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A Systematic Review of Autologous Fat Grafting in the Treatment of Acute and Chronic Cutaneous Wounds

Dean Malik, MSc, BMBS, BSc(Hons)*
Joshua Luck, MRCS, MSc, BMBCh, BA(Hons)*
Oliver J. Smith, MRCS, MBChB, BSc(Hons)*†
Afshin Mosahebi, PhD, FRCS(Plast), MBA, MBBS*†

Background: There is a growing interest in the regenerative potential of autologous fat. Adipose-derived stem cells, within the stromal vascular fraction of lipoaspirate samples, demonstrate anti-inflammatory, immunomodulatory, and angiogenic properties. This systematic review aimed to determine the efficacy and safety of autologous fat therapies for wound healing, with an evaluation of the quality of evidence provided by the literature.
Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we searched Ovid Medline, Embase, and Cochrane Library databases from inception to November 2018. We included all human studies where wounds were treated with lipotransfer, cell-assisted lipotransfer, stromal vascular fraction products, or isolated adipose-derived stem cells. Study screening and data extraction were performed by 2 authors. The quality of evidence was evaluated using the GRADE approach.
Results: The search strategy returned 5027 citations. From these, 10 observational case series were included in the qualitative synthesis; there were no randomized controlled trials. Patient characteristics, wound etiology, and intervention type differed markedly between studies, precluding formal meta-analysis. Autologous fat grafting was associated with satisfactory wound healing in all studies with low complication rates. However, the quality of evidence was consistently very low.
Conclusions: Autologous fat grafting is an emerging therapeutic option for challenging wounds, although there is insufficient evidence to conclusively demonstrate its effectiveness and adverse event profile. Based on the literature to date, it is unclear whether one type of autologous fat therapy is superior. Well-designed, blinded, prospective randomized controlled trials with adequate methodologic details and objective outcome measure reporting are essential. *(Plast Reconstr Surg Glob Open 2020;8:e2835; doi: 10.1097/GOX.0000000000002835; Published online 18 May 2020.)*
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INTRODUCTION

Autologous fat grafting (AFG) has long been used as an esthetic technique for correcting volume loss or contour defects.[1] The popularity of AFG increased significantly in the late 1980s, when an abundance of fat from liposuction procedures allowed surgeons to experiment with its therapeutic potential.[2] However, it was not until 2001 that mesenchymal stem/stromal cells—now termed adipose-derived stem cells (ADSCs)—were first isolated from lipoaspirate tissue.[3]

Over the past decade, there has been growing interest in the regenerative potential of AFG and related ADSC therapies.[4] ADSCs are capable of multilineage differentiation into various terminal phenotypes (including keratinocytes, fibroblasts, and endothelial cells) that contribute to cutaneous wound healing.[5] Unlike bone marrow–derived stem cells, ADSCs may be harvested with minimal donor site morbidity and used without culturing or expansion.[6,7] Adipose tissue also provides a markedly higher number of stem cells than bone marrow, with up

*From the *Division of Surgery and Interventional Science, Royal Free Hospital, University College London, London, United Kingdom; and †Department of Plastic and Reconstructive Surgery, Royal Free Hospital, London, United Kingdom.*

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to 5000 ADSC precursors per gram of fat.[2,5] As a result, ADSCs have already been trialed in various regenerative settings, including scar revision and wound healing.[1,8,9]

However, the literature is confusing when it comes to differentiating between conventional AFG and emerging cell therapy approaches. As such, it is important to clarify what is meant by AFG before elaborating on this review. Here, we define AFG as the transfer of lipoaspirate tissue (lipotransfer) from a donor site to a recipient site. The standard AFG procedure used is the Coleman technique, which may be subdivided into harvesting, refinement, and application steps. Fat harvesting sites are selected according to accessibility or esthetic factors, with studies showing similar outcomes between different donor regions.[2,10] Small incisions are made, and a blunt-tipped harvesting cannula is advanced into the donor region. Tumescent solution, containing saline with local anesthetic and/or adrenaline, may be infiltrated locally to ease aspiration and minimize bleeding. Harvested lipoaspirate is then typically processed by centrifugation to obtain a condensed adipose tissue pellet, although alternative refinement techniques exist.[11] The final lipoaspirate product is then injected in layers into the recipient site (Fig. 1).

Although the Coleman technique represents the standard AFG technique, several variations exist. One of these which has gathered considerable attention is cell-assisted lipotransfer (CAL). In CAL, either purified ADSCs or the mixed cellular components of the stromal vascular fraction (SVF) are added to processed lipoaspirate tissue before application. Alternatively, the SVF or isolated ADSCs may be injected without reconstitution; here, the intention is to provide equivalent regenerative effects while limiting the volume of fat injected (Fig. 2).

AFG is an emerging treatment option for cutaneous wounds, with preclinical evidence showing that AFG provides an abundance of cytokines and growth factors that promote soft-tissue regeneration and remodeling.[1] However, much of the literature supporting AFG for wound healing is based on animal studies, and, as yet, there has been no systematic evaluation of the literature in humans. Therefore, this systematic review aims to critically assess the efficacy and safety of AFG in acute and chronic cutaneous wounds, with an appraisal of the quality of evidence available. A secondary objective is to identify which approach to AFG is superior and whether this varies according to the characteristics of the wound. The protocol for this systematic review was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) (PROSPERO ID: CRD42017081499) and published in full before this review was conducted.[12]

METHODS

This systematic review was conducted in accordance with both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[13] and the Meta-analysis Of Observational Studies in Epidemiology guidelines.[14]

Search Methods

Bibliographic databases (Ovid Medline, Embase, and The Cochrane Library) were searched for relevant articles from inception to November 2018. Free-text terms and MeSH headings were combined with Boolean operators (Table 1).

Database results were merged before discarding duplicate entries. Titles and abstracts were then screened to eliminate unrelated results, and the remaining articles were read in full.

Study Selection

All authors agreed on the study selection criteria during the protocol stage (PROSPERO ID: CRD42017081499).[12] All primary clinical studies using AFG in human subjects

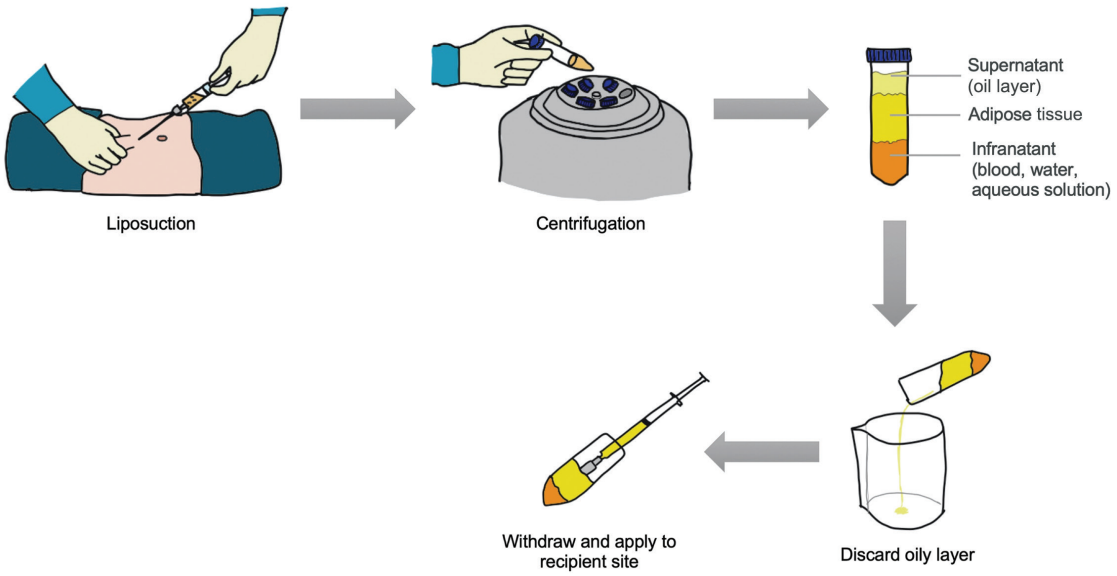

Fig. 1. Coleman technique for standard autologous fat grafting. The lipoaspirate is centrifuged with the supernatant and the infranatant is removed before grafting.

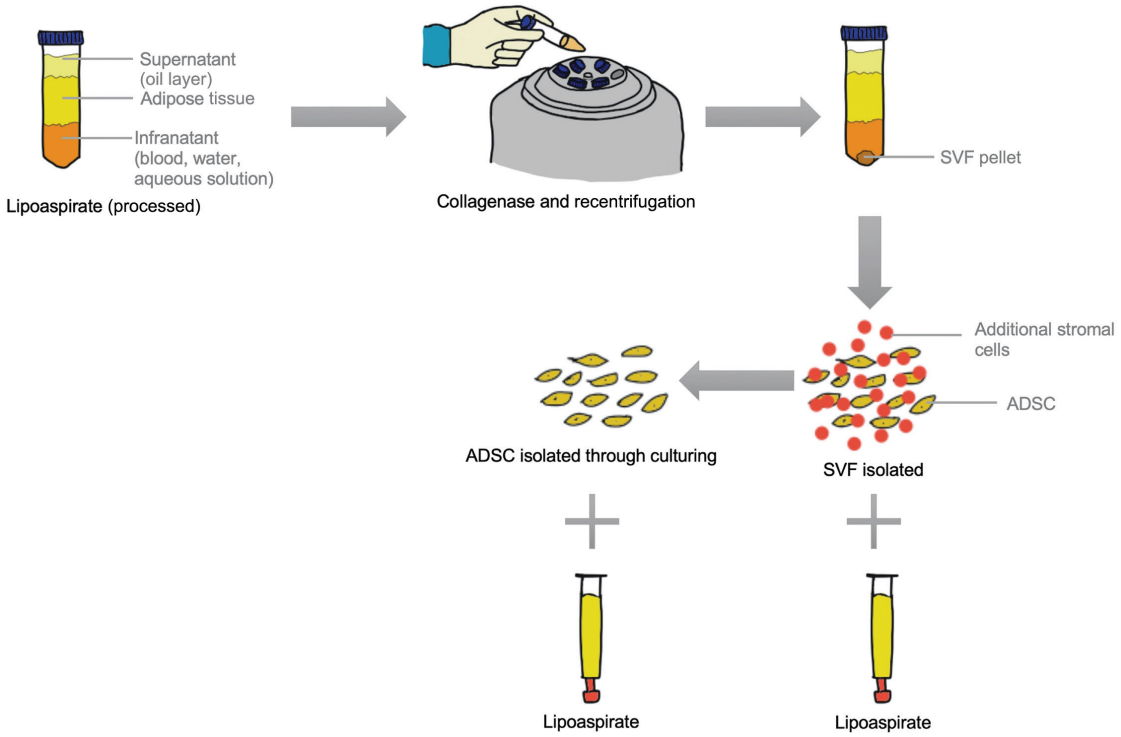

Fig. 2. CAL. Isolated SVF cells or cultured ADSCs may be recombined with lipoaspirate before application as CAL.

Table 1. Summary of the Search Terms Used

Search Terms	MeSH Terms
Fat graft*	Adipose tissue
Fat transf*	Lipectomy
Fat transplant*	Skin ulcer
Fat inject*	Transplantation, autologous
Adipose graft*	Wound healing
Adipose stem cell*	
Adipose derived stem cell*	
Adipose transplant*	
ASC*	
ADSC*	
Lipofill*	
Lipotransf*	
Lipomodell*	
Wound heal*	
Wound management	
Wound treat*	
Ulcer heal*	
Ulcer management*	
Ulcer treat*	
Search 1	(fat graft* OR fat transf* OR fat transplant* OR fat inject*) AND (wound heal* OR wound management OR wound treat*)
Search 2	(adipose graft* OR adipose stem cell* OR adipose derived stem cell* OR adipose transplant* OR ASC* OR ADSC*) AND (wound heal* OR wound management OR wound treat*)
Search 3	(Lipofill* OR lipotransf* OR lipomodell*) AND (wound heal* OR wound management OR wound treat*)
Search 4	(fat graft* OR fat transf* OR fat transplant* OR fat inject*) AND (ulcer heal* OR ulcer management OR ulcer treat*)
Search 5	(adipose graft* OR adipose stem cell* OR adipose derived stem cell* OR adipose transplant* OR ASC* OR ADSC*) AND (ulcer heal* OR ulcer management OR ulcer treat*)
Search 6	(Lipofill* OR lipotransf* OR lipomodell*) AND (ulcer heal* OR ulcer management OR ulcer treat*)

ASC, adipose stem cells.

for acute or chronic cutaneous wounds (defined as loss of epithelial continuity) of any depth were included. This included randomized controlled and observational studies with ≥3 participants. There were no restrictions applied to age, sex, defect location, harvesting site, processing technique, application method, or additional adjunct therapies.

Animal studies were excluded, as were those combining AFG with platelet-rich plasma, as this topic has already been reviewed by our research group.[15] Articles focusing on non-wound etiologies, including esthetic surgery, breast reconstruction, or scar revision, were excluded. The primary search was undertaken in English, and non-English articles not available for translation were excluded.

Letters, conference abstracts, and ongoing research were also excluded from the final analysis.

Data Extraction

Data collection and analysis was completed as per the Cochrane Handbook of Systematic Reviews of Interventions.[16] All data were recorded (in duplicates) onto a predesigned form by 2 authors to ensure accuracy. Disagreements were resolved by discussion and consensus. Data were collected on the following factors:

1. Study and demographic information
2. Preintervention wound characteristics
3. AFG application methodology
4. Postintervention wound healing outcomes

Where studies provided information from multiple interventions, only data relevant to the current research question were extracted. An additional objective of this systematic review was to assess the quality and details of published articles; therefore, no assumptions were made during data collection, and the authors were not contacted to provide missing information.

Summary Measures

The primary outcome measure specified in our protocol was the proportion of completely healed wounds at 12 weeks. However, owing to study reporting heterogeneity, this was modified to the proportion of completely healed wounds at follow-up times specified by individual authors.

Secondary outcome measures included: the proportion of partially healed wounds at reported endpoints (defined as a 1%–99% reduction in wound surface area); the time to complete wound healing (defined as complete re-epithelialization); and adverse event rates (related to either the donor or recipient site).

Quality of Evidence Appraisal

All authors appraised the quality of evidence across all included studies for each outcome using the systematic approach to rating the certainty of evidence in systematic reviews (GRADE).[17]

Statistical Analysis

We provide descriptive statistics for all relevant data related to the current research objective. A formal meta-analysis was not performed as a result of marked study heterogeneity. Where possible, summary data are presented as mean and range.

Additional Subgroup Analyses

A secondary aim was to establish if one or more techniques are superior; therefore, data are presented according to the type of intervention used.

RESULTS

Study Selection

The electronic search strategy returned a total of 5027 results. After removing duplicate citations, 4216 titles and abstracts were screened. Thirty-eight articles were read in full to determine their eligibility for inclusion. From this shortlist, 28 articles were excluded due to insufficient number of patients (n = 6), non-wound etiologies (n = 8), non-AFG treatment (n = 8), conference abstracts (n = 5), and unavailable English translation (n = 1). A total of 10 articles were included in the qualitative synthesis (Fig. 3).

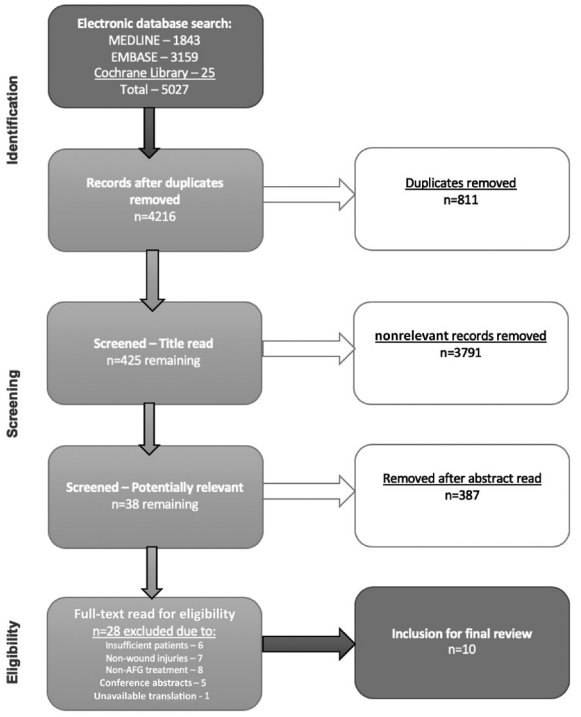

Fig. 3. The PRISMA study selection diagram. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Characteristics

All 10 included studies were observational case series; there were no randomized controlled trials (RCTs). Studies were undertaken from 2013 onward and across 4 different continents (Table 2).

Studies included an average of 62 patients (5–282) with a mean age of 53.1 (24–86) and followed them up for an average of 5.3 months.[3–10] The average number of total wounds treated, where reported, was 7.6.[5–26] Two studies did not report on the total number of wounds treated,[20,22] 3 did not report on the male-to-female ratio,[20,22,24] and 1 did not report on the age or length of follow-up of included participants.[22]

Wound etiology differed markedly between studies (Table 3). Only 1 study focused on acute wounds.[25] Six studies focused on lower limb wounds treated; the remaining studies focused on the face,[25] upper limb,[19,21] and buttocks.[20] One study did not describe the location or type of wounds treated.[22]

Where reported, the average preintervention wound surface area was 21.9 cm^2 (1.7–247.0 cm^2). Five studies did not provide any information on preintervention wound size.[19–22,24,25] Eight studies made no assessment of

Table 2. Summary of the 10 Included Studies

Year	Author	Title	Journal	Country	Study Design	Level of Evidence	M:F Ratio	Mean Age (Range)	Length of Follow-up (mo)
2013	Marino et al[18]	Therapy with autologous adipose-derived regenerative cells for the care of chronic ulcer of lower limbs in patients with peripheral arterial disease	*Journal of Surgical Research*	Italy	Case series, prospective	4	7:3	65.8 (61–70)	3
2014	Del Bene et al[19]	Autologous fat grafting for scleroderma-induced digital ulcers. An effective technique in patients with systemic sclerosis	*Handchir Mikrochir Plast Chir*	Italy	Case series, prospective	4	1:8	63 (43–76)	3
2014	Marangi et al[20]	Treatment of early-stage pressure ulcers by using autologous adipose tissue grafts	*Plastic Surgery International*	Italy	Case series, prospective	4	Unspecified	54 (44–65)	3
2015	Del Papa et al[21]	Regional implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting indolent digital ulcers in patients with systemic sclerosis	*Cell Transplantation*	Italy	Case series, prospective	4	0:15	55.4 (40–66)	6
2015	Piccolo et al[22]	Fat grafting for treatment of burns, burn scars, and other difficult wounds	*Clin Plast Surg*	Brazil	Case series, prospective	4	Unspecified	Unspecified	6
2015	Stasch et al[23]	Débridement and autologous lipotransfer for chronic ulceration of the diabetic foot and lower limb improves wound healing	*Plastic & Reconstructive Surgery*	Germany	Case series, prospective	4	17:9	59 (25–85)	4
2016	Caviglia et al[24]	Is it possible to use autologous adipose graft for wound repair in patients with coagulation disorders?	*Haemophilia*	Argentina	Case series, prospective	4	Unspecified	47.2 (27–62)	6
2016	Kim et al[25]	Early Intervention with highly condensed adipose-derived stem cells for complicated wounds following filler injections	*Aesth Plast Surg*	South Korea	Case series, retrospective	4	0:12	35.6 (24-52)	6
2017	Carstens et al[26]	Non-reconstructable peripheral vascular disease of the lower extremity in ten patients treated with adipose-derived stromal vascular fraction cells	*Stem Cell Research*	Nicaragua	Case series, prospective	4	1:5	73 (57–85)	10
2017	Chopinaud et al[27]	Autologous adipose tissue graft to treat hypertensive leg ulcer: a pilot study	*Dermatology*	France	Case series, prospective	4	7:3	78.3 (70–86)	6

F, female; M, male.

the wound depth. In the 2 studies that detailed wound depth,[18,20] this averaged 0.87 cm (0.2–3.0 cm).

Fat Harvesting

Fat was harvested from the abdomen in the majority of studies with additional sites, including the flank, buttocks, hip, thigh, and calf. Two studies did not specify the donor site.[19,26] This procedure, for the majority of cases, was performed under a general anesthetic approach, with only 2 studies using a local anesthetic approach.[19,21]

The liposuction approach used for harvesting fat was specified or described as a version of the Coleman technique in all studies except for 1 which did not provide this procedural details.[26] The majority of studies did not specify whether tumescent solution was administered. Five studies stated that they used tumescent solution, although only 4 provided details as to its constituents. Three of these studies used Klein's solution,[18,20,24] and 1 used adrenaline alone.[23]

Fat Processing

AFG processing varied considerably between included studies (Table 4). One study involved lipotransfer as per the Coleman technique, without a centrifugation step before administration.[23] Five studies used the standard Coleman technique for lipotransfer, centrifuging harvested lipoaspirate at 3000–3500 rpm for 1–4 minutes.[19,20,22,24,27]

Two studies used a CAL approach,[18,21] one of which used Celution, a commercial system for adipose isolation and processing.[18] Two studies used a purified SVF product, isolating the heterogenous cell pellet using an extended centrifugation protocol.[25,26] Of the 4 studies using either CAL or SVF-only approaches, only 2 determined cell viability before implantation.[18,26] There were no studies using isolated ADSCs only.

Application Method

Seven studies prepared the wound bed before AFG with either debridement or curettage (Table 4). Six studies injected the fat product into the wound edge.[18–20,24–26]

Table 3. Summary of Wound Data from Each Study

Author	Etiology	Wound Type	Location	Total No. Wounds	No. Patients With Wounds	No. Wounds per Patient	Wound Surface Area (cm^2)	Wound Depth (cm)
Marino et al[18]	Peripheral vascular disease and diabetes	Chronic	Lower limb	10	10	1	49.6 (3–247)	0.88 (0.2–3.0)
Del Bene et al[19]	Digital ulcers in systemic sclerosis	Chronic	Upper and lower limb	15	9	Unspecified	Unspecified	Unspecified
Marangi et al[20]	Pressure ulcers in paraplegia, spina bifida, multiple sclerosis, cerebrovascular accident, tetraplegia, and diabetes	Chronic	Ischium and sacrum	Unspecified	14	Unspecified	Unspecified	0.86 (0.52–1.13)
Del Papa et al[21]	Digital ulcers in systemic sclerosis	Chronic	Upper limb	15	15	1	4.1 (2.4–7.9)	Unspecified
Piccolo et al[22]	Burns, trauma, peripheral vascular disease, and diabetes	Unspecified	Unspecified	Unspecified	282	Unspecified	Unspecified	Unspecified
Stasch et al[23]	Pressure ulcers, peripheral vascular disease, and diabetes	Chronic	Lower limb	26	26	1	5.1 (1.7–10)	Unspecified
Caviglia et al[24]	Cutaneous fistulas in von Willebrand disease and hemophilia A	Chronic	Lower limb	5	5	1	Unspecified	Unspecified
Kim et al[25]	Postfiller necrosis	Acute	Face	12	12	1	Unspecified	Unspecified
Carstens et al[26]	Peripheral vascular disease and diabetes	Chronic	Lower limb	6	6	1	18.2 (7.5–35)	Unspecified
Chopinaud et al[27]	Hypertensive ulcers	Chronic	Lower limb	10	10	1	32.4 (13.8–59.4)	Unspecified

Two studies injected both the wound edge and the base,[22,23] and 1 study used microinjections into the wound edge and the base.[27] One study injected CAL products into the base alone.[21]

Where reported, the volume of fat injected varied markedly between studies, ranging from 0.5 to 21 mL. Three studies did not report on the volume of lipoaspirate tissue used.[22,24,25]

Most studies involved a single AFG intervention; only 3 studies used serial AFG treatments following failure to respond in a minority of cases.[22,23,25] Two studies did not report on the number of AFG applications.[18,20] All but one study used AFG at the same time of fat harvest,[18] with the storage of fat between harvest and application not being described. One study did not specify whether AFG was performed at the time of harvesting or as a delayed intervention.[22]

Additional Procedures

One study administered fat into the plane between soleus and gastrocnemius in patients with peripheral vascular disease in an attempt to promote revascularization while concurrently injecting lower limb wounds.[26]

Postoperative Care

Dressing type was reported in only 2 studies, including a hydrobalance biocellulose moist dressing[19] and negative pressure silicone dressing with topical negative pressure therapy for 4–5 days.[23] Three studies used concomitant antibiotics in the perioperative period.[19,23,25] The reasons for this were not detailed in all 3 articles, neither was the exact duration of antibiotic treatment. Immobilization post-AFG was only reported in 1 study, with 4–5 days bed rest.[23]

Wound Healing Outcomes

Lipotransfer

The majority of included studies used a lipotransfer technique (Table 5). One study administered unprocessed lipoaspirate without centrifugation.[23] In this study, 88% of wounds were fully healed and 12% of wounds were partially healed by 4 months. The average time to wound healing was 68 days (40–107), with an average reduction in wound surface area of 90%.

The remaining 5 studies used processed (ie, centrifuged) adipose tissue with follow-up lengths ranging from 3 to 6 months. One study did not report its follow-up duration.[22] The average number of wounds completely healed at primary follow-up was 65% (40%–100%); however, this was only reported in 3 studies.[19,24,27] In the 2 studies where partial healing of wounds was reported, this was achieved in 22%[19] and 60%[27] of cases. The average reduction in wound area was 85.7% in the only study where this was reported.[27] The average time to complete wound healing ranged from 4 to 16 weeks in the 2 studies where this was reported.[24,27]

Cell-assisted Lipotransfer

In the 2 studies using a CAL technique, complete wound healing was achieved in 60%,[18] and 100%[21] of wounds over a follow-up period of 3–6 months. Neither study reported on either partial healing rates or average reduction in wound area. The time to complete wound healing was 3 months[18] and 1 month.[21]

SVF Therapy

SVF treatment was used in postfiller necrosis and ulcers secondary to peripheral vascular disease and/or diabetes in 2 studies. Rates of complete healing differed markedly between these studies. By 8.5 months, 66% of

Table 4. Summary of the Fat Preparation Methods Used for Each Study

Components	Primary Author and Year	Donor Site	Liposuction Technique	Tumescent Solution	Anesthetic	Processing	Cell Viability Checked	Volume Used per Wound (mL)	Application Site	Wound Bed Preparation	No. Applications	Fat Graft in Index Procedure	Dressing	Additional Interventions
Lipotransfer (processed)	Del Bene et al[19]	Unspecified	Coleman	Unspecified	Local	Centrifuged for 3 min at 3000 rpm	N/A	2–3	Wound edge	Debridement	1	Yes	Yes	Antibiotics
Lipotransfer (processed)	Marangi et al[20]	Abdomen, hip, and calf	Coleman	Adrenaline with local anesthetic	Unspecified	Centrifuged for 1 min at 3000 rpm	N/A	1	Wound edge	Unspecified	Unspecified	Yes	Unspecified	None
Lipotransfer (processed)	Piccolo et al[22]	Abdomen, thigh, and buttocks	Coleman	Unspecified	Unspecified	Centrifuged for 3 min at 3000 rpm SVF and fat layer left together and injected	N/A	Unspecified	Wound edge and base	Unspecified	Multiple	Unspecified	Unspecified	Unspecified
Lipotransfer (processed)	Caviglia et al[24]	Unspecified	Coleman	Adrenaline with local anesthetic	General	Centrifuged for 3 min, unspecified rpm	N/A	Unspecified	Wound edge	Curettage	1	Yes	Unspecified	None
Lipotransfer (processed)	Chopinaud et al[27]	Abdomen, hip	Coleman	Unspecified	General	Centrifuged at 2–3000 rpm, time unspecified	N/A	9–21	Wound edge and base	Unspecified	1	Yes	Unspecified	None
Lipotransfer (unprocessed)	Stasch et al[23]	Abdomen, thigh	Coleman	Adrenaline without local anesthetic	General	Uncentrifuged	N/A	2–15	Wound edge and base	Debridement	Multiple	Yes	Yes	Antibiotics topical negative pressure dressing for 5 d
CAL	Marino et al[18]	Abdomen	Coleman	Adrenaline with local anesthetic	Unspecified	Celution extraction centrifuged for 5 min at 3000 rpm SVF pellet washed and recentrifuged for 5 min at 1500 rpm SVF pellet resuspended and injected	Yes—MTT method	5	Wound edge	Debridement	Unspecified	No (storage unspecified)	Unspecified	Unspecified
CAL	Del Papa et al[21]	Abdomen	Coleman	Unspecified	Local	Centrifuged for 3 min SVF pellet resuspended and injected	N/A	0.5–1	Wound base	Unspecified	1	Yes	Unspecified	Unspecified
SVF only	Kim et al[25]	Abdomen	Coleman	Unspecified	Unspecified	Centrifuged for 4 min at 3500 rpm mixed with collagenase for 30 min Recentrifuged for 3 min at 3500 rpm	No	Unspecified	Wound edge	Debridement	Multiple	Yes	Unspecified	Antibiotics (n = 11), composite graft (n = 1), steroids (n = 1), fat injections (n = 2)
SVF only	Carstens et al[26]	Abdomen, flank	Unspecified	Unspecified	General	Disassociated with collagenase for 40 min Recentrifuged for 10 min	Yes—image cytometer	3–4	Wound edge	Debridement	1	Yes	Unspecified	Concomitant administration in plane of gastrocnemius and soleus (n = 6)

N/A, not applicable; MTT, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) assay.

AQ10

Table 5. Summary of the Outcome Measures Reported for Each Study

Component	Author	Unit of Analysis	Frequency of Follow-up	Time of Primary Outcome (mo)	% of Wounds Completely Healed at Primary Outcome	% Wounds 50%–99% Healed at Primary Outcome	No. Treatment of Failures (<50% Reduction at Primary Outcome)	Average Reduction in Wound Area at Primary Outcome	% of Wounds Completely Healed at Total Follow-up	% of Treatment Failures	Average Reduction in Wound Area at Total Follow-up	Average Time to Wound Healing (wk)	Adverse Events
Lipotransfer (processed)	Del Bene et al[19]	Per patient	Unspecified	3	55.5	22.2	2	Unspecified	66	22.2	Unspecified	Unspecified	None
Lipotransfer (processed)	Marangi et al[20]	Per ulcer	Unspecified	3	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified
Lipotransfer (processed)	Piccolo et al[22]	Per patient	Unspecified	Unspecified	Unspecified	Unspecified	2	Unspecified	99.3	0.7	Unspecified	Unspecified	Unspecified
Lipotransfer (processed)	Caviglia et al[24]	Per ulcer	Alternate days in first week, weekly	6	100	Unspecified	Unspecified	Unspecified	100	None	Unspecified	4.5[4,5]	None
Lipotransfer (processed)	Chopinaud et al[27]	Per ulcer	1 wk, monthly	4	40	60	0	85.7%	40	0	85.7	16	Donor site hematoma (n = 1), lost to follow-up (n = 1)
Lipotransfer (unprocessed)	Stasch et al[23]	Per patient	Weekly	4	88	12	0	90%	88	12	90	9.7 (5.7–15.3)	Lost to follow-up (n = 1), skin graft (n = 1)
CAL	Marino et al[18]	Per ulcer	1 wk, 2–3 mo	3	60	Unspecified	4	Unspecified	60	40	Unspecified	Unspecified	None
CAL	Del Papa et al[21]	Per patient	1, 3, and 6 mo	1	100	100	0	Unspecified	100	0	Unspecified	4.2 (2–7)	None
SVF only	Carstens et al[26]	Per ulcer	N/A	10	66	Unspecified	1	Unspecified	66	16.7	Unspecified	34 (32–36)	Unrelated death (n = 1)
SVF only	Kim et al[25]	Per ulcer	Monthly	6	0	50	4	Unspecified	0	50	Unspecified	Unspecified	Scarring, erythema hypopigmentation

N/A, not applicable.

wounds had completely healed in 1 study.[26] In contrast, no wounds had completely healed by 6 months in the other.[25] Neither study reported a reduction in total wound area or average time to wound healing.

Adverse Events

Nine studies reported on whether there were complications related to either the donor or recipient site. In studies using a lipotransfer approach, there was 1 donor site hematoma[27] and 1 patient required additional skin grafting[23] (Table 5).

SVF monotherapies were associated with scarring, erythema, and hypopigmentation in 1 study,[25] although the number of patients affected was not specified.[26] There were no reported treatment-related adverse events in the articles using the CAL approach.

GRADE Score

Using the GRADE approach, the quality of evidence for each outcome of interest was assessed as very low. The evidence for AFG in wound healing is based on observational data only with low patient numbers, subjective endpoint evaluation, loss to follow-up, between-study heterogeneity, and unclear effect sizes. This is further confounded by generally poor reporting of methodologic and technical details (Table 6).

DISCUSSION

This study represents the first systematic review of AFG for cutaneous wound healing. To date, there have been no RCTs comparing AFG to other wound management options. There is insufficient evidence to demonstrate whether AFG is superior to standard wound care or alternative treatment options. There is also insufficient evidence to establish whether one type of AFG technique leads to superior wound healing and how this varies according to wound etiology.

The rationale for using AFG to enhance wound healing is based on the cellular composition of the SVF.[5] ADSCs within the SVF have been shown to modulate the wound microenvironment by the paracrine secretion of molecules that modify the inflammatory response, activate local stem cell niches, and promote revascularization.[28,29] The use of either isolated ADSCs or crude SVF is thought to recapitulate the regenerative potential of conventional lipotransfer without the need for large-volume fat injections. This underpins the rationale for CAL—here, the supplementation of harvested lipoaspirate with either purified ADSCs or the SVF is thought to enhance its regenerative capabilities. However, the absence of comparative RCT-level evidence prevents this review from establishing if CAL is superior to conventional lipotransfer and if ADSC- or SVF-only therapy can reproduce the effects of lipotransfer or CAL techniques in the clinical setting.[30]

It is possible that different cellular components within the SVF act synergistically to enhance wound healing[31]; however, no studies have compared SVF therapy to isolated ADSC therapies. Evidence from a murine myocardial infarction model suggests that they have similar regenerative effects,[32] while a small case series of Crohn's fistulas

Table 6. Evaluation of the Quality of Evidence from Each Study, Using the GRADE Method

Outcome	Studies	No. Wounds	Design	Quality	Consistency	Directness	Effect Size	Overall Assessment
% Wounds completely healed	Marino et al[18]	10	Observational	• Sparse data • Selective outcome reporting • Nonblinded • Inconsistency between interventions • No statistical analysis	• No evidence of dose response	• Different endpoints • Different disease states • Different regimens between studies	Unclear	Very low
	Del Bene et al[19]	15						
	Stasch et al[23]	26						
	Caviglia et al[24]	5						
	Kim et al[25]	12						
	Carstens et al[26]	6						
	Chopinaud et al[27]	10						
% Wounds partially healed	Del Bene et al[19]	15	Observational	• No statistical analysis • Uncertainty regarding included population • Subjective outcome assessment	• No evidence of dose response	• Narrow included population • Unclear enrolment • Clinical heterogeneity between studies	Unclear	Very low
	Stasch et al[23]	26						
	Kim et al[25]	12						
	Chopinaud et al[27]	10						
Time to complete wound healing	Stasch et al[23]	26	Observational	• No intention-to-treat analysis • Sparse data • Selective outcome reporting	• Different endpoints • Considerable heterogeneity	• Unclear outcome definitions • Clinical heterogeneity between studies	Unclear	Very low
	Caviglia et al[24]	5						
	Chopinaud et al[27]	10						
Adverse events	Marino et al[18]	10	Observational	• Loss to follow-up • Subjective assessment of outcomes	• Conflicting results with animal studies	• Narrow included population • Exclusion of drop-outs • Selective nonreporting	Unclear	Very low
	Del Bene et al[19]	15						
	Stasch et al[23]	26						
	Caviglia et al[24]	5						
	Carstens et al[26]	6						
	Chopinaud et al[27]	10						

found that expanded ADSCs were superior to uncultured SVF.[33] Conclusively demonstrating whether ADSCs alone lead to improvements in wound healing when compared with SVF (or vice versa) will be important both for SVF/ADSC monotherapy and for appropriately selecting which cell concentrate should be added to harvested fat for CAL approaches.

Although there is no universally accepted protocol for AFG, various factors related to lipoaspirate harvest,[28,34–37] processing,[38,39] and implantation[40] have been shown to affect both ADSC viability and graft retention. Unfortunately, all included studies omitted important technical details and inadequately characterized the fat product used. Together, these issues make meaningful cross-comparative evaluation of the literature challenging. Comprehensive methodologic reporting should be considered essential for all future research.[41] To ensure standardization of fat grafting research and outcome comparison, future studies should comply to a minimum of methodologic reporting standards, including: all details of fat processing [infiltration solution; location of harvest; harvest method (eg, cannula size, suction pressure, manual- or power-assisted); centrifugation; further processing into SVF/ADSC; method of grafting]; detailed patient demographics to allow subgroup analysis; and standardized outcome measures (the authors suggest time to wound healing and number of wounds healed to be the most straightforward to measure and clinically applicable).

Although the authors reviewed over 5000 citations and routinely screened the reference lists of all included articles, it remains possible that relevant studies have been missed. In comparison, publication bias represents a more likely source of error. No included studies reported unfavorable results (ie, either AFG improves wound healing or negative results are not reported). A recent systematic review of AFG and ADSC therapy for burn scars illustrates this concern. Based on largely qualitative data from 12 observational human studies, the authors concluded that the early evidence was encouraging[4]; however, the first prospective RCT of AFG for burn scars identified no benefit compared with saline injections.[42]

This review included an intentionally broad range of wound etiologies to establish whether AFG is more effective for particular wound types. For example, the behavior and regenerative potential of ADSCs have been shown to differ in acute and chronic wound microenvironments.[43] However, with insufficient studies for formal subgroup analysis, our narrative synthesis of the literature must be interpreted in the context of a marked between-study heterogeneity. It is also worth highlighting that the variability in outcome measures was used across the literature; broadly, endpoints have been subjectively assessed and do not provide robust quantitative data for a reliable comparative assessment.

CONCLUSIONS

This systematic review is the first to look at AFG as a treatment option for cutaneous wound healing. However, due to significant heterogeneity within the existing literature, there is an inability to delineate any superiority of AFG over traditional wound care or treatment options. Nonetheless, in some small, poorly reported studies, AFG has shown encouraging results for cutaneous wounds without unacceptably high complication rates. However, these findings must be interpreted in light of the quality of evidence available, and further larger studies are necessary to determine its efficacy.

Future research should aim to establish how AFG compares with alternative wound management options. Additionally, identifying which AFG technique is superior for wound healing and whether this varies according to wound characteristics will be essential.

There is an urgent requirement for well-designed, blinded, prospective RCTs with adequate methodologic details and objective outcome measure reporting. In the first instance, these should use alternative wound management options as a control before comparing different AFG procedures with one another.

Dean Malik, MSc, BMBS, BSc(Hons)
Division of Surgery and Interventional Science
Royal Free Hospital
University College London
9th Floor, Pond Street
London NW3 2QG, United Kingdom
E-mail: dean.malik@nhs.net

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