterization of Graft Cellularity

Samples of each adipose tissue graft were characterized per previously published methods.[29] In short, the stromal vascular fraction (SVF) was isolated using a combination of dissociation and differential centrifugation.[30,31] Each SVF sample was characterized in regard to total cell count, viability, and colony-forming unit quantification.[32] Cells plated at an initial density of 10,000 per cm^2 were cultured in a humidified, temperature- and gas-controlled incubator. At 2 weeks, cultures were trypsinized, and cells were subsequently counted. Cell counts were used to determine proliferation and doubling time.

Qualitative Assessment

The patient and observer scar assessment scale (POSAS) was used to evaluate scar quality by both patients and study personnel (ie, "observers").[33,34] The observer POSAS scale consists of 5 total items scored from 1 ("like normal skin") to 10 ("worst scar imaginable") for a sum total score ranging from 5 to 50. Scored items include vascularization, thickness, relief, pliability, and pigmentation. Pigmentation is also subscored categorically as hyper/hypo/mixed pigmentation. The patient POSAS scale consists of 6 total items also scored from 1 (like normal skin) to 10 (worst scar imaginable) for sum total score ranging from 6 to 60. Scored items include pain, itching, color, stiffness, thickness, and irregularity.

Statistical Considerations

Pre-and postoperative quantitative continuous variables and POSAS scores were compared using paired, two-tailed *t* tests. The ratios of categorical variable distribution were compared using χ^2 contingency analyses. Differences were considered statistically significant at the 5% level ($P < 0.05$). All statistics were completed with SPSS Statistics (International Business Machines Inc., Armonk, N.Y.), Prism (GraphPad Software Inc., San Diego, Calif.), and R (R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org/).

A power analysis was performed with an assumption that fat grafting could improve POSAS scores by 30% from baseline, relative to saline treatment. With each subject serving as an internal control, power calculation for a superiority trial yielded a need for 19 subjects to have an 80% chance of detecting a 30% improvement in POSAS compared with control, as significant at the 5% level.

RESULTS

Demographic Data

Seventeen subjects were successfully enrolled, treated, and evaluated during the study duration. The patient population was composed of 8 women and 9 men (47% women and 53% men) with an average age of 42.1 (±12.9) years. Three subjects did not show up for their 12-month assessment. For these 3 subjects, 6-month data were carried forward for final analysis. Scar anatomical location comprised ankle, thigh, abdomen, chest, and brachial distributions. Scars ranged in age from 9 months to 20 years. Treated scars were not related to chronic wounds, vasculopathy, diabetes, or radiation. Representative scars are presented in Figure 1.

Quantitative Scar Analysis

Scar Color

Although a single measured value (a*) exhibited a significant difference at 12 months versus baseline ($P < 0.05$) in AFT-treated scars, full dermal spectrophotometer analyses comparing AFT-treated scars to saline-treated scars demonstrated no significant differences in any parameter at baseline, 6 months, or 12 months.

Scar Firmness and Elasticity

Durometer and cutometer analyses demonstrated no significant difference in firmness or elasticity between saline- and fat-grafted scars at baseline ($P = 0.45$), 6 months ($P = 0.622$), or 12 months ($P = 0.80$).

Histology

A blinded, single-observer histologic 5-point scale ranking revealed no significant differences between AFT-treated

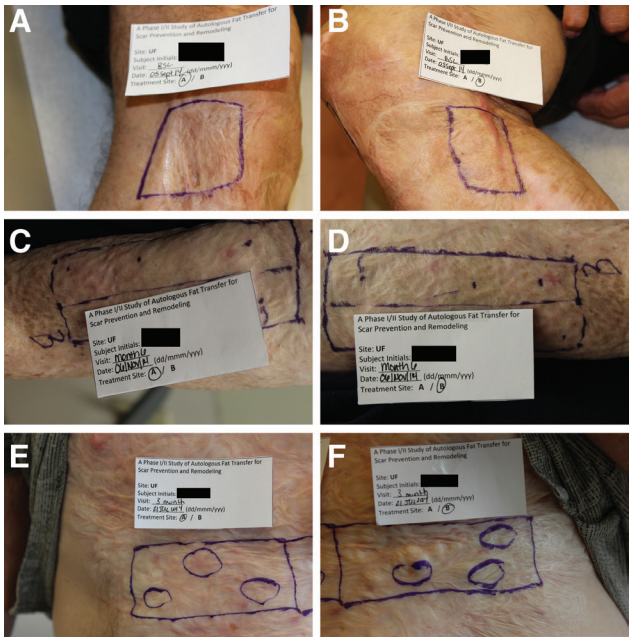


Fig. 1. Representative examples of 3 different scars/sites treated and evaluated in the study. A and B, Scars of a lower extremity before treatment. C and D, Scars of an upper extremity 6 months after treatment. E and F, Scars of the anterior trunk 3 months after treatment.

and saline-treated scar vascularity or inflammation, nor epidermal thickness at baseline, 6 months, or 12 months. Categorical evaluations, including vascular orientation, collagen organization, and remodeling, and chronicity of inflammation also revealed no statistically relevant differences.

Fat Graft Characterization

The SVF of all 17 lipoaspirate samples were obtained using previously published methods of collagenase digestion and differential centrifugation.[29] The average amount of tissue harvested for grafting and analysis was 35.87 g (±17.11). Grafts demonstrated a mean total cell count of 1.08×10^6 ($\pm 6.23 \times 10^5$) SVF cells/g of fat with a mean viability of 84.93% (±9.08) (Fig. 2). Colony-forming unit analyses revealed an average plate density of 2.23×10^4 cells/cm^2 ($\pm 1.34 \times 10^4$) after 2 weeks of culture and a calculated mean doubling time of 7.43 days (Fig. 3).

Qualitative Scar Analysis

Patient and Observer Scar Assessment

When evaluating the subjective/qualitative effects of AFT alone on scar quality over time, cumulative POSAS results demonstrate that patients but not observers noted a statistically significant improvement of their scar at 6 months posttreatment with AFT. However, at 12 months posttreatment, both the patient and a blinded observer judged the scars to be significantly enhanced (Fig. 4). The specific scar parameters that were judged to be the most improved over time by the patient are shown in Table 3. At 6 months posttreatment, patients judged the color ($P < 0.04$) and irregularity ($P < 0.03$) of their AFT-treated scars to be significantly improved (Table 3). The observed improvement in both these aforementioned scar parameters was durable at 12 months ($P < 0.001$ for both color and irregularity). Two additional parameters, including stiffness ($P < 0.001$) and thickness ($P < 0.02$), exhibited a statistically significant improvement at 12 months (Table 3).

In contrast, observers noted no significant difference in any of the scar parameters at the 6-month time point (Table 4), which is consistent with total POSAS scores (Fig. 4). At 12 months, observers judged statistically significant improvements in scar thickness ($P < 0.02$) and scar relief ($P < 0.01$) (Table 4), which is also consistent with the overall total POSAS scores/differences at this time point. When AFT-treated scars are compared with saline-treated scars, however, there were no statistically significant differences noted in patient- or observer-perceived scar quality at 6 or 12 months after treatment (Fig. 5).

DISCUSSION

A core principle of plastic and reconstructive surgery is to replace "like with like" to optimize cosmesis and function.[35] In the case of lost or scarred subcutaneous tissues, the ideal replacement is adipose tissue. German physician Franz Neuber first reported free AFT in 1893, and the technique has evolved notably over the years.[17,36–39] Today, AFT is a routine, safe surgical procedure, with >79,000 procedures performed in 2016 in the United States alone.[40]

Conventional AFT is an established approach to the correction (ie, "filling") of a wide variety of soft-tissue contour deficits.[16] However, several recent publications have drawn attention to the potential effect that AFT has on overlying tissues, including the quality and appearance of skin and scar tissue. In 2007, Sardesai and Moore[41] evaluated the impact of subdermal fat grafting on the maturation of facial scars for up to 1 year. Using subjective and objective scar assessment tools, they found that fat grafting improved dermal elasticity, patient and observer perception of scar thickness, patient perception of stiffness, and observer perception and pliability. The following year, Klinger et al[42] reported a small case series documenting

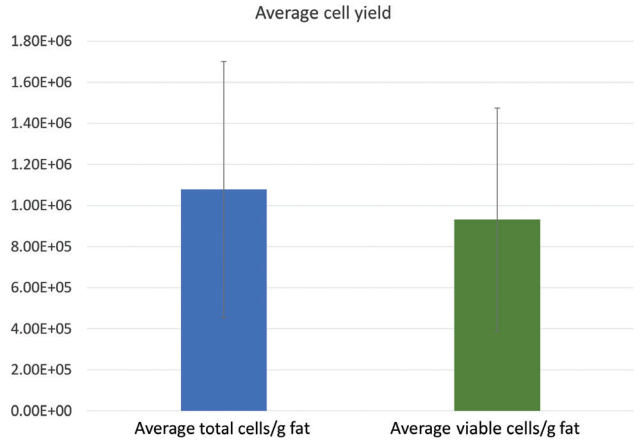


Fig. 2. Average yield of SVF cells isolated from a sample taken from each fat graft. The left column shows total cell yield and the right column shows viability. The mean amount of tissue processed was 35.87 g, with an average total cell yield of 1.1 million SVF cells per gram of tissue processed with an average viability of 85%. The wide range of cell yield is consistent with existing literature and reflection of the use/analysis of primary tissues from a variety of subject.

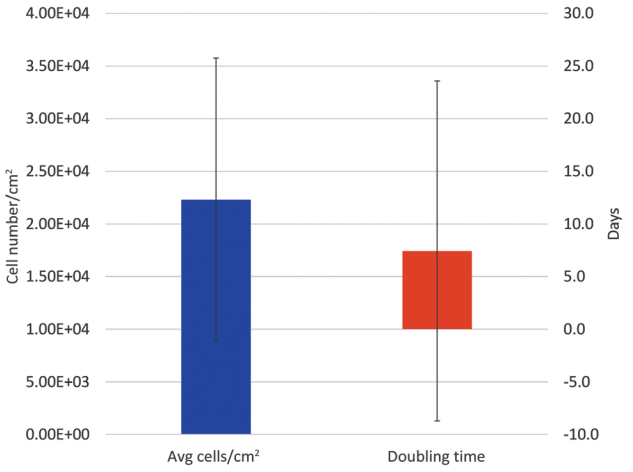


Fig. 3. Results of SVF cell culture and growth parameters. Isolated SVF cells were plated into culture at 10,000 cells per cm^2 and grown for 2 weeks. The cells were then lifted and counted. Average cell number after culture (left column) and average cell doubling time (right column) are shown.

	Time	Mean Difference of Total POSAS Scores	p-value
Patient Scar Scale	**6 Mo. – BSL**	8.500	**0.02**
	12 Mo. – BSL	15.100	**0.002**
	12 Mo. – 6 Mo.	6.545	0.07
Observer Scar Scale	6 Mo. – BSL	4.500	0.08
	12 Mo. – BSL	4.667	**0.01**
	12 Mo. – 6 Mo.	1.000	0.61

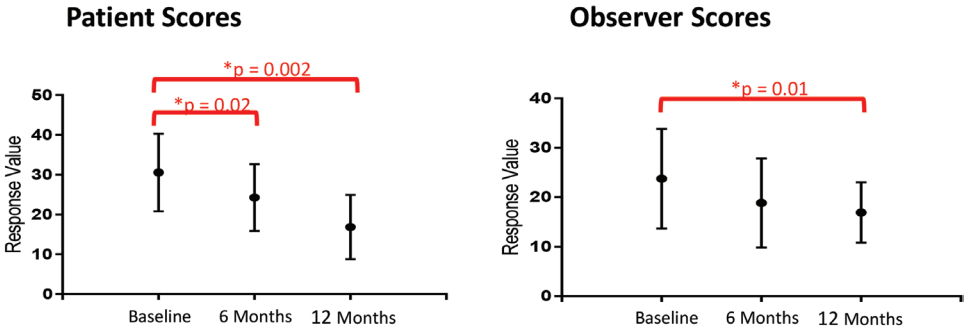


Fig. 4. Subjective scar analysis by patients and designated study personnel of fat-grafted scars over time. Using a validated scar assessment tool (POSAS), patients judged their scars to be statistically improved at both 6-month and 12-month timepoints compared to baseline (left). Study personnel judged scars to be statistically improved at the 12-month timepoint only (right). Both patients and study personnel were blinded to treatment. Specific scar parameters that were judged to be most changed are shown in Tables 3, 4. BSL indicates baseline.

Table 3. POSAS Patient Question Scores (Fat Grafted)

Time	Parameter	|Mean Difference|	*P*
6 mo to BSL	Pain	0.714	0.15
	Itch	0.143	0.81
	Color	2.000	**0.04**
	Stiffness	1.571	0.23
	Thickness	1.286	0.16
	Irregularity	2.786	**0.03**
12 mo to BSL	Pain	1.250	0.09
	Itch	0.167	0.86
	Color	4.167	**0.001**
	Stiffness	3.000	**0.001**
	Thickness	2.750	**0.02**
	Irregularity	4.083	**0.001**

Bold text indicates statistically significant values.
BSL, baseline.

Table 4. POSAS Observer Question Scores (Fat Grafted)

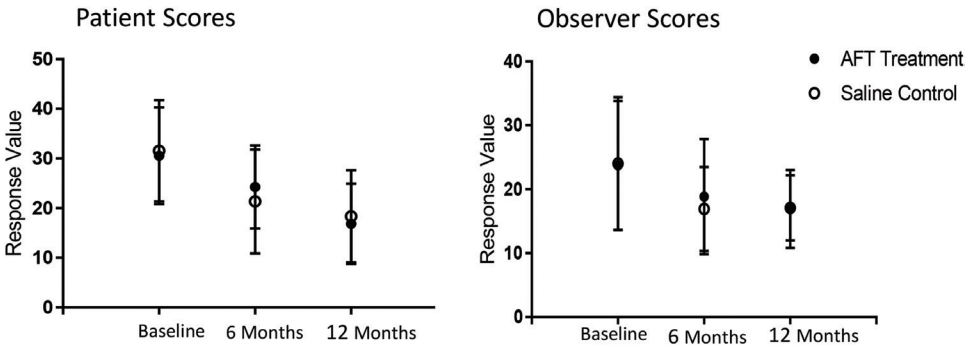
Time	Parameter	|Mean Difference|	*P*
6 mo to BSL	Vascularity	1.071	0.17
	Pigmentation	0.786	0.14
	Thickness	1.000	0.21
	Relief	0.857	0.10
	Pliability	0.786	0.15
12 mo to BSL	Vascularity	1.500	0.07
	Pigmentation	0.667	0.67
	Thickness	1.333	**0.02**
	Relief	0.833	**0.01**
	Pliability	0.417	0.29

Bold text indicates statistically significant values.
BSL, baseline.

improved burn scar quality, with histologic examinations showing local hypervascularity and dermal hyperplasia. Mojallal et al[43] demonstrated the neosynthesis of collagen fibers and subsequent dermal thickening in a nude murine model after subdermal injection of human fat tissue.

Despite an unclear mechanism of action, the results of the aforementioned publications were bolstered by subsequent studies that described improved quality in scars of various etiologies.[44–51] More often than not, these studies invoked a direct and/or indirect mechanistic effect mediated by cells within the SVF of adipose tissue, including putative mesenchymal stem cell populations (ASC).[31,52] ASCs have angiogenic, antiapoptotic, immunomodulatory, and matrix remodeling paracrine properties that are thought to be mediated primarily through paracrine signals.[29,31,53–55]

However, each of the aforementioned studies suffers from some element of bias related to study design. Only 2 of these studies include a control treatment method (eg, saline injection or no treatment) for comparison with AFT treatment.[48,51] In one of these studies, a battery of stains was used to evaluate grafted burn scars' cellular function and histology via surrogate markers. Along with subjective scar analysis, these histologic results demonstrated improved scar quality 6 months after fat grafting, with decreased inflammation, hypervascularization, and an improved histologic structure.[51] In the study by Klinger et al,[48] POSAS and durometer analyses revealed a significant improvement in hardness and all POSAS parameters (excluding pruritis) in fat-grafted burn scars versus saline controls (n = 20). However, neither of these studies compared fat



	Time	Mean Difference of Total POSAS Scores	p-value
Patient Scar Scale	BSL	1.000	0.54
	6 Mo.	2.929	0.22
	12 Mo.	1.500	0.49
Observer Scar Scale	BSL	0.250	0.82
	6 Mo.	1.929	0.18
	12 Mo.	0.167	0.94

Fig. 5. Comparison of subjective assessment of fat-grafted and (placebo) saline-treated scars over time. There are no statistical differences noted in perceived scar quality when fat-grafted scars are compared to saline-treated scars at either 6 or 12 months after treatment. BSL indicates baseline.

grafting directly with a control treatment in the setting of a randomized and blinded study design.

In 2017, Gal et al[56] published an 8-patient pilot trial in pediatric burn patients using a prospective, randomized, double-blinded, placebo-controlled study design. Sites were randomized to treatment with fat grafting or saline at a dose of 0.2 ml/cm^2, and follow-up ranged from 5 months to 1 year (average 8 months). Effects were evaluated using a subjective scar assessment (Vancouver Scar Scale) but no objective metrics. Based on the results of blinded patient and observer assessment (and unblinded surgeon assessment), they concluded that a "single treatment with autologous fat grafts did not improve mature pediatric burn scars when compared to normal saline injections."[56]

Our results extend the findings of Gal et al.[56] Qualitative results from our trial demonstrate a statistically significant improvement in scar quality over 12 months in the fat-grafted scars when blindly assessed by both the patient and a blinded observer. Specifically, patients reported significant improvement in scar color, irregularity, stiffness, and thickness at 12 months. Among blinded *observers*, there was a trend toward significance in improvements in scar surface irregularity and pliability. However, consistent with the findings reported by Gal et al,[56] these improvements were not statistically different from changes noted in scars treated with saline. Moreover, saline injection proved equally efficacious to autologous fat grafting when scars were objectively measured using durometer, cutometer, histology, and dermal spectrophotometry as evidenced by the lack of statistically significant differences. This lack of measurable objective differences between treatment methods is consistent with the absence of patient- and observer-reported qualitative differences between treatments.

The aforementioned qualitative data supporting subjective perception of AFT effects on scar quality are consistent with the results presented in several published studies that are not randomized, blinded, or placebo-controlled. In our study, however, like that of Gal et al,[56] improved subjective perceptions of scar quality were not unique to fat transfer and occurred with placebo saline treatments also. These findings argue strongly against any putative effect from mesenchymal stem cells or any other cell type within fat. Rather, given the similar effects of saline injection, one might hypothesize that the observed effects may be related to the act of needle injections/passes and associated inflammation and/or potentially to the mechanical/bulking effect of the injected material—regardless of its origin.

Indeed, some evidence indicates that dermal needling is efficacious (also known as needle dermabrasion) in the treatment of a variety of scars.[57–60] Similarly, the injection of saline and/or fat into tissue planes directly below a scar results in matrix distention within the surrounding tissue and scar. The fibroblasts within this collagen matrix can be biologically altered by the resulting strain through

mechano-transduction, a mechanism recognized as inductive to collagen production and scar remodeling.[61–63] In this scenario, mechanical forces alone may explain the findings in our study. Furthermore, the use of saline injections as a means to remodel scar has been published previously.[64]

Although this study attempts to provide high-level evidence related to the therapeutic impact of fat grafting on scars, there are several limitations that are worth of consideration. First, although the study design included an internal blinded placebo-controlled treatment group, the number of enrolled/treated subjects ("N") is limited, and therefore the lack of a significant difference between fat- and saline-treated scars may be the result of a type 2 error. Recruitment of adequate subjects for this study was difficult even with multi-institutional access, and full 12-month follow-up was challenging. Factors contributing to this difficulty included strict inclusion–exclusion criteria, "surgical fatigue", and significant time-burden required by the study. Second, the study involved only a single grafting treatment, whereas other studies and clinical practice often involves multiple treatment episodes spaced over several months. Third, the study did not include any type of scar release or "subdermal subcision" as part of the treatment protocol, which represents another technique often used in clinical practice to achieve maximal impact. Fourth, it remains possible that fat grafting may improve scar appearance relative to "innate" remodeling; however, this possibility was not specifically tested with our study design. Finally, the results of this study may differ depending on the specific etiology, age, or anatomical site of the scar, and the heterogeneity of the scars treated in this trial may limit the conclusions that can be drawn from the results. Despite these limitations, the study provides a solid foundation upon which to objectively and subjectively evaluate fat grafting and its outcomes in future studies. In conclusion, our longitudinal "within-group" analysis suggests that autologous fat grafting can improve the qualitative profile of a scar from both the patient and observer perspectives, which is consistent with a large body of level III and IV scientific work. However, there was no difference in improvement when compared to scars that were treated with saline. In addition, no statistical differences were noted when objective metrics such as hardness, elasticity, color, or histology were evaluated. Additional randomized, blinded, placebo-controlled trials are required to corroborate or challenge the putative beneficial effect(s) of adipose tissue on scar remodeling.

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REFERENCES

1. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen.* 2009;17:763–771.
2. de Bonnecaze G, Chaput B, Woisard V, et al. Adipose stromal cells improve healing of vocal fold scar: morphological and functional evidences. *Laryngoscope.* 2016;126:E278–E285.
3. Spiekman M, Przybyt E, Plantinga JA, et al. Adipose tissue-derived stromal cells inhibit TGF-β1-induced differentiation of human dermal fibroblasts and keloid scar-derived fibroblasts in a paracrine fashion. *Plast Reconstr Surg.* 2014;134:699–712.
4. Jeong JH. Adipose stem cells and skin repair. *Curr Stem Cell Res Ther.* 2010;5:137–140.
5. de Vries HJ, Middelkoop E, van Heemstra-Hoen M, et al. Stromal cells from subcutaneous adipose tissue seeded in a native collagen/elastin dermal substitute reduce wound contraction in full thickness skin defects. *Lab Invest.* 1995;73:532–540.
6. Meyers CA, Xu J, Zhang L, et al. Early immunomodulatory effects of implanted human perivascular stromal cells during bone formation. *Tissue Eng Part A.* 2018;24:448–457.
7. Liu X, Wang S, Wu S, et al. Exosomes secreted by adipose-derived mesenchymal stem cells regulate type I collagen metabolism in fibroblasts from women with stress urinary incontinence. *Stem Cell Res Ther.* 2018;9:159.
8. Li X, Xie X, Lian W, et al. Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. *Exp Mol Med.* 2018;50:29.
9. Cooper DR, Wang C, Patel R, et al. Human adipose-derived stem cell conditioned media and exosomes containing MALAT1 promote human dermal fibroblast migration and ischemic wound healing. *Adv Wound Care (New Rochelle).* 2018;7:299–308.
10. Ebrahimian TG, Pouzoulet F, Squiban C, et al. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing. *Arterioscler Thromb Vasc Biol.* 2009;29:503–510.
11. Nie C, Yang D, Xu J, et al. Locally administered adipose-derived stem cells accelerate wound healing through differentiation and vasculogenesis. *Cell Transplant.* 2011;20:205–216.
12. Sugihara H, Toda S, Yonemitsu N, et al. Effects of fat cells on keratinocytes and fibroblasts in a reconstructed rat skin model using collagen gel matrix culture. *Br J Dermatol.* 2001;144:244–253.
13. Sugihara H, Toda S, Miyabara S, et al. Reconstruction of the skin in three-dimensional collagen gel matrix culture. *In Vitro Cell Dev Biol.* 1991;27A:142–146.
14. Lee SH, Jin SY, Song JS, et al. Paracrine effects of adipose-derived stem cells on keratinocytes and dermal fibroblasts. *Ann Dermatol.* 2012;24:136–143.
15. Amos PJ, Shang H, Bailey AM, et al. IFATS collection: the role of human adipose-derived stromal cells in inflammatory microvascular remodeling and evidence of a perivascular phenotype. *Stem Cells.* 2008;26:2682–2690.
16. Gutowski KA; ASPS Fat Graft Task Force. Current applications and safety of autologous fat grafts: a report of the ASPS fat graft task force. *Plast Reconstr Surg.* 2009;124:272–280.
17. Coleman SR. Structural fat grafting: more than a permanent filler. *Plast Reconstr Surg.* 2006;118(3 Suppl):108S–120S.
18. Fearmonti R, Bond J, Erdmann D, et al. A review of scar scales and scar measuring devices. *Eplasty.* 2010;10:e43.
19. Ohshima H, Kinoshita S, Oyobikawa M, et al. Use of Cutometer area parameters in evaluating age-related changes in the skin elasticity of the cheek. *Skin Res Technol.* 2012;19:e238–e242.
20. Ahn S, Kim S, Lee H, et al. Correlation between a Cutometer and quantitative evaluation using Moire topography in age-related skin elasticity. *Skin Res Technol.* 2007;13:280–284.
21. Dobrev H. Application of Cutometer area parameters for the study of human skin fatigue. *Skin Res Technol.* 2005;11:120–122.
22. Fong SS, Hung LK, Cheng JC. The Cutometer and ultrasonography in the assessment of postburn hypertrophic scar—a preliminary study. *Burns.* 1997;23(Suppl 1):S12–S18.

23. Enomoto DN, Mekkes JR, Bossuyt PM, et al. Quantification of cutaneous sclerosis with a skin elasticity meter in patients with generalized scleroderma. *J Am Acad Dermatol.* 1996;35(3 pt 1):381–387.
24. Ryu HS, Joo YH, Kim SO, et al. Influence of age and regional differences on skin elasticity as measured by the Cutometer. *Skin Res Technol.* 2008;14:354–358.
25. Falanga V, Bucalo B. Use of a durometer to assess skin hardness. *J Am Acad Dermatol.* 1993;29:47–51.
26. Romanelli M, Falanga V. Use of a durometer to measure the degree of skin induration in lipodermatosclerosis. *J Am Acad Dermatol.* 1995;32(2 pt 1):188–191.
27. Kissin EY, Schiller AM, Gelbard RB, et al. Durometry for the assessment of skin disease in systemic sclerosis. *Arthritis Rheum.* 2006;55:603–609.
28. Merkel PA, Silliman NP, Denton CP, et al; CAT-192 Research Group; Scleroderma Clinical Trials Consortium. Validity, reliability, and feasibility of durometer measurements of scleroderma skin disease in a multicenter treatment trial. *Arthritis Rheum.* 2008;59:699–705.
29. Brown JC, Shang H, Li Y, et al. Isolation of adipose-derived stromal vascular fraction cells using a novel point-of-care device: cell characterization and review of the literature. *Tissue Eng Part C Methods.* 2017;23:125–135.
30. Katz AJ, Tholpady A, Tholpady SS, et al. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells. *Stem Cells.* 2005;23:412–423.
31. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7:211–228.
32. Aronoqitz JA, Ellenhorn JD. Adipose stromal vascular fraction isolation: a head-to-head comparison of four commercial cell separation systems. *Plast Reconstr Surg.* 2013;132:932e–939e.
33. Draaijers LJ, Tempelman FR, Botman YA, et al. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. *Plast Reconstr Surg.* 2004;113:1960–1965; discussion 1966.
34. Idriss N, Maibach HI. Scar assessment scales: a dermatologic overview. *Skin Res Technol.* 2009;15:1–5.
35. Millard DR. *Principlization of Plastic Surgery.* Boston, Mass.: Little Brown and Company; 1986.
36. Klein AW, Elson ML. The history of substances for soft tissue augmentation. *Dermatol Surg.* 2000;26:1096–1105.
37. Neuber F. Fettransplantation. *Chir Kongr Verhandl Dsch Gesellch Chir.* 1893;22.
38. Joseph M. *Handbuch der kosmetik.* Leipzig: Veit and Co; 1912.
39. Miller C. *Cannula Implants and Review of Implantation Techniques in Esthetic Surgery.* Chicago, Ill.: The Oak Press; 1926.
40. American Society of Plastic Surgeons. 2016 National Plastic Surgery Statistics: Cosmetic and Reconstructive Procedure Trends. 2016. Available at https://www.plasticsurgery.org/news/plastic-surgery-statistics. Accessed May 8, 2020.
41. Sardesai MG, Moore CC. Quantitative and qualitative dermal change with microfat grafting of facial scars. *Otolaryngol Head Neck Surg.* 2007;137:868–872.
42. Klinger M, Marazzi M, Vigo D, et al. Fat injection for cases of severe burn outcomes: a new perspective of scar remodeling and reduction. *Aesthetic Plast Surg.* 2008;32:465–469.
43. Mojallal A, Lequeux C, Shipkov C, et al. Improvement of skin quality after fat grafting: clinical observation and an animal study. *Plast Reconstr Surg.* 2009;124:765–774.
44. Caviggioli F, Villani F, Forcellini D, et al. Nipple resuscitation by lipostructure in burn sequelae and scar retraction. *Plast Reconstr Surg.* 2010;125:174e–176e.
45. Viard R, Bouguila J, Voulliaume D, et al. Fat grafting infacial burns sequelae. *Ann Chir Plast Esthet.* 2012;57:217–229.
46. Piccolo NS, Piccolo MS, Piccolo MT. Fat grafting for treatment of burns, burn scars, and other difficult wounds. *Clin Plast Surg.* 2015;42:263–283.
47. Sultan SM, Barr JS, Butala P, et al. Fat grafting accelerates revascularisation and decreases fibrosis following thermal injury. *J Plast Reconstr Aesthet Surg.* 2012;65:219–227.
48. Klinger M, Caviggioli F, Klinger FM, et al. Autologous fat graft in scar treatment. *J Craniofac Surg.* 2013;24:1610–1615.
49. Caviggioli F, Klinger FM, Forcellini D, et al. Scar treatment by lipostructure. *Update Plast Surg.* 2009;2:51–53.
50. Guisantes E, Fontdevila J, Rodríguez G. Autologous fat grafting for correction of unaesthetic scars. *Ann Plast Surg.* 2012;69:550–554.
51. Bruno A, Delli Santi G, Fasciani L, et al. Burn scar lipofilling: immunohistochemical and clinical outcomes. *J Craniofac Surg.* 2013;24:1806–1814.
52. Rigotti G, Marchi A, Galiè M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg.* 2007;119:1409–1422; discussion 1423.
53. Dahlman I, Elsen M, Tennagels N, et al. Functional annotation of the human fat cell secretome. *Arch Physiol Biochem.* 2012;118:84–91.
54. Shokrgozar MA, Fattahi M, Bonakdar S, et al. Healing potential of mesenchymal stem cells cultured on a collagen-based scaffold for skin regeneration. *Iran Biomed J.* 2012;16:68–76.
55. Rehman J, Traktuev D, Li J, et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation.* 2004;109:1292–1298.
56. Gal S, Ramirez JI, Maguina P. Autologous fat grafting does not improve burn scar appearance: a prospective, randomized, double-blinded, placebo-controlled, pilot study. *Burns.* 2017;43:486–489.
57. Fabbrocini G, Fardella N, Monfrecola A, et al. Acne scarring treatment using skin needling. *Clin Exp Dermatol.* 2009;34:874–879.
58. Park KY, Kim HK, Kim SE, et al. Treatment of striae distensae using needling therapy: a pilot study. *Dermatol Surg.* 2012;38:1823–1828.
59. Majid I. Microneedling therapy in atrophic facial scars: an objective assessment. *J Cutan Aesthet Surg.* 2009;2:26–30.
60. Schwarz M, Laaff H. A prospective controlled assessment of microneedling with the dermaroller device. *Plast Reconstr Surg.* 2011;127:146e–148e.
61. Costa AM, Peyrol S, Pôrto LC, et al. Mechanical forces induce scar remodeling. Study in non-pressure-treated versus pressure-treated hypertrophic scars. *Am J Pathol.* 1999;155:1671–1679.
62. Howard PS, Kucich U, Taliwal R, et al. Mechanical forces alter extracellular matrix synthesis by human periodontal ligament fibroblasts. *J Periodontal Res.* 1998;33:500–508.
63. Chiquet M, Gelman L, Lutz R, et al. From mechanotransduction to extracellular matrix gene expression in fibroblasts. *Biochim Biophys Acta.* 2009;1793:911–920.
64. Shumaker PR, Rao J, Goldman MP. Treatment of local, persistent cutaneous atrophy following corticosteroid injection with normal saline infiltration. *Dermatol Surg.* 2005;31:1340–1343.