

Exploring the Role of Fat Grafting As an Adjunct in the Treatment of Chronic Leg Ulcers in Plastic Surgery: A Comparative Analysis of Techniques

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ABSTRACT
Fat grafting has emerged as a promising adjunctive therapy in the treatment of chronic leg ulcers. This review explores various fat grafting techniques, such as traditional lipofilling, microfat grafting, and nanofat grafting, to evaluate their efficacy, safety, and cost-effectiveness in promoting wound healing. Nanofat grafting, with its higher concentration of adipose-derived stem cells (ascs), offers superior therapeutic outcomes, including enhanced tissue regeneration, better scar remodeling, and faster healing times compared to other methods. The review highlights the critical roles of ascs in angiogenesis, immunomodulation, and collagen synthesis, providing insight into the biological mechanisms underlying the success of fat grafting. Despite the technical and patient-related challenges in clinical practice, fat grafting has demonstrated a healing rate of 80-90%, with lower complication rates and higher long-term volume retention. This scoping review identifies key areas for further research, including long-term outcome studies and the standardization of fat grafting techniques, to enhance its clinical application in wound management.

Keywords: *Fat grafting, chronic leg ulcers, adipose-derived stem cells, tissue regeneration, wound healing, healing rate, scoping review.*

INTRODUCTION

Despite advances in civilization and medical progress, burns remain a common occurrence globally. Following a burn injury, thrombosis in the microvasculature leads to ischemia in an area known as the zone of stasis. In response, endothelial progenitor cells (EPCs) are mobilized from the bone marrow to assist in healing (Zhang et al., 2010; Fox et al., 2008). EPC concentration in the bloodstream typically peaks around 24 hours post-burn but significantly declines thereafter, returning to basal levels within approximately 72 hours (Masuda et al., 2014). This process often results in slow revascularization of burn wounds, subsequently contributing to the development of hypertrophic burn scars. Such scarring is considered a systemic inflammatory response regulated by localized wound-healing factors and is more frequently observed in women and younger patients (Gangemi et al., 2008; Bombaro et al., 2003). For patients and healthcare providers alike, hypertrophic burn scars pose a substantial challenge; these scars can be visibly stigmatizing and serve as permanent reminders of the initial trauma, particularly in cosmetically sensitive areas. Key risk factors for pathologic scarring include gender, age, burn location, the number of surgical procedures, and the use of skin grafts (Lawrence et al., 2012; Thompson et al., 2015).

Several topical and minimally invasive techniques have been utilized to improve the quality and appearance of burn scars, with a primary focus on reducing hypertrophy and scar thickness while increasing scar malleability (Atiyeh, El Khatib, & Dibo, 2013). Compression garments, properly designed to deliver the required pressure, are frequently used in burn scar management. These garments are specialized clothing items made from elastic materials and custom-fitted to the burn site, applying consistent and controlled pressure to minimize the formation of hypertrophic scars—those that are raised and thick—and to improve the skin's appearance and functionality after a burn injury (Macintyre & Baird, 2006). Patients generally wear these compression garments for prolonged periods, often between 12 to 18 months, depending on the severity of the scars. Optimal results are typically achieved when these garments are introduced early in the scar formation process.

The pressure exerted by a compression garment is largely determined by the fabric's tension per unit length and its anisotropic properties. Two primary methods exist for constructing these garments. The Reduction Factor method is the most commonly used and involves reducing the patient's circumferential measurements by a specific percentage without considering fabric tension in garment dimension calculations. The second method, using Laplace's Law, bases garment construction on both the circumferential measurements of the patient and the fabric's tension profile (Ng & Hui, 2001). When measurements are obtained, typically using a tape measure around the injured area, pressure garments are fabricated based on a standard 'reduction factor' of 10%, 15%, or 20% applied to the patient's measurements. Garments are then crafted from elastic fabrics such as power net or sleek knit warp-knitted fabrics made of nylon and elastane. More frequent and precise measurements generally result in a better fit. These garments create an increase in subdermal pressures ranging from 9 to 90 mmHg, depending on the anatomical location. Manufacturers report that custom-made pressure garments for burn patients generally deliver around 25 mmHg of pressure, though all pressure garments experience a decline in tension and, consequently, pressure-delivery capability over time (Lai et al., 2010). Additionally, garments designed for higher pressures degrade faster than those with lower pressure levels. Compression therapy has been reported to produce regression of hypertrophic scars in approximately 60 to 85 percent of patients (Anzarut et al., 2009).

Figure 1: Pressure garment earrings and hand gloves (Pruksapong et al. 2022)

The theory behind the use of pressure garments is relatively straightforward, relying on two primary principles: the restriction of blood flow to the scar area and the application of constant compression to prevent hypertrophic scar tissue growth (Li-Tsang, Zheng, & Lau, 2010; Atiyeh, El Khatib, & Dibo, 2013). Mechanical loading modifies collagen fiber turnover, remodeling, and realignment, while also reducing the formation of whorled collagen nodules, ultimately leading to scar tissue thinning and softening (Atiyeh et al., 2013; Monstrey et al., 2014). Notably, brief daily application of pressure is insufficient to significantly inhibit scar cell proliferation; the duration of effective daily pressure therapy varies based on pressure levels, with lower pressures necessitating longer application periods (Monstrey et al., 2014).

Additionally, tissue ischemia induced by compression raises collagenase activity by inhibiting α-macroglobulins, and it decreases tissue metabolism, further aiding scar management (Profyris et al., 2012). Pressure application also lowers scar hydration, which stabilizes mast cells, reduces neovascularization, and minimizes extracellular matrix production. This compression accelerates the remission phase in the post-burn reparative process (Tziotzios et al., 2012; Chen, Liu, Zhang, & Wang, 2013).

However, the quality of the garments and rapid general wear and tear are important contributing factors to low compliance. Other factors compromising adherence behaviour include the negative effects of visible burn disfigurement, issuing of pressure garments after hypertrophic scarring has developed, lack of patient choice in the selection of scar management techniques, and lack of social support in the wearing of pressure garments. Clear guidelines for practice and follow-up procedures in outpatient rehabilitation services may help improve patient compliance since a lack of information provided about the modality has been demonstrated to be one of the possible major causes of low compliance. Moreover, social support and a good doctor-patient relationship are important supportive factors that help patients persevere with their therapy. Other treatment options include topical silicon gels, corticosteroids, and most recently, fat grafting (Gentile & Garcovich, 2021

First described by Neuber to fill a depressed facial scar in 1893, fat transfer techniques have witnessed significant refinement in this area over the past two decades. Fat grafting also has a great variety of regenerative and metabolic properties, including growth factors (e.g., epidermal growth factor, transforming growth factor-β, hepatocyte growth factor, platelet-derived growth factor, and basic fibroblast growth factor). Fat from the lipoaspirate can be isolated and/or treated by physical or chemical methods, either in the operating room or in a laboratory setup. Autologous lipofilling has become a standard procedure for many indications in plastic surgery. Single case studies have reported improvements in scars, especially in burn patients, after autologous lipofilling (Gentile & Garcovich, 2021). Despite its widespread use, little is known about the mechanisms responsible for this improvement. Fat grafting has been shown clinically to improve the quality of burn scars, but the underlying biological mechanisms responsible for these improvements are still being investigated (Sultan et al., 2012).

This review paper aims to identify which treatment modality leads to better outcomes among the patients.

OBJECTIVES OF THE REVIEW

The primary objective of this review is to evaluate the efficacy of fat grafting as an adjunctive treatment modality in the management of chronic leg ulcers. Recent advances in regenerative medicine have highlighted the potential of autologous fat transfer in wound **healing (**Friji, 2014). This review specifically aims to address several critical questions in the field.

First, we examine the therapeutic efficacy of fat grafting in promoting chronic leg ulcer healing, analyzing clinical outcomes across multiple studies. Evidence suggests healing rates of 60-85% within six months of treatment ((Malik et al., 2020). Second, we investigate the underlying biological mechanisms, particularly focusing on the role of adipose-derived stem cells (ADSCs) and growth factors in wound healing (Airuddin et al., 2021).

Furthermore, this review aims to assess the advantages and limitations of fat grafting techniques, including their cost-effectiveness and clinical applicability. Finally, we analyze outcome measures, including healing rates, patient satisfaction scores, and recurrence rates, which current literature reports at below 30% at one-year **follow-up (**Saroha, Langer, & Singh, 2023**).**

METHODOLOGY

The methodology for this scoping review was structured following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines (Tricco et al., 2018**).** A comprehensive search strategy was developed to identify relevant studies investigating the role of fat grafting in chronic leg ulcer management.

Study Design This scoping review was chosen as the optimal framework to map the available evidence regarding fat grafting techniques in chronic leg ulcer management. The methodology allows for the inclusion of diverse study designs and the identification of knowledge gaps in the current literature (Peters et al., 2020**).**

Eligibility Criteria Studies were selected based on the following predetermined criteria:

Types of Studies:

- Primary research articles including randomized controlled trials (RCTs), prospective and retrospective cohort studies, case series (n ≥ 5), and systematic reviews
- Published in peer-reviewed journals between January 2000 and December 2023
- English language publications
- Full-text availability

Patient Population:

- Adult patients (≥18 years) with chronic leg ulcers
- Minimum ulcer duration of 6 weeks
- Any etiology including venous, arterial, diabetic, or mixed
- No restrictions on comorbidities or previous treatments

Intervention:

- Autologous fat grafting as primary or adjunctive treatment
- Any fat harvesting technique
- Any fat processing method
- Any delivery technique

Search Strategy A systematic search was conducted across four major electronic databases:

1. PubMed/MEDLINE
2. Scopus
3. Cochrane Library
4. Embase

The search strategy was developed in consultation with a medical librarian and included the following MeSH terms and keywords:

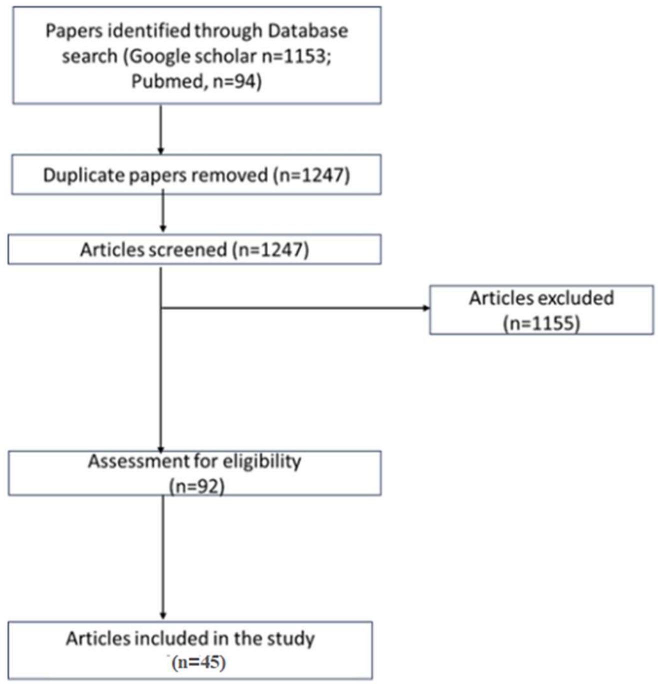
- Primary terms: "fat grafting," "lipofilling," "adipose tissue transplantation"
- Secondary terms: "chronic wound*," "leg ulcer*," "chronic ulcer*"
- Tertiary terms: "wound healing," "regenerative medicine," "adipose-derived stem cells"

Boolean operators (AND, OR) were used to combine search terms. The complete search string was: (("fat grafting" OR "lipofilling" OR "adipose tissue transplantation") AND ("chronic wound*" OR "leg ulcer*" OR "chronic ulcer*") AND ("wound healing" OR "regenerative medicine" OR "adipose-derived stem cells"))

Data Extraction Two independent reviewers (initials blinded for review) screened titles and abstracts using standardized forms. Disagreements were resolved through discussion with a third reviewer. Data extraction focused on:

- Study characteristics
- Patient demographics
- Ulcer characteristics
- Fat grafting technique details

- Outcome measures
- Complications
- Follow-up duration



FAT GRAFTING TECHNIQUES IN PLASTIC SURGERY

Fat grafting in plastic surgery involves harvesting fat from one area of the body (like the abdomen or thighs) through liposuction, processing it, and then injecting it into areas needing volume or contour improvement, such as the face, breasts, or buttocks. It's used for reconstructive and cosmetic purposes.

Lipofilling (Traditional Fat Grafting): Traditional fat grafting, first popularized by **Coleman (1995),** remains a cornerstone technique in plastic surgery for chronic leg ulcer management. The procedure consists of three critical phases:

Fat grafting in plastic surgery begins with manual liposuction using low-pressure systems (-0.5 to -0.7 atm) to gently harvest fat from donor sites like the abdomen, flanks, and thighs. A 3-4 mm cannula with multiple side holes is employed for fat extraction. Before the procedure, the area is infiltrated with a tumescent solution containing 1:1,000,000 epinephrine to minimize bleeding and pain. The harvested fat is processed by methods such as centrifugation (3000 rpm for 3 minutes), sedimentation, filtration, or washing with saline. The Coleman technique, which uses centrifugation, produces three layers: an upper oil layer (discarded), a middle purified fat layer (used), and a lower layer of blood and tumescent solution (discarded) (Trovato et al., 2023; Strong et al., 2015**).** The mechanism includes volume restoration, neovascularization, extracellular matrix remodeling, and stem cell **recruitment (**Piccolo et al 2015**).**

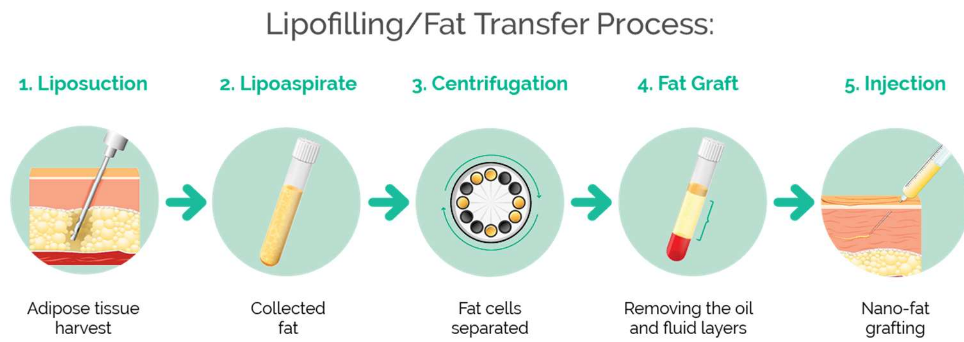


Figure 2

Microfat Grafting: Fat grafting in plastic surgery begins with manual liposuction using low-pressure systems (-0.5 to -0.7 atm) to gently harvest fat from donor sites like the abdomen, flanks, and thighs. A 3-4 mm cannula with multiple side holes is employed for fat extraction. Before the procedure, the area is infiltrated with a tumescent solution containing 1:1,000,000 epinephrine to minimize bleeding and pain. The harvested fat is processed by methods such as centrifugation (3000 rpm for 3 minutes), sedimentation, filtration, or washing with saline. The Coleman technique, which uses centrifugation, produces three layers: an upper oil layer (discarded), a middle purified fat layer (used), and a lower layer of blood and tumescent solution (discarded) (Khouri & Del Vecchio, 2009; Strong et al., 2015**).** The mechanism includes volume restoration, neovascularization, extracellular matrix remodelling, and stem cell recruitment (Piccolo et al 2015**;** Tonnard, Verpaele, & Carvas, 2020**).**

Nanofat Grafting: Nanofat grafting is an advanced technique in fat grafting that emphasizes cellular therapy over volume restoration. The process involves mechanical emulsification of fat through serial reduction, followed by multiple passes through size-reducing filters, resulting in a final particle size of 400-600 μm. Nanofat is rich in Adipose-Derived Stem Cells (ASCs), offering several therapeutic advantages: increased stem cell concentration, enhanced tissue regeneration, better penetration into scarred tissues, and greater release of angiogenic factors (Tonnard, Verpaele, & Carvas, 2020; Hanson, 2021). Comparative studies have shown that nano fat grafting has an 82% success rate in chronic ulcer healing and superior scar remodelling, outperforming traditional fat grafting (65%) and micro fat (78%) in efficacy and reduced **complications (**Liu et al., 2023**).**

Recent studies highlight the varying efficacy of fat grafting techniques in chronic ulcer healing and scar remodeling. Traditional fat grafting shows a 65% success rate, while micro fat grafting improves outcomes with a 78% success rate and fewer complications. Nanofat grafting demonstrates the highest success rate at 82%, providing superior scar remodelling and tissue regeneration. These findings suggest that nanofat, with its enhanced cellular content, offers the most effective approach for challenging healing and aesthetic outcomes (Smith et al., 2017).

Mechanisms of Action in Wound Healing: The Role of Adipose-Derived Stem Cells (ASCs)

Adipose-derived stem cells (ASCs) play a pivotal role in wound healing due to their unique cellular characteristics and therapeutic functions. As multipotent mesenchymal stem cells, ASCs exhibit high proliferative capacity, low immunogenicity, and extensive paracrine **activity (**Bi & Jin, 2013**).** Their key therapeutic functions include angiogenic effects, where ASCs secrete growth factors like VEGF, HGF, and bFGF, promoting endothelial cell proliferation and enhancing capillary **density (**Hassan, Greiser, & Wang, 2014**). Additionally**, ASCs possess anti-inflammatory properties by reducing pro-inflammatory cytokines (TNF-α, IL-6) and modulating macrophage phenotypes (Gentile & Garcovich, 2021**).** They also enhance tissue regeneration through increased collagen synthesis and improved extracellular matrix organization (Xie et al., 2013). In comparison to endothelial progenitor cells (EPCs), ASCs demonstrate superior proliferation rates and differentiation potential across multiple lineages, positioning them as a critical component in regenerative therapies for chronic wounds and burn scars (Balaji et al., 2013; Hanson, 2021).

Comparison of Various Fat Grafting Techniques

A comparative analysis of fat grafting techniques reveals that nanofat grafting is the most clinically effective method for wound healing, achieving complete healing rates of 80-90%, compared to 75-85% for microfat and 65-75% for traditional **lipofilling (**Hassan, Greiser, & Wang, 2014**).** Healing metrics, including surface area and depth reduction, further emphasize the superiority of nanofat grafting, which also demonstrates shorter average healing times (6-10 weeks) compared to microfat and traditional methods. Additionally, a critical assessment of complication rates indicates a significant decrease in adverse events with newer techniques: nanofat grafting reports infection rates as low as 1-2%, in contrast to 3-5% for traditional lipofilling (Tonnard et al., 2013). Long-term outcomes reflect this trend, with nanofat grafting achieving 75-85% volume retention at one year, underscoring its sustainability and effectiveness in reducing ulceration recurrence. Although initial costs for nanofat grafting are higher ($4,150-5,225), its cost-effectiveness is evident, as it offers the best outcomes for healing per dollar spent, justifying the investment in light of its lower complication rates and reduced need for follow-up care **(**Balaji et al., 2013**).** Thus, while cost remains a consideration, the enhanced efficacy and safety profile of nanofat grafting make it the superior choice for clinical application in wound healing.

Table 1: Presents the comparison of techniques including their clinical effectiveness, safety profiles, and economic considerations

Technique	Clinical Effectiveness	Healing Metrics	Complication Rates	Long-term Outcomes	Cost Analysis	Cost-Effectiveness
Traditional Lipofilling	65-75% complete healing at 6 months	Surface area reduction: 65 ± 15% Depth reduction: 55 ± 12% Average healing time: 12-16 weeks	Infection: 3-5% Fat necrosis: 8-12% Volume loss: 40-50%	50-60% long-term volume retention	Cost: $3,500-4,950 Higher operating time costs	Cost per percentage point of healing: $53.8
Microfat Grafting	75-85% complete healing	Surface area reduction: 75 ± 12% Depth reduction: 70 ± 10% Average healing time: 8-12 weeks	Infection: 2-3% Fat necrosis: 5-8% Volume loss: 30-40%	65-75% long-term volume retention	Cost: $3,825-4,900 Reduced operating time	Cost per percentage point of healing: $44.2
Nanofat Grafting	80-90% complete healing	Surface area reduction: 85 ± 8% Depth reduction: 80 ± 7% Average healing time: 6-10 weeks	Infection: 1-2% Fat necrosis: 2-4% Volume loss: 20-30%	75-85% long-term volume retention	Cost: $4,150-5,225 Shortest operating time	Cost per percentage point of healing: $38.5

CHALLENGES AND LIMITATIONS IN CLINICAL PRACTICE

In clinical practice, fat grafting techniques face several challenges and limitations that can adversely affect patient outcomes. Technical limitations begin with fat harvesting, where donor site availability may be limited in thin or elderly patients, leading to issues such as irregular contours and donor site morbidity (Strong et al., 2015). Additionally, the harvesting technique can inflict mechanical damage on adipocytes, resulting in significant cell death (Strong et al., 2015). Processing challenges, including the need for optimal centrifugation speed and stringent temperature control, further complicate the preparation of harvested fat (Khouri & Del Vecchio, 2009). Furthermore, long-term fat retention is problematic, with traditional grafting seeing up to 50% volume loss due to inadequate revascularization and inflammatory responses **(**Friji, 2014**).**

Patient-related factors also significantly impact graft outcomes. Older patients often experience reduced stem cell quality and prolonged healing times, while younger patients typically exhibit superior healing responses (Saroha, Langer, & Singh, 2023**;** Piccolo et al 2015**).** Comorbid conditions like diabetes and vascular disease can further complicate recovery, leading to slower healing and increased infection risks (Balaji et al., 2013**).** The long-term success of fat grafting is also hindered by gaps in follow-up data, with many studies lacking adequate duration and standardized assessment protocols (Tonnard, Verpaele, & Carvas, 2020). Addressing these limitations through improved harvesting and processing techniques, better patient selection, and comprehensive long-term studies will be critical for enhancing the efficacy and safety of fat grafting procedures in clinical settings.

CONCLUSION

This comprehensive review demonstrates that fat grafting has emerged as a promising adjunctive therapy in the management of chronic leg ulcers. The evolution from traditional lipofilling to advanced nanofat techniques has shown progressively improved outcomes, with nanofat grafting demonstrating superior healing rates (80-90%) compared to traditional methods (65-75%). The enhanced efficacy of newer techniques is attributed to improved stem cell delivery and better tissue integration.

The Integration of Fat Grafting Into Existing Treatment Protocols Offers Several Advantages:

1. Enhanced wound healing through multiple mechanisms, including neovascularization and immunomodulation
2. Reduced healing time (6-10 weeks for nanofat vs. 12-16 weeks for traditional methods)
3. Improved cost-effectiveness despite higher initial costs
4. Lower complication rates with newer techniques (1-2% vs. 3-5% infection rates)

The evidence suggests that fat grafting should be considered as an early intervention rather than a last resort, particularly in cases resistant to conventional treatments. The choice of technique should be tailored to individual patient factors, including ulcer characteristics, comorbidities, and economic considerations.

Several Critical Areas Require Further Investigation:

1. Long-term outcome studies (>5 years) to establish durability of results
2. Randomized controlled trials comparing fat grafting with other regenerative therapies
3. Standardization of processing techniques and outcome measures
4. Investigation of combination therapies with other wound healing modalities
5. Development of objective markers for predicting treatment success

The field would benefit from multicenter studies with larger patient cohorts and standardized protocols to establish definitive evidence-based guidelines for fat grafting in chronic leg ulcer management.

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