Fat Grafting and Adipose-Derived Regenerative Cells in Burn Wound Healing and Scarring: A Systematic Review of the Literature


Background: There is an abundance of literature supporting the efficacy of fat grafting in aesthetic and reconstructive cases. There has been a recent emphasis on the regenerative capacity of adipose-derived stem cells and their utility in the improvement of wound healing and scarring provided by their cytokine and growth factor profiles. Despite the wealth of evidence supporting their efficacy, little attention has been paid to their utility in burn treatment. The authors’ purpose was to provide an analysis of the literature regarding the use of fat grafting and regenerative cells in the treatment of burn wounds to guide surgeons and scientists on their clinical use.

Methods: A systematic review of the literature was performed by a thorough search of 12 terms using the PubMed, Medline, and Cochrane databases. Two hundred forty-one articles were subject to evaluation by predetermined inclusion and exclusion criteria.

Results: Six murine and 12 human studies were selected, including case-control studies, case series, and case reports. They describe histologic and clinical effects of fat grafting and regenerative cell therapy, including improvements in burn scar size and texture, enhanced angiogenesis, decreased inflammation, alleviation of pain, and return of function.

Conclusions: There is a dearth of randomized controlled trials and quantitative analysis supporting the efficacy of fat grafting and adipose regenerative cells in burns. However, the subjective improvements in scars are encouraging. The authors hope that this review will be a foundation for future studies and will highlight the breadth of knowledge yet to be explored by this therapy. (Plast. Reconstr. Surg. 137: 302, 2016.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

A
tologous fat grafting is a commonly used technique for treating volume and contour defects in aesthetic and reconstructive surgery. First described in the early 1900s, this procedure became popular in the late 1980s, when liposuction increased the availability of fat stores and allowed surgeons to experiment with the therapeutic potential of autologous fat.¹ There has been a recent emphasis on not only the filling capability of fat but also its regenerative capacity.² The stromal vascular fraction of processed fat grafts contains multipotent stem cells that express adipogenic, osteogenic, and chondrogenic genes.³ Many studies have demonstrated the angiogenic, immunomodulatory, and

Disclosure: The authors declare no conflicts of interests with respect to the authorship and/or publication of this article. The authors received no financial support for the research and/or authorship of this article.
Volume 137, Number 1 • Burn Wound Healing and Scarring

antiapoptotic capabilities of these cells, making them a valuable and effective tool in restoring devitalized tissue, as evidenced by their efficacy in improving radiation-damaged skin.4,5 Adipose-derived stem cells have also been shown to play a role in antiaging6 and skin regeneration by forming tissue consisting of hypodermis, dermis, and epidermis.7 It is this regenerative capacity that is of particular interest in burn wound therapy.

There is an abundance of literature supporting the efficacy of fat grafting in both aesthetic and reconstructive cases. Recent studies have shown the utility of adipose-derived stem cells in the improvement of wound healing, describing their ability to regenerate soft tissues and their remodeling capacity provided by their unique cytokine and growth factor profiles. Despite the wealth of evidence supporting their efficacy in wound healing, little attention has been paid to their utility in the treatment of thermal injury. The purpose of this study was to provide a thorough analysis of the literature regarding the use of fat grafting and adipose-derived stem cells in the treatment of burn wounds to guide surgeons and scientists on their clinical use in burn wound healing and scar remodeling, and in pursuing further investigation.

PATIENTS AND METHODS

The foundation for this review was a systematic method for finding and evaluating the literature on the efficacy of fat and adipose stem cell therapy in the treatment of thermal injury. A comprehensive search was conducted by two independent reviewers in April of 2015 using the following terms alone or in combination in the PubMed, MEDLINE, and Cochrane databases: “burn,” “fat grafting,” “fat transplant,” “fat harvesting,” “fat transfer,” “adipose stem cell,” “lipofilling,” “lipoinjection,” “lipotransfer,” “wound healing,” and “scar treatment.” In addition, the terms “exp burn/” and “exp adipose tissue/” were used in MEDLINE to search all articles including burn and adipose tissue exploded subheadings. Because one of the authors is fluent in Portuguese and French, filters were set to include all articles in English, Portuguese, and French.

Prospective inclusion criteria were the use of fat or adipose stem cell therapy and reporting of the effects on wound healing when used as an early intervention, the effects on scar formation when used on an old wound, and the effects on quality of life. Studies included were case-control studies, case series, case reports, animal studies using human fat, animal studies using animal fat, clinical trials, and randomized controlled trials. Exclusion criteria were articles on fat grafting for nonburn wounds, burn to a surface other than skin (e.g., cornea, bone), fat transfer as part of another graft (dermal grafts), and radiation injury. Necessarily excluded were articles we were not able to access and those in languages other than English, Portuguese, and French.

A formal statistical analysis of the eligible studies was not performed because of the methodologic and clinical heterogeneity. A detailed systematic review of the diverse outcomes was undertaken instead.

RESULTS

The primary search yielded 544 articles. After removal of duplicates, 241 of these were found to be distinct. The titles of remaining articles were screened for relevance, after which 75 abstracts were reviewed according to our inclusion criteria. The remaining 28 articles were read in their entirety and their references scoured for articles that escaped our primary search criteria. Of these, 12 were excluded based on predetermined criteria, and the remaining 16, along with one article that was discovered by review of references, were included in this review (Fig. 1). Thus, we present a total of 17 articles describing 18 studies, as one of the articles described two distinct studies.8

Human Studies

Twelve human studies were selected, including case control studies (n = 3), case series (n = 7), and case reports (n = 2). Adipose tissue was harvested from one or multiple sites, including the abdomen (n = 9), trochanteric region (n = 3), inner thigh (n = 1), and medial knee (n = 1), and discarded burn tissue (n = 1). Adipose tissue was processed by high-speed centrifugation (n = 9) and low-speed centrifugation (n = 2). Further processing included mincing and processing for adipose-derived stem cell isolation (n = 1), and supplementation of fat with stromal vascular fraction (n = 1) or platelet-rich plasma (n = 1).

Case-Control Studies

Bruno et al. conducted a study on 93 chronic burns scars divided into two halves, where half of each scar was treated with lipofilling and the other half served as a control.9 Improved vascularization of the dermal papillae and better collagen organization were shown in scars treated with lipofilling after 6 months. There was a statistically
significant decrease in S100-positive cells on immunohistochemistry, indicating that lipofilling correlates with reduction of melanocytes in the wounds. There was a decrease in Langerin-positive cells, most likely resulting from efflux of trapped cells secondary to loose connective tissue. Increased visualization of Ki-67 in the basal layer of lipofilled wounds indicated that there was increased proliferation. A modified Vancouver Scar Scale was used to provide objective clinical evaluation of scars. Scores of 41 before treatment, 29 at 3 months, and 15 at 6 months were reported (range, 5 to 50, with low numbers representing close to normal skin).

Klinger et al. conducted two separate studies described in one article8 (which is reflected in a footnote in Table 1).10–24 The case-control study evaluated scars of 20 randomly selected patients. Each scar was treated half with fat and half with saline injection and evaluated by the Patient and Observer Scar Assessment Scale25 and Durometer measurement for scar firmness. Significant improvement of color, shape, thickness, and movement was seen as early as 3 months postoperatively in the fat-grafted side.

Gentile et al. compared fat grafts to fat-enhanced grafts with stromal vascular fraction or platelet-rich plasma in 30 patients with burn and posttraumatic scars.10 In stromal vascular fraction- and platelet-rich plasma–enhanced groups, 63 percent and 69 percent of wounds maintained their volume after 1 year, respectively, compared with 39 percent of the control group, indicating less fat resorption in enhanced grafts.

The first case-control study9 was the strongest, as clinical results following treatment with fat grafting were corroborated by immunohistochemical findings achieving statistical significance, and clinical evaluation was double blinded. The second case-control study8 showed objective statistically significant clinical findings in treated scars, but there was no histologic confirmation. The third study10 exposed three different preparation techniques of fat grafting to scars and showed that fat supplemented with stromal vascular fraction or platelet-rich plasma achieved better contour maintenance, with increased graft take. However, they did not compare them to untreated controls with no fat grafting.

Case Series

Klinger et al. reported improvement in mimic features, skin texture, and skin thickness in three burn patients with facial hypertrophic scars and keloids after fat injection into the dermohypodermal junction performed twice, 3 months apart.11 Although findings were not compared to controls or subjected to statistical analysis, new collagen deposition, increased vascularity, and dermal hyperplasia were observed. Although the sample size was small, the clinical results were corroborated with histologic findings.

Caviggioli et al. performed fat grafting in the nipple-areola complex of 12 patients who specifically suffered burns to the chest.12 The average nipple projection was 4.6 mm at 2 weeks, with patients rating the results as excellent; and the projection was 2.9 mm at 2 years, with the majority rating the results as good. These were objective clinical findings with a good follow-up period; however, there was no control, histologic report, or statistical analysis.

Brongo et al. reported evidence of new collagen deposition, angiogenesis, and dermal hyperplasia in scars of 18 burned patients treated with lipofilling three times at 3-month interval.13 Improvements in texture, softness, thickness, and color of treated scars based on a questionnaire completed
by patients, surgeons, and external observers 1 year after treatment were reported. Clinical improvement of scars was supported by histologic findings with a good follow-up period, but there was no control, and no statistical analysis was conducted.

Viard et al. treated 15 patients with postburn facial scars that had an average of 7.5 operations 1 year before fat grafting.14 Patients received two to three sessions. Subjective improvements in mimic features, skin texture, and skin thickness were reported without controls or statistical analysis of the results.

The second study of the 2013 article of Klinger et al. reported improvements in scar elasticity, skin softening, and mobility in periarticular regions of 376 patients with retractile and painful scars treated with lipofilling.8 This was a large study where subjective clinical findings were reported; however, the authors did analyze a group of 20 patients that we mentioned above in the case-control study group.

Keck et al. harvested adipose tissue from discarded burn tissue. It was spread on a bovine collagen-elastin scaffold and applied on the fascia of previously excised wounds covered with skin graft in five patients.15 Ninety percent of the skin graft was viable at postoperative day 10 in three patients. Flow cytometry, microscopy, and AdipoRed (Lonza, Walkersville, Md.) staining revealed that adipose cells from debrided tissues were comparable to abdominal fat in quantity, proliferative capacity, and differentiation. This study lacked controls, was limited in number of cases, but represents a novel technique with much potential.

Piccolo et al. described their 3-year experience using fat grafting in acute and subacute burn wounds, and burn scars. They treated 240 patients who presented with burn, vascular, or traumatic injuries. For acute and subacute wounds, fat was injected at 2- to 4-week intervals until a definitive procedure such as skin graft or flap coverage was performed. Subsequent scars were treated at 3-month intervals. The authors reported subjective improvements in wound healing, fibrosis, and scar suppleness.16 This study was large, with adequate follow-up, but lacked statistical analysis and controls.

Table 1. List of Articles Included in This Systematic Review According to Inclusion and Exclusion Criteria, Stratified by Level of Evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Level of Evidence</th>
<th>No. of Subjects or Burn Scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno et al., 20136</td>
<td>Case-control</td>
<td>III</td>
<td>93 burn scars</td>
</tr>
<tr>
<td>Klinger et al., 2013*</td>
<td>Case-control</td>
<td>III</td>
<td>20 patients with scars†</td>
</tr>
<tr>
<td>Gentile et al., 2014</td>
<td>Case-control</td>
<td>IV</td>
<td>30 patients with scars†</td>
</tr>
<tr>
<td>Klinger et al., 2008</td>
<td>Case series</td>
<td>IV</td>
<td>3 patients with burn scars</td>
</tr>
<tr>
<td>Caviggioli et al., 2010</td>
<td>Case series</td>
<td>IV</td>
<td>12 patients with burn scars</td>
</tr>
<tr>
<td>Brongo et al., 2012</td>
<td>Case series</td>
<td>IV</td>
<td>18 patients with burn scars</td>
</tr>
<tr>
<td>Viard et al., 2012</td>
<td>Case series</td>
<td>IV</td>
<td>15 patients with burn scars</td>
</tr>
<tr>
<td>Klinger et al., 2013*</td>
<td>Case series</td>
<td>IV</td>
<td>376 patients with scars†</td>
</tr>
<tr>
<td>Keck et al., 2013</td>
<td>Case series</td>
<td>IV</td>
<td>5 patients with burns</td>
</tr>
<tr>
<td>Piccolo et al., 2015</td>
<td>Case series</td>
<td>IV</td>
<td>240 patients†</td>
</tr>
<tr>
<td>Caviggioli et al., 2008</td>
<td>Case report</td>
<td>V</td>
<td>1 patient with burn scar</td>
</tr>
<tr>
<td>Khouri et al., 2013</td>
<td>Case reports</td>
<td>V</td>
<td>5 patients with burn scars†</td>
</tr>
<tr>
<td>Sultan et al., 2012</td>
<td>Murine</td>
<td>—</td>
<td>20 mice</td>
</tr>
<tr>
<td>Shokrgozar et al., 2012</td>
<td>Murine</td>
<td>—</td>
<td>10 rats</td>
</tr>
<tr>
<td>Huang et al., 2014</td>
<td>Murine</td>
<td>—</td>
<td>30 rats</td>
</tr>
<tr>
<td>Loder et al., 2014</td>
<td>Murine</td>
<td>—</td>
<td>20 mice</td>
</tr>
<tr>
<td>Karimi et al., 2014</td>
<td>Murine</td>
<td>—</td>
<td>30 mice</td>
</tr>
<tr>
<td>Atalay et al., 2014</td>
<td>Murine</td>
<td>—</td>
<td>20 rats</td>
</tr>
</tbody>
</table>

*Two studies were part of the same article.
†Three studies included burns and other types of wounds (trauma, ulcers).

Case Reports

Caviggioli et al. reported lasting correction of epiphora, xerophthalmia, and lagophthalmos, 1 year after performing fat grafting in one patient with medial ectropion secondary to chemical burn.17 Khouri et al. reported scar softening and increased range of motion after performing lipofilling and percutaneous aponeurotomy (transforming a restrictive scar into a neomatrix scaffold into which fat grafts can settle) in patients with retractile scars of the upper extremity, hands, and chest secondary to burns, radiation therapy, and congenital restriction bands.18 Five of the patients presented scars from burns, with objective measurement of functional improvement, but lacked controls.
Murine Studies

Six murine studies assessing clinical and biochemical outcomes of applying fat (n = 2) or adipose stem cells (n = 4) to burn wounds were selected. Subjects were delivered burn injury by contact with a metal object submerged in hot water (n = 4) or by direct exposure to hot water (n = 2). The injury was located on a depilated dorsum (n = 5) or a hind paw (n = 1). Adipose tissue was harvested from mice or rats, as autografts (n = 5); or discarded human fat, as a xenograft (n = 1).

Sultan et al. conducted a controlled study describing the physical and biochemical effects of human fat on burn scars of 20 mice, where they injected saline in one half and fat in the other. Fat-grafted mice expressed significantly elevated levels of stromal cell–derived factor-1, vascular endothelial growth factor, and CD31 expression (indicative of greater vascularity), and wound remodeling expressed by transforming growth factor-β and matrix metalloproteinase-9, compared with controls. They showed greater flux on laser Doppler scanning and less fibrosis.19 This study was the strongest murine study, as there were untreated control animals, and objective and statistically significant macroscopic and histologic evaluations.

Shokrgozar et al. supplemented collagen scaffolds with adipose-derived stem cells and showed epidermal regeneration in burn wounds treated in 10 rats compared with controls.20 Wound surface area and histopathologic findings with formation of dermis and epidermis on the scaffolds supplemented with adipose-derived stem cells were reported; however, statistical analysis was not mentioned.

Huang et al. investigated the effects of autologous fat on burn-induced neuropathic pain in 30 rats.21 Rats that received fat grafting had reduced burn-induced neuropathic mechanical allodynia by suppression of phosphorylation of p38 in microglial cells. The clinical and histologic findings were statistically significant, and there were untreated controls.

Loder et al. studied the effects of isolated autologous adipose-derived stem cells, fat, adipose-derived stem cells and fat, and phosphate-buffered saline grafts on burns of 20 mice.22 There was a significant decrease in wound surface area in all groups compared to controls, but not to each other. Adipose-derived stem cells and mixed groups showed significant decrease in wound depth apoptosis.

Karimi et al. reported significant increases in fibroplasia and collagen remodeling and a decrease in surface area of wounds treated with adipose-derived stem cells in comparison with fat grafts in 30 mice.23 The differences in eschar thickness, inflammatory cell counts, epithelialization, and angiogenesis were not significant.

Atalay et al. showed statistically significant decreased inflammation and fibroplastic proliferation, and increased vascular endothelial growth factor expression, vascularization, and proliferating cell nuclear antigen index (suggesting improved wound healing) in acute burns of rats injected with stromal vascular fraction.24 There was no macroscopic evaluation of the wounds.

The first three murine studies were conducted in burn scars,19–21 and the last three were conducted in acute burns showing the effects of fat and adipose regenerative cells on wound healing.22–24 The last two studies had histologic results reported by pathologists that were blinded to study groups (Tables 1 and 2).

DISCUSSION

Although limited in number, studies detailing the use of fat grafts or adipose-derived regenerative cells on burn wounds and scars have had positive results. Murine studies have suggested that fat grafting therapy can enhance vascularity, promote wound remodeling, and diminish neuropathic pain when administered weeks after injury.19,22 Such attributes are of particular utility when considering the common features of burn wounds: hypertrophic scars are characterized by an overactive proliferative phase and an impaired remodeling phase of wound healing,26 and neuropathic pain may occur in more than 50 percent of burn victims.27 Murine studies have also suggested that adipose-derived stem cell therapy may improve outcomes when applied on a newly acquired burn wound. Although some studies had conflicting results regarding the effect on wound surface area, most concluded that the early use of adipose-derived stem cell therapy altered the course of the remodeling phase of healing through decreased apoptosis22 and increased fibroplasia.24 Murine studies have limited applicability in human treatment; however, the human case-control studies, case series, and case reports have corroborating results.

With regard to treatment of burn scars, histologic analysis in human studies revealed that fat grafting may increase vascularity, new collagen deposition, and reorganization.9,11,13 Studies also reported improvements in mimic features, skin texture, thickness, color,11,13,14 and patient satisfaction.11,12,14 The utility of lipofilling as a secondary measure to improve previous treatments is also considerable. Although the regenerative capacity
<table>
<thead>
<tr>
<th>References</th>
<th>Processing Techniques</th>
<th>Acute Wounds vs. Scars</th>
<th>Clinical/Macroscopic Findings</th>
<th>Microscopic Findings</th>
<th>Study Strengths</th>
<th>Study Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human studies</td>
<td>Bruno et al., 2013</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Functional and aesthetic improvement, Increase patient satisfaction score</td>
<td>Improved vascularization of dermal papillae, Better organization of collagen, Significant decrease in S100-positive cells and Langerin-positive cells</td>
<td>Comparison to controls (half scar treated vs. half scar untreated), Double-blinded assessment of clinical evaluation, Statistical significance for histology and IHC, Objective measurement of clinical findings (Vancouver Scar Scale) confirmed by histologic findings, Adequate follow-up period, All scars resulted from burn injury</td>
</tr>
<tr>
<td>Klinger et al., 2013</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Pain relief, improved scar elasticity, mimic features, mobility, filling of volume deficits, Improved softness (Durometer), Improved POSAS</td>
<td>None reported</td>
<td>Comparison to controls (half scar injected with fat vs. half scar injected with saline), Randomized selection of patients, Objective measurement of clinical findings (POSAS and Durometer), Statistical significance for clinical findings</td>
<td>Scars resulting from various injuries (trauma, after surgery, radiotherapy, burns)</td>
</tr>
<tr>
<td>Gentile et al., 2014</td>
<td>Three methods: High-speed centrifugation, High speed centrifugation plus PRP, SVF enhancement</td>
<td>Scars</td>
<td>Restoration of contour, Improved texture, softness, Improved patient satisfaction</td>
<td>No microscopic evaluation of scars</td>
<td>Comparison of multiple fat-processing techniques, Objective measurement of contour maintenance by MRI/ultrasound, Statistical significance of clinical findings when compared to non-enhanced fat grafting, Adequate follow-up period (60 mo)</td>
<td>No comparison to untreated controls, Scars resulting from various injuries (trauma and burns)</td>
</tr>
<tr>
<td>Klinger et al., 2008</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Improved mimic features, skin texture, thickness, Soft-tissue contour documented by MRI</td>
<td>New collagen deposition, increased local vascularity, dermal hyperplasia</td>
<td>One of the earliest studies showing clinical improvement, All scars resulted from burn injury</td>
<td>Small sample size (n = 3), Lack of controls or statistical analysis</td>
</tr>
<tr>
<td>Caviggioli et al., 2010</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Improved nipple projection, skin texture, softness, color, elasticity, Improved patient satisfaction</td>
<td>None reported</td>
<td>Objective measurement of clinical findings, Adequate follow-up (2 yr)</td>
<td>Lack of controls or statistical analysis</td>
</tr>
<tr>
<td>References</td>
<td>Processing Techniques</td>
<td>Acute Wounds vs. Scars</td>
<td>Clinical/Macroscopic Findings</td>
<td>Microscopic Findings</td>
<td>Study Strengths</td>
<td>Study Weaknesses</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brongo et al., 201213</td>
<td>Low-speed centrifugation</td>
<td>Scars</td>
<td>Improved texture, softness, thickness, color Reduction of scar contracture Improved symptomatology per questionnaire</td>
<td>New collagen deposition, neoangiogenesis, dermal hyperplasia</td>
<td>All scars resulted from burn injury Adequate follow-up period (15 mo) Objective measurement of clinical findings (by means of questionnaire)</td>
<td>Lack of controls or statistical analysis</td>
</tr>
<tr>
<td>Viard et al., 201214</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Improved mimic features, skin texture, thickness Improved patient satisfaction</td>
<td>None reported</td>
<td>All scars resulted from burn injury</td>
<td>Lack of controls or statistical analysis Lack of objective clinical evaluation</td>
</tr>
<tr>
<td>Klinger et al., 2012*</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Pain relief, improved scar elasticity, mimic features, mobility in periarticular scars</td>
<td>None reported</td>
<td>Large sample size (n = 376) Added small group of 20 patients analyzed objectively, with statistical analysis (shown above*)</td>
<td>Lack of controls or statistical analysis Lack of objective clinical evaluation Scars resulting from various injuries (trauma, after surgery, radiotherapy, burns)</td>
</tr>
<tr>
<td>Keck et al., 201315</td>
<td>ASC isolation (from débrided burn skin)</td>
<td>Acute burns</td>
<td>Improved skin graft take (n = 3)</td>
<td>Histology showed débrided burn fat comparable to abdominal fat Adipose tissue detected in reconstructed areas</td>
<td>Novel therapeutic technique Potential for patients with large burn surface area</td>
<td>Lack of controls Small sample size (n = 5)</td>
</tr>
<tr>
<td>Piccolo et al., 201516</td>
<td>High-speed centrifugation</td>
<td>Acute, subacute burns, and scars</td>
<td>Improved wound healing, fibrosis, scar suppleness</td>
<td>Increase in elastic fibers</td>
<td>Large sample size (n = 240) Adequate follow-up (3-yr experience)</td>
<td>Lack of controls or statistical analysis Lack of objective clinical evaluation Scars resulting from various injuries (trauma, ulcers, burns)</td>
</tr>
<tr>
<td>Caviggioli et al., 200817</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Correction of functional deficits in periorbital region Improved skin texture, softness, elasticity</td>
<td>None reported</td>
<td>Adequate follow up (1 yr) One of the earliest studies showing clinical improvement</td>
<td>Small sample size (n = 1) Lack of objective clinical evaluation</td>
</tr>
<tr>
<td>Khouri et al., 201318</td>
<td>Low-speed centrifugation</td>
<td>Scars</td>
<td>Softened scar, increase mobility, texture</td>
<td>None reported</td>
<td>Objective measurement of functional improvement Small sample size (n = 5) Lack of controls</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>References</th>
<th>Processing Techniques</th>
<th>Acute Wounds vs. Scars</th>
<th>Clinical/Macroscopic Findings</th>
<th>Microscopic Findings</th>
<th>Study Strengths</th>
<th>Study Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sultan et al., 2012</td>
<td>High-speed centrifugation</td>
<td>Scars</td>
<td>Improved color, texture</td>
<td>Increase CD31&lt;sup&gt;+&lt;/sup&gt; cells, Picrosirius Red staining</td>
<td>Comparison to untreated control animals</td>
<td>Objective macroscopic evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greater flux by means of Doppler</td>
<td>Increased SDF-1, VEGF, TGF-β, and MMP9</td>
<td>Statistical significance for macroscopic and histologic findings</td>
<td></td>
</tr>
<tr>
<td>Shokrgozar et al., 2012</td>
<td>ASC isolation</td>
<td>Scars</td>
<td>Improved wound surface area</td>
<td>Increased epidermal regeneration</td>
<td>Comparison to untreated controls</td>
<td>Objective macroscopic evaluation</td>
</tr>
<tr>
<td>Huang et al., 2014</td>
<td>Mechanical mincing</td>
<td>Scars</td>
<td>Decreased force required to produce mechanical allodynia</td>
<td>Decreased p38&lt;sup&gt;+&lt;/sup&gt; and OX42&lt;sup&gt;+&lt;/sup&gt; cells, Increased collagen deposition, decreased cellularity</td>
<td>Comparison to untreated controls</td>
<td>Lack of statistical analysis</td>
</tr>
<tr>
<td>Loder et al., 2014</td>
<td>High-speed centrifugation plus ASC</td>
<td>Acute burns</td>
<td>Decreased wound surface area (all treatment groups) Decreased wound depth (ASC and mixed groups)</td>
<td>Decreased caspase staining and increased CD31 (ASC and mixed groups)</td>
<td>Comparison of ASC, fat graft, fat plus ASC, and untreated controls</td>
<td>Objective macroscopic evaluation Statistical significance for clinical and histologic findings</td>
</tr>
<tr>
<td>Karimi et al., 2014</td>
<td>Washing plus low-speed centrifugation ASC</td>
<td>Acute burns</td>
<td>Decreased wound surface area for ASC group (not significant)</td>
<td>Significantly increased fibroplasia, collagen remodeling</td>
<td>Comparison of ASC, fat graft, and untreated controls Pathologist blinded to study groups</td>
<td>Lack statistical significance for macroscopic findings</td>
</tr>
<tr>
<td>Atalay et al., 2014</td>
<td>SVF isolation</td>
<td>Acute burns</td>
<td>None reported</td>
<td>Decreased inflammation, fibroblastic proliferation, increased vascularization Increased PCNA index (wound healing), VEGF expression</td>
<td>Comparison to untreated controls Pathologist blinded to study groups</td>
<td>Lack objective macroscopic evaluation</td>
</tr>
</tbody>
</table>

IHC, immunohistochemistry; POSAS, Patient and Observer Scar Assessment Scale; PRP, platelet-rich plasma; SVF, stromal vascular fraction; MRI, magnetic resonance imaging; ASC, adipose-derived stem cells; SDF-1, stromal cell-derived factor 1; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; MMP9, matrix metalloproteinase 9; PCNA, proliferating cell nuclear antigen.

*Two studies were part of the same article.
of adipose-derived stem cells is an alluring concept, there are notably few human studies detailing the use of adipose-derived stem cell-supplemented grafts in burns. There were two human studies that investigated wound healing in its acute phase. The large series studied by Piccolo et al. showed improved wound healing and fibrosis in acute and subacute wounds. Although there was lack of controls, this article had pertinent details on the procedure, and adequate follow-up. The case series using adipose cells from discarded burned tissue was a small case series that was difficult to assess, but these cells were shown to share the adipogenic, osteogenic, and chondrogenic potential of their abdominally derived counterparts. Therefore, they may represent a source of multipotent cells in patients with extensive burns, for whom there may not be enough viable tissue to perform subcutaneous liposuction to obtain such cells from noninjured sites. Indeed, as the percentage of total body surface area affected by burn injury increases, so does the availability of these adipose-derived stem cells from discarded burn tissue.

Adipose-derived regenerative cells have been used in the treatment of other burn sequelae such as heterotopic ossification. These studies were not included, as we focused on the effects on burn wounds.

Although nearly all documented uses of this therapy on burn wounds have had positive results, it should be noted that much of the current literature consists of case reports or case series that lack rigorous statistical analysis (only two human studies included statistical analysis) or power. There has yet to be a large, prospective, randomized, controlled study detailing its use in patients with burn wounds and scars.

We have attempted to summarize all articles relevant to this subject. Our inclusion criteria were necessarily broad and our search terms were diverse, and we included articles in languages other than English. Still, we may have missed studies that have been undertaken with the use.
of fat grafting and burns. Even so, the results are encouraging. Reports of clinical and histologic improvements highlight the potential of this therapy (Fig. 2), and show that much is yet to be explored in this field.

CONCLUSIONS

After careful review of the literature regarding the utility of fat grafting and adipose-derived regenerative cells in the treatment of burns, it is apparent that this therapy has many documented benefits. Murine studies have shown histologic improvements in angiogenesis, collagen organization, and neuropathic pain. Human studies have shown similar biochemical effects in addition to improvements in clinical features such as skin texture, softness, coloration, and function, bearing in mind that the human experience is anecdotal and the laboratory experiences are questionable because of experimental design and number of subjects. This review suggests that, at this time, there is no significant literature to suggest that fat grafting in acute burn wounds facilitates wound healing and ameliorates subsequent scarring. There is substantial evidence that fat grafting in burn scars is helpful in modifying scar tissue. There is a dearth of randomized controlled trials and quantitative analysis supporting the efficacy of fat and adipose-derived stem cells in burns. However, this emerging therapy is encouraging. It is our hope that this review will be a foundation for future studies and highlight the breadth of knowledge yet to be explored by this therapy.

Alexandra Condé-Green, M.D.
Division of Plastic Surgery
Department of General Surgery
Rutgers New Jersey Medical School
Newark, N.J. 07103
acondegreen@yahoo.com

REFERENCES


学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：
图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具